Programma voorjaarsvergadering 21 en 22 maart 2013
NH Conference Centre Koningshof Veldhoven

NEDERLANDSE VERENIGING VOOR GASTROENTEROLOGIE

Sectie Gastrointestinale Endoscopie
Netherlands Society for Parenteral and Enteral Nutrition
Sectie Neurogastroenterologie en Motiliteit
Sectie Experimentele Gastroenterologie
Sectie Gastrointestinale Oncologie
Sectie Inflammatoire Darmziekten IBD
DEGH-Meeting
Sectie Kinder-MDL
V&VN MDL

NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

NEDERLANDSE VERENIGING VOOR GASTROINTESTINALE CHIRURGIE

NVGIC Nederlandse Vereniging voor GastroIntestinale Chirurgie

NEDERLANDSE VERENIGING VAN MAAG-DARM-LEVERARTSEN

MDL

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Dutch Experimental Gastroenterology and Hepatology Meeting (DEGH) 14
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Tijdstippen diverse ledenvergaderingen tijdens voorjaarsvergadering:

Nederlandse Vereniging voor Gastroenterologie	21 maart, 11.30 uur – Brabantzaal
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Tijdstippen diverse ledenvergaderingen tijdens voorjaarsvergadering:

Nederlandse Vereniging van Maag-Darm-Leverartsen 22 maart, 08.00 uur – Brabantzaal
V&VN MDL 22 maart, 11.45 uur – Diezezaal
Vergadering Sectie Inflammatoire Darmziekten (IBD) 22 maart, 11.15 uur – Parkzaal

Belangrijke mededeling
over de aanwezigheid van farmaceutische industrieën

Aan alle deelnemers aan de voorjaarsvergadering op 21 en 22 maart 2013

De Nederlandse Vereniging voor Gastroenterologie kent een jarenlange samenwerking met de farmaceutische industrie. De vereniging stelt de farmaceutische industrie in de gelegenheid aanwezig te zijn bij de wetenschappelijke vergaderingen met een stand. Mede hierdoor kan de vereniging haar wetenschappelijke bijeenkomsten organiseren.

De Geneesmiddelenwet zegt dat - onder strikte voorwaarden - de farmaceutische industrie alleen reclame mag maken voor receptgeneesmiddelen voor personen die bevoegd zijn om dergelijke geneesmiddelen voor te schrijven. Alle andere personen (inclusief bijvoorbeeld verpleegkundigen, endoscopie-assistenten en biochemici) worden beschouwd als “publiek”. De farmaceutische industrie mag geen reclame maken voor receptgeneesmiddelen voor publiek.
De Nederlandse Vereniging voor Gastroenterologie is een wetenschappelijke vereniging voor personen die beroepsmatig betrokken zijn bij zorg, onderwijs en onderzoek ten behoeve van patiënten met maag-, darm- en leveraandoeningen. Dat betekent dat ook personen die geen arts zijn, lid van de NVGE zijn. De aanwezigheid van artsen, niet-artsen en farmaceutische industrieën tijdens de voorjaarsvergadering kan de NVGE ongewild in aanraking brengen met de inspectie voor de gezondheidszorg, sectie reclametoezicht, en daarmee in diskrediet worden gebracht.
Dat willen wij uiteraard voorkomen.

In verband met de Gedragscode Geneesmiddelenreclame van de CGR en de aan het NVGE-congres verbonden expositie van farmaceutische producten, medische instrumenten en voedingsmiddelen, zal bij uw congresregistratie via de NVGE-website worden gevraagd naar uw bevoegdheid om medicijnen voor te schrijven.

Alle congresdeelnemers dragen verplicht een congresbadge waarop behalve de naam ook beroep/ functie staat aangegeven. Farmaceutische standhouders benaderen uitsluitend congresdeelnemers die de bevoegdheid hebben om receptgeneesmiddelen voor te schrijven of ter hand te stellen. Om dit extra te verduidelijken zal vanaf komend voorjaarscongres worden gekozen voor verschillende kleuren congresbadges.

Uit het bovenstaande volgt dat aanwezige reclame-uitingen en merkproductinformatie van farmaceutische industrieën alleen gericht zijn op personen die bevoegd zijn om de betreffende geneesmiddelen voor te schrijven. Wij maken u erop attent dat het voor niet-artsen dan ook niet is toegestaan de stands van de aanwezige farmaceutische industrieën te bezoeken.

De NVGE en farmaceutische industrie (sponsoren) vertrouwen erop u met bovenstaande voldoende te hebben geïnformeerd.

Het bestuur van de NVGE

VOORWOORD

Hierbij treft u het volledige programma aan van de voorjaarsvergadering op 21 en 22 maart 2013 in NH Conference Center Koningshof te Veldhoven. Zoals gebruikelijk wordt ons congres vooraf gegaan door het cursorisch onderwijs op 20 maart, waarvan u het programma aantreft op bladzijde 6 en 7.

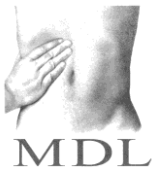
Op donderdag 21 maart zijn er vrije voordrachten van de Nederlandse Vereniging voor Gastroenterologie in de Brabantzaal. Parallel hieraan vinden in de Parkzaal vrije voordrachten plaats van de sectie Inflammatoire Darmziekten, gevolgd door voordrachten van de NVGE en voordrachten van de sectie Neurogastroenterologie en Motiliteit.
De Nederlandse Vereniging voor Gastrointestinale Chirurgie start om 9.00 uur met een lustrum-symposium in het Auditorium. Het thema voor dit symposium is 'Borders & Customs in colorectal surgery'.
In de Baroniezaal is zowel op donderdag als op vrijdag de Dutch Experimental Gastroenterology and Hepatology Meeting, een gezamenlijk initiatief van de Sectie Experimentele Gastroenterologie van de NVGE en de Sectie Basale Hepatologie van de NVH, voor het zesde achtereenvolgende jaar. Vanaf 12.00 organiseert de DEGH postersessies in de Meierij. U vindt van deze posters een overzicht vanaf pagina 59.
Om 17.00 uur vindt in de Brabantzaal de uitreiking plaats van de Janssen Research Prijs 2012. Aansluitend volgt om 17.30 uur de President Select, zoals gebruikelijk ook plenair. Deze sessie duurt tot 18.30 uur en sluit daarmee het programma van de donderdag af. In de avond zijn er geen verdere lezingen meer ingepland, zodat er gelegenheid is voor diner en ontspanning.

Op vrijdagochtend zijn er vanaf 09.30 uur vrije voordrachten van de Sectie Gastrointestinale Endoscopie en parallel daaraan vrije voordrachten van de Nederlandse Vereniging voor Gastrointestinale Chirurgie in het Auditorium en van de sectie Oncologie in de Parkzaal. In Zaal 80 start vanaf 09.00 uur de abstract meeting van NESPEN, gevolgd door het NESPEN Symposium. Na de koffiepauze vindt in de Brabantzaal een symposium plaats over de Richtlijn Coloscopie Surveillance. Parallel zijn er vrije voordrachten van de Nederlandse Vereniging voor Gastrointestinale Chirurgie en van de Sectie Inflammatoire Darmziekten respectievelijk in het Auditorium en de Parkzaal. Gedurende de gehele vrijdag zijn er genodigde sprekers en vrije voordrachten van de DEGH.
Na de lunch wordt de dag afgesloten met het Symposium Oncologie in de Brabantzaal en voordrachten van de Nederlandse Vereniging voor Gastrointestinale Chirurgie en de Nederlandse Vereniging voor Gastroenterologie in het Auditorium. In de Diezezaal wordt door de Vereniging Verpleegkundigen en Verzorgenden Nederland MDL (V&VN MDL) een eigen programma met lezingen verzorgd, met in de middag een keuze uit verschillende subsessies.

Dr. J.J. Keller, secretaris NVGE

Woensdag 20 maart 2013

Cursorisch onderwijs in maag-darm-leverziekten **Auditorium**



Cursuscommissie
Prof. dr. P.D. Siersema (voorzitter), MDL-arts, UMCU
Mevr. dr. C.M. Bakker, MDL-arts, Atrium MC, Heerlen
Prof. dr. U.H.W. Beuers, MDL-arts, AMC, Amsterdam
Drs. M.P.J. van den Broek, AIOS MDL, LUMC, Leiden
Dr. J. Heisterkamp, chirurg, St. Elisabeth Ziekenhuis Tilburg
Mevr. dr. A.M.J. Langers, MDL-arts, LUMC, Leiden
Drs. M.C.P. Pennings, AIOS MDL, UMC St Radboud, Nijmegen
Dr. B.J. Veldt, MDL-arts, Reinier de Graaf Gasthuis Delft
Dr. R.A. de Vries, MDL-arts, VUmc, Amsterdam
Dr. P.J. Wahab, MDL-arts, Rijnstate Ziekenhuis, Arnhem

Oncologie van de bovenste tractus digestivus

15.00 – 15.15 Opening met toets

15.15 – 15.40 Principes van chemotherapie van oncologische aandoeningen
Dr. A. van der Gaast, oncoloog, Erasmus MC Rotterdam

Oesofagus-maag oncologie

15.40 – 16.05 Diagnostiek en stadiering oesofagus-maagcarcinoom
Dr. F.P. Vleggaar, MDL-arts, UMC Utrecht

16.05 – 16.30 Chirurgie van het oesofagus-maagcarcinoom
Dr. M.I. van Berge Henegouwen, chirurg, AMC, Amsterdam

16.30 – 16.55 Centralisatie van behandeling van MDL-maligniteiten
Prof. dr. R. van Hillegersberg, chirurg, UMC Utrecht

16.55 – 17.20 Casuïstiek door aios MDL, UMCGroningen, gevolgd door paneldiscussie
Panel: Dr. F.P. Vleggaar, Dr. A. van der Gaast en Dr. M.I. van Berge Henegouwen

17.20 – 17.30 Kennistoets

17.30 – 18.00 Pauze

Cursorisch onderwijs in maag-darm-leverziekten, vervolg **Auditorium**

HPB-oncologie

18.00 – 18.10	Kennistoets
18.10 – 18.35	Differentiaal diagnose focale levertumoren *Dr. M.J. Coenraad, MDL-arts, LUMC Leiden*
18.35 – 19.00	Differentiaal diagnose cysteuze en solide afwijkingen in pancreas/galwegen *Dr. H.M. van Dullemen, MDL-arts, UMC Groningen*
19.00 – 20.15	Diner
20.15 – 20.40	Chirurgische mogelijkheden en onmogelijkheden bij de behandeling van het cholangio- en pancreascarcinoom *Prof. dr. C.H.C. Dejong, chirurg, MUMC Maastricht*
20.40 – 21.05	Opereren zonder snijden: radiologische behandeling van maligne levertumoren *Dr. W. Prevoo, radioloog, AvL Amsterdam*
21.05 – 21.30	Casuïstiek door aios MDL, Reinier de Graaf Gasthuis, Delft, gevolgd door paneldiscussie *Panel: Dr. H.M. van Dullemen, Prof. dr. C.H. Dejong, Dr. W. Prevoo*
21.30 – 21.55	Als curatie niet meer mogelijk is: optimale palliatie van patiënten met MDL-tumoren *Prof. dr. C.C. van der Rijt, oncoloog, Erasmus MC, Rotterdam*
21.55 – 22.05	Kennistoets
22.05	Einde programma

De cursuscommissie verwacht van de MDL-artsen i.o. dat ze de Cursus Klinische Hepatologie (NVH) éénmaal bezoeken in het tweede deel van de MDL-opleiding (jaar vier tot zes).

Op het cursorisch onderwijs zijn conform de eisen van het Centraal Register Kort Beroepsonderwijs leveringsvoorwaarden van toepassing. Informatie vindt u op de onderwijspagina van www.mdl.nl en www.nvge.nl.

Programma donderdag 21 maart 2013

Donderdag	Brabantzaal	Baroniezaal	Auditorium	Parkzaal
09.00	Ontvangst en koffie	Ontvangst en koffie	Lustrumsymposium NVGIC: Borders & Customs in colorectal surgery'. pagina 12	Ontvangst en koffie
10.00 - 11.30	Vrije voordrachten Ned. Vereniging voor Gastro-enterologie pagina 10	DEGH-meeting (aanvang 10.30 uur) Gastspreker: Prof. T.H. Karlsen pagina 14		Vrije voordrachten Sectie Inflammatoire Darmziekten pagina 16
11.30 - 12.00	Ledenvergadering NVGE			Geen programma i.v.m. Ledenvergadering NVGE
12.00 - 13.00	Lunch in expositiehal	Lunchbuffet en postersessie	Lunch in expositiehal	Lunch in expositiehal
13.00 – 15.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie pagina 18	DEGH-meeting Gastspreker: Prof. A. Kaser pagina 26	Lustrumsymposium NVGIC: Borders & Customs in colorectal surgery'. pagina 24	Vrije voordrachten Ned. Vereniging voor Gastroenterologie pagina 29
15.00 - 15.30	Theepauze	Theepauze + ALV NVH	Theepauze	Theepauze
15.30 - 17.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie pagina 20	DEGH-meeting pagina 27	Lustrumsymposium NVGIC: Borders & Customs in colorectal surgery'. pagina 24	Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit pagina 31
17.00 - 17.30	Uitreiking Janssen Gastrointestinale Research Prijs 2012 pagina 22			
17.30 - 18.30	President Select pagina 22			
18.30 - 19.30	Borrel in expositiehal			
19.30 - 22.00	Diner Genderzaal			
22.00 - 01.00	Borrel / Muziek in foyer			

Vrijdag 22 maart 2013

Vrijdag	Brabantzaal	Baroniezaal	Auditorium	Parkzaal
08.30 09.30 – 11.00	Vrije voordrachten sectie Gastrointestinale Endoscopie pagina 33	DEGH-meeting Gastspreker: Prof. M. Neunlist pagina 39	Vrije voordrachten Ned. Vereniging voor Gastrointestinale Chirurgie pagina 36	Vrije voordrachten Sectie Gastrointestinale Oncologie pagina 42
		Koffiepauze (10.25)		
11.00 - 11.30	Koffiepauze	DEGH-meeting Gastspreker: M. Huch pagina 40	Koffiepauze	Vergadering + koffie
11.30 - 13.00	Symposium Richtlijn Coloscopie Surveillance pagina 35		Vrije voordrachten Ned. Vereniging voor Gastrointestinale Chirurgie pagina 37	Vrije voordrachten Sectie Inflammatoire Darmziekten pagina 44
		Lunchbuffet en postersessie		
13.00 – 14.00	Lunch expositiehal		Lunch expositiehal	Lunch expositiehal
14.00 – 15.30	Symposium: Oncologische behandelingen en hun bijwerkingen in de tractus digestivus pagina 46	DEGH-meeting Gastspreker: S. Withoff pagina 49	Vrije voordrachten Ned. Vereniging voor Gastroenterologie en Gastrointestinale Chirurgie -pagina 47	Geen programma in deze zaal in de middag
15.30 – 16.00	Afsluiting in expositiehal	Abstract and Poster Prizes and goodbye	Afsluiting in expositiehal	

Vrijdag 22 maart 2013 - programma V&VN MDL en NESPEN

Vrijdag	Diezezaal	Zaal 52	Zaal 58	Zaal 57	Zaal 80
10.00 – 12.15	Plenair ochtendprogramma V&VN MDL pagina 55				Voordrachten NESPEN, om 10.30. gevolgd door Symposium Oncology and Nutrition - p. 51-53
12.15	Lunch in expo				Lunchbuffet 13.10
13.45 – 15.30	Parallel programma Endoscopie-verpleegkundigen pagina 56	Parallel programma Lever- en IBD-verpleegkundigen pagina 56	Parallel programma Voedings-verpleegkundigen pagina 57	Parallel programma MDL – kliniek verpleegkundigen pagina 58	Geen programma in deze zaal in de middag
15.30	Einde programma	Einde programma	Einde programma	Einde programma	

Donderdag 21 maart 2013

Nederlandse Vereniging voor Gastroenterologie — Brabantzaal

09.30 Inschrijving, koffie

Voorzitter: J.J. Keller en M.E. van Leerdam

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

10.00 Increased prevalence of proximal and multiple adenomas in patients with diabetes mellitus (p. 65)

S. de Kort[1] , M. Bouwens[1], M. Weijenberg[2], P.A. van den Brandt[2], R. Riedl[3], A. Masclee[1], S. Sanduleanu[1], [1]Dept. of Gastroenterology & Hepatology, Maastricht University Medical Centre, Maastricht, Limburg, The Netherlands, [2]Dept. of Epidemiology, Maastricht University, Maastricht, Limburg, The Netherlands[3], Dept. of Pathology, Maastricht University Medical Centre, Maastricht, Limburg, The Netherlands

10.10 Microsatellite instability, BRAF and KRAS mutation in postcolonoscopy cancers: an explorative study (p. 66)

C.M.C. le Clercq[1] , R.G. Riedl[2] , M.W.E. Bouwens[1] , B. Carvalho[3] , G.A. Meijer[3] , M. van Engeland[2] , B. Winkens[4] , A.A.M. Masclee[1] , S. Sanduleanu[1], [1]Division of Gastroenterology and Hepatology, Dept. of Internal Medicine, Maastricht University Medical Center, The Netherlands, [2]Dept. of Pathology, Maastricht University Medical Center, The Netherlands, [3]Dept. of Pathology, VU Medical Center Amsterdam, The Netherlands, [4]Dept. of Methodology and Statistics, Maastricht University Medical Center, The Netherlands

10.20 Efficacy of EUS-implanted fiducial markers to diminish margins in radiation of pancreatic cancer (p. 67)

J. van Hooft[1], A. van der Horst[2], S. Wognum[2], R. de Jong[2], G. van Tienhoven[2], R. Davila Fajardo[2], P. Fockens[1], A. Bel[2], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Dept. of Radiotherapy, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

10.30 Prevalence of small bowel neoplasia in Lynch syndrome as assessed by capsule endoscopy (p.68)

J.F. Haanstra[1], A. Al-Toma[2], E. Dekker[3], A. Cats[4], F.M. Nagengast[5], M.E. van Leerdam[4,6], W.H. de Vos tot Nederveen Cappel[7], S. Sanduleanu[8], S.A. Vanhoutvin[4], E.M. Mathus- Vliegen[3], R.A. Veenendaal[9], H.F.A. Vasen[9,10], J.H. Kleibeuker[1], J.J. Koornstra[1] , [1]Dept. of gastroenterology and hepatology, University Medical Center Groningen, Groningen, [2]Dept. of gastroenterology and hepatology, St Antonius Hospital, Nieuwegein, [3]Dept. of gastroenterology and hepatology, Amsterdam Medical Center, Amsterdam, [4]Dept. of gastroenterology and hepatology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, [5]Dept. of gastroenterology and hepatology, Radboud University Nijmegen Medical Center, Nijmegen, [6]Dept of gastroenterology and hepatology, Erasmus Medical Center, Rotterdam, [7]Dept. of gastroenterology and hepatology, Isala Clinics, Zwolle, [8]Dept. of gastroenterology and hepatology, Maastricht University Medical Center, Maastricht, [9]Dept of gastroenterology and hepatology, Leiden University Medical Center, Leiden, [10]The Netherlands Foundation for the Detection of Hereditary Tumours, Leiden

10.40 Delineating the PMS2 cancer risk (p. 69)

S. ten Broeke[1], M. Nielsen[1], R.M. Brohet[2] , C.M. Tops[1] , H. van der Klift[1], M.G. Ausems[3], E. Gómez García[4], F.J. Hes[1], N. Hoogerbrugge[5], F.H. Menko[6], R.C. Niessen[7], T.A. van Os[8], R.H. Sijmons[7], L. Spruijt[5], S. Verhoef[9], A. Wagner[10], The Mallorca Group, M. Velthuizen[3] , H.F. Vasen[11], J.T. Wijnen[1], [1]Centre of Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands, [2]Spaarne Hospital, Hoofddorp, The Netherlands, [3]Dept. of Medical Genetics, University Medical Centre, Utrecht, The Netherlands, [4]Dept. of Clinical Genetics, University Hospital, Maastricht, The Netherlands, [5]Dept. of Human Genetics and Hereditary Cancer Clinic, University Medical Centre, Nijmegen, The Netherlands, [6]Dept. of Clinical Genetics and Human Genetics, VU University Medical Centre, Amsterdam, [7]Dept. of Clinical Genetics, University Medical Centre, Groningen, The Netherlands, [8]Dept. of Clinical Genetics, Academic Medical Centre Amsterdam, Netherlands, [9]Family Cancer Clinic, Netherlands Cancer Institute, Amsterdam, [10]Dept. of Clinical Genetics, Erasmus University Medical Centre, Rotterdam, [11]The Netherlands Foundation for the Detection of Hereditary Tumours, Leiden, The Netherlands

10.50 Prevalence and characteristics of serrated lesions in individuals undergoing primary screening colonoscopy (p. 70)

Y. Hazewinkel [1], T.R de Wijkerslooth[1] , E.M. Stoop[2] , P.M. Bossuyt[3] , K. Biermann[4] , M.J. van de Vijver[5] , P. Fockens[1] , M.E. van Leerdam[2] , E.J. Kuipers[2], E. Dekker [1] Y.[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Dept. of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, The Netherlands, [4]Dept. of Pathology, Erasmus University Medical Center, Rotterdam, The Netherlands, [5]Dept. of Pathology, Academic Medical Center, Amsterdam, The Netherlands

11.00 Proximal Colorectal Cancers Have Distinct Clinicopathologic Features: A 10-Year Population-Based Survey (p. 71)

C.M.C. le Clercq[1], F.J.J.M. van Proemeren[1], M.W.E. Bouwens[1] , C.M. Bakker[2] , E.T.P. Keulen[3] , B. Winkens[4] , A.A.M. Masclee[1] , S. Sanduleanu[1], [1]Division of Gastroenterology and Hepatology, Dept. of Internal Medicine, Maastricht University Medical Center, The Netherlands, [2]Dept. of Gastroenterology, Atrium Medical Center Heerlen, The Netherlands, [3]Dept. of Internal Medicine and Gastroenterology, Orbis Medical Center Sittard, The Netherlands, [4]Dept. of Methodology and Statistics, Maastricht University Medical Center, The Netherlands

11.10 Current surgical strategies for patients with acute left-sided colonic cancer; analysis of a large prospective Dutch cohort (p. 72)

M.A.W. Stam[1] (presenting author) N.R. Paulino Pereira[1] , W.A. Draaisma[1] , E.C.J. Consten , P.J. Tani[2] , W.A. Bemelman[2], [1] Meander Medisch Centrum, locatie Lichtenberg (Amersfoort) [2]AMC Amsterdam, The Netherlands

11.20 Missed Flat Lesions: A Major Contributor To Postcolonoscopy Cancers (p.73)

C.M.C. le Clercq[1] , M.W.E. Bouwens[1], E.J.A. Rondagh[1], R.J.J. de Ridder[2], C.M. Bakker[3], E.T.P. Keulen[4], B. Winkens[5], A.A.M. Masclee[1], S. Sanduleanu[1], [1]Dept. of Gastroenterology and Hepatology, Internal Medicine, Maastricht University Medical Center, The Netherlands, [2]Dept. of Pathology, Maastricht University Medical Center, The Netherlands, [3]Dept. of Internal Medicine and Gastroenterology, Atrium Medical Center Heerlen, The Netherlands, [4]Dept. of Internal Medicine and Gastroenterology, Orbis Medical Center Sittard, The Netherlands, [5]Dept. of Methodology and Statistics, Maastricht University Medical Center, The Netherlands

11.30 Einde abstractsessie, aansluitend in deze zaal de ALV van de NVGE

Donderdag 21 maart 2013

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Auditorium**

Lustrum NVGIC 2013

Exploring Borders in GI surgery
Borders & Customs in colorectal surgery

Ochtendprogramma

9.00 Opening

Customs in colorectal surgery (voordrachten in het Nederlands)

Voorzitters: P.P. Coene en W.M.U. van Grevenstein

9.05 Het Zorgpad, de naakte feiten
Dr. J.M. Klaase, chirurg, Medisch Spectrum Twente, Enschede

9.20 Peri-operatieve management van de colorectale patiënt
Prof. Dr. M. Hollmann, anesthesist, AMC, Amsterdam

9.40 NSAID's en naadlekkage, feit of fabel?
Dr. M.D.P. Luyer, chirurg, Catharina Ziekenhuis, Eindhoven

10.00 Koffiepauze expositiehal

Borders in colorectal surgery (voordrachten in het Engels)

Voorzitters: T. Karsten en C. Verhoef

10.30 APR, the approach
Dr. P.J. Tanis, chirurg, AMC, Amsterdam

10.45 APR, the closure
Dr. G. Nieuwenhuijzen, chirurg, Catharina Ziekenhuis, Eindhoven

Lustrum NVGIC 2013

Exploring Borders in GI surgery
Borders & Customs in colorectal surgery

11.10 - 11.25 Innovations in colorectal surgery round 1
11.35 - 11.50 Innovations in colorectal surgery round 2

12.00 - 12.20 Towards non invasive treatment of rectal cancer
Dr. G. Beets, chirurg, MUMC+, Maastricht

12.20 - 13.00 Lunchbuffet in de expositiehal

Donderdag 21 maart 2013

DEGH-Meeting **Baroniezaal**

Voorzitters: T.H. Karlsen en R.K. Weersma

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

Theme **Primary Sclerosing Cholangitis**

10.30 Chronic antigenic stimulation may be an etiological feature of IgG4-Associated Cholangitis (p.74)
L. Maillette de Buy Wenniger[*1], M.E. Doorenspleet*[*2], J. Verheij[3], N. de Vries[2], U. Beuers[1], [1]Dept. of Gastroenterology and Hepatology, Tytgat Institute of Liver and Intestinal Research, [2]Dept. of Experimental Immunology and Rheumatology, [3]Dept. of Pathology, all at the Academic Medical Center of the University of Amsterdam, Amsterdam, The Netherlands, *these authors contributed equally to this work*

10.42 Increased IL8 in bile and increased MUC5AC and CFTR expression in the gallbladder of patients with primary sclerosing cholangitis (p.75)
S.J.L.B. Zweers[1], A. Shiryaev[2], T.H. Karlsen[2], P.L.M. Jansen[1,3], F.G. Schaap[1,4], [1]Tytgat Institute for Intestinal and Liver Research, Academic Medical Center, Amsterdam, The Netherlands, [2]Norwegian PSC Research Center, Clinic for Specialized Medicine and Surgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [3]Dept. of Hepatology and Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands, [4]Dept. of Surgery, Maastricht University, The Netherlands

10.54 Molecular aspects of rifampicin treatment in severe persistent hepatocellular secretory failure (p. 76)
R. van Dijk[1], A. E. Kremer[1], W. Smit[1], P.L.M. Jansen[1], U. Beuers[1], [1]Dept. of Gastroenterology & Hepatology, Tytgat Institute for Liver and Intestinal research, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

11.06 Specific biological pathways lead to distinct extra-intestinal manifestations and complications in inflammatory bowel disease (p.77)
S. van Sommeren[1,2], M. Janse[2], J. Karjalainen[1], R. Fehrmann[1], L. Franke[1], J. Fu[1], R.K. Weersma[2], [1]University of Groningen, University Medical Centre Groningen, Dept. of Genetics, The Netherlands, [2]University of Groningen, University Medical Centre Groningen, Dept. of Gastroenterology and Hepatology, The Netherlands

11.18 **Invited Speaker**
"PSC - what have we learned from genetics?"
T.H. Karlsen, professor of Gastroenterology, Oslo University Hospital, Norway

12.00 Lunch en postersessie

Postersessie DEGH — Meierij Foyer

12.00 De postersessie van de DEGH vindt plaats tussen 12.00 en 13.30 uur met vanaf 12.45 de mogelijkheid om u aan te sluiten bij een begeleide sessie langs de posters. Vier tot vijf posters per categorie, 7 minuten per poster, zie pagina 59 e.v.

De posters moeten tot aan het eind van het programma op vrijdagmiddag blijven hangen. Over de posterprijzen wordt vrijdag tijdens de lunch beslist.

13.30 Vervolg DEGH-programma.

Sectie Inflammatoire Darmziekten — Parkzaal

Voorzitters: A.E. van der Meulen en P.C.F. Stokkers

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

10.00 Active inflammation of the appendix in ulcerative colitis (p. 78)

T.J. Gardenbroek[1], C.J. Buskens[1] , JP van Straalen[2], GR van den Brink[3], G.R.A.M. D'Haens[3], W.A. Bemelman[1], [1]Dept. of Surgery, [2]Clinical Chemistry, [3]Dept. of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands

10.10 Long term response to infliximab treatment and its effect on disease course in ulcerative colitis – A population-based cohort study (0. 79)

S.F.G. Jeuring[1], P.H.A. Bours[1], A.W. Ambergen[2], T.R.A. van den Heuvel[1], M.J.L. Romberg- Camps[3], L.E. Oostenbrug[4], S.O. Breukink[5], A.A.M. Masclee[1], D.M.A.E. Jonkers[1], M.J. Pierik[1], [1]Dept. of Internal Medicine, Division of Gastroenterology & Hepatology, Maastricht University Medical Center, Maastricht, [2]Dept. of Methodology & Statistics, Maastricht University, Maastricht, [3]Dept. of Internal Medicine, Orbis Medical Center, Sittard, [4]Dept. of Internal Medicine, Atrium Medical Center, Heerlen, [5]Dept. of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

10.20 A Phase 2/3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Subcutaneous Golimumab Induction Therapy in Patients with Moderately to Severely Active Ulcerative Colitis: PURSUIT SC (p. 80)

P. Rutgeerts[1], B. G. Feagan[2], C. Marano[3], R. Strauss[3], J. Johanns[3], H. Zhang[3], C. Guzzo[3], J.-F. Colombel[4], W. Reinisch[5], P. Gibson[6], J. Collins[7], G. Jarnerot[8], W. Sandborn[9], [1]University of Leuven, Leuven, Belgium, [2]Robarts Research Institute, London, Ontario, Canada, [3]Janssen Research and Development, Spring House, PA, USA, [4]CHU, Lille, France, [5]Universitätsklinik für Innere Medizin IV, Vienna, Austria, [6]Alfred Hospital, Melbourne, VIC, Australia, [7]Oregon Health Sciences University ,Portland, OR, USA, [8]Orebro University Hospital, Orebro, Sweden, [9]University of California San Diego, La Jolla, CA, USA, Submitted and presented by dr. A.A. van Bodegraven, on behalf of the PURSUIT SC investigators

10.30 Fecal loss of Infliximab as a cause of lack of response in severe Inflammatory Bowel Disease (p. 81)

J.F. Brandse[1,2], M.E. Wildenberg[2], J.R. de Bruyn[1,2], G.J. Wolbink[3], M. Löwenberg[1], C.Y. Ponsioen[1], G.R. van den Brink[1,2], G.R.A.M. D'Haens[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands, [3]Sanquin Research Laboratory, Amsterdam, The Netherlands

10.40 Re-evaluation of anti-TNF use in a cohort of IBD patients in a non-academic hospital (p. 82)

L.A. van der Waaij, Martini Ziekenhuis Groningen, The Netherlands

10.50 Adalimumab for Crohn's disease: sustained benefit in a Dutch multicentre cohort (p. 83)

C.P. Peters[1], E. J. Eshuis[1,2], F.M. Toxopeus[1], J. M. Jansen[3] , G.R.A.M. D'Haens[1], P. Fockens[1], P.C.F. Stokkers[4], H.A.R.E. Tuynman[5], A.A. van Bodegraven[6], C.Y. Ponsioen[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept. of Surgery, Academic Medical Center, Amsterdam, [3]Dept. of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, [4]Dept. of Gastroenterology and Hepatology, St Lucas Andreas Hospital, Amsterdam, [5]Dept. of Gastroenterology and Hepatology, Medical Center Alkmaar, [6]Dept. of Gastroenterology and Hepatology, Free University Medical Centre, Amsterdam, The Netherlands

11.00 Re-introduction of Infliximab after consecutive failure of Infliximab and Adalimumab is beneficial in Refractory Crohn's Disease (p. 84)

J.F. Brandse[1], C.P. Peters[1], E.J. Eshuis[1], M. Löwenberg[1], C.Y. Ponsioen[1], G.R. van den Brink[1], G.R.A.M. D'Haens[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

11.10 ATG16L1 genotype is associated with response to anti-TNF (p. 85)

M.E. Wildenberg, A.D. Levin, A.C.W. Vos, J.F. Brandse, J.R. de Bruyn, G.R.A.M. D'Haens and G.R. van den Brink, Dept. of Gastroenterology and Hepatology and Tytgat Institute for Intestinal and Liver Research Academic Medical Center, Amsterdam, The Netherlands

11.20 Serial Magnetic Resonance Imaging for Monitoring Anti-TNF Treatment Effects in Crohn's Disease (p. 86)

J.A.W. Tielbeek[1], M. Löwenberg[2], S. Bipat[1], K. Horsthuis[1], C.Y. Ponsioen[2], G.R. D'Haens[2], J. Stoker[1], Academic Medical Center, Dept. of Radiology, Amsterdam, The Netherlands, [2]Academic Medical Center, Dept. of Gastroenterology and Hepatology, Amsterdam, The Netherlands

11.30 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie in de Brabantzaal

12.00 Lunchbuffet in de expositiehal

Nederlandse Vereniging voor Gastroenterologie — Brabantzaal

Voorzitters: M.J. Bruno en J.C.H. Hardwick

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

13.00 P53 immunohistochemistry for predicting neoplastic progression in patients with Barrett's esophagus: results from a large multicentre prospective cohort (p. 87)

F. Kastelein[1], S. van Olphen[1], K. Biermann[2], E.W. Steyerberg[3], J. Verheij[4], M. Kalisvaart[1], L.H.J. Looijenga[2], J.A. Stoop[2], L. Walter[2], E.J. Kuipers[1,5], H. Geldof[6], H. van der Valk[7], P.C.J. ter Borg[8], R.J.F. Felt[9], G.A. Meijer[10], J. Alderliesten[11], R. Heinhuis[12], F. ter Borg[13], J.W. Arends[14], J.J. Kolkman[15], J. van Baarlen[16], B. den Hartog[17], A.H. Mulder[18], A.J.P. van Tilburg[19], L.G.J.B. Engels[20], W. Vos[21], F.T.M Peters[22], A. Karrenbeld[23], B.E. Schenk[24], F. Moll[25], M.C.W. Spaander[1], M.J. Bruno[1], [1]Dept. of Gastroenterology & Hepatology, [2]Dept. of Pathology, [3]Dept. of Public health, Erasmus Medical Center, Rotterdam, [4]Dept. of Pathology, Academic Medical Center, Amsterdam, [5]Dept. of Internal medicine, Erasmus Medical Center, Rotterdam, [6]Dept. of Gastroenterology & Hepatology, IJsselland, Capelle aan den IJssel, [7]Pahology laboratory Pathan, Rotterdam, [8]Dept. of Gastroenterology & Hepatology, Ikazia, Rotterdam, [9]Dept. of Gastroenterology & Hepatology, VU University Medical Center, Amsterdam, [10]Dept. of Pathology, VU University Medical Center, Amsterdam, [11]Dept. of Gastroenterology & Hepatology, [12]Dept. of Pathology, Albert Schweitzer, Dordrecht, [13]Dept. of Gastroenterology & Hepatology, [14]Dept. of Pathology, Deventer Hospital, Deventer, [15]Dept. of Gastroenterology & Hepatology, Medical Spectrum Twente, Enschede, [16]Pathology laboratory East Netherlands, Enschede, [17]Dept. of Gastroenterology & Hepatology, [18]Dept. of Pathology, Rijnstate, Arnhem, [19]Dept. of Gastroenterology & Hepatology, Sint Franciscus Gasthuis, Rotterdam, [20]Dept. of Gastroenterology & Hepatology, [21]Dept. of Pathology, Orbis Medical Center, Sittard, [22]Dept. of Gastroenterology & Hepatology, [23]Dept. of Pathology, University Medical Center, Groningen, [24]Dept. of Gastroenterology & Hepatology, [25]Dept. of Pathology, Isala Clinics, Zwolle, The Netherlands

13.10 A randomised trial comparing multiband mucosectomy and ER-cap for endoscopic piecemeal resection of early squamous neoplasia of the esophagus (p. 88)

D.F. Boerwinkel[1], Y.M. Zhang[2], S. He[2], L. Xue[3], B.L.A.M. Weusten[1,4], S.M. Dawsey[5], D.E. Fleischer[6], X. Qin[2], L.Z. Dou[2], Y. Liu[2], N. Lu[3], J.J.G.H.M. Bergman[1], G.Q. Wang[2], [1]Gastroenterology and Hepatology, Academic Medical Centre Amsterdam, The Netherlands, [2]Endoscopy, Cancer Institute and Hospital, Chinese Academy of Medical Sciences Beijing, PR China, [3]Pathology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences Beijing, PR China, [4]Gastroenterology and Hepatology, St Antonius Hospital Nieuwegein, The Netherlands, [5]Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda MD, USA, [6]Gastroenterology and Hepatology, Mayo Clinic, Scottsdale AZ, USA

13.20 Low-grade dysplasia in Barrett's esophagus has a high risk of progression when confirmed by a panel of expert pathologists (p. 89)

L.C. Duits[1], K.Y.N. Phoa[1], W.L. Curvers[1], F.J. Ten Kate[2], G.A. Meijer[3], C.A. Seldenrijk[4], G.J. Offerhaus[2], M. Visser[2], S.L. Meijer[2], K.K. Krishnadath[1], R.C. Mallant-Hent[5,1], J.J.G.H.M. Bergman[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands, [2]Dept. of Pathology, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept. of Pathology, VU University Medical Center, The Netherlands, [4]Dept. of Pathology, St. Antonius Hospital, Nieuwegein, The Netherlands, [5]Dept. of Gastroenterology and Hepatology, Flevoziekenhuis, Almere, The Netherlands

13.30 The impact of active monitoring of quality of colonoscopy on adenoma detection rates and caecum intubation rates (p. 90)

S.A. van Essen[1], W.A. Marsman[1], V.M.D. Struben[2], T. van der Ploeg[2], E.J. van Soest[1], [1]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [2]Linaeus Instituut, Haarlem, The Netherlands

13.40 Adenoma detection rates vary greatly between gastroenterology fellows (p.91)

Y. Hazewinkel[1], R.B. Klanderman[1], D.M.F van den Buijs[1], P.Fockens[1], E. Dekker[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

13.50 Deep sequencing of paired colorectal cancers and metastases: Detection of novel miRs and colonization specific miRs (p. 92)

M. Neerincx[1], T.E. Buffart[1], D.L.S. Sie[2], M.A. van de Wiel[3], H. Dekker[1], B. Diosdado[2], P.P. Eijk[2], N.C.T. van Grieken[2], G.A. Meijer[2], H.M.W. Verheul[1], [1]Dept. Medical Oncology VU University Medical Center, [2]Dept. Pathology VU University Medical Center, [3]Dept. Epidemiology and Biostatistics VU University Medical Center, Amsterdam, The Netherlands

14.00 Ex Vivo Sentinel Lymph Node Mapping in Colorectal Cancer Combining both Conventional Blue Dye and Near-Infrared Fluorescence (p. 93)

B.E. Schaafsma[1], F.P.R. Verbeek[1], Q.R.J.G. Tummers[1], J.R. van der Vorst[1], M. Hutteman[1], J.V. Frangioni[2], C.J.H. van de Velde[1], A.L. Vahrmeijer[1], [1]Leiden University Medical Center, Leiden, The Netherlands, [2]Beth Israell Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

14.10 Participation, FIT-result and yield in three rounds of biannual FIT-based screening in The Netherlands (p. 94)

I. Stegeman[1], S.C. van Doorn[2], R.C. Mallant-Hent[3], M.W. Mundt[3], P. Fockens[2], A.K. Stroobants[4], P.M. Bossuyt[1], E. Dekker[2], [1]Dept. of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, Netherlands, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, [3]Dept. of Gastroenterology and Hepatology, Flevoziekenhuis Almere, [4]Dept. of Clinical Chemistry, Academic Medical Centre Amsterdam, The Netherlands

14.20 Can endoscopists correctly predict polyp histopathology in FIT based screening? (p. 95)

I. Stegeman[1], S.C. van Doorn[2], R.C. Mallant-Hent[3], M.W. Mundt[3], P. Fockens, P.M. Bossuyt[1], E. Dekker[2], [1]Dept. of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic, Medical Center, Amsterdam, Netherlands, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, [3]Dept. of Gastroenterology and Hepatology, Flevoziekenhuis Almere, The Netherlands

14.30 **MLDS-project**

27-Hydroxycholesterol: a novel approach for inhibition of hepatic inflammation (p. 96)

T. Hendrikx[1], V. Bieghs[1], S.M.A. Walenbergh[1], P.J. van Gorp[1], F. Verheyen[2], M.L.J. Jeurissen[1], M. Gijbels[1,3], M.H. Hofker[4], D. Lütjohann[5], R. Shiri-Sverdlov[1], [1]Dept of Molecular Genetics, [2]Dept of Electron Microscopy, [3]Dept of Pathology, Maastricht University, Netherlands. [4]Dept of Pathology & Laboratory Medicine, University Medical Center Groningen, Netherlands. [5]Institute of Clinical Chemistry and Pharmacology, University of Bonn, Germany

14.40 **MLDS-project**

The role of the ABC-transporters MRP1 and PMP70 in liver fibrosis in vitro and in vivo (p. 97)

A.U. Rehman[1], B. Mikuš[1], C. Reker-Smit[2], K. Poelstra[2], A.J. Moshage[1], K.N. Faber[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, [2]Pharmacokinetics, Toxicology and Targeting - Groningen Research Institute of Pharmacy, University of Groningen, The Netherlands

14.50 **MLDS-project**

Probiotics and enteral nutrition in acute pancreatitis - the POST-PATRIA project (p. 98)

M.C. van Baal[1], M.G. Besselink[4], K. Venema[2], L.M. Akkermans[5], G.T. Rijkers[3], H.G. Gooszen[1], [1]UMC St Radboud Nijmegen, [2]TNO Zeist, [3]Roosevelt Academy Middelburg, [4]AMC, Amsterdam, [5]UMC Utrecht, The Netherlands

15.00 Theepauze expositiehal

Nederlandse Vereniging voor Gastroenterologie — Brabantzaal

Voorzitters: F.P. Vleggaar en J. Tuynman

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

15.30 Adherence to anti-TNF therapy in patients with inflammatory bowel disease (p. 99)

M. van der Have[1], B. Oldenburg[1], A.A. Kaptein[2], J.M. Jansen[3], R.C.H Scheffer[4], S.A. van Tuyl[5], A.E. van der Meulen-de Jong[6], M. Pierik[7], M.G.H. van Oijen[8,9], P.D. Siersema[1], H.H. Fidder[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands, [2]Section Medical Psychology, Leiden University Medical Center, The Netherlands, [3]Dept. of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands, [4]Dept. of Gastroenterology and Hepatology, Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands, [5]Dept. of Gastroenterology and Hepatology, Diakonessenhuis, Utrecht, The Netherlands, [6]Dept. of Gastroenterology and Hepatology, Leiden University Medical Center, The Netherlands, [7]Dept. of Gastroenterology and Hepatology, Maastricht University Medical Center, The Netherlands, [8]Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, CA, [9]UCLA/VA Center for Outcomes Research and Education (CORE), Los Angeles, CA*

15.40 Faecal hemoglobin and calprotectin are equally effective in predicting whether surveillance can be performed in patients with long-standing ulcerative or Crohn's colitis (p. 100)

E. Mooiweer[1], H.H. Fidder[1], K.J. van Erpecum[1], P.D. Siersema[1], R.J.F. Laheij[1], B. Oldenburg[1], [1]Dept. of Gastroenterology, University Medical Center Utrecht, Utrecht, The Netherlands

15.50 Ethnicity is the strongest predictor for Helicobacter pylori infection in young women in a multi-ethnic European city: the Generation R study (p. 101)

W.J. den Hollander[1], I.L. Holster[1], C.M. den Hoed[1], F. van Deurzen[1], V.W. Jaddoe[3], G.I. Perez-Perez[4], M.J. Blaser[4], H.A. Moll[3], E.J. Kuipers[1,2], Depts. of [1]Gastroenterology and Hepatology, [2]Internal Medicine, and [3]Pediatrics, Erasmus MC University Medical Centre, Rotterdam, The Netherlands, [4]Depts. of Medicine and Microbiology, New York University School of Medicine, New York, US

16.00 The effect of viral, bacterial and parasitic infections on the intestinal microbiota (p. 102)

M.E. Grasman[1], A.E. Budding[2], P.H.M. Savelkoul[2], A.A. van Bodegraven[1], [1]Afd. Maag-, darm- en leverziekten, [2]Afd. Medische Microbiologie en Infectiepreventie, VU medisch centrum, Amsterdam, The Netherlands

16.10 Rectal swabs as feasible and reproducible sampling method of the intestinal microbiota in a clinical setting (p. 103)

M.E. Grasman[1], A.E. Budding[2], P.H.M. Savelkoul[2], A.A. van Bodegraven[1], [1]Afd. Maag-, Darm- en Leverziekten, [2]Afd. Medische Microbiologie en Infectiepreventie, VU medisch Centrum, Amsterdam, The Netherlands

16.20 Diagnostic value of multiple auto(antibodies) and carbohydrate antigen 19.9 in discriminating between autoimmune pancreatitis, malignancy and other disorders (p. 104)

M. van Heerde[1], L. Bakker-Jonges[2], M. Batstra[2], K. van Ettinger[2], M. Gilbert[2], B. Hansen[1], A. van Toorenenbergen[1], H. Hooijkaas[1], M. Bruno[1], J. Poley[1], C. van Eijck[1], G. Kazemier[2], C. Pek[1], J. Buijs[1], E. Kuipers[1], H. van Buuren[1], [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Reinier de Graaf Hospital, Delft, Netherlands, [3]VU University Medical Center, Amsterdam, The Netherlands

16.30 The Reflux Finding Score for Infants (RFS-I): Inter- and intraobserver variability (p. 105)

R.J. van der Pol[1], M.M.J. Singendonk[1*], H. Hoeve[3], Q. Kammeijer[2], B. Pullens[3], E. van Spronsen[2], G Thomas[2], L. Vermeeren[2], A.M. König[2], M.A. Benninga[1], M.P. van Wijk[1], [*]Both authors contributed equally,[1]Dept. of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital and [2]Dept. of Pediatric Otorhinolaryngology AMC, Amsterdam, The Netherlands, [3]Dept. of Otorhinolaryngology-Head and Neck Surgery, Erasmus Medical Center, Rotterdam, The Netherlands*

16.40 The value of Golgi protein 73 as a marker to differentiate between solid benign and malignant liver tumours (p. 106)

M.E.E. Bröker MD[1], J.N.M. IJzermans MD PhD[1], C.D.M. Witjes MD, PhD[1], A.J. van Vuuren[2], R.A. de Man MD, PhD[2], [1]Dept. of Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands, [2]Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands

16.50 Human small intestinal barrier function and tight junction integrity during ischemia reperfusion (p. 107)

I.H.R. Hundscheid[1,2], D.H.S.M. Schellekens[1,2], J. Grootjans[3], F.K. Verheyen[4,5], R.M. Van Dam[1], J.P.M. Derikx[1], C.H.C. Dejong[1,2], K. Lenaerts[1,2], [1]Dept. of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands, [2]School for Nutrition, Toxicology and Metabolism (NUTRIM), Maastricht, The Netherlands, [3]Dept. of Internal Medicine, Slotervaart Ziekenhuis, Amsterdam, The Netherlands, [4]Dept. of Molecular Cell Biology and Electron Microscopy, Maastricht University Medical Center, Maastricht, The Netherlands, [5]Center for Research Innovation, Support and Policy (CRISP), Maastricht

Plenaire sessie — Brabantzaal

17.00 **Uitreiking Janssen Gastrointestinale Research prijs 2012**
De prijs wordt uitgereikt door de voorzitter van de jury, Dr. H. Boot, gevolgd door ere-voordracht door de prijswinnaar.

President Select (plenaire sessie) — Brabantzaal

Voorzitter: C.J.J. Mulder

Voordrachten in het Nederlands, spreektijd 10 minuten, discussietijd 5 minuten

17.30 Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile infection, results of a randomized controlled trial (p. 108)
E. van Nood[1], A. Vrieze[1], M. Nieuwdorp[1], S. Fuentes[6], E.G. Zoetendal[6], W.M. de Vos[6,7], C.E. Visser[2], E.J. Kuijper[8], J.F.W.M. Bartelsman[5], J.G.P. Tijssen[3], P. Speelman[1], M.G.W. Dijkgraaf[4], J.J. Keller[5,9], [1]Dept. of Internal Medicine, [2]Dept. of Microbiology, [3]Dept. of Cardiology, [4]Clinical Research Unit, [5]Dept. of Gastroenterology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [6]Laboratory of Microbiology, Wageningen University, Wageningen, The Netherlands, [7]Dept. of Bacteriology and Immunology, Medical Faculty, University of Helsinki, Finland, [8]Dept. of Experimental and Medical Microbiology, Leiden University Medical Center, Leiden, The Netherlands, [9]Dept. of Gastroenterology, Hagaziekenhuis, The Hague, The Netherlands

17.45 Prucalopride decreases esophageal acid exposure and accelerates gastric emptying in healthy subjects (p. 109)
B.F. Kessing[1], A.J.P.M. Smout[1], R.J. Bennink[2], N. Kraaijpoel[1], J.M. Oors[1], A.J. Bredenoord[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Nuclear medicine, Academic Medical Center, Amsterdam, The Netherlands

18.00 A multicenter retrospective head-to-head comparison of adalimumab and infliximab for Crohn's disease (p. 110)
C. Kestens[1], M. van Oijen[1,7], C. Mulder[1], C. Ponsioen[2], A. van Bodegraven[3], G. Dijkstra[4], D. de Jong[5], B. van Tuyl[6], P. Siersema[1], H. Fidder[1], B. Oldenburg[1], [1]Gastroenterology, University Medical Center Utrecht, Utrecht, [2]Gastroenterology, Academic Medical Center, [3]Gastroenterology, VU University Medical Center, Amsterdam, [4]Gastroenterology, University Medical Center Groningen, Groningen, [5]Gastroenterology, Radboud University Medical Center, Nijmegen, [6]Gastroenterology, Diakonessenhuis Hospital, Utrecht, The Netherlands, [7]Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, CA

18.15 Estrogens promote development of colitis-associated cancer (p. 111)
M.C.B. Wielenga[1,], J. Heijmans[1,*], S.L. Rosekrans[1], J.F. van Lidth de Jeude[1], J. Roelofs[3], P. Groothuis[4], A. Ederveen[4], E.S.M. de Jonge-Muller[2], I. Biemond[2], J.C. Hardwick[2], D.W. Hommes[2,5], V. Muncan[1] and G.R. van den Brink[1], [1]Tytgat Institute for Liver & Intestinal Research and dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology and*

*Hepatology, Leiden University Medical Center, Leiden, The Netherlands, [3]Dept. of Pathology, Academic Medical Center, Amsterdam, The Netherlands, [4]MSD, Oss, The Netherlands, [5]Center for Inflammatory Bowel Diseases, University of California Los Angeles, Los Angeles, USA, * these authors contributed equally*

18.30 Einde programma, congresborrel in expositiehal

19.30 Diner in de Genderzaal

Donderdag 21 maart 2013

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Auditorium**

Lustrum NVGIC 2013

middagprogramma:

Borders in colorectal surgery (voordrachten in het Engels)

Voorzitters: G. Beets en A. van de Ven

13.10 Management of colocarcinoma in the elderly
Dr. G.J. Liefers, chirurg, LUMC, Leiden

13.30 Downstaging colon carcinoma – Does it work (FOxTROT trial)?
Prof. Dion Morton, chirurg, Birmingham, UK

13.50 Treatment options in visceral colorectal metastasis, how far can we go?
Dr. C. Verhoef, chirurg, DDHK, Rotterdam

14.10-14.30 DSCA update, achievements and future improvements of colorectal cancer surgery *Prof. dr. T. Wiggers, chirurg, UMCG, Groningen*

14.40-14.55 Innovations in colorectal surgery round 3
15.10-15.25 Innovations in colorectal surgery round 4

15.25 Theepauze

Sessie Borders chirurgie/MDL (voordrachten in het Nederlands)

Voorzitters: E. Dekker en G. Patijn

16.00 Genetica in colorectale chirurgie, surveillance of opereren
Prof. dr. H.F.A. Vasen, internist, LUMC, Leiden

16.20 Obstructie van het colon, de waarde van stenten als bridge to surgery
Prof. dr. W.A. Bemelman, chirurg, AMC, Amsterdam

16.40 Behandeling van colorectale aandoeningen in 2025: visie van de MDL-arts
Prof. dr. B.L.A.M. Weusten, MDL-arts, St. Antonius Ziekenhuis, Nieuwegein

17.00 Behandeling van colorectale aandoeningen in 2025: visie van de chirurg
Prof. dr. J.F. Lange, chirurg, Erasmus MC, Rotterdam

17.20 Pauze

Voor de president select en de uitreiking van de Janssen Gastrointestinale Researchprijs 2012 kunt u zich begeven naar de Brabantzaal

Disasters in Colorectal surgery

18.30 Video sessie met mogelijkheid tot commentaar bij de borrel (expositiehal)
Dr. J.W.T. Dekker, Dr. E. van der Harst en Dr. C. Hoff

19.30 Diner in de Genderhal

DEGH-Meeting **Baroniezaal**

Voorzitters: A. Kaser en G. Bouma

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

Theme **Inflammatory signalling**

13.30 Defective CSF2RB signaling in Crohn's disease patients bearing the NCF4 risk allele (p. 112)

R. Somasundaram[1], C.J. van der Woude[1], M.P. Peppelenbosch[1], G.M. Fuhler[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

13.42 JAK inhibitor tofacitinib interferes with interferon alpha mediated inhibition of hepatitis C replication (p. 113)

P.E. de Ruiter[1], C.C. Baan[2], Q. Pan[3], J. Kwekkeboom[3], H.J. Metselaar[3], R.W.F. de Bruin[1], H.W. Tilanus[1], L.J.W. van der Laan[1], [1]Dept. of Surgery and Laboratory of Experimental Transplantation and Intestinal Surgery, [2]Internal Medicine, [3]Dept. of Gastroenterology & Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

13.54 Functional consequences of a novel IL-10 receptor alpha mutation on innate and adaptive immunity in early-onset inflammatory bowel disease (p. 114)

M.A. van Leeuwen[1,4], S. Veenbergen[1,4], R. Kersseboom[2], L.F. de Ruiter[1], H.C. Raatgeep[1], D.J. Lindenbergh-Kortleve[1], Y. Simons-Oosterhuis[1], L. de Ridder[1], G.J. Driessen[3], J.C. Escher[1], J.N. Samsom[1], [1]Dept. of Paediatric Gastroenterology, Erasmus Medical Centre- Sophia Children's Hospital, Rotterdam, The Netherlands, [2]Dept. of Clinical Genetics, Erasmus Medical Centre, Rotterdam, The Netherlands, [3]Dept. of Paediatric Infectious Disease and Immunology, Erasmus Medical Centre, Rotterdam, The Netherlands, [4]Authors share first authorship

14.06 First multi-ethnic genetic analyses in inflammatory bowel disease show transferability of loci and population specific variants associated in non-Caucasian populations (p. 115)

S. van Sommeren[1,2], E.A.M. Festen[1,2], H. Huang[3], O. Jazayeri[1], K. Fransen[1,2], M. Mitrovic[4], A. Sood[5], R. Malekzadeh[6], B.K. Thelma[7], B. Alizadeh[8], R.K. Weersma[2], [1]Dept. of Genetics, [2]Dept. of Gastroenterology and Hepatology, University of Groningen, University Medical Centre Groningen, The Netherlands, [3]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA, [4]Center for Human Molecular Genetics and Pharmacogenomics, Medical Faculty, University of Maribor, Maribor, Slovenia, [5]Dayanand Medical College and Hospital, Ludhiana, Punjab, India, [6]Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran, [7]Dept. of Genetics, University of Delhi, South Campus, New Delhi, India, [8]Dept. of Epidemiology, University of Groningen, University Medical Centre Groningen, The Netherlands

14.18 **Invited Speaker**

Endoplasmic reticulum stress, inflammation & tumourigenesis in the intestine - implications for IBD and beyond

Arthur Kaser, professor of Gastroenterology, University of Cambridge, UK

15.00 Theepauze en ALV Nederlandse Vereniging voor Hepatologie

DEGH-Meeting **Baroniezaal**

Voorzitters: M. Peppelenbosch en A.A. te Velde

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

Theme Cancer

15.30 **Inleider / Invited Speaker**
Theme introduction by Maikel P. Peppelenbosch, Rotterdam.

15.42 Low molecular weight protein tyrosine phosphatase (LMW-PTP) is upregulated in primary colorectal cancer and affects cancer signaling pathways (p. 116)
E. Hoekstra[1], L.L. Kodach[2], J.C. Hardwick[2], E.J. Kuipers[1], M. Bruno[1], M.P. Peppelenbosch[1], G.M. Fuhler[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands, [2]Dept. of Gastroenterology-Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

15.54 Hyperactivation of the endoglin/TGF-β pathway plays a role in CRC invasion and metastasis (p. 117)
M. Paauwe[1], A. Garcia de Vinuesa[1], H. Verspaget[2], G. van Pelt[3], W. Mesker[3], C. Sier[3], P. ten Dijke[1], L. Hawinkels[1], [1]Dept. of Molecular Cell Biology, [2]Dept. of Gasteroenterology-Hepatology, [3]Dept. of Surgery, Leiden University Medical Center, Leiden, The Netherlands

16.06 Loss of Bone Morphogenetic Protein Receptor IA predicts poor survival in patients with pancreatic cancer and is responsible for invasiveness and proliferation of cancer cells (p. 118)
P. Voorneveld[1], R.J. Jacobs[1], S. Lam[3], N. de Mirandal[2], H. Morreau[2], L.L. Kodach[1], J.C. Hardwick[1], [1]Gastroenterology & Hepatology, Leiden University Medical Center, Leiden, Netherlands, [2]Pathology, Leiden University Medical Center, Leiden, Netherlands, [3]Molecular Cell Biology, Leiden University Medical Center, Leiden, Netherlands

16.18 Abrogation of tumor-associated immunosuppression by targeting tumor-infiltrating regulatory T-cells restores impaired T cell responses in patients with liver cancer (p. 119)
A. Pedroza-Gonzalez[1], J. Kwekkeboom[1], E.T. Tjwa[1], W.G. Polak[2], D.J. Grünhagen[2], J.N.M. IJzermans[2], H.L.A. Janssen[1], D. Sprengers[1,3], [1]Dept Gastroenterology and Hepatology, [2]Dept. Surgery, Erasmus MC University Medical Center, Rotterdam, [3]Dept. Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

16.30 Perioperative selective decontamination of the digestive tract (SDD) decreases tumor cell adhesion in the liver post-operatively (p. 120)
N. Gül[1], S. Grewal[1,2], R. Braster[1], S. Pouw[1], M. Bögels[1,2], N. Grewal[1,2], R. Beelen[1], J. Bonjer[2], M. van Egmond[1,2], [1]Dept. of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands, [2]Dept. of Surgery, VU University Medical Center, Amsterdam, The Netherlands

16.42 Aurora kinase A (AURKA) expression in colorectal cancer liver metastasis is associated with poor prognosis (p. 121)

J.A.C.M. Goos, V.M.H. Coupé, B. Diosdado, P.M. Delis-Van Diemen, C. Karga, J.A.M. Beliën, B. Carvalho, M.P. van den Tol, H.M.W. Verheul, A.A. Geldof, G.A. Meijer, O.S. Hoekstra and R.J.A. Fijneman on behalf of the DeCoDe PET group, VU University Medical Center, Amsterdam, The Netherlands

17.00 Einde programma, voor de Janssen Gastrointestinale Research Prijs 2012 en de aansluitende President Select kunt u zich begeven naar de Brabant-zaal

18.30 Congresborrel in de expositiehal.

19.30 Diner in de Genderzaal

Nederlandse Vereniging voor Gastroenterologie — Parkzaal

Voorzitters: J.Ph. Kuijvenhoven en A.A.M. Masclee

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

13.00 Right versus left-sided ischemic colitis: different presentation and worse prognosis; a study in a cohort of 474 patients (p. 122)

L.B. ten Heggeler[1], L.J.H. van Dam[2], A. Bijlsma[3], M.C. Visschedijk[2], M.G.J. Brusse-Keizer[4], R.H. Geelkerken[5], M.A.C. Meijssen[2], J.J. Kolkman[1,3], [1]Dept. of Gastroenterology, Medical Spectrum Twente, Enschede, [2]Dept. of Gastroenterology, Isala Clinics Zwolle, [3]Dept. of Gastroenterology, University Medical Centre Groningen, [4]Dept. of Epidemiology, Medical Spectrum Twente, Enschede, [5]Dept. of Vascular surgery, Medical Spectrum Twente, Enschede, The Netherlands

13.10 Follow-up endoscopy for benign appearing gastric ulcers has no additive value in detecting malignancy (p. 123)

E.A.R. Gielisse, J.P. Kuyvenhoven, Kennemer Gasthuis, Haarlem, The Netherlands

13.20 The impact of sexual abuse in the Gastroenterology practice A multi-centered cross-sectional study among colonoscopy patients (p. 124)

M.P.J Nicolai[1], L. de Vries[1], J.J. Keller[2], A.E. van der Meulen[3], J.J. Nicolai[2], R.C.M. Pelger[1], H. Putter[4], H.W. Elzevier[1], [1]Dept. of Urology, Leiden University Medical Centre, Leiden, [2]Dept. of Gastroenterology, HAGA teaching hospital, The Hague, [3]Dept. of Gastroenterology, Leiden University Medical Centre, Leiden, [4]Dept. of Medical Statistics, Leiden University Medical Centre, Leiden, The Netherlands

13.30 Long-term quality of life and sexual function after ileal pouch-anal anastomosis in adults with ulcerative colitis or familial adenomatous polyposis (p. 125)

P.H.A. Bours[1,], J.M. Bakia[2,*], D.M.A.E. Jonkers[1], M.J.L. Romberg-Camps[3], A.A.M. Masclee[1], E. van Heurn[4], M.J. Pierik[1], S.O. Breukink[2], [1]Division Gastroenterology and Hepatology, Dept. of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Division Gastro-Intestinal Surgery, Dept. of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands, [3]Dept. of Internal Medicine and Gastroenterology, Orbis Medical Center, Sittard-Geleen, The Netherlands, [4]Division Pediatric Surgery, Dept. of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands, *Both authors contributed equally to this abstract*

13.40 Towards non-invasive diagnosis and monitoring of celiac disease: a prospective study to the usefulness of I-FABP (p. 126)

M. Adriaanse[1], A. Mubarak[2], D. Leffler[3], C. Kelly[3], D. Schuppan[3], A. van de Neucker[1], W. Buurman[4], R. Houwen[2], A.Vreugdenhil[1], [1]Pediatrics, Maastricht University Medical Centre, Maastricht, [2]Pediatrics, Wilhelmina Children's Hospital, Utrecht, [3]The Celiac Disease Center, Department of Gastroenterology, Beth Israel Deaconess Medical Centre, Boston, United States of America, [4]General Surgery, Maastricht University Medical Centre, Maastricht, Netherlands

13.50 Differential IL-13 production by lamina propria derived leucocytes in uncomplicated and refractory celiac disease (p. 127)

S. Gross[1], R.L. van Wanrooij[2], P. Nijeboer[2], C.J. Mulder[2], G. Bouma[2], B.M.E. von Blomberg[1], H.J. Bontkes[1], Depts. of [1]Pathology and [2]Gastroenterology, VU University Medical Hospital, Amsterdam, The Netherlands

14.00 Gastroenterologist's gut feeling versus Blatchford risk score to predict the need for a medical intervention in suspected upper GI bleeding: results of a multicenter prospective cohort study (p. 128)

N.L. de Groot[1], P.D. Siersema[1], M.G.H. van Oijen[1], A.J. Bredenoord[1,2], on behalf of the RASTA study group, [1]Dept. Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands, [2]Dept. Gastroenterology and Hepatology, Academic Medical Center Amsterdam, The Netherlands

14.10 The simplified Forrest classification for the prediction of rebleeding of peptic ulcer bleeds: results of a prospective cohort study (p. 129)

N.L. de Groot[1], P.D. Siersema[1], M.G.H. van Oijen[1,2], A.J. Bredenoord[1,2], on behalf of the RASTA study group, [1]Dept. Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands, [2]Dept. Gastroenterology and Hepatology, Academic Medical Center Amsterdam, The Netherlands

14.20 Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily clinical practice? (p. 130)

G.M.C. Masclee[1,2], V.E. Valkhoff[1,2], E.M. van Soest[1], R. Schade[1], G. Mazzaglia[3], M. Molokhia[4], G. Trifirò[1,5], J.L. Goldstein[6], S. Hernández-Díaz[7], E.J. Kuipers[2,8], M.C.J.M. Sturkenboom[1,9], [1]Dept. of Medical Informatics, Erasmus, University Medical Centre, Rotterdam, The Netherlands, [2]Dept. of Gastroenterology and Hepatology, Erasmus, University Medical Centre, Rotterdam, The Netherlands, [3]Health Search, Italian College, of General Practitioners, Florence, Italy, [4]Primary Care & Public Health Sciences, Kings College London, London, United Kingdom, [5]Dept. of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy, [6]Dept. of Medicine, Division of Gastroenterology, NorthShore University HealthSystem, Evanston, Illinois, USA, [7]Dept. of Epidemiology, Harvard School of Public Health, Boston, USA, [8]Dept. of Internal Medicine, Erasmus University, Medical Centre, Rotterdam, The Netherlands, [9]Dept. of Epidemiology, Erasmus University, Medical Centre, Rotterdam, The Netherlands

14.30 Long-term outcome of treatment with temperature-controlled radiofrequency energy (SECCA) in patients with faecal incontinence (p. 131)

A.P. Visscher, T.J. Lam, M. Meurs-Szojda, C.J. Mulder, R.J. Felt-Bersma, VUmc, Amsterdam, The Netherlands

14.40 Feacal incontinence, sexual complaints, and anorectal function in patients with a third degree anal sphincter rupture: long term follow-up (p. 132)

A.P. Visscher, T.J. Lam, N.A. Hart, C.J. Mulder, R.J. Felt-Bersma, VUmc, Amsterdam, The Netherlands

14.50 Improvement of plasma parameters linked to nonalcoholic fatty liver disease after weight loss induced by proximal small intestinal exclusion by duodenal-jejunal bypass liner (p. 133)

C. de Jonge[1,2], S.S. Rensen[1], G.H. Koek[3], M.F. Joosten[1], W.A. Buurman[1], N.D. Bouvy[1], J.W.M. Greve[2], [1]Dept. of General Surgery and NUTRIM School for Nutrition, Toxicology and Metabolism Research, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Dept. of General Surgery, Atrium Medical Center Parkstad, Heerlen, The Netherlands, [3]Dept. of Gastroenterology and NUTRIM School for Nutrition, Toxicology and Metabolism Research, Maastricht University Medical Centre, Maastricht, The Netherlands

15.00 Theepauze expositiehal

Sectie Neurogastroenterologie en Motiliteit — Parkzaal

Voorzitters: J.M. Conchillo en D.P. Hirsch

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

15.30 A subgroup of achalasia patients with manometrically normal LES relaxation can be identified by measurements of esophagogastric junction distensibility (P. 134)

F.A.M. Ponds[1], A.J. Bredenoord[1], B.F. Kessing[1], W.O. Rohof[1], A.J.P.M. Smout[1], [1]Gastroenterology & Hepatology, Academic Medical Center University of Amsterdam, Amsterdam, The Netherlands

15.40 Does post-procedure Esophagogastric Junction (EGJ) Distensibility predict treatment success in newly diagnosed achalasia patients? (p.135)

F.G. Smeets[1] , E.T. Tjwa[2] , A.A. Masclee[1] , J.M. Conchillo[1], [1]Dept. of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Dept. of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

15.50 Acid suppression restores impaired esophageal mucosal integrity in patients with esophageal eosinophilia (p. 136)

B.D. van Rhijn[1,2], P.W. Weijenborg[1,2], J. Verheij[3], M.A. van de Bergh Weerman[3], W.J. de Jonge[2], A.J.P.M. Smout[1], A.J. Bredenoord[1], [1]Dept. of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Tytgat Institute for Liver and GI research, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept. of Pathology, Academic Medical Center, Amsterdam, The Netherlands

16.00 First results of the BaroSense ACE stapler procedure for the treatment of morbid obesity: effect on food intake and satiety (p. 137)

M. van Avesaat[1], G. Paulus[2], JM. Conchillo[1], ND. Bouvy[2], AA. Masclee[1], [1]Division of Gastroenterology and Hepatology, Dept. of Internal Medicine, Maastricht University Medical Center, The Netherlands, [2]Dept. of General Surgery, Maastricht University Medical Center, The Netherlands

16.10 Neuronal modulation of intestinal inflammation during Postoperative ileus (p. 138)

L.M.M. Costes[1], J. van der Vliet[1], M.A. Nolte[2], S.H.W. van Bree[1], G.E. Boeckxstaens[3], C. Cailotto[1], [1]Tytgat Institute for Liver and Intestinal Research, AMC, Amsterdam, [2]Dept of Hematology, Sanquin, Amsterdam, The Netherlands, [3]Dept Gastroenterology, University Hospital Leuven, Belgium

16.20 The effect of chewing gum before and directly after surgery on postoperative ileus in colorectal surgery; a randomized controlled trial (p. 139)

D. van der Lee Bsc[1], T. van den Heijkant MD[1], B. Aerts MD[1], M. Osinga - de Jong MD[2], H. Rutten MD PhD[1], I. de Hingh MD PhD[1], G. Nieuwenhuijzen MD PhD[1], K. Hulsewé MD PhD[3], T. Hoofwijk MD PhD[3], W. Buurman PhD[4], M. Luyer MD PhD[1], [1]Dept. of Surgery, Catharina Hospital Eindhoven, [2]Dept. of Radiology, Orbis Medical Centre Sittard, [3]Dept. of Surgery, Orbis Medical Centre Sittard, [4]Institute Nutrim, Maastricht University, The Netherlands

16.30 Effect of a multispecies probiotic on visceroperception in hypersensitive IBS patients (p. 140)

S. Ludidi[1], D. Jonkers[1], C.J. Koning[2], J. Kruimel[1], L. Mulder[2], I. Besseling - van der Vaart[2], J.M. Conchillo[1], A. Masclee[1], [1]Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, Netherlands, [2]Winclove Bio Industries BV, Amsterdam, Netherlands

16.40 Does colonic transit time predict the result of colonic manometry in patients with chronic obstipation? (p. 141)

M. van Avesaat[1], EA. van Hoboken[2], NF. Rinsma[1], AA. Masclee[1], [1]Division of Gastroenterology and Hepatology, Dept. of Internal Medicine, Maastricht University Medical Center, The Netherlands, [2]Dept. of Gastroenterology-Hepatology, Leiden University Medical Center, The Netherlands

16.50 Brain processing of rectal sensation in children with chronic functional constipation (p. 142)

S.M. Mugie[1], M.M. van den Berg[2], P.F.C. Groot[3], L. Reneman[3], A.J. Nederveen[3], M.A. Benninga[1], [1]Dept. of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital AMC, Amsterdam, [2]Dept. of Pediatrics, Wilhelmina Children's Hospital UMCU, Utrecht, [3]Dept. of Radiology, Academic Medical Centre, Amsterdam, The Netherlands

17.00 Einde abstractsessie, voor de Janssen Research Prijs en de aansluitende President Select kunt u zich begeven naar de Brabantzaal

Sectie Gastrointestinale Endoscopie **Brabantzaal**

08.00 Ledenvergadering NVMDL in de Genderzaal (met ontbijt)

Voorzitters: J-W. Poley en T.E.H. Römkens

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

09.30 Assessment of ERCP performance in novice trainees (p. 143)
V.E. Ekkelenkamp[1], A.D. Koch[1], E.A.J. Rauws[2], R.A. de Man[1], E.J. Kuipers[1,3], [1]Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept. of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

09.40 Optical diagnosis of colorectal polyps using HD i-scan is feasible and correctly predicts surveillance intervals (p. 144)
M. Bouwens[1], A. Masclee[1], R. de Ridder[1], T. Kaltenbach[2], R. Soetikno[2], B. Winkens[3], S. Sanduleanu[1], [1]Division of Gastroenterology and Hepatology, Dept. of Internal Medicine, Maastricht University Medical Center, The Netherlands, [2]Veterans Affairs Palo Alto Health Care System, Palo Alto, California, USA, [3]Dept. of Methodology and Statistics, Maastricht University Medical Center, The Netherlands

09.50 Computer-Aided Delineation of Early Neoplasia in Barrett's Esophagus using High Definition Endoscopic Images (p. 145)
F. van der Sommen[1], S. Zinger[1], P. de With[1], E.J. Schoon[2], [1]Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands, [2]Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, The Netherlands

10.00 Preoperative Esophagogastric Junction (EGJ) Distensibility predicts treatment outcome after endoscopic fundoplication in GERD patients (p. 146)
F.G. Smeets[1], N.D. Bouvy[2], A.A.M. Masclee[1], J.M. Conchillo[1], [1]Dept. of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Dept. of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

10.10 An endoscopic grasp-and-traction device is helpful for gastric endoscopic submucosal dissection in the forward, but not in the retroflex approach: an ex-vivo comparative study on the usefulness of Endolifter® (p. 147)
O. Goto[2,3], D.W. Schölvinck[1,2], J.J.G.H.M. Bergman[2], N. Yahagi[3], B.L.A.M. Weusten[1], [1]St. Antonius Ziekenhuis, Nieuwegein, Netherland, [2]Academisch Medisch Centrum, Amsterdam, The Netherlands, [3]Cancer Centre Keio University, Tokyo, Japan

10.20 A large International Multicenter Experience with an Over-The-Scope Clipping Device for Endoscopic Management of Gastrointestinal Perforations, Fistulae, and Leaks in 188 Patients (p. 148)
J.W. Poley[1], F.P. Vleggaar[2], Y. Haito Chavez[3], T. Kratt[4], J.K. Law[3], A. Arezzo[5], R.Z. Sharaiha[6], M.

Kahaleh[6], C.C. Thompson[7], M.B. Ryan[7], N. Choksi[8], B.J. Elmunzer[8], S. Gosain[9], E.M. Goldberg[9], R.J. Modayil[10], S. Stavropoulos[10], D.B. Schembre[11], C.J. DiMaio[12], V. Chandrasekhara[13], M. Hasan[14], S. Varadarajulu[14], R. Hawes[14], V. Gomez[15], T.A. Woodward[15], S. Rubel Cohen[16], F. Fluxa[16], G.S. Raju[17], M. Khashab[3], [1]Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, Netherlands, [2]University Medical Center Utrecht, Netherlands, [3]Johns Hopkins Medical Institute, Baltimore, MD, United States, [4]University Hospital of Tuebingen, Germany, [5]University of Turin, Italy, [6]Dept. of Internal Medicine Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY, United States, [7]Brigham and Women's Hospital, Boston, MA, United States, [8]University of Michigan Medical Center, Ann Arbor, MI, United States, [9]University of Maryland Medical Center, Baltimore, MD, United States, [10]Winthrop University Hospital, Mineola, NY, United States, [11]Swedish Medical Center, Seattle, WA, United States, 12Mount Sinai School of Medicine, New York, NY, United States, 13Hospital of the University of Pennsylvania, Philadelphia, PA, United States, 14Florida Hospital Orlando, FL, United States, 15Mayo Clinic, Jacksonville, FL, United States, 16Clinica Las Condes, Santiago, Chile, 17University of Texas MD Anderson Cancer Center, Houston, TX, United States

10.30 Placement of a fully covered metal stent (AXIOS) for EUS-guided drainage of peripancreactic fluid collections; a prospective European cohort study (p. 149)

D. Walter[1], U. Will[2], A. Sanchez-Yague[3], D. Brenke[4], J. Hampe[5], J.M. H. Wollny[6], J.M. Esteban López-Jamar[7], G. Jechart[8], P. Vilmann[9], J.B. Gornals[10], H.S. Ullrich[11], M. Fähndrich[12], A. Herreros de Tejada[13], F. Junquera[14], H. Schlieker[15], F. Gonzalez-Huix[16], P.D. Siersema[1], F.P. Vleggaar[1], [1]Dept. Gastroenterology and Hepatology, UMC Utrecht, Utrecht, Netherlands, [2]Dept. of Gastroenterology, Municipal Hospital, Gera, Germany, [3]Endoscopy Unit, Hospital Costa del Sol, Marbella, Spain, [4]Dept. of Internal Medicine II, Dept. of Gastroenterology, Hepatology and Diabetology, SKK Teaching Hospital , Karlsruhe, Germany, [5]Dept. of Internal Medicine I, UKSH, Kiel, Germany, [6]Dept. of Internal Medicine and Gastroenterology, Medical Center Städte Region, Aachen, Germany, [7]Dept. of Endoscopy, Hospital Clinico San Carlos, Madrid, Spain, [8]Dept. of Gastroenterology, Klinikum Augsburg, Augsburg, Germany, [9]Dept. of Surgery, University Hospital Herlev, Copenhagen, Denmark, [10]Dept. of Endoscopy, Hospital Universitari de Bellvitge-IDIBELL, Barcelona, Spain, [11]Dept. of Internal Medicine I, Klinikum Asklepios Altona, Hamburg, Germany, [12]Dept. of Interventional Endoscopy, Klinikum Dortmund, University Münster, Dortmund, Germany, [13]Dept. of Gastroenterology, Puerta de Hierro University Hospital, Madrid, Spain, [14]Dept. of Digestive Disease, Hospital Parc Tauli, Barcelona, Spain, [15]Dept. of Gastroenterology, Klinikum Lippe-Detmold, Detmold, Germany, [16]Endoscopy Unit, Clinica Girona, Girona, Spain

10.40 A fully covered self-expandable metal stent, Niti-S, for benign biliary strictures: a prospective multi-center follow-up study (p. 150)

D. Walter[1], W. Laleman[2], J.M. Jansen[3], A.W.M. van Milligen de Wit[4], B.L. Weusten[5], F.P.Vleggaar[1], P.D. Siersema[1], [1]Gastroenterology and Hepatology, UMC Utrecht, Utrecht, The Netherlands, [2]Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands, [3]Gastroenterology and Hepatology, Amphia Hospital, Breda, The Netherlands, [4]Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, The Netherlands, [5]Hepatology and biliopancreatic disorders, University Hospital Gasthuisberg, Leuven, Belgium

10.50 Self-expandable metal stents as definite treatment for esophageal variceal bleeding (p. 151)

I.L. Holster[1], E.J. Kuipers[1,2], H.R. van Buuren[1], V.M.C.W. Spaander[1], E.T.T.L. Tjwa[1], Depts. of [1]Gastroenterology and Hepatology and [2]Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

11.00 Koffiepauze in de expositiehal

Symposium Richtlijn Coloscopie Surveillance — Brabantzaal

Voorzitter: E. Dekker en S. Sanduleanu

11.30	Introductie door de voorzitter *Dr. E. Dekker, MDL-arts, Academisch Medisch Centrum, Amsterdam*
11.40	Coloscopie-surveillance na adenomen *Dr. M.E. van Leerdam, MDL-arts, NKI Antoni van Leeuwenhoekhuis, Amsterdam*
12.05	Coloscopie-surveillance na geserreerde poliepen *Drs. Y. Hazewinkel, arts-onderzoeker, Academisch Medisch Centrum, Amsterdam*
12.20	Coloscopie-surveillance na CRC *Dr. A.M. van Berkel, MDL-arts, Medisch Centrum Alkmaar*
12.35	Coloscopie-surveillance bij personen met erfelijke belasting *Prof. dr. H.F.A. Vasen, internist, Leids Universitair Medisch Centrum*
12.50	Discussie *geleid door Dr. E. Dekker en Dr. S Sanduleanu*
13.00	Lunchpauze in de expositiehal

Nederlandse Vereniging voor Gastrointestinale Chirurgie — Auditorium

Voorzitter: M.I. van Berge Henegouwen en J.E. van Hooft

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

09.30 Incidence and management of late postpancreatectomy haemorrhage (p. 152)
J.A.M.G. Tol, O.R.C. Busch, O.M. van Delden, T.M. van Gulik, D.J. Gouma, Academisch Medisch Centrum, Amsterdam, The Netherlands

09.40 Long-term survival after palliative resection and bypass procedure in patients with periampullary adenocarcinoma (p. 153)
J.A.M.G. Tol, O.R.C. Busch, T.M. van Gulik, D.J. Gouma, Academisch Medisch Centrum, Amsterdam, The Netherlands

09.50 Near-infrared fluorescence-guided resection of otherwise undetectable hepatic colorectal metastases using indocyanine green (p. 154)
B.E. Schaafsma[1], J.R. van der Vorst[1], M. Hutteman[1], F.P.R. Verbeek[1], J.S.D. Mieog[1], G.J. Liefers[1], H.H. Hartgrink[1], J.V. Frangioni[2], C.J.H. van de Velde[1], A.L. Vahrmeijer[1], [1]Leiden University Medical Center, Leiden, The Netherlands, [2]Beth Israell Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

10.00 Hepatocyte and cholangiocyte-derived microRNAs in serum as early markers for ischemia & reperfusion injury in pigs (p. 155)
C.J. Verhoeven[1], J. de Jonge[1], J. Kwekkeboom[2], H.J. Metselaar[2], R.W.F. de Bruin[1], H.W. Tilanus[1], G. Kazemier[1,3], L.J.W. van der Laan[1], [1]Dept. of Surgery and Laboratory of Experimental Transplantation and Intestinal Surgery, [2]Dept. of Gastroenterology & Hepatology, Erasmus MC-University Medical Center, Rotterdam, [3]Dept. of Surgery, VU Medical Center Amsterdam, The Netherlands

10.10 Efficacy of absorbable embolization materials for portal vein embolization to induce liver regeneration in a rabbit model (p. 156)
F. Huisman[1], L.T. Hoekstra[1], K.P. van Lienden[2], J. Verheij[3], T.M. van Gulik[1], [1]Dept of Surgery, [2]Dept of Radiology, [3]Dept of Pathology, Academic Medical Center, Amsterdam, The Netherlands

10.20 Risk factors for bleeding in hepatocellular adenoma (p. 157)
M. Bieze[1], S.K.S. Phoa[2], J. Verheij[2], K.P. van Lienden[4], T.M. van Gulik[1], [1]Dept. of Surgery, Academic Medical Center, The Netherlands, [2]Dept. of Radiology, Academic Medical Center, The Netherlands, [3]Dept. of Pathology, Academic Medical Center, The Netherlands, [4]Dept. of Interventional Radiology, Academic Medical Center, The Netherlands

10.30 Is oesophagogastroduodenscopy prior to Roux-en-Y gastric bypass surgery mandatory? (p. 158)
U.K. Coblijn[1], A. Schigt[1], S.M. Lagarde[1], P. Scholten[2], S.D. Kuiken[2], B.A. van Wagensveld[1], [1]Afdeling Heelkunde, [2]Afdeling Maag, Darm en Leverziekten, Sint Lucas Andreas Ziekenhuis, Amsterdam, The Netherlands

10.40 The role of hospital of diagnosis in offering curative surgery and the impact on survival in resectable oesophageal cancer (p. 159)
M. Koëter[1], L.N. van Steenbergen[2], V.E.P.P. Lemmens[2,3], H.J.T. Rutten[1], J.A. Roukema[4], G.A.P. Nieuwenhuijzen[1], [1]Dept. of Surgery, Catharina Hospital Eindhoven, The Netherlands, [2]Eindhoven Cancer Registry, Comprehensive Cancer Centre South, Eindhoven, The Netherlands, [3]Dept. of Public Health, Erasmus University Medical Centre, Rotterdam, The Netherlands, [4]Dept. of Surgery, St. Elisabeth Hospital Tilburg, The Netherlands

10.50 PET-CT after neoadjuvant chemoradiotherapy can prevent non-curative surgical interventions in esophageal cancer patients (p. 160)
M.C.J. Anderegg[1], R.J. Bennink[2], H.W.M. van Laarhoven[3], J.H.G. Klinkenbijl[1], M.C.C.M. Hulshof[4], J.J.G.H.M. Bergman[5], M.I. van Berge Henegouwen[1], [1]Dept. of Surgery, [2]Nuclear Medicine, [3]Medical Oncology, [4]Radiation Oncology [5]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

11.00 Koffiepauze in de expositiehal

Nederlandse Vereniging voor Gastrointestinale Chirurgie — Auditorium

Voorzitter: R. van Hillegersberg en K. Peters

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

11.30 How to treat an appendicular mass: operatively or conservatively? (p. 161)
J.D. Deelder, M.C. Richir, W.H. Schreurs, Medisch Centrum Alkmaar, The Netherlands

11.40 Complications after laparoscopic cholecystectomy: did we reach critical view of safety. A video evaluation study (p. 162)
M. van Nieuwenhuizen, MD, J.M.J. Schreinemakers, MD, PhD, Z. Meyer, MD, G.P. van der Schelling, MD, R.M.P.H. Crolla, MD, A.M. Rijken, MD, PhD,Amphia Ziekenhuis, Breda, The Netherlands

11.50 Longer disease-free survival following colorectal cancer when operation is performed by a high-volume surgeon (p. 163)
M. Buurma, H.M. Kroon, M.S. Reimers, P.A. Neijenhuis, Rijnland Ziekenhuis, Leiderdorp, The Netherlands

12.00 Resection of the primary tumor in the treatment of synchronous peritoneal carcinomatosis from colorectal cancer with hyperthermic intraperitoneal chemotherapy (p. 164)
H.J.W. Braam[1], D. Boerma[1], M.J. Wiezer[1], B. van Ramshorst[1], [1]Dept. of surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

Vrijdag 22 maart 2013

12.10 Cyclooxygenase-2 (cox-2) is essential for colorectal anastomotic healing (p. 165)

K.W. Reisinger[1], D.H. Schellekens[1], M.F. von Meyenfeldt[1], M. Poeze[1], [1]Dept. of Surgery, Maastricht University Medical Center & Nutrim School for Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, The Netherlands

12.20 The Accuracy of Computed Tomography in Detecting Anastomotic Leakage After Colorectal Surgery (p. 166)

M.M. Tjeenk Willink[1], L. Pietersen[1], L.M. Dijksman[2], S.C. Donkervoort[1], [1]Dept. of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands, [2]Onze Lieve Vrouwe Gasthuis, Teaching Hospital, Amsterdam, The Netherlands

12.30 Early closure of anastomotic leakage after ileal pouch-anal anastomosis: a novel solution to an old problem (p. 167)

T.J. Gardenbroek, G.D. Musters, C.J. Buskens, P.J. Tanis, W.A. Bemelman, Dept. of Surgery, Academic Medical Center, Amsterdam, The Netherlands

12.40 Plasma markers for anastomotic leakage after colorectal surgery (p. 168)

K.W. Reisinger[1], J.P. Derikx[1], K.W. Hulsewé[2], A.A. van Bijnen[1], M.F. von Meyenfeldt[1], M.Poeze[1], [1]Dept. of Surgery, Maastricht University Medical Center & Nutrim School for Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, The Netherlands, [2]Dept. of Surgery, Orbis Medical Center, Sittard, The Netherlands

12.50 Surgical treatment for complex perianal fistulas combined with platelet rich plasma. Long-term results (p. 169)

K.W.A. Göttgens[1], S. van der Hagen[2], R. Smeets[1], G. van Gemert[3], L. Stassen[1], G. Beets[1], C.G.M.I. Baeten[1], S.O. Breukink[1], [1]Dept. of general and colorectal surgery, Maastricht University Medical Center+, Maastricht, The Netherlands, [2]Dept. of general and colorectal surgery, Refaja Hospital, Stadskanaal, The Netherlands, [3]Dept. of general and colorectal surgery, Atrium Medical Center Parkstad, Heerlen, The Netherlands

13.00 Lunchpauze in de expositiehal

DEGH-Meeting **Baroniezaal**

Voorzitters: M. Neunlist en D. Jonker

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

Theme Epithelial Barrier and cholestasis

08.30 Lipid raft modulation in rat visceral hypersensitivity: proof of principal study (p. 170) *S.A. van Diest[1], Z. Yu[1], S. Botschuijver[1], O. Welting[1], A. Strik[1], G. Jennings[2], R.P.J. Oude Elferink[1], C.C. Paulusma[1], G.E. Boeckxstaens[3], W. de Jonge[1], R.M. van den Wijngaard[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, University of Amsterdam, The Netherlands, [2]Jado Technologies GmbH, Dresden, Germany, [3]Division of Gastroenterology, University Hospital Gasthuisberg, Catholic University of Leuven, Leuven, Belgium*

08.42 The microbiota in mouse colon is causal for dietary heme-induced epithetlial hyperproliferation and hyperplasia (. p 171) *N. IJssennagger, R. van der Meer, TI Food and Nutrition and Dept. of Human Nutrition, Wageningen University, Wageningen, The Netherlands*

08.54 Activation of snail via reactive oxygen species mediates acetaldehyde-induced disruption of tight junctions in Caco-2 cell monolayer (p. 172)
E. Elamin[1,2,3], A. Masclee[1,2,3], HJ. Pieters[1,2,3], F. Troost[1,2,3], J. Dekker[1,4], D. Jonkers[1,2,3], [1]Top Institute Food and Nutrition (TIFN), Wageningen, The Netherlands, [2]Division Gastroenterology-Hepatology, [3]School for Nutrition, Toxicology and Metabolism, Maastricht University Medical center, The Netherlands, [4]Dept. of Animal Sciences, Wageningen UR, Wageningen, The Netherlands

09.06 Novel treatment options to improve protein folding and enhance pre-mRNA splicing in ATP8B1 deficiency (p. 173)
W.L. van der Woerd[1,2], I.T.G.W. Bijsmans[1], B. Spee[3], N. Geijsen[4], R.H.J. Houwen[2], S.F.J. van de Graaf[1], [1]Dept. of Metabolic Diseases, University Medical Center Utrecht, The Netherlands, [2]Dept. of Paediatric Gastroenterology, University Medical Center Utrecht, The Netherlands, [3]Dept. of Clinical Sciences of Companion Animals, Utrecht University, Utrecht, The Netherlands, [4]Hubrecht Institute, Utrecht, The Netherlands

09.18 27-Hydroxycholesterol: a potential treatment for non-alcoholic steatoheaptitis in mice (p. 174)
S.M.A. Walenbergh[1], V. Bieghs[1], T. Hendrikx[1], P.J. van Gorp[1], F. Verheyen[1], Y.D. Guichot[1], M.L.J. Jeurissen[1], M.J. Gijbels[1], S.S. Rensen[1], A. Bast[1], J. Plat[1], S.C. Kalhan[2], E. Leitersdorf[3], G.H. Koek[1], M.H. Hofker[4], D. Lütjohann[5], R. Shiri-Sverdlov[1], [1]Depts. of Molecular Genetics, Molecular Cell Biology, Electron Microscopy, Pathology, General Surgery, Toxicology, Internal Medicine and Human Biology; Nutrition and Toxicology Research (NUTRIM) and Cardiovascular Research (CARIM) Institutes of Maastricht, University of Maastricht, Maastricht University Medical Center (MUMC), Maastricht, The Netherlands, [2]Dept. of Pathobiology, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, Ohio, [3]Dept. of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [4]Dept. of Pathology and Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [5]Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Bonn, Germany

Vrijdag 22 maart 2013

09.30 Exploring a role for Cyp17a1 in the pathogenesis of cholestasis (p. 175)
A. Milona[1], B.M. Owen[2], E.C.L. Willemsen[1], C. Williamson[3], S.W.C. van Mil[1], [1]Dept. of Molecular Cancer Research, section Metabolic Diseases Metabolic and Endocrine Diseases, University Medical Centre Utrecht and Netherlands Metabolomics Centre, The Netherlands, [2]Dept. of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [3]Dept. of Surgery and Cancer, Institute of Reproductive and Developmental Biology, Imperial College London, London, United Kingdom

09.42 **Invited Speaker**
Targeting the enteric nervous system
Michel Neunlist, Professor French National Institute of Health and Medical Research (INSERM), Nantes, France

10.25 Koffiepauze

DEGH-Meeting **Baroniezaal**

Voorzitters: M. Huch en S.W.C. van Mil

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

Theme Stem cells

11.00 Indian Hedgehog is required for intestinal adenoma formation (p. 176)
N.V.J.A. Büller[1], S.L. Rosekrans[1], J. Heijmans[1], G.J. Offerhaus[3], B. Lanske[4], V. Muncan[1], M.E. Wildenberg[1], G.R. van den Brink[1,2], [1]Tytgat Institute for Liver and Intestinal Research and Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept. of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands, [4]Dept. of Developmental Biology, Harvard School of Dental Medicine, Boston, USA

11.12 Human liver carcinomas recruit mesenchymal stem/stromal cells that can promote tumor growth via paracrine signalling (p. 177)
P.Y. Hernanda[1], A. Pedroza-Gonzalez[1], M.E.E. Bröker[2], M.J. Hoogduijn[3], J.N.M. IJzermans[2], L.J.W. van der Laan[2], H.L.A. Janssen[1], M.P. Peppelenbosch[1], Q. Pan[1], [1]Dept. of Gastroenterology and Hepatology and [2]Dept. of Surgery and Laboratory of Experimental Transplantation and Intestinal Surgery, [3]Dept. of Internal Medicine Erasmus MC-University Medical Center, Rotterdam, The Netherlands

11.24 Induction of ER stress identifies potential esophageal stem cell markers (p. 178)
S.L. Rosekrans[1,2], J. Heijmans[1,2], E.J. Westerlund[1], C. Puylaert[1], V. Muncan[1], G.R. van den Brink[1,2], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, The Netherlands

11.36 The Bone Morphogenetic Protein Pathway either enhances or inhibits the Wnt pathway depending on SMAD4 and p53 status in colorectal cancer (p. 179)

P. Voorneveld[1], L.L. Kodach[1], R.J. Jacobs[1], S. Lam[2], J. C. Hardwick[1], [1]Gastroenterology & Hepatology, Leiden University Medical Center, Leiden, Netherlands, [2]Molecular Cell Biology, Leiden University Medical Center, Leiden, Netherlands

11.48 **Invited Speaker**

Stem/progenitor cells of the liver and gastrointestinal tract. In vitro expansion and therapeutic uses

Meritxell Huch, senior postdoctoral researcher, Hubrecht Institute for Developmental Biology and Stem Cell Research, Utrecht, The Netherlands

12.30 Lunch en postersessie

Postersessie DEGH **Meierij Foyer**

12.30 De postersessie van de DEGH vindt plaats tussen 12.30 en 14.00 uur met vanaf 12.45 de mogelijkheid om u aan te sluiten bij een begeleide sessie langs de posters. Vier tot vijf posters per categorie, 7 minuten per poster, zie pagina 59 e.v.

14.00 Vervolg DEGH-programma op bladzijde 49.

Sectie Gastrointestinale Oncologie — Parkzaal

Voorzitter: M. Bigirwamungu-Bargeman en K.M.A.J. Tytgat

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

09.30 Preoperative chemoradiotherapy for esophageal or junctional cancer (p. 180)

P. van Hagen[1], M.C.C.M. Hulshof[2], J.J.B. van Lanschot[1,3], E.W. Steyerberg[4], M.I. van Berge Henegouwen[3], B.P.L. Wijnhoven[1], D.J. Richel[5], G.A.P. Nieuwenhuijzen[6], G.A.P. Hospers[7], J.J. Bonenkamp[8], M.A. Cuesta[9], R.J.B. Blaisse[10], O.R.C. Busch[3], F.J.W. ten Kate[11,12], G. J.Creemers[13], C.J.A. Punt[14], J.Th.M. Plukker[15], H.M.W. Verheul[16], E.J. Spillenaar Bilgen[17], H. van Dekken[11,18], M.J.C. van der Sangen[19], T. Rozema[20,21], K. Biermann[11], J.C. Beukema[22], A.H.M. Piet[23], C.M. van Rij[24], J.G. Reinders[25], H.W. Tilanus[1], A. van der Gaast[26], for the CROSS-study Group, [1]Dept. of Surgery, Erasmus MC Rotterdam, [2]Dept. of Radiation Oncology, [3]Dept. of Surgery, Academic Medical Center Amsterdam, [4]Dept. of Public Health, Erasmus MC Rotterdam, [5]Dept. of Medical Oncology, Academic Medical Center Amsterdam, [6]Dept. of Surgery, Catharina Hospital Eindhoven, [7]Dept. of Medical Oncology, University Medical Center Groningen, [8]Dept. of Surgery, Radboud University Nijmegen Medical Center Nijmegen, [9]Dept. of Surgery, VU Medical Center Amsterdam, [10]Dept. of Medical Oncology, Rijnstate Hospital Arnhem, [11]Dept. of Pathology, Erasmus MC Rotterdam, [12]Dept. of Pathology, Academic Medical Center Amsterdam, [13]Dept. of Medical Oncology, Catharina Hospital Eindhoven, [14]Dept. of Medical Oncology, Radboud University Nijmegen Medical Center Nijmegen,[15]Dept. of Surgery, University Medical Center Groningen, [16]Dept. of Medical Oncology, VU Medical Center Amsterdam, [17]Dept. of Surgery, Rijnstate Hospital Arnhem, [18]Dept. of Pathology, St. Lucas Andreas Hospital Amsterdam, [19]Dept. of Radiation Oncology, Catharina Hospital Eindhoven, [20]Dept. of Radiation Oncology, Radboud University Nijmegen Medical Center Nijmegen, [21]Verbeeten Institute Tilburg, [22]Dept. of Radiation Oncology, University Medical Center Groningen, [23]Dept. of Radiation Oncology, VU Medical Center Amsterdam, [24]Dept. of Radiation Oncology, Erasmus MC Rotterdam, [25]Arnhem Radiotherapeutic Institute ARTI, [26]Dept. of Medical Oncology, Erasmus MC Rotterdam/ Daniel den Hoed Cancer Center, The Netherlands

09.40 Prediction of disease-free survival using relative change in FDG-uptake early during neoadjuvant chemoradiotherapy for potentially curable esophageal cancer (p. 181)

P. van Hagen[1], M. van Heijl[2], M.I. van Berge Henegouwen[2], R. Boellaard[3], P.M.M. Bossuyt[4], F.J.W. ten Kate[5,6], H. van Dekken[6,7], O.S. Hoekstra[3], G.W. Sloof[8,9], J.J.B. van Lanschot[1,2], [1]Dept. of Surgery, Erasmus Medical Center, Rotterdam, [2]Dept. of Surgery, Academic Medical Center, Amsterdam, [3]Dept. of Nuclear Medicine and PET research, VU Medical Center, Amsterdam, [4]Dept. of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, [5]Dept. of Pathology, Academic Medical Center, Amsterdam, [6]Dept. of Pathology, Erasmus Medical Center, Rotterdam, [7]Dept. of Pathology, St. Lucas Andreas Hospital, Amsterdam, [8]Dept. of Nuclear Medicine, Academic Medical Center, Amsterdam, [9]Dept. of Nuclear Medicine, Groene Hart Hospital, Gouda, The Netherlands

09.50 Timing of surgery and location of residual tumor after neoadjuvant chemoradiotherapy for esophageal cancer (p. 182)

J. Shapiro[1], F.J.W. ten Kate[2], P. van Hagen[1], B.P.L. Wijnhoven[1], J.J.B. van Lanschot[1], [1]Dept. of Surgery, Erasmus MC, Rotterdam, [2]Dept. of Pathology, Erasmus MC, Rotterdam, The Netherlands

10.00 A new fully covered metal stent (HANARO-ECT stent) for the treatment of malignant esophageal strictures: a prospective follow-up study (p. 183)

D. Walter[1], M.W. van de Berg[2], J.E. van Hooft[2], H. Boot[3], R.C.H. Scheffer[4], F.P Vleggaar[1], P.D. Siersema[1], [1]Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands, [2]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [3]Gastroenterology and Hepatology, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands, [4]Gastroenterology and Hepatology, Jeroen Bosch Hospital, Den Bosch, The Netherlands

10.10 Early pain detection and management after self-expandable esophageal stent placement in incurable cancer patients: a prospective observational cohort study (p. 184)

A.N. Reijm, P. Didden, E.J. Kuipers, M.J. Bruno, M.C.W. Spaander, Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

10.20 Limited diagnostic value of microsatellite instability associated pathology features in colorectal cancer (p. 185)

P.G. van Putten[1] , M.G.F. van Lier[1] , M. Hage[2] , K. Biermann[3] , R.H. van Rijssel[4] , P.J. Westenend[5] , J. Morreau[6] , W.N.M. Dinjens[3] , E. J. Kuipers[1, 7] , M.E. van Leerdam[1] and J.H. van Krieken[8] , [1]Dept. of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, [2]Dept. of Pathology, Pathan Foundation, Rotterdam, [3]Dept. of Pathology, Erasmus MC, University Medical Center, Rotterdam, [4]Dept. of Pathology, Isala Clinics, Zwolle, [5]Laboratory for Pathology, Dordrecht, [6]Dept. of Pathology, Leiden University Medical Center, Leiden, [7]Dept. of Internal Medicine, Erasmus MC, University Medical Center, Rotter-dam, [8]Dept. of Pathology, University Nijmegen Medical Center, Nijmegen, The Netherlands

10.30 The prognostic value of micrometastases and isolated tumour cells in histologically negative lymph nodes of patients with colorectal cancer: a systematic review and meta-analysis (p. 186)

D.A.M. Sloothaak, MD[1,2], S. Sahami, MD[2], H.J. van der Zaag-Loonen, MD PhD[3], P.J. Tanis, MD PhD[2], W.A. Bemelman, MD PhD[2], C.J. Buskens, MD PhD[2], [1]Dept. of Surgery, Gelre Hospital, Apeldoorn, The Netherlands, [2]Dept. of Surgery, AMC, Amsterdam, The Netherlands, [3]Dept. of Epidemiology, Gelre Hospital, Apeldoorn, The Netherlands

10.40 VEGF Expression in lesions of Patients with Colorectal Peritoneal Metastases is Correlated to Survival (p. 187)

E.M.V. de Cuba[1], I.H.J.T de Hingh[2], R. Kwakman[1], P.M. Delis-van Diemen[3], R. Bouwe[3], H.J. Bonjer[1], G.A. Meijer[3], E.A. te Velde[1], [1]Dept. of Surgical Oncology, VU University Medical Center Amsterdam, [2]Dept. of Surgery, Catharina Ziekenhuis Eindhoven, [3]Tumor Profiling Unit Dept. of Pathology, VU University Medical Center

10.50 Optimal time interval between neo-adjuvant chemo radiotherapy and surgery for rectal cancer (p. 188)

D.A.M. Sloothaak[1], D.E. Geijsen[2], N.J. van Leersum[3], C.J.A. Punt[4], C.J. Buskens[1], W.A. Bemelman[1], P. J. Tanis[1], On behalf of the Dutch Surgical Colorectal Audit., [1]Dept. of Surgery, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Radiotherapy, Academic Medical Centre, Amsterdam, The Netherlands, [3]Dept. of Surgery, Leiden University Medical Centre, Leiden, [4]Dept. of Medical Oncology, Academic Medical Centre, Amsterdam, The Netherlands

11.00 Koffiepauze expositiehal

11.15 Vergadering Sectie Inflammatoire Darmziekten

Voorzitters: G. Dijkstra en R.L. West

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

11.30 A history of colorectal neoplasia is associated with an increased risk of ileo-anal pouch neoplasia in a nationwide inflammatory bowel disease cohort (p. 189)

L.A.A.P. Derikx[1], W. Kievit[1], D.J. de Jong[1], C.Y. Ponsioen[2], B. Oldenburg[3], A.E. van der Meulen -de Jong[4], G. Dijkstra[5], M.J.A.L. Grubben[6], C.J.H.M. van Laarhoven[7], I.D. Nagtegaal[8], F. Hoentjen[1], Dutch Initiative on Crohn and Colitis, [1]Inflammatory Bowel Disease Center, Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept. of Gastroenterology and Hepatology, University Medical Center, Utrecht, The Netherlands, [4]Dept. of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands, [5]Dept. of Gastroenterology and Hepatology, University Medical Center, Groningen, The Netherlands, [6]Dept. of Gastroenterology and Hepatology, St Elisabeth Hospital, Tilburg, The Netherlands, [7]Dept. of Surgery, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [8]Dept. of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

11.40 Surveillance for colorectal cancer in colitis patients: effect of the implementation of new British and American guidelines on neoplasia yield (p. 190)

E. Mooiweer[1], M.G.H. van Oijen[1], A.E. van der Meulen[2], A.A. van Bodegraven[3], J.M. Jansen[4], N. Mahmmod[5], J. Nijsten[1], P.D. Siersema[1], B. Oldenburg[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, [2]Dept. of Gastroenterology and Hepatology, Leiden University Medical Center, [3]Dept. of Gastroenterology and Hepatology, VU University Medical Center Amsterdam, [4]Dept. of Gastroenterology and Hepatology, OLVG Amsterdam, [5]Dept. of Gastroenterology and Hepatology, Antonius Hospital Nieuwegein, The Netherlands

11.50 TPMT genotyping before thiopurine treatment results in lower leucopenia occurrence in a prospective randomized strategy study in 850 patients with inflammatory bowel disease (p. 191)

M.J.H. Coenen[1], C.J. van Marrewijk[1], L. Derijks[2], S.H. Vermeulen[1], H. Scheffer[1], B. Franke[1], H.J. Guchelaar[3], D.J. de Jong[4], on behalf of the TOPIC study group, Dept. of [1]Genetics and [4]Gastroenterology , Radboud University Medical Centre, Nijmegen, [2]Dept of Clinical Pharmacy, Maxima Medical Centre Veldhoven, [3]Dept of clinical Pharmacy and Toxicology , Leiden Univerisity Medical Centre, The Netherlands

12.00 Mercaptopurine therapy in IBD patients modulates GTPase Rac (p. 192)

M. L. Seinen[1], G. P. van Nieuw Amerongen[2], N. K. H. de Boer[1], J. van Bezu[2], C. J .J Mulder[1], A.A. van Bodegraven[1], [1]Gastroenterology and Hepatology, VU University medical center, Amsterdam, [2]Dept of Physiology, ICaR-VU, VU University medical center, Amsterdam, The Netherlands

12.10 Relapse rates during pregnancy in ulcerative colitis are higher than in Crohn's disease (p. 193)

A. De Lima[1], Z. Zelinkova[1], C. Van der Ent[1], C.J. Van der Woude[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

12.20 Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease (p. 194)

T.G.J. De Meij, B. Jharap, C.M.F. Kneepkens, A.A. van Bodegraven, N.K.H. de Boer, and the Dutch Initiative on Crohn and Colitis, Pediatric Gastroenterology, VU University medical centre, Amsterdam, The Netherlands, Gastroenterology and Hepatology, VU University medical centre, Amsterdam, The Netherlands

12.30 Magnetic resonance imaging of the hands and knees in patients with inflammatory bowel disease and arthralgia (p. 195)

L.K.P.M. Brakenhoff[1], W. Stomp[2], F.A. van Gaalen[3], H.H. Fidder[4], J.L. Bloem[2], D.M.F.M. van der Heijde[3], M. Reijnierse[2], D.W. Hommes[1,5], [1]Dept. of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands, [2]Dept. of Radiology, Leiden University Medical Center, Leiden, The Netherlands, [3]Dept. of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands, [4]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands, [5]Center for Inflammatory Bowel Diseases, University of California Los Angeles, Los Angeles, USA

12.40 Adding fuel to the fire – Neutrophils as antigen presenting cells in Crohn`s disease (p. 196)

R. Somasundaram[1], C.J. Van der Woude[1], M.P. Peppelenbosch[1], G.M. Fuhler[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

12.50 Fecal gas analysis by electronic nose of pediatric IBD patients and healthy controls: a pliot study (p. 197)

T.G.J. de Meij[1], Y.E. Lentferink[1], M.P.C. van der Schee[2], T. Paff[3], C.M.F. Kneepkens[1], A.A. van Bodegraven[4], N.K.H. de Boer[4], [1]Paediatric Gastroenterology, VU University medical centre, Amsterdam, [2]Pulmonology, Academic Medical Centre, Amsterdam, [3]Paediatric pulmonology, VU University medical centre, Amsterdam, [4]Gastroenterology and Hepatology, VU University medical centre, Amsterdam, The Netherlands

13.00 Lunchpauze in de expositiehal

Vrijdag 22 maart 2013

Symposium MDL-oncologie **Brabantzaal**

Voorzitters: A. Cats en G.H. de Groot

Oncologische behandelingen en hun bijwerkingen in de tractus digestivus

14.00 (Neo-)adjuvante behandeling bij het cholangio- en pancreascarcinoom
Dr. J. Wilmink, medisch oncoloog, Academisch Medisch Centrum, Amsterdam

14.25 Ondervoeding bij kanker
Dr. S. Beijer, diëtist / epidemioloog, IKZ

14.50 Bijwerkingen van chemotherapie en doelgerichte therapie in het colon
Drs. R.M.E. Slangen, MDL-arts, HagaZiekenhuis, Den Haag

15.15 Bijwerkingen van radiotherapie in de tractus digestivus
Dr. H. Boot, MDL-arts, NKI Antoni van Leeuwenhoekhuis, Amsterdam

15.40 Einde symposium

Ned. Ver. voor Gastroenterologie en Gastrointestinale Chirurgie — Auditorium

Voorzitters: C.H.C. Dejong en M.A.J.M. Jacobs

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

14.00 A vascular calcification scoring model in the prediction of anastomotic leakage after oesophagectomy for cancer (p. 198)
P.S.N. van Rossum[1,2], L. Haverkamp[1], M.S. van Leeuwen[3], M.J.A. Gondrie[3], R. van Hillegersberg[1], J.P. Ruurda[1], [1]Dept. of Surgery, University Medical Center Utrecht, Utrecht, [2]Dept. of Radiotherapy, University Medical Center Utrecht, Utrecht, [3]Dept. of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

14.10 Colonic stenting or emergency surgery for acute malignant colonic obstructtion: comparison of long-term outcomes in two general hospitals (p. 199) *M.W. van den Berg[1,2], D.A.M. Sloothaak[3,4], M.G.W. Dijkgraaf[5], E. van der Zaag[4], W.A. Bemelmam[3], P.J. Tanis[3], R.J.I. Bosker[6], P. Fockens[1], F. ter Borg[2], J.E. van Hooft[1], [1]Dept. of Gastroenterology & Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology & Hepatology, Deventer Hospital, Deventer, The Netherlands, [3]Dept. of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [4]Dept. of Surgery, Gelre Hospital, Apeldoorn, The Netherlands, [5]Clinical Research Unit, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [6]Dept. of Surgery, Deventer Hospital, Deventer, The Netherlands*

14.20 The N0 stage in colon cancer: how many nodes are enough? (p. 200)
D.W. da Costa[1], H. van Dekken[2], B. Witte[3], B.C. Vrouenraets[1], [1]Dept. of Surgery, Sint Lucas Andreas Hospital, Amsterdam, [2]Dept. of Pathology, Sint Lucas Andreas Hospital, Amsterdam, [3]Dept. of Epidemiology and Biostatistics, VU Medical Center, Amsterdam, The Netherlands

14.30 Who determines the N-stage in colon carcinoma: Pathologist or Surgeon? (p. 201). *D.W. da Costa[1], B.A. van Wagensveld[1], K. Wassenaar[2], W.F. van Tets[1], K. Keizer[2], B. Witte[3], H. van Dekken[2], B.C. Vrouenraets[1], [1]Dept. of Surgery, Sint Lucas Andreas Hospital, Amsterdam, [2]Dept. of Pathology, Sint Lucas Andreas Hospital, Amsterdam, [3]Dept. of Epidemiology and Biostatistics, VU Medical Center, Amsterdam. The Netherlands*

14.40 Randomized Controlled Trial of Transoral Incisionless Fundoplication versus Proton Pump Inhibitors for Treatment of GERD: Preliminary data (p. 202). *B.P.L. Witteman[1], J.M. Conchillo[2], N.F. Rinsma[2], R. Vijgen[1], F. Nieman[3], A. Peeters[3], G.H. Koek[2], L.P.S. Stassen[1], N.D. Bouvy, [1]Afdeling Gastro-intestinale Chirurgie, Maastricht Universitair Medisch Center, Maastricht, [2]Afdeling Maag-darm-leverziekten, Maastricht Universitair Medisch Center, Maastricht, [3]Afdeling Epidemiologie, Maastricht Universitair Medisch Center, Maastricht, The Netherlands*

14.50 Genome-wide screening of microRNAs as predictors for response to neoadjuvant chemoradiotherapy in oesophageal adenocarcinoma (p. 203)
E.L.A. Toxopeus[1], K.C. Mahabier[1], K. Biermann[2], H.W. Tilanus[1], J.J.B. van Lanschot[1], B.P.L. Wijnhoven[1], L.J.W. van der Laan[1], [1]Dept. of Surgery and Laboratory of Experimental Transplantation and Intestinal Surgery and [2]Dept. of Pathology, Erasmus MC – University Medical Centre, Rotterdam, The Netherlands

Vrijdag 22 maart 2013

15.00 Epidural analgesia: associated with survival in colon cancer? (p. 204)

F.J. Vogelaar[1,2], V.E. Lemmens[3], J.C. van der Linden[4] , H.G.J.M. Cornelisse[5], F.R.C. van Dorsten[5], K. Bosscha[1], [1]Dept. of Surgery, Jeroen Bosch Hospital, The Netherlands, [2]Dept. of Surgery, VieCuri Medical Centre, The Netherlands, [3]Dept. of Research, Comprehensive Cancer Centre South, The Netherlands, [4]Dept. of Pathology, Jeroen Bosch Hospital, The Netherlands, [5]Dept. of Anaesthesiology, Jeroen Bosch Hospital, The Netherlands

15.10 The role of biological markers of epithelial to mesenchymal transition (EMT) in esophageal adenocarcinoma (p. 205)

M.J.D. Prins[1], J.P. Ruurda[1], M.J.P. Lolkema[3], F.J.W. Kate ten[2], R. van Hillegersberg[1], [1]Dept. of Surgery, University Medical Center Utrecht, The Netherlands, [2]Dept. of Pathology, University Medical Center Utrecht, The Netherlands, [3]Dept. of Medical Oncology, University Medical Center Utrecht, The Netherlands

15.20 Laparoscopic Total Gastrectomy versus Open Total Gastrectomy for Cancer: A Systematic Review and Meta-Analysis (p. 206)

L. Haverkamp, T.J. Weijs, P.C. van der Sluis, I. van der Tweel, J.P. Ruurda, R. van Hillegersberg, Universitair Medisch Centrum Utrecht, Utrecht, The Netherlands

15.30 Einde programma

DEGH-Meeting **Baroniezaal**

Voorzitters: C.C. Paulusma en S. Withoff

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

Theme **miRNA and Immunology**

14.00 **Inleider / Invited Speaker**
Theme introduction by Sebo Withoff, Groningen

14.12 MiR-214 is a key-regulator and therapeutic target in colitis-associated colorectal carcinogenesis (p. 207)
W.K. van Deen[1,3], C. Polytarchou[2], H.W. Verspaget[1], T. Palumbo[2], G. Koukos[2], A.E. van der Meulen-de Jong[1], M. Hatziapostolou M[2], C. Pothoulakis[3], D.W. Hommes[1,3], D. Iliopoulos[2], [1]Dept. of Gastroenterology and Hepatology, LUMC The Netherlands, [2]Division of Digestive Diseases, Center for Systems Biomedicine, UCLA USA, [3]Division of Digestive Diseases, Center for Inflammatory Bowel Diseases, UCLA USA

14.24 MicroRNA-142-5P and mast cell biology in experimental colitis (p. 208)
M.M.W. Slaman[1], F.H. van Dooren[1], S.L. Meijer[2], K. Fluiter[3], E.W. Vogels[1], P. D. Moerland[4], A.A. te Velde[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, [2]Dept. of Pathology, Academic Medical Center, Amsterdam, [3]Dept. of Neurogenetics, Academic Medical Center, Amsterdam, [4]Cinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands

14.36 Stool-based microRNA expression profiling discriminates colorectal cancer patients from healthy individuals (p. 209)
L.M. Timmer[1], M.A. van de Wiel[2], A.S. Bolijn[1], L.J.W. Bosch[1], B. Carvalho[1], C.J.J. Mulder[3], R.Q.J. Schaapveld[4], E. Berezikov[4,5], E. Cuppen[4,5], G.A. Meijer[1], B. Diosdado[1], [1]Dept. of Pathology, VU University Medical Center, Amsterdam, [2]Dept. of Epidemiology & Biostatistics, VU University Medical Center, Amsterdam, [3]Dept. of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [4]InteRNA Technologies BV, Utrecht, [5]Hubrecht Institute, Cancer Genomics Center, and University Medical Center Utrecht, Utrecht, The Netherlands

14.48 Bi-directional release of microRNAs by hepatocytes to bile and blood: Relation with liver injury and bilirubin secretion (p. 210)
W.R.R. Farid[1], H.P. Roest[1], C.J. Verhoeven[1], P.E. de Ruiter[1], V. Ramakrishnaiah[1], J. de Jonge[1], R.W.F. de Bruin[1], J. Kwekkeboom[2], H.J. Metselaar[2], H.W. Tilanus[1], G. Kazemier[3], L.J.W. van der Laan[1], [1]Dept. of Surgery and Laboratory of Experimental Transplantation and Intestinal Surgery, [2]Dept. of Gastroenterology & Hepatology, Erasmus MC-University Medical Center and Postgraduate School Molecular Medicine, Rotterdam, [3]Dept. of Surgery, VU University Medical Center, Amsterdam, The Netherlands

Vrijdag 22 maart 2013

15.00 IFNα and IFNλ induce distinct response patterns in TLR-activated human macrophages (p. 211)

R.A. de Groen[1], B-S. Liu[1], A. Boltjes[1], H.L.A. Janssen[1], A. Boonstra[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

15.12 Recruited inflammatory monocytes, but not Kupffer cells, play a crucial role in early virus-induced intrahepatic immune responses (p. 212)

D. Movita[1], P. Biesta[1], B. Haagmans[2], E. Zuniga[3], H.L.A. Janssen[1], A. Boonstra[1], T. Vanwolleghem[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Virology, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Division of Biological Sciences, University of California San Diego, La Jolla, San Diego, California

15.24 Abstract and Poster prizes and goodbye

Voorzitters: M.E. Klos en G.J.A. Wanten

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

09.00 Single centre evaluation of nasojejunal feeding tube placement by nurses using the Cortrak® electromagnetic imaging system (p. 213)
J.M.J. Geesing, J.Z. Kuper, M.S. Postema-Stiksma, M. Hoekstra-Wilts, H.R. Noordhoff, J.J. Koornstra, G. Dijkstra, University Medical Centre Groningen, The Netherlands

09.10 Medical doctors underestimate daily calcium intake in patients with osteoporosis (p. 214) *L. Rasch[1,2], M. van Bokhorst - de van der Schueren[2], L. van Tuyl[1], I. Bultink[1], W. Lems[1], [1]Dept. of Rheumatology, [2]Dept. of Nutrition and Dietetics, VU University Medical Center, Amsterdam, The Netherlands*

09.20 Systematic screening for undernutrition; predictive factors for success (p. 215). *E. Leistra[1,2], A. van der Hout[1], M.A.E. van Bokhorst-de van der Schueren[1,2], M. Visser[2,3], H.M. Kruizenga[1,2,3], [1]Dept. of Nutrition and Dietetics, Internal Medicine, VU University Medical Center[2], Dutch Malnutrition Steering Group, [3]Dept. of Health Sciences, Faculty of Earth and Life Sciences, VU University, Amsterdam, The Netherlands*

09.30 Nutritional status in patients with chronic pancreatitis. The value of a nutritional assessment (p. 216)
B.P.M. Verhaegh[1], P.L.M. Reijven[2], M.H. Prins[3], J.H.M. Brouns[2], A.A.M. Masclee[1], J.C.A. Keulemans[1], [1]Dept. of Gastroenterology, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Dept. of Dietetics, Maastricht University Medical Center, Maastricht, The Netherlands, [3]Dept. of Epidemiology, Maastricht University Medical Center, Maastricht, The Netherlands

09.40 Validity of bioelectrical impedance analysis to assess fat-free mass in head and neck cancer patients: an exploratory study (p. 217).
H. Jager-Wittenaar[1,2], P.U. Dijkstra[2,3], C.P. Earthman[4], W.P. Krijnen[1], J.A. Langendijk[5], B.F.A.M. van der Laan[6], J. Pruim[7], J.L.N. Roodenburg[2], [1]Hanze University of Applied Sciences, Professorship in Health Care and Nursing, Groningen, The Netherlands, [2]University Medical Center Groningen, Dept. of Oral and Maxillofacial Surgery, University of Groningen, The Netherlands, [3]University Medical Center Groningen, Dept. of Rehabilitation, University of Groningen, The Netherlands, [4]University of Minnesota, Dept. of Food Science and Nutrition, St. Paul, MN, USA, [5]University Medical Center Groningen, Dept. of Radiation Oncology, University of Groningen, The Netherlands, [6]University Medical Center Groningen, Dept. of Otorhinolaryngology/Head & Neck Surgery, University of Groningen, The Netherlands, [7]University Medical Center Groningen, Dept. of Nuclear Medicine and Molecular Imaging, University of Groningen, Groningen, The Netherlands

09.50 Leukocyte activation by medium-chain triglycerides is not modulated by fish oil-based lipids (p. 218)
E.D. Olthof[1], H.M.J. Roelofs[1], G.J.A. Wanten[1], [1]Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Vrijdag 22 maart 2013

10.00 Features of cachexia in patients with advanced cancer scheduled for treatment with chemotherapy (p. 219)

S. Blauwhoff-Buskermolen[1,2], H.M.W. Verheul[2], M.J.P. Admiraal[1], J.A.E. Langius[1], M.A.E. van Bokhorst-de van der Schueren[1], [1]Dept. of Nutrition and Dietetics, Internal Medicine, [2]Dept. of Medical Oncology VU University Medical Center, Amsterdam, The Netherlands

10.10 Evaluation of optimal protein and energy nutrition in mechanically ventilated critically ill patients (p. 220)

P.J.M. Weijs, S.N. Stapel, A.R.J. Girbes, A. Beishuizen, [1]Dept. of Nutrition and Dietetics, VU University Medical Center, [2]Dept. of Nutrition and Dietetics, Amsterdam University of Applied Sciences, [3]Dept. of Intensive Care Medicine, VU University Medical Center Amsterdam, The Netherlands

10.20 The impact of duodenal-jejunal exclusion on satiety hormones (p. 221)

C. de Jonge[1,2], S.S. Rensen[1], F.J. Verdam[1,2], R.P. Vincent[3], S.R. Bloom[4], W.A. Buurman[1], C.W. le Roux[4], N.D. Bouvy[1], J.W.M. Greve[2], [1]Dept. of General Surgery and NUTRIM School for Nutrition, Toxicology and Metabolism Research, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Dept. of General Surgery, Atrium Medical Center Parkstad, Heerlen, The Netherlands, [3]Dept. of Clinical Biochemistry, King's College Hospital NHS Foundation Trust, London, UK, [4]Dept. of Medicine, Imperial College London, London, UK

10.30 Koffiepauze

Symposium Oncology and Nutrition

Chairs: Dr. G. Ligthart-Melis, dietitian VUmc
Dr. G. Wanten, gastroenterologist UMCN

11.00 Introduction and goals of symposium
(Platform research dietitians and nurse practioners)
Dr. M.A.E. van Bokhorst-de van der Schueren

11.10 Optimizing nutrition and functional capacity in patients with foregut tumors
Dr. L. Gramlich, PhD MD, associate professor University of Alberta, Edmonton, Canada

11.50 Discussion

Short presentations of research dietitians and nutritionists on their studies in relation to body composition, body function and energy expenditure

(7 minutes presentation / 3 minutes discussion)

12.10 Diet optimizes treatment hepatitis C
Drs. E. Huisman (UMCU)

12.20 Malnutrition and oropharyngeal cancer
J.A.E. Langius, VUmc

12.30 From decreasing malnutrition to improving quality of life in head and neck cancer patients
Drs. M. van den Berg (UMCN)

12.40 Prevalence of cachexia in head and neck cancer patients: an exploratory study
Dr. H. Jager (UMCG / Hanze Hogeschool)

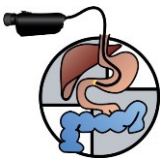
Vrijdag 22 maart 2013

12.50 Design of the COBRA-study, an observational study on changes in body composition during chemotherapy for breast cancer
Dr. ir. R. Winkels (Wageningen UR)

13.00 What have we learned today, where do we want to go?
Mrs. C. Jonkers, secretary NESPEN

Programma V&VN MDL **Diezezaal**

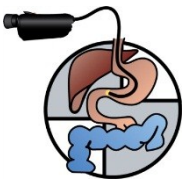
Beroepsvereniging van zorgprofessionals
Maag Darm Lever



10.00	Opening door de voorzitter *Mevr. P. Bol, voorzitter V&VN MDL, Meander Medisch Centrum, Amersfoort*
10.00	Complementaire zorg binnen MDL *Mw. M. Busch, directeur Praag Instituut*
10.25	RIVM – colonscreening *Mw. M. van Wieren, programmamedewerker invoering bevolkings-onderzoek darmkanker RIVM*
10.55	Algemene Ledenvergadering *Mw. P. Bol, voorzitter V&VN MDL*
11.25	Lancering v-logs van de Colitis Collectie *Mw. T. Markus, CCUVN*
11.45	Beeldvorming van het darmpakket *Mw. H.M. Dekker, radioloog, Universitair Medisch Centrum St Radboud, Nijmegen*
12.15	Lunchbuffet in de Kempenhal

Vrijdag 22 maart 2013

Programma Endoscopieverpleegkundigen — Diezezaal



Beroepsvereniging van zorgprofessionals
Maag Darm Lever

Voorzitter: P. Bol

13.45 Doktersassistenten in de endoscopie
Mw. G. van Baggum, voorzitter NVDA

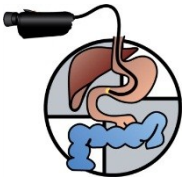
14.25 Behandeling van GI-bloedingen: de Coil methode
Dr. L. Meiss, radioloog, Meander MC, Amersfoort

14.45 Verpleegkundig endoscopisten opleiding
Mw. M. Fokker, verpleegkundig endoscopist, Diaconessenhuis Leiden

15.05 Praktische toepassing sedatierichtlijn
Dhr. J. Turner, PSA specialist en anesthesiemedewerker, Flevoziekenhuis Almere

15.30 Einde programma

Programma Lever-/IBD verpleegkundigen — Zaal 52



Beroepsvereniging van zorgprofessionals
Maag Darm Lever

Voorzitter: M. van Kouwen

13.45 Zelfmanagement, hoe kan ik dit inpassen in mijn praktijk?
Mw. M. van Halm, projectadviseur V&VN

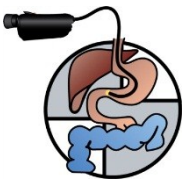
14.30 Leverfunctietesten
Dr. J.J. Kloek, MDL-arts i.o., Academisch Medisch Centrum, Amsterdam

15.00 Primaire Scleroserende Cholangitis
Dr. A. Inderson, maag-darm-leverarts, Leids Universitair Medisch Centrum

15.30 Einde programma

Programma Voedingsverpleegkundigen — Zaal 58

Beroepsvereniging van zorgprofessionals
Maag Darm Lever



Voorzitter: W. Kuin

13.45 TPV, complicaties en voorwaarden voor het regelen van TPV thuis
Mw. W. Kuin, verpleegkundig specialist i.o., Medisch Centrum Alkmaar

14:05 Het organiseren van kortdurende TPV in de thuissituatie
Mw. M. Klos, voedingsverpleegkundige, Gelre Ziekenhuizen Apeldoorn

14.25 Het vervolgen van patiënten in de thuissituatie
Mw. T. Tas, voedingsverpleegkundige, Academisch Medisch Centrum, Amsterdam

14.45 TPV thuis, invalshoek van de thuiszorg
Mw. M. Wilms, VTHT team EVEAN Alkmaar

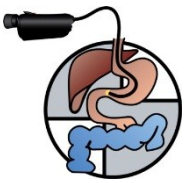
15.05 Casussen, valkuilen, tips & trics discussie
Mw. T. Tas, voedingsverpleegkundige, Academisch Medisch Centrum, Amsterdam

15.30 Einde programma

Vrijdag 22 maart 2013

Programma MDL – kliniek verpleegkundigen **Zaal 57**

Beroepsvereniging van zorgprofessionals
Maag Darm Lever



Voorzitter: J. Elzerman

13.45 Tractus Digestivus bloedingen
Dhr. J.M. Kersten, AIOS MDL, Universitair Medisch Centrum St Radboud, Nijmegen

14.15 Verpleegkundige aandachtspunten bij tractus digestivus bloedingen in de kliniek
Mw. A. Pouwelsen, verpleegkundige, Universitair Medisch Centrum St Radboud, Nijmegen

14.45 Colorectale chirurgie, soorten OK's en risico's op complicaties
Dhr. J. Deelder, AIOS chirurgie, Medisch Centrum Alkmaar

15.15 Einde programma

Theme **Regulation and Intervention –** Chairs: K.N. Faber and A.A. te Velde

1. Identification of a novel gene associated with polycystic liver and kidney diseases

W.R. Cnossen[1], R.H.M. te Morsche[1], A. Hoischen[2], C. Gilissen[2], M. Chrispijn[1], H. Venselaar[3], S. Mehdi[4], C. Bergmann[5], J.A. Veltman[2], J.P.H. Drenth[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Human Genetics, [3]Center for Molecular and Biomolecular Informatics, Radboud University Nijmegen Medical Center, [4]Dept. of Surgery, Hôpital Avicenne Chu Rabat, d'Oujda, Morrocco, [5]Center for Human Genetics, Bioscientia, Ingelheim, Germany

2. IFN-γ abrogates endotoxin tolerance in human macrophages via an HDAC-dependent mechanism

J. Duarte, R. Schilderink, W.J. de Jonge, Tytgat Institute, AMC, Amsterdam, The Netherlands

3. Nociception induced by duodenal capsaicin infusion in healthy volunteers: a potential protective role for serotonin?

D. Keszthelyi[1,2], M. van Avesaat[1,2], F. Troost[1,2], D. Jonkers[1,2], J. Dekker[1,3], A. Masclee[1,2], [1]Top Insitute Food and Nutrition, Wageningen, [2]Maastricht Universitair Medisch Centrum, Maastricht, [3]Wageningen Universiteit, Wageningen, The Netherlands

4. High Pregnane X Receptor expression in human intestinal cancer cells inhibits proliferation and prolongs survival

J.J. Deuring[1], M.P. Peppelenbosch[1], E.J. Kuipers[1], C. de Haar[1], C. Janneke van der Woude[1]*, [1]Dept. of Gastroenterology and Hepatology, Erasmus MC - University Medical Centre, Rotterdam, The Netherlands, *CdH and CJvdW share senior author ship*

Theme **Hepatic Insult / Immunity –** Chairs: U.H.W. Beuers and C.C. Paulusma

5. Dopamine infusion protects rat liver *in vivo* against hypothermia and re-warming-induced damage

E.M. Verhaag[1,2], G.J. Dugbartey[2], H. Moshage[1], R.H. Henning[2], K.N. Faber[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [2]Dept. of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

6. Hepatitis B virus-induced activation of Kupffer cells as first step towards virus-specific immunity?

A. Boltjes[1], N. van Montfoort[1], M.L. op den Brouw[1], H.L.A. Janssen[1], A. Boonstra[1], A.M. Woltman[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

7. A preoperative amino acid free diet protects against hepatic ischemia reperfusion injury

T.C Saat, T.M van Ginhoven, M. Verweij, L.J.W. van der Laan, J.N.M. IJzermans, R.W.F. de Bruin, Laboratory for Experimental Transplantation and Intestinal Surgery (LETIS) – University Medical Center Rotterdam, The Netherlands

8. Hyaluronic acid as a marker of hepatic sinusoidal obstruction syndrome secondary to oxaliplatin-based chemotherapy in patients with colorectal liver metastases

M.A.J. van den Broek[1], C.P.H. Vreuls[2], A. Winstanley[4], R.L.H. Jansen [3], A.A. van Bijnen[1], S.A.W.G. Dello[1], M.H. Bemelmans[1], C.H.C. Dejong[1], A. Driessen[2], S.W.M. Olde Damink[1,5], [1]Dept. of Surgery, [2]Dept. of Pathology and [3]Dept. of Medical Oncology, Maastricht University Medical Centre, Maastricht, The Netherlands, [4]Dept. of Pathology and [5]Dept. of HPB Surgery, Royal Free Hospital, London, United Kingdom

Theme **Metabolism –** Chairs: R.K. Weersma and S.W.C. van Mil

9. Amelioration of fatty liver by a novel FXR agonist is not due to inhibition of LXR activation

M. Boesjes[1], T. Bos[1], R. Havinga[1], R. Boverhof[1], F. Kuipers[1,2], B. Groen[1,2], [1]Laboratory of Pediatrics and [2]Laboratory Medicine, Center for Liver, Digestive and Metabolic Diseases, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

10. Genetic inactivation of the bile salt export pump in mice profoundly increases fecal cholesterol excretion

M.Y.M. van der Wulp[1,2], T.H. van Dijk[2], V.W. Bloks[2], A.K. Groen[1,2], H.J. Verkade[1,2], *[1]Top Institute Food and Nutrition, Wageningen, The Netherlands, [2]Pediatric Gastroenterology and Hepatology, Dept. of Pediatrics, Beatrix, Children's Hospital, Groningen University Institute for Drug Exploration, University Medical Center Groningen, Groningen, The Netherlands*

11. Acute effect of plant stanol esters on hepatic sterol metabolism in mice

E. de Smet[1], R.P. Mensink[1], M. Konings[1], G. Brufau[2], B. Groen[2], R. Havinga[2], M. Schonewille[2], A. Kerksiek[3], D. Lütjohann[3], J. Plat[1], [1]Dept. of Human Biology, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, The Netherlands, [2]Dept. of Pediatrics, University Medical Center Groningen, The Netherlands, [3]Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Bonn, Germany

12. Vitamin A promotes the synthesis of biliary beta-muricholic acid in rats

M. Hoekstra[1], M.O. Hoeke[1], J. Heegsma[1], V.W. Bloks[2], H. Moshage[1], K.N. Faber[1], [1]Dept. of Gastro-enterology and Hepatology, [2]Dept. of Pediatrics, University Medical Center Groningen, Groningen, University of Groningen, The Netherlands

13. A novel mathematical modelling approach to analyze complex metabolic path-way dynamics; application to LXR activated lipoprotein metabolism

C.A. Tiemann[1,4], J. Vanlier[1,4], M.H. Oosterveer[2], P.A.J. Hilbers[1,4], A.K. Groen[2,3,4], N.A.W. van Riel[1,4], [1]Dept. of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands, [2]Dept. of Pediatrics, Center for Liver Digestive and Metabolic Diseases, University Medical Center Groningen, Groningen, The Netherlands, [3]Dept. of Laboratory Medicine, Center for Liver Digestive and Metabolic Diseases, University Medical Center Groningen, Groningen, The Netherlands, [4]Netherlands Consortium for Systems Biology, University of Amsterdam, Amsterdam, The Netherlands

Theme **Mucosal Immunology –** Chairs: D. Jonkers and G. Bouma

14. Fecal microbial composition of inflammatory bowel disease (IBD) patients with changing disease activity over time

E. Wills[1,2], D. Jonkers[1,3], P. Savelkoul[2,3], A. Masclee[1,3], M. Pierik[1,3], J. Penders[2,3], [1]Division Gastroenterology-Hepatology, [2]Dept. of Medical Microbiology, [3]School for Nutrition, Toxicology and Metabolism (NUTRIM), Maastricht University Medical Center, Maastricht, The Netherlands

15. Crohn's disease patients with the ATG16L1T300A allele are unable to modify their mucosal microbiota profile upon inflammation

A. Regeling[1#], M. Sadaghian[1,2#], M.C. de Goffau[2], K.N. Faber[1], H.J.M. Harmsen[2], G. Dijkstra[1*], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Medical Microbiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, [#]Both first authors contributed equally, [*]Both last authors contributed equally*

16. Cytokine Profiles In Peripheral Blood Of IBD Patients; Correlation With Genotypes And Clinical Phenotypes

N.W. Duijvis[1], F.H. van Dooren[1], D. Oudejans[1], S.C. Wolfkamp[1], E.W. Vogels[1], F.W. Vergouwe[1], P.C. Stokkers[2], A.A. te Velde[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, [2]Sint Lucas Andreas Ziekenhuis, Amsterdam, The Netherlands

17. Cytokine profiles of Crohn's disease responders and non-responders to adalimumab

C.P. Peters[1,2], F.H. van Dooren[1], N.W. Duijvis[1,2], E.W. Vogels[1], C.Y. Ponsioen[1,2], A.A te Velde[1,2], [1]Tytgat Institute for Liver and Intestinal Research, AMC, Amsterdam, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

18. Prevalence of Brachyspira species in stool-samples of patients with gastroenteritis

L.J. Westerman[1], R.F. de Boer[2], J.H. Roelfsema[3], I.H.M. Friesema[3], L.M. Kortbeek[3], J.A. Wagenaar[4], M.J.M. Bonten[1], J.G. Kusters[1], [1]Dept. of Medical Microbiology, University Medical Centre Utrecht, Utrecht, The Netherlands, [2]Laboratory for Infectious Diseases, Dept. of Research & Development, Groningen, The Netherlands, [3]National Institute for Public Health, Centre for Infectious Disease Control, Bilthoven, The Netherlands, [4]Dept. of Infectious Diseases and Immunology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

Theme **Regulation and Intervention –** Chairs: K.N. Faber and A.A. te Velde

19. Bromodomain inhibition enhances tolerogenic properties in dendritic cells; application in colitis

R. Schilderink[1], L.E. Nijhuis[1], F.W. Hilbers[1], R.K. Prinjha[2], W.J. de Jonge[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands, [2]Epinova DPU, GlaxoSmithKline, Stevenage, United Kingdom

20. The proton pump inhibitor esomeprazole increases transepithelial resistance in Caco-2 cells but does not affect paracellular permeability

D. Keszthelyi, A.A.M. Masclee, Maastricht Universitair Medisch Centrum, Maastricht, The Netherlands

21. Identification of two pathways by which intravenous immunoglobulin modulates dendritic cells in humans in vivo

A.S.W. Tjon[1], H. Jaadar[1], R. van Gent[1], P. M. van Hagen[2], L.J.W. van der Laan[3], P.A.W. te Boekhorst[4], H.J. Metselaar[1], J. Kwekkeboom[1], Depts. of Gastroenterology and Hepatology[1], Internal Medicine and Immunology[2], Surgery[3] and Hematology[4], Erasmus MC-University Medical Centre, Rotterdam, The Netherlands

22. Feasibility of pathway analysis in EUS-FNA obtained tissue of pancreatic cancer patients: a step towards personalized based medicine

W.K. Utomo[1], V. Narayanan[1], K. Biermann[2], C.H.J. van Eijck[3], M.J. Bruno[1], M.P. Peppelenbosch[1], H. Braat[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [2]Dept. of Pathology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [3]Dept. of Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands

23. MMP-2 CT/TT genotype is a disease modifier in Primary Sclerosing Cholangitis

K. Sebib Korkmaz[1], B.J. de Rooij[1], B. van Hoek[1], M. Janse[2], M.J. Coenraad[1], J.J. van der Reijden[1], R.K. Weersma[2], R.J. Porte[3], A.G. Baranski[4], H.W. Verspaget[1], [1]Dept. of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands, [2]Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, The Netherlands, [3]Dept. of Hepatobiliary Surgery and Liver Transplantation, University Medical Groningen, The Netherlands, [4]Dept. of Surgery, Leiden University Medical Center, Leiden, The Netherlands

Theme **Hepatic Insult / Immunity –** Chairs: U.H.W. Beuers and C.C. Paulusma

24. Mesenchymal stem cell-derived trophic factors promote liver regeneration but does not protect against ischemia reperfusion injury

S.M.G. Fouraschen[1], L.J.W. van der Laan[1], J. Wolf[2], H.J. Metselaar[3], R.W.F. de Bruin[1], H.W. Tilanus[1], K.M. Olthoff[2] and J. de Jonge[1], [1]Dept. of Surgery and Laboratory of Experimental Transplantation and Intestinal Surgery, Erasmus MC-University Medical Center, Rotterdam, The Netherlands, [2]Penn Transplant Institute, University of Pennsylvania, Philadelphia, USA, [3]Dept. of Gastroenterology & Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

25. T follicular helper cells: do they play a role in chronic HCV?

M. Spaan, K. Kreefft, W.P. Brouwer, R.J. de Knegt, T. Vanwolleghem, H.L.A. Janssen, A. Boonstra, Department of Gastroenterology and Hepatology, Erasmus Medical Center Rotterdam, the Netherlands

26. The TNF-alpha -238 G-allele predisposes to severe bacterial infection in patients with end-stage liver disease enlisted for liver transplantation

E. de Mare-Bredemeijer[3], R. Bartáková[1]*, S. Fraňková[1], D. Roelen[4], T. Visseren[3], P. Trunečka[1], J. Špičák[1], H. Metselaar[3], M. Jirsa[2], J. Kwekkeboom[3], J. Šperl[1], [1]Dept. of Hepatogastroenterology, Inst for Clin and Exp Med and [2] Laboratory of Experimental Medicine, Prague, Czech Republic, [3]Dept. of Hepatogastroenterology, University Medical Center, Rotterdam, [4]Dept. of Immunohematology and Blood Transfusion, University Medical Center, Leiden, The Netherlands, *These authors contributed equally*

27. Tumor-infiltrating IL-10 producing cells are potent suppressors of the local anti-tumor immunity in patients with liver cancer

A. Pedroza-Gonzalez[1], J. Kwekkeboom[1], E. Vargas-Mendez[1], C. Verhoef[2], J. de Jonge[2], K. Biermann[3], J.N.M. IJzermans[2], H.L.A. Janssen[1], D. Sprengers[1,4], [1]Dept Gastroenterology and Hepatology, [2]Dept. Surgery, [3]Dept. Pathology, Erasmus MC University Medical Center, Rotterdam, [4]Dept. Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Theme **Metabolism –** Chairs: R.K. Weersma and S.W.C. van Mil

28. Colectomy enhances tumor cell adhesion in the liver and subsequent out-growth of metastases

S.S. Grewall[1,2], N. Gül[1], R. Braster[1], S. Pouw[1], M. Bögels[1,2], R. Beelen[1], J. Bonjer[2], M. van Egmond[1,2], [1]Dept. of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, [2]Dept. of Surgery, VU University Medical Center, Amsterdam, The Netherlands

29. Multiple intraperitoneal injections of human bone marrow-derived mesenchymal stromal cells does not improve treatment efficacy in experimental colitis.

I. Molendijk[1], V.L. van Zuylen[2*], H.W. Verspaget[1], H. Roelofs[2], A.E. van der Meulen-de Jong[1], W.E. Fibbe[2], D.W. Hommes[3], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Immunohematology and Blood transfusion, Leiden University Medical Center, Leiden, The Netherlands, [3]Div. of Digestive Diseases, University of California Los Angeles, USA, *Contributed equally*

30. Smooth muscle protein 22 (SM22) as potential marker for the diagnosis of transmural intestinal ischemia: an experimental study in rats

D.H.S.M. Schellekens[1,2], K.W. Reisinger[1,2], J.P.M. Derikx[1,2], K. Lenaerts[1,2], W.A. Buurman[2], C.H.C. Dejong[1,2], [1]Dept. of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands, [2]NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, Maastricht, The Netherlands

31. Plasma cathepsin D: a novel way to improve diagnosis of non-alcoholic steatohepatitis

V. Bieghs[*1], S.M.A. Walenbergh*[*1], T. Hendrikx[1], P.J. van Gorp[1], M.L.J. Jeurissen[1], P. Lindsey[1], S.S. Rensen[1], S.W.M. Olde Damink[1], W.A. Buurman[1], A.C.E. Vreugdenhil[1], J.W.M. Greve[2], J. Plat[1], M.H. Hofker[3], G.H. Koek[4], R. Shiri-Sverdlov[1], [1]Depts. of Molecular Genetics, Population Genetics, General Surgery, Human Biology, Nutrition and Toxicology Research (NUTRIM) and Cardiovascular Research (CARIM) Institutes of Maastricht, University of Maastricht, Maastricht, The Netherlands, [2]Dept. of Surgery, Atrium Medical Center Parkstad, Heerlen, The Netherlands, [3]Dept. of Pathology and Medical Biology, Molecular Genetics, Medical Biology Section, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, [4]Dept. of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Center (MUMC), Maastricht, The Netherlands, *These authors contributed equally to this work.*

32. Evidence for intestinal oxidative stress in patients with compensated liver cirrhosis?

K.E. Pijls[1,3], D.M.A.E. Jonkers[1,3], M. Elizalde[1,3], MJ. Drittij-Reijnders[2,3], G.R. Haenen[2,3], A.A.M. Masclee[1,3], A. Bast[2,3], G.H. Koek[1,3], [1]Division of Gastroenterology and Hepatology, Dept. of Internal Medicine, [2]Dept. of Toxicology, [3]School for Nutrition, Toxicology and Metabolism (NUTRIM), Maastricht University Medical Center+, The Netherlands

Theme **Mucosal Immunology –** Chairs: D. Jonkers and G. Bouma

33. Vitamin D potentiates the immunosuppressive effect of anti-TNF induced regulatory macrophages

A.D. Levin, M.E. Wildenberg, A.C. Vos, J.R. de Bruyn, J.F. Brandse, G. D'Haens, G.R. van den Brink, AMC, Tytgat Instituut, Amsterdam, The Netherlands

34. Levels of vitamin A metabolism correlate with mucosal immune function

G. Goverse[1,], B.J. Olivier[1,*], R. Molenaar[1,*], M. Knippenberg[1], M. Greuter[1], T. Konijn[1], E.C.L. Cook[1], G. Bouma[2], R.E. Mebius[1], [1]Dept. of Molecular Cell Biology and Immunology, VU medical center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, VU University Medical Center, Amsterdam, The Netherlands, [*]These authors contributed equally to this work*

35. Induction of mucosal tolerance in the small and large intestine is mediated by distinct immune processes

S. Veenbergen, M.F. du Pré, L.A. van Berkel, F. Luk, Y. Simons-Oosterhuis, J.N. Samsom, Dept. of Pediatrics, Division Gastroenterology and Nutrition, Erasmus Medical Center – Sophia Children's Hospital, Rotterdam, The Netherlands

36. Intestinal stem cell derived organoids as a novel model for studying host-microbiota interactions

S. Lukovac[1], M. Hassan Zade Nahjari[1], B.J.F. Keijser[1], R. Montijn[1], F.H.J. Schuren[1], G. Roeselers[1], [1]TNO Microbiology & Systems Biology, Zeist, The Netherlands

37. Effect of interleukin-17 on gene expression profile of fibroblasts from Crohn's disease patients

Z. Kerami[1], N.W. Duijvis[1], E.W. Vogels[1], F.H. van Dooren[1], P.D. Moerland[2], A.A. te Velde[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, [2]Cinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands

Increased prevalence of proximal and multiple adenomas in patients with diabetes mellitus

S. de Kort[1] , M. Bouwens[1], M. Weijenberg[2], P.A. van den Brandt[2], R. Riedl[3], A. Masclee[1], S. Sanduleanu[1], [1]Dept. of Gastroenterology & Hepatology, Maastricht University Medical Centre, Maastricht, Limburg, The Netherlands, [2]Dept. of Epidemiology, Maastricht University, Maastricht, Limburg, The Netherlands[3], Dept. of Pathology, Maastricht University Medical Centre, Maastricht, Limburg, The Netherlands

Introduction: Although diabetes mellitus (DM) and colorectal cancer (CRC) are highly prevalent worldwide, with approximately 5-15% of the adult population having diabetes and 30-60% colorectal adenomas, the impact of this association on colonoscopic cancer prevention remains unclear. In this study, we aimed to identify endoscopic and histopathologic characteristics of colorectal adenomas in patients with diabetes mellitus. Methods: We conducted a cross-sectional study of all consecutive patients who underwent elective colonoscopy at our university hospital from February 2008 to February 2012. We collected data about risk factors for colorectal cancer, i.e. demographics, presence of DM at the time of colonoscopy, BMI, smoking, alcohol consumption, fruit and vegetable consumption, NSAID/aspirin use and personal/family history of CRC using standard questionnaires. Endoscopic (size, location and morphology) and histopathologic data about colorectal neoplasms were recorded. For multivariable analysis and estimation of adjusted prevalence ratios (PR), cox-regression analyses with constant time at risk and robust variance option were used. We adjusted for age, gender, BMI and other relevant risk factors. Results: We examined a total of 3335 symptomatic and asymptomatic patients (mean age± SD: 61.9 ± 11.9 years, 48.3% males). Of them, 326 (9.8%) had diabetes mellitus (mean age ±SD: 66±10 years, 54.0% males). Mean BMI was significantly higher in diabetic patients compared to non-diabetic patients (28.8±5.0 vs. 25.7±4.0 kg/m2, P<0.001). The prevalence of colorectal adenomas (41.9% vs. 32.4%, p<0.001), as well as the prevalence of multiple (≥3) adenomas (12.9% vs. 7.2%, p<0.001) was higher in patients with DM than in those without DM. The prevalence of both proximal (30.4% vs. 19.2%, p<0.001) and distal adenomas (26.0% vs. 21.2%, p=0.045) was significantly higher in DM versus non-DM patients. No significant differences were found with regard to size of adenomas or presence of high-grade dysplasia between DM versus non-DM patients. Multivariable analysis showed that the prevalence ratios for multiple (PR 1.39, 95% CI; 1.02-1.90) and proximal (PR 1.33, 95% CI; 1.11-1.58) adenomas, but not distal adenomas (PR 1.11, 95% CI; 0.91-1.35) were statistically significant when comparing diabetic patients with non-diabetic patients.

Conclusion: Patients with diabetes mellitus more frequently harbor multiple colonic adenomas, preferentially located in the proximal colon than those without diabetes mellitus. Close colonoscopic surveillance of diabetic patients, with careful inspection of the proximal colon are therefore important to ensure protection against CRC.

Microsatellite instability, BRAF and KRAS mutation in postcolonoscopy cancers: an explorative study

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A subset of postcolonoscopy colorectal cancers (PCCRCs) may evolve through alternative molecular mechanisms, yet the biologic features of these cancers are largely unknown. We therefore retrospectively examined the histopathologic and molecular characteristics of PCCRCs diagnosed at our institution. Methods: We identified all patients diagnosed with CRC at our university hospital from Jan 2001 to Dec 2010 using the national pathology database (PALGA) and the Netherlands Cancer Registry. We collected and reviewed digital colonoscopy and histopathology records. We excluded patients with hereditary forms of CRC, IBD or previous history of CRC. We defined PCCRCs as CRCs occurring within 5 years after an index colonoscopy. According to location, CRCs were categorized into proximal or distal to the splenic flexure. We defined advanced adenomas, as adenomatous polyps ≥1cm, containing high grade dysplasia or a villous component. Histology of PCCRCs was revised by an experienced GI-pathologist and microsatellite instability (MSI), mismatch repair gene expression, hypermethylation of MLH1 and mutation analyses of KRAS (exon 2) and BRAF (V600E) genes were performed. Results: Out of a total of 1,218 patients, we identified 28 patients (mean age, 73.3 years; 71% men) with PCCRCs. Overall, 68% of PCCRCs were proximally located and all of them were adenocarcinomas. Of the 19 proximal PCCRCs, 5 were MSI, showing loss of expression of both MLH1 and PMS2 proteins by immunohistochemistry, all in combination with hypermethylation of MLH1. Five were BRAF mutated (2 of them being MSI) and in 3 cases KRAS mutation was found (all of them being MSS). Of the 9 distal PCCRCs, 1 was BRAF mutated and 1 was KRAS mutated, all of them were MSS. Mean (range) size of PCCRCs was 2.9 (0.5-5.5) cm, 48% of them were poorly differentiated, 11% were mucinous cancers and 32% contained lymphoid aggregates. TNM-stage was I, II, III and IV in 9, 6, 9 and 3 cases respectively, while in 1 case was unclear. At the time of the index colonoscopy, 12 patients had adenomas with 9 having advanced adenomas, 4 had hyperplastic polyps only, while 12 had no abnormalities. No SSA/Ps or TSAs were identified. Interestingly, 3 out of the 4 patients with hyperplastic polyps only developed BRAF mutated PCCRC (1 was MSI).

Conclusion: In this population, 21% of the postcolonoscopy cancers were BRAF mutated MSS/MSI cancers suggesting an alternative biology might contribute to a minor proportion of these cancers. Comprehensive studies of the (epi)genetic molecular alterations of PCCRCs are needed to clarify their biology, as this information might provide the basis for personalized surveillance in the future.

Efficacy of EUS-implanted fiducial markers to diminish margins in radiation of pancreatic cancer

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Introduction: Radiation treatment of pancreatic tumors uses target volume margins tocorrect for the substantial day-to-day position variation of the pancreas. Modern linear accelerators (linacs) are equipped with Cone-Beam CT (CBCT), a CT device with reasonable image quality enabling imaging during treatment. Fiducial markers in the pancreas are well visible on CBCT. These markers can help diminish the error in daily patient treatment, thereby reducing the large margins. Consequently the radiation exposure of surrounding healthy tissue can be reduced. The aim of our study is to study the feasibility of EUS-guided placement of fiducial markers and to quantify interfractional position variation using these markers. Materials & Methods: Eleven consecutive patients with borderline-resectable pancreatic cancer were included in our study. Each patient had 2 or 3 flexible gold fiducials (Visicoil; 10–20 mm, 0.35mm diameter; 27 in total) implanted under EUS-guidance using a 22-gauge needle. Daily CBCTs were obtained before each of 25 radiation fractions and registered with the reference CT on bony anatomy and on each of the fiducials. From this, the position variation of the fiducials relative to the vertebrae was measured as well as the distancebetween the markers. Results: In 10 out of 11 patients fiducial markers could be detected on the treatment planning CT, 0 to 5 (average 3.4) days after implantation, as well as on all 242 CBCTs obtained during treatment. A clear shift inthe distance between markers that would indicate marker migration was not seen for any of the 20 pairs. Position variations (displacements) were largest in the cranio-caudal direction. For 51/242 (21%) of fractions, the variation in at least one direction was >10mm.
Conclusion: The large position variation and its range between patients strongly supports the benefit and necessity of EUS-implanted fiducial markers for better focusing the radiation to the pancreas tumor, enabling smaller safety margins.

Prevalence of small bowel neoplasia in Lynch syndrome as assessed by capsule endoscopy

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Lynch syndrome (LS) is caused by germ mutations in one of the mismatch repair (MMR) genes MLH1, MSH2/Epcam, MSH6 or PMS2. Patients with LS have an increased lifetime risk of small bowel cancer of about 4%. Surveillance of the small bowel is until now not recommended for these patients, because of limited possibilities of small bowel visualization in the past and paucity of data on the prevalence and incidence of small bowel neoplasia. Capsule enteroscopy nowadays allows for surveillance of the small bowel. However, robust data on the prevalence of small bowel neoplasia in LS are still lacking. Aim of this prospective multicentre trial was to determine the prevalence of small bowel neoplasia in asymptomatic LS patients. After obtaining informed consent, asymptomatic proven gene mutation carriers aged 35-70 years were included. Patients with previous small bowel surgery were excluded. After bowel preparation, capsule endoscopy was performed. The videos of these procedures were read by two independent investigators. In case significant lesions were detected, a balloon-assisted enteroscopy was subsequently performed to obtain histology and, if possible, remove the lesion. In total 193 patients (mean age 50 years [range 35-72], M/F 88/105), with proven mutations were included. These concerned MLH1 (n=49), MSH2 (n=64), MSH6 (n=74), PMS2 (n=3), and Epcam (n=3) mutation carriers. In 5% of the procedures no cecal visualization was achieved. Small bowel neoplasms were detected in two patients: one adenocarcinoma (TisN0Mx) and one adenoma, both localized in the duodenum. In another patient, a duodenal cancer (T2N0Mx) was diagnosed six months after a negative capsule endoscopy procedure. All neoplastic lesions were within reach of a conventional gastroduodenoscope. All patients with neoplasia were males, with mutations of different genes (MSH6, MSH2, MLH1), over 50 years of age and without a family history of small bowel cancer.

Conclusions: The prevalence of small bowel neoplasia in asymptomatic Lynch syndrome patients in this study was1.5%. All neoplastic lesions were localized in the duodenum and in reach of conventional gastroduodenoscopy. No neoplastic lesions were detected in patients aged under 50 years. Although capsule endoscopy has the potential to detect these neoplastic lesions at an early stage, small bowel neoplasia may still be missed.

Delineating the PMS2 cancer risk

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Introduction: Lynch syndrome is an inheritable cancer syndrome caused by mutations in one of the mismatch repair (MMR) genes. The clinical phenotype for mutations in the MLH1, MSH2 or MSH6 is comprehensively described, but the consequences of a PMS2 mutation are less well understood. We aim to establish the cancer risk for PMS2 mutation carriers in the largest cohort reported so far. Methods: Data were used from 100 PMS2 families, including approximately 367 mutation carriers and more than 2500 family members, assembled by our centre in cooperation with Dutch university hospitals and several genetic clinics in other European countries. A Kaplan Meier analysis calculating cancer risk in proven or obligated PMS2 carriers will be done. Results: The result Kaplan Meier analysis will be shown during the presentation. In the 367 mutation carriers analyzed, CRC was most frequently diagnosed (n=108). In 200 female mutation carriers endometrial (n=28) and breast cancers (n=11) (after CRC) were most frequent. Other cancers were reported in a total of 26 cases.
Discussion: In this study we analyze the cancer risks in a large cohort of PMS2 mutation carriers. The tumor spectrum in total group of family members is diverse and families seem less severely affected than other MMR deficient families, suggesting a lower penetrance for PMS2 mutation carriers.

Prevalence and characteristics of serrated lesions in individuals undergoing primary screening colonoscopy

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Serrated lesions comprise a heterogeneous group of polyps with different premalignant potential that are further subdivided into hyperplastic polyps (HPs), sessile serrated adenomas/polyps (SSA/Ps) and traditional serrated adenomas (TSAs). Data on prevalence rates of the different serrated subtypes are scarce. The aim of the study was to determine the prevalence and to specify polyp characteristics of the different serrated subtype lesions in a large cohort of individuals undergoing primary screening colonoscopy. Data were collected from subjects who participated in the randomized, multicenter Colonoscopy or Colonography for screening (COCOS) trial. Screen-naïve individuals, aged 50-75 years, were randomly selected and invited to undergo primary screening by colonoscopy. Colonoscopies were performed at two referral medical institutions by expert endoscopists (experience > 1000 colonoscopies). Bowel preparation was scored using the Ottawa scale ranging from excellent (score 0) to very poor (score 14). The proximal colon was defined as proximal to the splenic flexure. Tissue specimens were evaluated by one of the two study pathologists. Serrated polyps were classified as HPs, SSA/Ps or TSAs based on criteria incorporated in the WHO classification for serrated polyps. The prevalence rate was defined as the proportion of screened subjects in whom at least one serrated lesion was found. Univariable and multivariable logistic regression analysis were performed to identify associations between patients' age and gender, and presence of serrated subtype lesions. A total of 1,426 subjects (51% male) with a median age of 60 years (IQR 55-65) underwent a colonoscopy. Unadjusted cecal intubation rate was 98.7%, median withdrawal time after subtracting polypectomy time was 10 minutes (IQR 8-15) and the median Ottawa bowel preparation score was 5 (IQR 3-8). One or more adenomas were detected in 29% (419/1426) of individuals. The prevalence of HPs, SSA/Ps and TSAs was 24% (339/1426), 4.8% (68/1426) and 0.1% (1/1426), respectively. SSA/Ps comprised 7% (111/1521) of all histopathological classified polyps, 15% (111/744) of all serrated polyps and 48% (34/71) of all proximal serrated lesions larger than 5 mm. Multivariable analysis, adjusted for quality of bowel preparation, showed that neither patient age (OR 0.99 95% CI 0.95-1.03) nor male gender (OR 1.07 0.95% CI 0.65-1.75) was independently associated with the presence of SSA/Ps.

Conclusion: Serrated polyps, including SSA/Ps, are frequently encountered in a primary colonoscopy screening program. Endoscopists should be aware of these lesions and should acquire sufficient competence in recognizing and removing them.

Proximal Colorectal Cancers Have Distinct Clinicopathologic Features: A 10-Year Population-Based Survey

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Colonoscopy is less effective in reducing incidence of and mortality from proximal versus distal colorectal cancer (CRC). The underlying explanations are yet unclear. Aim of this study was to examine the clinicopathologic characteristics of proximal versus distal CRCs. Methods: We conducted a population-based study of all patients diagnosed with CRC in South Limburg, the Netherlands, from Jan 2001 to Dec 2010. We used clinical records, a national pathology database (PALGA) and data from the Netherlands Cancer Registry. Digital colonoscopy, histopathology reports and medical records from all patients were studied. Patients with hereditary forms of CRC, inflammatory bowel disease and unknown CRC localization were excluded. We categorized CRCs according location into proximal (from cecum to splenic flexure) or distal (from descending colon to rectum), according to macroscopic appearance into flat or protruded, and according to stage into early (TNM I) and advanced (TNM II, III or IV). Results: We included a total of 5,133 patients (mean age 70.0 years, 53.8% males) with 5,375 CRCs. Of all patients, 1682 (32.8%) had proximally located CRC. Patients with proximal CRCs were more likely females (54.3% vs 42.3%, p<.001) of older age (72.0 vs 69.1 years, p<.001) than those with distal CRC. With regard to size, at the time of diagnosis, proximal CRCs were larger (mean size 5.0 cm vs 4.1cm, p<.001), and with regard to histopathology were more often poorly differentiated (31.9% vs 21.0%, p<.001), and contained mucinous histology (13.2% vs 6.1%, p<.001) than distal CRCs. In addition, proximal CRCs were less often at early stage at the time of diagnosis (12.4% vs 25.6%, p<.001) than the distal CRCs. Logistic regression analysis after adjusting for age, sex and TNM stage showed that proximal CRCs were larger (OR 1.19, 95% CI 1.15-1.22), more likely poorly differentiated (OR 1.62, 95% CI 1.40-1.88) and more often contained mucinous histology (OR 2.20, 95%CI 1.80-2.68) than distal CRCs. Sub analysis of early stage CRCs only, showed proximal CRC were more likely to have a flat macroscopic appearance than the distal CRCs (36.0% vs 26.7%, p=0.007). Cox regression analyses adjusted for age, sex and TNM stage, showed no significant differences with regard to survival between patients with proximal versus distal CRCs.

Conclusions: In this cohort, proximal colorectal cancers were more likely diagnosed in older females, were poorly differentiated and more often contained mucinous histology than the distal cancers. These findings strengthen the hypothesis that differences might exist in the biologic mechanisms underlying carcinogenesis in the proximal versus distal colon.

Current surgical strategies for patients with acute left-sided colonic cancer; analysis of a large prospective Dutch cohort

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Background: Discussion persists regarding what treatment should be offered to patients with acute left-sided obstructive colonic cancer. Primary resection is regarded the standard therapy in the Netherlands, however it is associated with high morbidity and mortality rates. Studies analysing other treatment modalities, such as diverting loop colostomy or colonic stenting as bridge to elective resection, remain contradictory in morbidity and mortality rates. Therefore this study aims to evaluate the clinical outcome of acute primary resection, stenting as bridge to elective surgery and diverting loop colostomy as bridge to elective surgery in a large prospective Dutch cohort. Methods: Through the DSCA (Dutch Surgical Colorectal Audit), operation data for patients with acute left-sided obstructive colonic cancer were prospectively gathered in all hospitals in the Netherlands from 2009 to 2011. Resection related morbidity and mortality rates were measured and compared for the three different treatment modalities. Results: In total, 1265 patients presented with acute left-sided obstructive colorectal cancer, from which 1002 (79.2%) underwent primary resection, 166 (13.1%) stenting as bridge to elective resection and 97 (7.7%) diverting loop colostomy as bridge to elective resection. Postoperative complications were measured in 43.4%, 33.3% and 35.1% for primary resection, elective resection after stenting and elective resection after colostomy respectively (p= 0.02). Thirty-day mortality occurred in 8.1% after primary resection, 6.7% after stenting as bridge to elective resection and 4.2% after colostomy as bridge to elective resection (p= 0.19).
Conclusion: Acute primary resection is accompanied by significantly more postoperative complications and higher mortality rates than the other two treatment modalities. This indicates that stenting and diverting loop colostomy seem attractive alternatives to elective resection.

Missed Flat Lesions: A Major Contributor To Postcolonoscopy Cancers

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Postcolonoscopy colorectal cancers (PC-CRCs) are of legitimate concern as these events might jeopardize the outcome of screening and lead to waste of economic resources. Recognition of procedural factors is especially important for establishing potential improvements. Herein, we reviewed the most common causes of post-colonoscopy cancers in our experience. Methods: We conducted a population-based study of all patients diagnosed with CRC in South Limburg, the Netherlands, from Jan 2001 to Dec 2010. We used digital colonoscopy and histopathology reports from all patients, a national pathology database (PALGA) and data from the Netherlands Cancer Registry. We excluded patients with hereditary forms of CRC, inflammatory bowel disease or previous history of CRC. We defined PC-CRCs as cancers diagnosed within 5 years after an index colonoscopy. According to the macroscopic aspect, CRCs were categorized into flat or protruded and according to location into proximal or distal to the splenic flexure. Possible etiologic factors for PC-CRCs were subdivided into i) procedural factors such as missed lesions (large ≥20mm or advanced stage cancer found <36 months after index colonoscopy); incomplete resection (cancer in the same segment as a previously resected advanced adenoma; or mixed (patient and endoscopist-related) factors i.e. incomplete colonic visualization or inadequate surveillance and ii) newly developed cancers (<20mm in size or early stage cancer found >36 months). Results: We examined a total of 5,110 patients with 5,307 CRCs (mean age 70.0 yrs, 53.8% males), of whom 145 patients (mean age 72.8 yrs, 54.5% males, 2.8% of all patients) underwent an index colonoscopy within the previous 5 years and were considered PC-CRC. The PC-CRCs were diagnosed on average 25.9 months after the index colonoscopy. Of them, 58.6% were possibly due to missed lesions, 9.0% to incomplete resection, 13.8% cases could be related to incomplete colonic visualization or 5.5% to inappropriate surveillance. Thirteen % of the cases may represent newly developed cancers. Logistic regression analyses, adjusting for age and gender, showed that PC-CRCs were significantly smaller in size (OR 0.82, 95%CI 0.75-0.91), more often flat (OR 2.19, 95%CI 1.57-3.06) and proximally located (OR 3.15, 95%CI 2.23-4.45) than non-PC-CRCs. Of note, 51.2% of the missed cancers had a flat macroscopic appearance.

Conclusion: In our experience, 87% of all postcolonoscopy cancers might be explained by procedural factors, especially missed lesions. Quality improvements in performance of colonoscopy are needed, with particular attention for the detection and management of flat lesions.

Chronic antigenic stimulation may be an etiological feature of IgG4-Associated Cholangitis

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IgG4-associated cholangitis (IAC) is the biliary manifestation of the spectrum of IgG4-related diseases (IgG4-RD). The etiology of IgG4-RD, and the origin of the elevated serum IgG4, is enigmatic. Considering the odd nature of IgG4, which is known to have immunomodulatory properties even while antigen-specific IgG4-levels may rise following prolonged antigenic exposure, we wondered if prolonged antigenic exposure could play a role in the pathogenesis of IgG4-RD. If elevated serum IgG4 titers would be caused by antigen-driven immune responses in the affected tissues, clonally expanded, class-switched B cells could be identifiable in the peripheral blood (PB) and/or affected tissue. In a parallel effort, we reasoned that as IgG4 production could be dependent on chronic antigenic stimulation, there might be a common denominator amongst patients in terms of exposures to potential antigens.Using a next-generation sequencing protocol, we assessed the B-cell receptor (BCR) repertoire as reported in a pilot study in PB and several paired tissue samples of IAC patients (currently n=10). mRNA was isolated and full-repertoire sequencing of the BCR heavy-chain was performed with primers for all V(ariable)- and C(onstant)-genes. A customized bioinformatics algorithms (>10,000 sequences/sample) allowed for the determination of Ig class and IgG subtype and for the detection of overlapping clones in PB and tissue. Furthermore, we noted which chemical substances the cohort of IgG4-RD patients at our department (n=25) had been significantly exposed to.In IAC patients but not in any healthy or disease controls (n=6 each), we detected highly abundant IgG4+ BCR clones in the PB. The majority of the identified CDR3 regions contained base substitutions highly suggestive of somatic hypermutation, which is indicative of antigen-driven clone expansion. In cases where tissue samples were available the identical dominant IgG4+ clones from the blood were also dominant in the infiltrate BCR repertoire, implying that specific B cell responses may be pivotal to the pathogenesis of IAC. This is supported by the finding that the vast majority (91%) of the successfully contacted patients with IgG4-RD had a history of manual labour of at least one year, but often of a whole career. Solvents, industrial and metal dusts, pigments and industrial oils were among the most often mentioned potential occupational hazards.
Conclusions: The finding of highly expanded IgG4+ BCR clones in patients with IAC but not controls suggests that IgG4-RD is caused by chronic antigenic stimulation. Prolonged exposure to occupational antigens could be contributing to the occurrence of these clones.

Increased IL8 in bile and increased MUC5AC and CFTR expression in the gallbladder of patients with primary sclerosing cholangitis

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Introduction: Primary sclerosing cholangitis (PSC) is characterized by inflammation and fibrosis of extrahepatic and segmental branches of the intrahepatic bile ducts. We recently observed that gallbladder bile -but not ERCP (ductal) bile- of PSC patients has decreased concentrations of bile salts, phospholipids, cholesterol and FGF19, suggestive of defective concentration of bile in PSC. This concentration defect may be caused by factors from the inflamed biliary tree. This study was undertaken to elucidate the underlying mechanism. Methods: Gallbladder bile and tissue of PSC (n=12-13) and non-PSC liver disease patients (n=13-14) were collected at the time of liver transplantation (LTx). IL8 levels in bile were measured by ELISA. Additional cytokines and chemokines in bile were studied by Luminex multiplex bead array. Transcript levels of genes involved in mucus formation and chloride/bicarbonate secretion were measured by RT-qPCR using mucosal epithelium-specific cytokeratins 7 and 19 as reference genes. Cultured primary human gallbladder epithelial cells (HGBECs) were incubated with a pro-inflammatory cytokine mix (TNF-α, IL-1β and IL-6) for 3 hours before gene expression analysis. Results: IL-8, but not TNF-α, IL-1β and IL-6, was strongly elevated in PSC gallbladder bile (7.6, [2.1-16.5] vs. 2.3, [0.6-3.4] ng/mL in non-PSC patients; $p=0.02$) and ERCP bile (4.5, [1.4-19.7] vs. 0.2, [0.005-0.6]; $p<0.0001$). Expression of MUC5AC and CFTR was upregulated in gallbladder of PSC patients (3.9-fold, $p<0.007$ and 1.8-fold, $p<0.03$, resp.). In addition, Trefoil factors (TFFs) 1, 2 and 3, known to stabilize the mucus layer, were also upregulated (4.0, 17.1 and 4.3-fold, resp.; $p<0.001$). HGBECs incubated with cytokine mix showed upregulation of MUC5AC, CFTR and TFF1 (5.6, 3.4 and 1.7-fold, resp.; $p<0.02$).
Conclusions: Elevated gallbladder expression of MUC5AC, TFFs and CFTR may underlie dilution of gallbladder bile in PSC patients by increased secretion of mucus and chloride/bicarbonate and accompanying flow of water. The strongly increased IL8 levels in PSC bile –even at the time of liver transplantation- are suggestive of a persistent and ongoing inflammatory process in the biliary tree that may affect mucus and chloride/bicarbonate secretion by MUC5AC and CFTR in the gallbladder. The persistent inflammatory stimulus in PSC may originate from the compromised gut.

Molecular aspects of rifampicin treatment in severe persistent hepatocellular secretory failure

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Severe persistent hepatocellular secretory failure (PHSF) with extreme jaundice (serum bilirubin > 255 µmol/L) induced by drugs, toxins or transient biliary obstruction may incidentally persist for months after removal of the initiating factor and may be fatal. Until recently no effective treatment existed except for transplantation. Recently we showed that rifampicin dramatically improved hepatobiliary secretion and clinical outcome in 11 consecutive patients with severe PHSF. To obtain a better molecular understanding of the remarkable effects of rifampicin treatment in PHSF, we investigated the effect of PXR activation by rifampicin on genes involved in biotransformation and secretion in the enterohepatic circulation (biotransformation phase 1-3) of potential toxins in primary human hepatocytes and human HepG2 hepatoma cells, HepG2 cells overexpressing PXR (HepG2PXR), HepG2 cells after PXR knock down (HepG2PXRkd) and the human colon adenocarcinoma HT-29 cell line.Primary human hepatocytes, HepG2, HepG2PXR, HepG2 PXRkd and differentiated HT-29 cells were incubated with 10µmol/L rifampicin for 24 hrs or 0.1% DMSO as control. To investigate if PXR activation also had a beneficial effect under FXR activation HepG2 cells were incubated besides rifampicin, with the potent FXR agonist 6-ECDC (10µmol/L) and with rifampicin + 6-ECDC (both 10µmol/L) for 24 hours. The mRNA expression levels of CYP3A4, UGT1A1, MRP2, MRP3, OSTα/β were determined after RNA isolation and reverse transcription by real-time PCR. In primary human hepatocytes, human HepG2 cells and HT-29 cells, rifampicin (10µmol/L, 24 hrs) induced a PXR-dependent upregulation of biotrans–formation phase 1 and 2 enzymes, CYP3A4 and UGT1A1, and phase 3 apical conjugate export pump MRP2 as well as the basolateral bile salt exporter OSTβ. PXR activation had no effect on OSTα expression. On the other hand, both OSTα and OSTβ were significantly induced by 6-ECDC (6,2- and 39.0-fold, respectively). Addition of the PXR agonist rifampicin had a substantial additive effect on OSTβ expression leading to a 49.8-fold induction in comparison to vehicle control. Rifampicin alone induced OSTb expression 2.0-fold in comparison to vehicle control.

In conclusion, this in vitro study showed that rifampicin enhanced detoxification and transport capacity in human hepatic and intestinal cells by upregulating CYP3A4, UGT1A1, MRP2 and OSTβ by PXR-dependent mechanisms. These PXR-dependent effects of rifampicin on key detoxification enzymes as well as apical and basolateral exporters may contribute to the striking improvement of hepatobiliary secretion in patients with severe PHSF.

Specific biological pathways lead to distinct extra-intestinal manifestations and complications in inflammatory bowel disease

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Genetic studies have shown numerous associations for inflammatory bowel diseases (IBD). Increasing insight is also available for conditions that are known to be extraintestinal manifestations or complications (here together called EIM) of IBD such as Ankylosing Spondylitis (AS), Bone Mineral Density (BMD), Primary Sclerosing Cholangitis (PSC) and Colorectal Cancer (CRC).The aim of the current study is to assess genetic overlap between IBD and EIM, and to identify shared biological pathways. First a literature search was performed to assess genetic overlap. We then performed an extensive pathway analysis searching for protein-protein and co-expression interaction between IBD genes and EIM genes within the genetic loci. The InWeb database was used to assess protein-protein interactions. The analysis was performed with a newly developed R-script. To check statistical robustness of the protein-protein interactions 1000 permutations were performed at comparable genomic regions and then a p-value of less then 0.05 was considered a specific protein-protein interaction between an IBD gene and an EIM gene. To assess co-expression interactions we performed principal component analysis on microarray expression data from the Gene Expression Omnibus (GEO) to derive a regulatory model of the trans-criptome. Second, we described co-regulation between all pairs of genes by calculating a Pearson correlation coefficient for each pair of genes and examined co-regulation by finding pairs of genes that showed the strongest co-regulation in each pair of loci between the phenotypes. The robustness of the interactions was checked in the same matter as the protein-protein interactions.99 genetic risk loci are now known in IBD. In AS 12/18 risk loci are shared with IBD. In CRC this is 2/15, BMD 2/23 and PSC 8/14. We identified numerous statistically significant protein-protein and co-expression interactions clustering in several shared biological pathways. These include TGF-B signaling and epithelial barrier function in CRC and IBD, WNT signaling and TNFSF11 signaling in BMD and IBD, and T-cell signaling in PSC, AS and IBD.
In conclusion, we show that the pathogenetic overlap between IBD and its EIM or complications extends substantially beyond purely shared risk genes to shared biological pathways and protein-protein and co-expression interactions. Hereby we further highlight the genetic background as a risk factor for IBD-EIM or complications next to known mechanisms as e.g. malabsorption, chronic inflammation or medication.

Active inflammation of the appendix in ulcerative colitis

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Several studies suggest that the appendix plays a causative role in ulcerative colitis (UC). Nowadays, appendectomy is sometimes offered as experimental treatment in these patients. Some studies show histologically normal appendices in UC, whereas others suggest mucosal inflammation in the appendix comparable to the disease activity in the colon. The objective of this study was to analyze T cell infiltration in the appendices of UC patients undergoing colectomy and compare these to patients with Crohn's disease (CD), acute appendicitis and non-inflammatory controls. The appendix was removed from the surgical resection specimen and flushed with 2cc of phosphate buffered saline. The number of CD4 and CD8 lymphocytes in the lavage fluid was determined by FACS analysis and the CD4/CD8 ratio was calculated. The appendix was histologically evaluated by assessing the degree of inflammation (mucosal, submucosal or transmural) and mucosal ulceration. In addition, slides were immunohistochemically stained for CD4 and CD8, and scored according to the number of positive cells per high power field (graded 1-4). Ten patients with UC, 8 with CD, 4 with appendicitis and 5 control patients (FAP or right sided colon cancer) were included. In UC patients all appendices appeared macroscopically normal, although at histological evaluation 7 patients showed mucosal based inflammation with lymphocyte infiltration. This differed from the more extensive infiltration of granulocytes and oedema in the mucosa and submucosa of CD patients and the transmural inflammation present in the macroscopically affected appendices of the appendicitis patients. No granulocytes or signs of inflammation were seen in the controls. Immunohistochemical staining showed extensive influx of CD4 lymphocytes (grade 3 or 4) in 6 UC patients, 7 CD patients, all appendicitis patients and none of the controls. CD4/CD8 ratio in the lavage fluid was determined in 22 patients. The median ratio of 4.7 in UC was increased compared to 2.7 in the control group ($p=0.06$), but not significantly different from the ratio of 5.8 in the CD and 4 in the appendicitis group. In 82% of patients, a high CD4/CD8 ratio (ratio ≥ 3) correlated with increased influx of CD4 lymphocytes, confirming inflammation. Despite a macroscopically normal appearance, the appendix shows increased numbers of CD4 lymphocytes in the mucosa in patients with UC. The CD4/ CD8 ratio in the lavage fluid can be used as a measure of this inflammatory process.

Long term response to infliximab treatment and its effect on disease course in ulcerative colitis – A population-based cohort study

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Infliximab is an effective treatment for steroid-refractory and steroid-dependent ulcerative colitis (UC). Information about long term response is scarce and it is still unclear whether the natural disease course of UC has improved since the introduction of anti-TNF agents. Since anti-TNF treatment is expensive and has potentially severe side effects, it is important to evaluate its efficacy and to optimise treatment by identifying markers for response. This study evaluates the effect of anti-TNF availability on the natural disease course of UC in a population-based cohort and aims to identify clinical predictive markers for response to infliximab. Since 1991, all newly diagnosed IBD patients are included in our population-based cohort. Medical records of all UC patients were reviewed with regard to hospitalisation, colectomy, medication, disease location at diagnosis, and smoking status and disease location at first infliximab infusion. Two cohorts were distinguished to analyse the effect of anti-TNF introduction, based on the date of diagnosis and separated by the year of introduction (i.e. diagnosis in 1991-2004 vs. diagnosis in 2006-2010). Patients were followed until December 31, 2005 and December 31, 2011, respectively. A Cox proportional hazards regression model was used to analyse differences in hospitalisation and colectomy between the cohorts and to assess markers for response to infliximab. Associations were presented as Hazard ratios (HR). In this study, 1464 UC patients were included. Cohort 1991-2004 comprised 908 patients and cohort 2006-2010 comprised 454 patients. Of the 1464 patients, 109 patients (7.4%) were exposed to infliximab. Primary response to infliximab was seen in 100 patients (91.7%). Sixty-two patients (56.9%) still used infliximab 24 months after first infusion. No predictive markers for sustained response to infliximab were found. The risk of colectomy 12 months after diagnosis, decreased threefold (HR 0.32; 95%CI 0.13-0.79) since the introduction of anti-TNF treatment. Twenty-four months after diagnosis, the risk of colectomy decreased 1.5-fold (HR 0.64; 95%CI 0.35-1.18) since anti-TNF introduction. No differences were found in risk of hospitalisation.
Conclusion:This study showed that since the introduction of anti-TNF agents, the risk of colectomy is decreased threefold for at least 12 months after diagnosis, thereby providing new evidence for the efficacy of anti-TNF in UC. Although costs associated with anti-TNF are high, prevention of colectomies in UC patients is important since complications after surgery are frequent and patients' quality of life is often impaired.

A Phase 2/3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Subcutaneous Golimumab Induction Therapy in Patients with Moderately to Severely Active Ulcerative Colitis: PURSUIT SC

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The aim was to evaluate SC golimumab (GLM) induction in patients (pts) with moderately to severely active UC despite current adequate treatment or who had previously failed to respond to or tolerate treatment with 6-MP, AZA, corticosteroids and/or 5-ASAs or were corticosteroid dependent and naïve to anti-TNF. PURSUIT SC had an adaptive design with Phase 2 dose ranging followed by a confirmatory Phase 3. Pts with Mayo scores of 6-12 inclusive, including endoscopic subscore >2 were randomized to placebo (PBO)/PBO; GLM 100mg/50mg (before dose selection only); GLM 200mg/100mg; GLM 400mg/200mg at wks 0&2. Primary endpoint was clinical response at wk6 in pts enrolled after dose selection. Secondary endpoints at wk6 were clinical remission, mucosal healing, and change from base in IBDQ. Primary analysis population for efficacy consisted of pts randomized after dose selection (n=774); for safety, all treated pts in Phase 2&3 combined (n=1065). 774 pts were randomized in primary analysis population; 759 pts (98%) completed through wk6. Sig higher prop of GLM-tx pts achieved endpoints. Randomized pts after dose selection (n): 256(PBO); 257(GLM200/100mg); 258 (GLM400/200mg). Clinical response wk6: 76(29.7%,PBO), 133 (51.8%, GLM200/100mg) p<0.0001*, 142(55.0%,GLM400/200mg) p<0.0001* (*Based on Chi-square test). Clinical remission wk6: 16(6.3%,PBO), 48(18.7%,GLM200/100mg) p<0.0001, 46(17.8%,GLM400/200mg) p<0.0001. Mucosal healing wk6: 73(28.5%,PBO), 111(43.2%,GLM200/100mg) p=0.0005, 117(45.3%,GLM400/200mg) p<0.0001. Mean change from base in IBDQ wk6: 14.6(PBO), 27.4(GLM200/100mg) p<0.0001, 27.0(GLM400/200mg) p<0.0001. Through wk6, AEs proportions were similar for the combined GLM and PBO grps (39.1% & 38.2%,resp); 3.0% and 6.1% of pts, resp, had SAEs. 1 death reported in GLM 400mg/200mg grp; 1 case of demyelination was reported in this grp. Injection site reactions were uncommon and comparable across GLM grps. Malignancy rates were 0.3%. 0.0%, and 0.3% in the PBO, GLM 200mg/100mg, and GLM 400/200mg grps, resp. Conclusion: Induction regimens of SC GLM induced clinical response, clinical remission, mucosal healing and improved QoI in anti-TNF naïve UC pts. Safety of GLM induction was consistent with the safety in labeled rheumatologic indications and other anti-TNFs.

Fecal loss of Infliximab as a cause of lack of response in severe Inflammatory Bowel Disease

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Although Infliximab (IFX) has proven its efficacy both in Crohn's disease (CD) and Ulcerative Colitis (UC), still a considerable group of patients fails to respond to induction therapy. One of the hypotheses behind this phenomenon is increased clearance or loss of the drug. In severe CD and UC, the mucosa is diffusely denuded and ulcerated, leading to massive loss of proteins, electrolytes and other nutrients. We hypothesized that, even after intravenous administration, IFX may be lost through this 'leaky gut'. Fecal loss of IFX in this context has not been investigated up to date and this was the focus of the current study In this pilot study we prospectively collected repeated fecal samples of IBD patients within the first 14 days after starting IFX therapy. Fecal samples were weighed and homogenized in PBS containing bovine serum albumin. Supernatant was collected after centrifugation and tested with a well established ELISA to detect the presence of Infliximab. Clinical response in these patients was assessed 3 months after the initiation of IFX therapy. 9 IBD patients (3 CD, 6 UC) with different disease localizations (5 Ulcerative Pancolitis, 1 Proctitis, 2 Ileocecal CD, 1 Crohn's Colitis) starting on IFX 5 mg/kg at week 0-2-6 were included. One patient (Crohn's colitis) received an extra infusion (5mg/kg) at day 4 because of initial non response. IFX could be detected in the feces of all patients. The highest concentrations were measured in the first days after initiation of therapy, meaning in the most acute phase of the disease. In non responders (3/9) the amount of drug detected in stool at the first day after infusion was significantly (p: 0.024) higher than in patients who had clinical response.
Conclusion: IFX can be detected in the feces of patients with severe IBD, especially short after infusion. This phenomenon may contribute to rapid disappearance of the drug out of the gut and the circulation leading to insufficient response.

Re-evaluation of anti-TNF use in a cohort of IBD patients in a non-academic hospital

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Anti-TNF can be an effective therapy for IBD, especially Crohns disease. Since it is very expensive, it is reasonable that only patients that failed (adverse events or lack of efficacy) on thiopurines may use anti-TNF. Thiopurine drug monitoring and metabolite adjusted dosing is associated with an increased efficacy of thiopurine therapy in IBD. Recently, the value of thiopurine metabolites and correction of the 6-TG/6-MMP ratio with allopurinol has been recognised and introduced in our clinic. In 2011 our hospital has spent €1,500,000 for anti-TNF in IBD patients which accounts for 30% of the total budget of our department. Restart of an optimised thiopurine therapy may allow stopping anti-TNF treatment. Therefore, we critically re-evaluated the anti-TNF use in our current IBD cohort with the current insights. Thiopurine failure is defined as: (1) allergic adverse events (f.i. pancreatitis) or (2) rechallenge with 6-mercaptopurine in case of other adverse events, (3) optimisation of the thiopurine dose guided by thiopurine metabolites and, if necessary, correction of the 6-TG/6-MMP ratio with allopurinol in case of therapeutic failure or elevated transaminases. 74 of our 455 (16%) Crohns patients and 15 of 597 (3%) ulcerative colitis patients use anti-TNF. 41 0f these 89 patients (46%) fulfil the criteria of thiopurine failure: 13 had therapeutic failure despite therapeutic metabolite levels, 9 had allergic adverse events, 17 adverse events despite rechallenge with 6-mp, 2 had other reasons to stop thiopurines. 49 other patients did not fulfil the criteria of thiopurine failure: 11 had therapeutic failure and insufficient 6-TG levels but the thiopurine dose was not adjusted, 16 had therapeutic failure without measurement of metabolite levels, 11 had non-allergic adverse events without rechallenge, 4 had elevated liver functions without measurement of metabolite levels, in 5 anti-TNF was started as an induction therapy and thereafter continued, 1 patient did not want to continue 6-mercaptopurine, 1 had elevated transaminases of unknown cause which precluded initiation of thiopurine therapy.
In conclusion, thiopurine therapy can possibly be optimised in 54% of our IBD patients on anti-TNF therapy. This suggests that in some of these patients anti-TNF can be stopped which will result in a considerable reduction in costs.

Adalimumab for Crohn's disease: sustained benefit in a Dutch multicentre cohort

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Background Adalimumab is an effective therapy for Crohn's disease. This study aimed to assess real-life sustained benefit of adalimumab in a large cohort of Crohn's patients, covering approximately 20% of the Dutch population. MethodsAll Crohn's patients treated with adalimumab were included. Endpoints were sustained benefit, influence of patient and disease specific factors, immunosuppressive co-medication, dose escalation, safety, and efficacy after previous infliximab therapy. Sustained benefit was determined by failure-free survival of adalimumab therapy in Kaplan-Meier analysis. ResultsIn total 438 patients were included. Successful remission induction was achieved in 405 patients (92.5%). After one year 83.3% of patients experienced sustained benefit, followed by 74.0% and 62.0% after two and three years respectively. A trend in higher rates of sustained benefit was noted for concomitant thiopurine use. Concomitant steroids were prescribed in 26.5% of patients during the first six months of treatment. Dose escalation was deemed necessary in 175 patients (40.0%) after a median period of 5.7 months (IQR: 2.8-13.6). Infliximab naïve and patients previously failing infliximab showed similar responses to adalimumab, however the latter category more often needed dose escalation (26.8% and 49.8%, p<0.001; OR 2.82; 95% CI 1.87-4.25).
Conclusions Adalimumab induction therapy was successful in the majority of patients (92.5%). After three years of maintenance treatment, 62.0% showed sustained benefit, which is comparable to our recent findings for infliximab. Prior failure of infliximab should not preclude adalimumab treatment, since this did not influence adalimumab outcome. Thiopurines may be beneficial as concomitant therapy however this needs to be confirmed in future prospective trials.

Re-introduction of Infliximab after consecutive failure of Infliximab and Adalimumab is beneficial in Refractory Crohn's Disease

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In the last decade, Infliximab (IFX) and Adalimumab (ADA) have dramatically improved the management of steroid refractory Crohn's disease (CD). In clinical practice a considerable group of patients are switched from one agent to the other because of failure, intolerance and patient preference. There are no data regarding the long term clinical response of re-exposure to IFX in patients who sequentially used and discontinued IFX and ADA. Therefore we retrospectively assessed clinical response to IFX in CD patients that failed subsequently IFX and ADA and were re-exposed to IFX.For this survey we used a multicenter cohort of 438 CD patients treated with ADA. Twenty-nine of these had previously been treated with IFX and received a second IFX treatment after failing ADA. Short-term and prolonged response to IFX was assessed retrospectively by reviewing clinical records.29 patients (62% luminal CD, 7% fistulizing CD, 31% both) from 8 hospitals were included with complete follow-up data up to 18 months. IFX was re-started at 5mg/kg in 20/29 (69%), 7.5 mg/kg in 1 patient and at 10 mg/kg in 8/29 (28%), at intervals varying between 4 and 8 weeks. Dose escalation was done in 8/29 (28%) of patients during retreatment with IFX. Twenty patients (69%) were on concomitant immune modulators at the re-introduction of IFX and 3 (10%) patients experienced adverse events: acute infusion reaction (n=2, 7%) and delayed hypersensitivity reaction (n=1, 3%).20/29 (69%) patients were still on continued Infliximab therapy after 18 months. Reasons for discontinuing the second Infliximab therapy included: non-response (n=2, 7%), loss of response (n=3, 10%), intolerance (n=3, 10%) or non-compliance (n=1, 3%).
Conclusion: The majority of CD patients, failing prior treatment with IFX and ADA, benefit from re-introduction of Infliximab for at least 18 months. Only a small proportion of 9 patients failed on retreatment with IFX.Retreatment with Infliximab is to be considered a valuable strategy in this group of refractory CD patients.

ATG16L1 genotype is associated with response to anti-TNF

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Background: We have previously shown that infliximab (IFX) treatment of mixed lymphocytes reactions results in the induction of macrophages with immunosuppressive and wound healing properties, the number of these macrophages increases significantly in the intestine of patients who respond to IFX treatment compared to non-responders. Genetic studies have shown an association between various autophagy related genes and the development of Crohn's disease. The aim of this study was to determine whether autophagy is involved in the induction of regulatory macrophages by IFX and whether autophagy related polymorphisms influence the response to IFX in vitro. Methods: Peripheral blood was isolated from 29 healthy volunteers and rs_2241880 genotype was determined by pcr. After isolation of PBMC mixed lymphocyte reactions containing cells from 2 donors were established for 150 separate donor combinations. Cultures were treated with IFX or control IgG and incubated for 6-7 days. Cells were analyzed by gene array, immunofluorescence, flow cytometry and thymidine incorporation. ResultsAnti-TNF induced regulatory macrophages displayed increased numbers of autophagosomes as well as an increased expression of autophagy related transcripts including atg5, atg7, atg9 and atg16l2, suggesting induction of autophagy by IFX treatment. Of all donors, 7 were homozygously carrying the CD associated risk allele, 14 were heterozygous and 7 were homozygous for the WT allele. The number of CD14+ regulatory macrophages correlated significantly with the number of WT alleles present in each individual culture, with the largest number of macrophages found in cultures containing 3 or 4 WT alleles (2 WT donors or 1 WT and 1 heterozygous). Similarly, expression of CD206, which is associated with the immunosuppressive function of macrophages, positively correlated with the number of WT alleles present. To confirm the functional consequences of these findings, IFX mediated suppression of T cell proliferation was determined. Again, the level of suppression correlated significantly with the number of WT alleles present in the respective donor combinations.
Conclusion: Induction of regulatory macrophages by IFX is associated with induction of autophagy. In vitro, the number and function of IFX induced macrophages correlated with the number of WT alleles for the autophagy related gene ATG16L1. This suggests that an intact autophagy pathway is important for effectiveness of anti-TNF therapy.

Serial Magnetic Resonance Imaging for Monitoring Anti-TNF Treatment Effects in Crohn's Disease

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Background Tumor necrosis factor (TNF) antagonists can induce mucosal healing in patients with Crohn's disease (CD), but the effects on transmural inflammation and stenotic lesions are largely unknown. Aim To assess the evolution of CD inflammation and stenosis in patients treated with anti-TNF agents using serial Magnetic Resonance Imaging (MRI) scans. Methods We performed a retrospective study in 50 patients (54% female, median age 37 years) with CD who had undergone serial MRI examinations while receiving infliximab or adalimumab. Patients were grouped as clinical responders or non-responders based on physician's assessment, laboratory and endoscopic appearance. MRI scoring was performed by two radiologists in consensus blinded to clinical data using a validated MRI scoring system. In total 64 lesions on MRI were identified for analysis. Analyses were performed using paired t-test and Wilcoxon rank test. Results During anti-TNF treatment, MRI inflammation scores improved in 29 out of 50 patients (45.3%), remained unchanged in 18 out of 50 (28.1%) or deteriorated in 17 out of 50 (26.6%) over time. In the anti-TNF responder group, the mean intestinal inflammation score of all lesions improved from 5.19 to 3.12 ($p<0.0001$). Mean inflammation scores in stenotic lesions in anti-TNF responders improved also significantly, from 6.33 to 4.58 ($p=0.01$). In contrast, inflammation scores deteriorated from 5.55 to 5.92 ($p=0.49$) in non-responders.
Conclusions: Improved inflammatory activity on serial MRI scans correlated with clinical response to treatment with anti-TNF agents in luminal CD. MRI can be used as a complementary approach to measure transmural inflammation in CD patients and guide the optimal use of TNF antagonists in daily clinical practice.

P53 immunohistochemistry for predicting neoplastic progression in patients with Barrett's esophagus: results from a large multicentre prospective cohort

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Surveillance is recommended for Barrett's esophagus (BE) to detect esophageal adenocarcinoma (EAC) at an early stage, but is problematic given the overall low incidence of EAC and lack of discriminative tests for risk stratification. Histological diagnosis of low-grade dysplasia (LGD) is currently the only accepted predictor for progression, but has a low predictive value. The aim of this study was therefore to evaluate the value of p53 immunohistochemistry for predicting neoplastic progression in Barrett's esophagus. We conducted a case-control study within a multicenter prospective cohort of 720 BE patients. Patients were followed according to the ACG guidelines and during follow-up incident cases of high-grade dysplasia (HGD) and EAC were identified. Patients who developed HGD or EAC during follow-up were classified as cases and patients without neoplastic progression as controls. P53 protein expression was determined by immunohistochemistry in more than 12.000 biopsies from 635 patients and was scored (normal expression, overexpression, loss of expression) independently by two expert pathologists who were blinded for long-term outcome. Data were analyzed in Loglinear regression models adjusted for age, gender, BE length and esophagitis. In this study 635 BE patients (73% male, median age 60 years (IQR 53-69)) were included and followed during surveillance for a median duration of 6.6 years (IQR 5.1-7.3). Forty-nine (8%) patients developed HGD or EAC during follow-up and were classified as cases. The remaining 586 (92%) patients were classified as controls. Aberrant p53 expression was associated with an increased risk of neoplastic progression (RRa 6.4; 95%CI 3.6-11.3) in both BE without dysplasia and BE with LGD. Not only p53 overexpression was associated with neoplastic progression (RRa 5.6; 95% CI 3.1-10.3), but the risk was even higher with loss of p53 expression (RRa 14.0; 95% CI 5.3-37.2). Aberrant p53 expression was already seen up to 5 years before progression. The sensitivity for predicting neoplastic progression was 49% with a specificity of 86%. Interobserver agreement was good (κ = 0.79; 95%CI 0.75-0.83). The positive predictive value for neoplastic progression increased from 15% with histological diagnosis of LGD to 33% with LGD and concurrent aberrant p53 expression.

Conclusion: Aberrant P53 protein expression is associated with an increased risk of neoplastic progression in BE patients and appears to be a more powerful predictor for neoplastic progression than histological diagnosis of LGD. Implementation of p53 immunohistochemistry could improve risk stratification and hence the cost-effectiveness of BE surveillance programs.

A randomised trial comparing multiband mucosectomy and ER-cap for endoscopic piecemeal resection of early squamous neoplasia of the esophagus

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Introduction: Endoscopic Resection (ER) for esophageal high-grade intraepithelial neoplasia (HGIN) or esophageal squamous cell carcinoma (ESCC) is usually performed with the ER-cap technique. This requires submucosal lifting and multiple snares for piecemeal resections and is therefore technically relatively difficult. Multi Band Mucosectomy (MBM) is an ER technique that uses a modified variceal-band ligator for piecemeal resection without submucosal lifting. In China, in certain high-risk areas where ESCC is extremely prevalent and limited endoscopic expertise is available, MBM might be a more easily applicable ER technique.Aim: We prospectively compared MBM to ER-cap for piecemeal ER of squamous neoplasia of the esophagus.Methods: Patients with HGIN or ESCC (size ≥2, ≤6 cm, max 2/3 of the circumference) and no signs of submucosal invasion or metastatic disease were included. Lesions were delineated with electrocoagulation after 1.25% Lugol staining. The patient was then randomised to MBM or ER-cap followed by piecemeal resection. Endpoints: complete endoscopic resection (ie complete removal of the lesion including all electrocoagulation markers), procedure time, costs, adverse events, absence of HGIN/ESCC at 3 months follow-up. Calculated sample size: 84 patients.Results: In 88 patients (62 male, mean age 60 yrs) ER was performed with MBM (n=46, 12 ESCC) or ER-cap (n=42, 13 ESCC). There was no difference in the size of lesions between groups (5cm vs. 5cm, p=NS; 42% vs. 33% of the circumference, p=NS). Endoscopic complete resection was achieved in all lesions. Procedure time was less with MBM (11 vs. 22 minutes, p<0.001), for a median of 5 vs. 4 resections (p=0.03). MBM resulted in smaller (18x12mm vs. 20x15mm; p=NS), but thicker (2200 µm vs. 1700µm; p=0.04) resection specimens. No difference in submucosal thickness was observed (900 µm vs. 800 µm; p=NS). Four patients were referred for surgery, based on the ER histology. Total costs of disposables was significantly less for MBM compared with ER-cap ($260 vs. $325, p=0.04).No clinically significant bleeding episodes occurred. One perforation was seen after ER-cap, which was treated conservatively. No clinically relevant stenoses were observed.At 3 months FU none of the patients demonstrated HGIN/ESCC at the resection site.
Conclusion: Piecemeal ER of early esophageal squamous neoplasia with MBM is faster and cheaper compared to ER-cap. Both techniques are highly effective and safe. Given its low complexity and costs, MBM may have significant advantages over the ER-cap technique, especially in countries where ESCC is highly prevalent but endoscopic expertise and resources are limited.

Low-grade dysplasia in Barrett's esophagus has a high risk of progression when confirmed by a panel of expert pathologists

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There is uncertainty regarding the natural history of low-grade dysplasia (LGD) in Barrett's esophagus (BE). Reported progression rates to high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) range from 0.6% to 13.4% per year. These divergent results may be explained by the reliability of the base LGD diagnosis and/or differences in the quality of endoscopic follow-up.We investigated the natural history of LGD confirmed by an expert panel of pathologists organised in our regional Barrett's Advisory Committee (BAC) to which all Dutch centers have free access.All BE cases referred to the BAC for pathology review of LGD diagnosed at community hospitals between 2000 and 2011 were included in this study. Slides were evaluated by two or three pathologists with extensive experience in BE neoplasia. In case of discordance a consensus diagnosis was reached in a dedicated consensus meeting.All follow-up endoscopy and pathology reports were retrieved from the referring hospitals. The expert panel diagnosis was then compared to the histological outcome during endoscopic follow-up.466 LGD patients (76% males; mean 62 yrs (SD 11.9)) underwent pathology review. 71% was downstaged to non-dysplastic BE (NDBE) or indefinite for dysplasia. In 28% the initial diagnosis was confirmed and 9 patients (2%) were upstaged to HGD/EAC.36 patients were excluded from endoscopic follow-up due to base HGD/EAC (n=9), participation in a randomized ablation study (n=7), comorbidity (n=9) or declined informed consent (n=11). Of the remaining 430 patients, 33 (8%) were lost to follow-up.397 patients were analyzed for outcome during endoscopic follow-up (mean follow-up: 59 months (SD 39.6); 1,933 patient-years). Based on the initial LGD referral diagnosis, the incidence rate for HGD/EAC during follow-up was 2.4% per patient year. In patients with a confirmed diagnosis of LGD the incidence rate for HGD/EAC during follow-up was 9.0% per patient year, compared to an incidence rate of 0.9% for patients with a consensus diagnosis of NDBE.

Conclusions: This is the largest cohort of LGD patients undergoing an expert pathology revision with the longest patient-years of follow-up described to date. The results indicate that patients with a confirmed diagnosis of LGD in BE have a markedly increased risk for progression to HGD/EAC. However, the vast majority of patients diagnosed with LGD by community pathologists will be downstaged after expert revision. These patients have a low risk of progression, similar to the reported progression rates for NDBE patients. All BE patients with LGD, therefore, should undergo review of the histopathological diagnosis by an expert panel.

The impact of active monitoring of quality of colonoscopy on adenoma detection rates and caecum intubation rates

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The Dutch government obliges monitoring of several quality indicators during colonoscopy, including adenoma detection rates (ADR) and caecum intubation rates (CIR). Knowing quality indicators are being monitored, may improve the quality of a colonoscopy. The aim of this study was to assess whether implementation of a monitoring program influences the ADR and CIR and, secondarily, to assess whether ADR and CIR meet the national requirements. We analyzed colonoscopy reports of 1085 colonoscopies before the introduction of the monitoring programme and 820 colonoscopies after the introduction of the programme. The colonoscopies were performed by 8 endoscopists in a large, non-academic teaching hospital. Patients with a history of colorectal surgery were excluded (36 patients in 2011; 25 in 2012). Colonoscopies performed by endoscopists who were not employed in our hospital during one of the periods of time are excluded as well (80 patients in 2011; 13 in 2012). Main endpoints were ADR and CIR. In total, 969 unmonitored colonoscopies and 782 monitored colonoscopies were included. The ADR in both cohorts (unmonitored: 34%; monitored 40%) were significantly higher than the national requirement of 20% (P<0.001). The CIR in both cohorts (unmonitored: 95%; monitored: 97%) were significantly higher than the national requirement of 90% (P<0.001). Both the mean ADR and CIR were significantly higher in the monitored cohort than the ADR and CIR in the unmonitored cohort (ADR: 34% vs. 40%, P<0.001, CIR: 95% vs. 97%, P<0.001). Monitoring was a significant factor of influence on the ADR (P=0.014) and on the CIR (P=0.022) after adjusting for the confounders age and sex.
In conclusion, our ADR and CIR both meet the national requirements. This study shows that monitoring the quality indicators ADR and CIR during colonoscopy is associated with a significant effect on the ADR and the CIR.

Adenoma detection rates vary greatly between gastroenterology fellows

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The adenoma detection rate (ADR) is an independent predictor of interval cancer and varies between colonoscopists. This variability within the ADR might already start during endoscopical training. Although Dutch training guidelines prescribe 100 fully supervised procedures, in the past at our institution, fellows inspected the colon unsupervised after approximately their first 50 procedures. This setting enabled us to measure ADR levels of starting colonoscopists. The aim of the study was to monitor ADRs of fellows withdrawing autonomously during their entire fellowship in a retrospective setting. Colonoscopies performed by 7 fellows between May 2004 and Feb 2012 were reviewed. To identify a learning curve, consecutive procedures were stratified into a ''training set" (first 140 procedures) and "post training set" (141 till end of fellowship). For ADR analysis, emergency procedures as well as patients with IBD, polyposis and a positive faecal blood test were excluded. These procedures, however, did count as gained experience in the training set. Individual ADRs were compared with the highest level detector, adjusted for patient's age, gender and indication. Regression analysis was used to determine the association of training ADRs on the detection of advanced neoplasia (≥ 1 cm, high grade dysplasia, villous structure or CRC) during the remaining fellowship. A total of 3252 colonoscopies were performed by 7 fellows. The number of procedures performed per fellow ranged from 389 to 612. After exclusion, data of 2050 procedures could be used for ADR analysis. In this cohort (mean age 59 yrs SD ± 15, 48% male) the overall ADR was 23% whereas individual ADRs ranged from 15% to 32%. Compared with the highest level detector, the odds for detecting ≥ 1 adenoma for individual fellows ranged from 0.73 to 0.29. None of the 7 individual ADRs increased significantly after the first 140 procedures. Fellows with a training ADR ≥20% (n=4) detected significantly more advanced neoplasms during the remaining course of their fellowship compared to fellows with a training ADR <20% (OR 1.88 95% CI 1.33 2.66). CONCLUSION The detection of adenomas varies greatly between fellows. We observed no increase in ADR levels after the first 140 colonoscopies, suggesting that adequate withdrawal technique is specifically learned during this novice period. The significance of this finding is underlined by the observation that fellows with an ADR ≥20%, during this period, go on to detect more advanced neoplasms during the remaining course of their fellowship. In an effort to improve detection performance it seems therefore advisable to intensify training during the beginning of a fellowship.

Deep sequencing of paired colorectal cancers and metastases: Detection of novel miRs and colonization specific miRs

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Introduction: Biomarkers are increasingly used for selecting the most optimal therapy for each patient. MiRs have recently been recognized as promising candidate biomarkers because of their role in cancer biology while being protected from degradation. It is unknown whether miRs are differentially expressed between primary colorectal cancers (CRC) and metastatic lesions. Such a comparison may provide information on the potential use of miRs for therapy selection. Moreover, the full miR ome of CRC has not been elucidated and consequently miR expression have not been studied in a thoroughly manner. AIMS: 1)Elucidate the miRNA expression of known and potential novel candidate miRs in mCRC and 2) Compare miR expression of primary CRCs and metastases from the same patients. METHODS: RNA was isolated from 64 snap frozen resection specimens, including 16 primary CRCs with 17 corresponding metastases. All tumor samples contained >70% tumor cells. Next generation sequencing was performed on the Illumina Highseq 2000 platform. Sequence data were aligned to miRBase v19. Prediction of novel candidate miRs was based on specific folding characteristics of the precursor sequences and fit of sequenced RNAs to the model of miRNA biogenesis. Cluster analysis and differential expression analysis for known and novel miRs were performed using EdgeR in a paired manner. RESULTS: 622.183.482 small RNA sequences were obtained for 64 samples, identifying 1634 known and 401 potential novel unique mature or complementary strand miRs expressed in mCRC. Unsupervised clustering showed a trend of close relationship between samples of the same patient, indicating that expression profiles of metastases resemble those of primary CRCs. 10 miRs were upregulated and 9 miRs were downregulated (FDR <0.1) in the metastases compared to their paired primary tumors. Including one novel candidate miR and miRs known in metastasis formation (miR 10b), tumor suppression (miR 133, miR 486) or associated with worse prognosis (miR 199b). Interestingly, subgroup analysis revealed specific expression changes for different organs of metastases, indicating that these miRs might contribute to organ specific colonization.
CONCLUSION: Using NGS, 401 potential novel miRs were identified in mCRC. MiR expression profiles of primary CRCs resemble those of their metastases. Only 1.15% of the miRs may be differentially expressed between primary CRCs and corresponding metastases, which is most likely determined by organ specificity. Based on our results, we expect that miR expression can be used as a biomarker for therapy selection irrespective of a primary or secondary origin of the CRC tissue.

Ex Vivo Sentinel Lymph Node Mapping in Colorectal Cancer Combining both Conventional Blue Dye and Near Infrared Fluorescence

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Lymph node status is the most important prognostic factor in colon cancer. The sentinel lymph node (SLN) procedure has been proposed in colon cancer to improve nodal staging. The aim of this study was to combine the use of blue dye staining and near infrared (NIR) fluorescence imaging for SLN biopsy in colon cancer patients. Twenty two consecutive patients undergoing surgery for colon cancer were included. Directly after resection, a premixed cocktail of 1 cc of 50 μM HSA800 (IRDye 800CW conjugated to human serum albumin) diluted in patent blue was submucosally injected around the tumor for detection of the sentinel lymph node. The Mini FLARE near infrared camera system was used for fluorescence imaging. In 95% of the patients at least one sentinel lymph node was identified. On average, per specimen, 3.5 ± 1.9 sentinel lymph nodes were identified. A total of 77 sentinel lymph nodes were identified, of which 77 were fluorescent and 70 were blue. Histological analysis showed lymph node metastases in 5 patients. In all but 1 case, at least 1 of the sentinel lymph nodes contained tumor cells.
Conclusions: This study demonstrated the successful use of the near infrared fluorescence tracer HSA800 in combination with conventional blue dye for the ex vivo sentinel lymph node procedure in colon cancer.

Participation, FIT result and yield in three rounds of biannual FIT based screening in the Netherlands

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Most European colorectal cancer (CRC) screening programs rely on fecal occult blood testing (FOBT), of which fecal immunochemical tests (FIT) have the best accuracy and adherence rates. The effectiveness of these FOBT based programs is not only influenced by the participation and yield of the initial screening round, but also by program adherence during consecutive rounds. FIT sensitivity is relatively low and is increased by repeated screening rounds. We aim to evaluate the participation rate, yield and progression of FIT screening for CRC over three rounds of CRC screening . A total number of 10,050 average risk individuals (50 to 75 years of age) were invited to participate in a third round of biennial FIT based CRC screening, using OC Sensor with a cut off of 50 ng/ml buffer(or 10 ug/mg feces). They received an invitation, including an information leaflet, a FIT test, and a pre paid return envelope. All FIT positives were recommended to undergo a colonoscopy unless contraindicated. Colonoscopy findings were classified as CRC, advanced adenoma, advanced neoplasia (CRC plus advanced adenoma) or other. Participation rates, FIT positivity rate, FIT positive predictive value and mean level of FIT result were calculated, and compared to the results of the first two screening rounds. Within this cohort, 5,671 invitees (56%) returned the FIT in this third screening round, compared to 52% in the second round and 56% in the first round ($p<0.001$). Overall, 377 (6.8%) of the third round participants had a positive FIT result, versus 7.4% in the second round and 8.1% in the first round ($p <0.01$). Of the FIT positives, 316 (84%) underwent colonoscopy. 59 could not undergo colonoscopy because of medical reasons or did not want to undergo colonoscopy. 88 participants had at least one advanced adenoma (28% of positives) and 17 had cancer (5%). The FIT positive predictive value for advanced neoplasia was 30%, compared to 44% in the second round and 55% in the first round; a significant dec ($p<0.01$)The average FIT result decreased in consecutive screening rounds from 430 ng/ml in the first round to 370 ng/ml in the second and 348 ng/ml in the third round. This decrease was not significant (round one versus round 2 p= 0.16; round one versus round three: 0.08).
Conclusion In consecutive CRC screening rounds with FIT, the participation rate stays stable, but both FIT positivity rate for advanced neoplasia and its positive predictive value dec significantly. Which means there is a positive effect on the chances on having advanced neoplasia in repeated FIT based screening. The average concentration of Hb in Feces decreased over several rounds of FIT based screening, though not significant.

Can endoscopists correctly predict polyp histopathology in FIT based screening?

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Screening would be more efficient and cost effective if polyps were accurately diagnosed on site by the endoscopist. Discarding these lesions without histopathologic evaluation would reduce time and costs for a final diagnosis. The accuracy of optical diagnosis of endoscopists is compared with the histopathological diagnosis in a screening setting. Data were collected in the third round of a FIT based CRC screening pilot program in the Netherlands, in which 10,050 average risk individuals (50 to 75 years of age) were invited to participate in a third round of FIT based CRC screening. In this study, 318 FIT positives underwent colonoscopy with Olympus (160 and 180 series) endoscopes without (virtual) chromoendoscopy. Endoscopists in this study had no special training in polyp assessment. They made an on site diagnosis of all detected lesions and classified these as a hyperplastic polyp, adenoma or carcinoma. All lesions were subsequently sent for histopathology, which was used as reference standard. We calculated the sensitivity and specificity for each category, as well as the overall accuracy. Colonoscopies were performed by 24 endoscopists in two hospitals. Of these, 259 (74%) were performed by 8 endoscopists. In the 318 patients with a positive FIT, a total of 839 lesions were detected. These were classified by the pathologist as 185 hyperplastic polyps, 523 adenomas and 17 carcinomas (39 serrated adenomas excluded). Optical diagnosis was correct for 460 of 523 adenomas (sensitivity 88% and specificity of 48%). For hyperplastic polyps, optical diagnosis was correct in 74 of 185 (sensitivity 40% and specificity 14%). Of 17 carcinomas, 12 were correctly diagnosed by the endoscopist (sensitivity 71%, specificity 99%). Classifying the cancers into AJJC stadia, 7 were stage I, of which 2 were correctly identified (sensitivity 29%, specificity 99%). In stages II and III, all cancers were correctly diagnosed by the endoscopists.
Conclusion: In a FIT based screening setting in routine practice, accuracy of optical diagnosis with regular white light endoscopy was suboptimal, especially for hyperplastic polyps and stage I cancers. This suboptimal sensitivity suggests that histopathology for lesions detected at colonoscopy for repetitive FIT based colorectal cancer screening should not be omitted.

27 Hydroxycholesterol: a novel approach for inhibition of hepatic inflammation (MLDS -project)

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Non alcoholic steatohepatitis (NASH) is a disorder which is characterized by fat accumulation in the liver (steatosis) combined with hepatic inflammation. Recently, we demonstrated a clear association between hepatic inflammation and lysosomal fat accumulation inside the Kupffer cells (KC's). 27 hydroxycholesterol (27HC), a derivative of cholesterol formed by CYP27A1A1, has been shown in vitro to mobilize cholesterol from the lysosomes to the cytoplasm. Here, we hypothesized that 27HC can redirect the intracellular cholesterol distribution in vivo, thereby influencing hepatic inflammation To investigate whether expression of CYP27A1A1 in Kupffer cells can modulate lysosomal cholesterol accumulation and thereby influence hepatic inflammation. For this purpose, Ldlr / mice were transplanted with bone marrow from mice lacking Cyp27a1 or wild type (Wt) bone marrow as control. After a recovery period of 9 weeks, the mice were put on chow or high fat high cholesterol (HFC) diet for 3 months. To examine whether exogenous 27HC influences intracellular cholesterol distribution and hepatic inflammation, 27HC was administered to Ldlr / mice that received regular chow or an HFC diet for 3 weeks. In with our hypothesis, electron microscopy analysis of KC's revealed increased lysosomal cholesterol accumulation in Cyp27a1 / tp mice compared to Wt tp mice after 3 months of HFC diet. Liver histology demonstrated that Cyp27a1 / tp mice had increased hepatic inflammation compared to Wt tp mice as indicated by the elevated numbers of infiltrated macrophages, neutrophils and T cells. These findings were confirmed by hepatic expression of Tnf, Il 6 and Il 1b. In with these data, administration of 27HC to Ldlr / mice on an HFC diet led to reduced lysosomal cholesterol accumulation and hepatic inflammation. Our data point towards a causal role for lysosomal cholesterol accumulation in hepatic inflammation and under the potential of 27HC to modulate the intracellular cholesterol distribution inside KCs, and thereby to reduce hepatic inflammation.

The role of the ABC transporters MRP1 and PMP70 in liver fibrosis in vitro and in vivo (MLDS-project)

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Background Liver fibrosis invariably develops during chronic liver disease and may progress to cirrhosis and liver cancer. Two main cell types are involved: hepatic stellate cells (HSCs) and portal myofibroblasts (PMFs). These cells become proliferative, contractile and produce excessive amounts of extracellular matrix proteins. Thus, HSCs and MFBs are prime targets to treat fibrosis. Activated HSCs and PMFs express increased levels of the multidrug resistance associated Protein 1 (MRP1) and the non selective MRP inhibitor MK571 inhibits expression of fibrosis markers (α SMA and Col1a1). MRP1 is an ATP binding cassette (ABC) transporter that transports glutathione (GSH) and GSH conjugates, including leukotriene C4. Here, we extended our studies to 1) identify the MRP1 substrate causing reversal of HSC/PMF activation and to establish the role of Mrp1 in a mouse model of fibrosis and 2) determine de function of an additional ABC transporter, the 70 kDa peroxisomal membrane protein (PMP70), in activation of HSCs and PMFs. Methods Primary rat HSCs and PMFs were used as in vitro model of fibrosis. MRP1 activity was inhibited by MK571, Reversan or RNA interference and confirmed by CMFDA transport assays. Glutathione depletion/repletion experiments and LTC4 synthesis inhibitors were used to identify the potential MRP1 substrate. In addition, PMP70 expression was suppressed by siRNA or enhanced by transient transfection of GFP PMP70 encoding plasmids. Mrp1 knock out and appropriate wild type FVB control mice were injected with CCL4 or corn oil for 12 weeks. After 12 weeks livers were excised for qPCR, western blot and histological (Sirius red for collagens) analysis. Results 1. MRP inhibition reduced CMFDA export, α SMA and Col1a1 mRNA levels. Partial inhibition of MRP1 by RNA interference lead to reduced expression of a SMA. Manipulation of glutathione levels did not affect the Reversan induced reduction of α SMA and Col1a1 expression in LX 2 cells. AA861 treatment, like MK571, suppressed α Sma and Col1a1 expression. Both α Sma protein and collagen deposition was strongly reduced in CCl4 treated Mrp1 / mice vs. WT. 2. PMP70 shows an aberrant subcellular location in HSCs/PMFs when compared to hepatocytes. It resides in fibrillous strands that lay parallel to the aSma network, whereas it is a peroxisomal protein in hepatocytes. PMP70 siRNA reduces PMP70 and aSma expression with no significant effects on Col1a1.
Conclusions: Inhibition of MRP1 leads to suppression of liver fibrosis by preventing leukotriene export from HSCs. PMP70 is required for HSC/PMF activation. MRP1 and PMP70 are therefore highly relevant targets for the treatment of liver fibrosis. This work was supported by MLDS grant WO 09 54. Ms Ing. B. Mikuš was employed by the MLDS grant.

Probiotics and enteral nutrition in acute pancreatitis the POST PATRIA project (MLDS-project)

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Background: Bacterial translocation (BT) through the bowel wall is held responsible for infection of (peri)pancreatic necrosis and mortality in acute pancreatitis (AP). Probiotics were thought to reduce BT and mortality. Clinical prophylactic application of probiotics did not reduce the infection rate but was associated with an increase in mortality and a higher rate of fatal bowel ischemia. Based on these results, the following questions were raised: is small bowel ischemia a pivotal process in the higher mortality rate and if so, what role is played by probiotics, enteral nutrition or the combination. Aim of the project: To unravel the effects of probiotics and enteral nutrition on small bowel ischemia, necrosis and death. Material and methods: In the MLDS project, three studies were conducted: I) a retrospective study in a cohort of patients treated with probiotics, (II) an experimental study in rats (4 groups: 1) AP, n=9, 2) AP and probiotic prophylaxis, n=10, 3) AP and enteral nutrition, n=10, and 4) AP, probiotic prophylaxis and enteral nutrition, n=11), to investigate the interaction between probiotic prophylaxis and enteral nutrition in an experimental rat model for severe AP and (III) in vitro study (a}, with and without pancreatic enzymes and bile salts, simulating functioning and non functioning of pancreas secretion, b} with and without probiotics/placebo, and c} using two enteral nutrition 'Fibre rich' and 'protein rich') to investigate the interaction between enteral nutrition and probiotics during passage through the small intestine using a dynamic, computer controlled model of the small intestine (TIM 1), in order to show whether or not lactate is produced. Results: In study (I) again no beneficial effect of the use of probiotics on the rate of infections was demonstrated, but also, no harmful effects of the use of probiotics could be demonstrated. In study (II) histological severity of AP in all groups was similar, no difference between groups was observed in histology of the small bowel, no significant difference was found between the groups in rRNA gene copies per gram pancreatic tissue and no difference in over all mortality was observed between the 4 groups (11% in group 1, 0% in group 2, 18% in group 3, and 9% in group 4, P=0.54). Conclusion: in the patients with AP studied, the findings of the PROPATRIA study on the infection rate was supported, the effect on mortality was not. Neither in the animal experiment nor in the in vitro study could any adverse effect of probiotics, enteral nutrition or the combination be documented. So all questions remaining after the PROPATRIA study are still awaiting an adequate answer

Adherence to anti TNF therapy in patients with inflammatory bowel disease

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More than one third of patients with inflammatory bowel disease (IBD) are non adherent to oral medication, leading to poor health outcomes and increased health care costs. However, data regarding non adherence to anti TNF therapy are limited. Therefore, we assessed the rate and risk factors of non adherence to infliximab (IFX) and adalimumab (ADA) in patients with IBD.In this multicenter observational study, consecutive IBD patients using IFX or ADA were included. Patients completed the validated Modified Morisky Adherence Scale 8 with a score on this scale of <6 indicating low adherence. Clinical disease activity was assessed by the modified Harvey Bradshaw Index (Crohn's disease) or the Simple Clinical Colitis Activity Index (ulcerative colitis). We also assessed demographic and behavioural characteristics, including attitudes towards maintenance therapy (Beliefs about Medicines Questionnaire) and illness beliefs (Brief Illness Perception Questionnaire). A hierarchical logistical regression analysis was performed to determine factors associated with low adherence.Seventy three patients were included, median age 35 years (IQR 24 51), 27 males (37%). Median disease duration was 11 years (IQR 3 18). Nineteen patients (26%) were in clinical remission. Of the 51 patients on maintenance anti TNF therapy, 6 out of 18 patients on ADA (33%) and 14 out of 33 patients on IFX (42%) reported a low adherence (p = 0.37). Attitudinal analysis showed that while 38% of the patients was "accepting" maintenance therapy, including anti TNF therapy (high necessity, low concerns), more than half of patients (58%) was "ambivalent" about maintenance therapy (high necessity, high concerns). Factors independently associated with low adherence were high perceived personal control over the illness (OR 1.38, 95% CI 1.01 1.89) and symptoms attributed to the illness (OR 0.60, 95% CI 0.39 0.93), and strong beliefs about how the illness affects one's emotional well being (OR 1.61, 95% CI 1.12 2.32). Non adherence was not affected by young age, male gender, disease activity, disease duration or concerns about anti TNF therapy.
Conclusions:The overall non adherence rate of anti TNF therapy is comparable to rates found in oral medication. A substantial proportion of patients were ambivalent about maintenance therapy, including anti TNF therapy and several illness beliefs were significantly associated with non adherence. As illness beliefs are potentially modifiable factors, they may provide a relevant target for interventions aimed at improving adherence and health outcomes.

Faecal hemoglobin and calprotectin are equally effective in predicting whether surveillance can be performed in patients with long standing ulcerative or Crohn's colitis.

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Introduction: In patients with inflammatory bowel disease (IBD) active colitis impairs neoplasia detection in the setting of colonoscopic surveillance for colorectal cancer (CRC). Therefore, current guidelines recommend repeated colonoscopy after induction of remission in these cases, thereby increasing costs and burden for the patient. We investigated whether faecal hemoglobin and calprotectin testing prior to surveillance colonoscopy might prevent ineffective surveillance in colitis patients. METHODS: All consecutive patients with either Crohn's colitis or ulcerative colitis scheduled for surveillance colonoscopy were asked to collect a stool sample prior to the start of bowel cleansing. Three experienced endoscopists scored inflammation in each colonic segment. The cut off for ineffective surveillance was defined as at least one colonic segment with moderate or severe inflammation. Hemoglobin and calprotectin were quantitatively analyzed using an enzyme linked immunosorbent assay (R Biopharm, Germany). Stool samples were analyzed without reference to the colonoscopy findings and vice versa. ROC statistics were used to determine cut off values for hemoglobin and calprotectin. RESULTS: A total of 119 patients were included, of which 54 patients had Crohn's colitis, 59 had ulcerative colitis and 6 indeterminate colitis. A total of 14 patients (12%) had an endoscopic score of moderate (n=9) or severe (n=5) inflammation (ineffective surveillance). The remaining 105 patients had either mild inflammation (n=29) or no active inflammation (n=76) and were grouped as effective surveillance. Median hemoglobin and calprotectin levels were significantly higher in patients in the ineffective surveillance group as compared to patients in the effective surveillance group 133 (IQR 34 468) µg/g vs 0.4 (IQR 0.3 1.5) µg/g and 2318 (IQR 691 4118) µg/g vs 84 (IQR 27 276) µg/g respectively (both $p<0.01$, Mann Whitney U test). Using ROC statistics, the predictive accuracy of hemoglobin and calprotectin in identifying patients with ineffective surveillance was 0.96 and 0.92 respectively (area under the curve). For hemoglobin a cut off value of 11 µg/g indicated patients with ineffective surveillance with 93% sensitivity and 89% specificity. For calprotectin a cut off value of 545 µg/g indicated patients with ineffective surveillance with 86% sensitivity and 89% specificity.
CONCLUSION: Faecal hemoglobin and calprotectin testing prior to a scheduled surveillance colonoscopy are equally effective in identifying IBD patients with active endoscopic inflammation in whom surveillance will probably be ineffective. Routine use of either of these tests might prevent useless colonoscopies and can therefore be cost effective.

Ethnicity is the strongest predictor for Helicobacter pylori infection in young women in a multi ethnic European city: the Generation R study.

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Background: The prevalence of H. pylori infection has been declining in Western countries over recent decades. During this same period, however, many immigrants from developing countries with high H. pylori prevalence have settled in Western urban areas. Knowledge about the epidemiology of H. pylori in a migrant community may help in realizing a more selective approach to assess H. pylori related diseases. Aim: The objective of this study was to define H. pylori and CagA prevalence and risk factors related to H. pylori in pregnant women living in a multiethnic European city. Methods: We measured IgG anti H. pylori and CagA antibodies in serum of pregnant women of the Generation R study, a population based prospective cohort study. Information on demographics, education, lifestyle and socio economic status was collected by questionnaires. Chi square tests and multivariate logistic regression were used. Results: Serum of 7185 pregnant women was analyzed (mean age 29.8 ± SD 5.2). In total, 3248 (45%) subjects were H. pylori positive and 1142 (35%) of them were CagA positive. H. pylori positivity was found in 92% of Moroccan (OR 10.8; 95% CI 6.6 17.6), 81% of Cape Verdean (OR 4.4; 95% CI 2.9 6.8), 80% of Turkish (OR 5.2; 95% CI 3.9 7.0), 61% of Dutch Antillean (OR 1.6 95% CI 1.0 2.3), and 57% of Surinamese women (OR 1.3; 95% CI 1.0 1.6), while subjects of Dutch or other European origin had an infection rate of 26% ($p<0.001$). Multivariate analysis revealed, in addition to ethnicity, the following independent risk factors for H. pylori positivity: first generation immigrant (OR 2.2; 95% CI 1.9 2.7), low education level (OR 1.8; 95% CI 1.4 2.5), and low income (OR 1.6; 95% CI 1.3 2.0). H. pylori positive Dutch subjects were CagA positive in 18% of the cases compared with 40% of the non Dutch subjects ($p<0.001$). Conclusions: Migrant communities in a European city still have high H. pylori positivity rates. Since maternal H. pylori status is a strong predictor of childhood H. pylori status, these results imply that H. pylori will be prevalent in migrant communities for the coming decades. The high prevalence of H. pylori and in addition the higher CagA positivity rate will permit assessment of disease risks, and will offer opportunities for targeted interventions.

The effect of viral, bacterial and parasitic infections on the intestinal microbiota

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Objectives: While investigation of the intestinal microbiota with molecular techniques has become a topic of intense research in recent years, relatively little is still known about the effect of pathogens on the intestinal microbiota. Here we analysed the effect of a number of bacterial, viral and parasitic pathogens on the intestinal microbiota in diarrheal samples. We compared the effects of the different types of pathogens on the intestinal microbiota to each other and to a set of control samples in which no pathogen was present. Methods: We prospectively collected 101 diarrheal samples that tested positive for gastrointestinal pathogens with conventional methods (culture, serology and/or PCR). Most common pathogens present were Campylobacter sp, Salmonella sp, Norovirus, Rotavirus and Giardia lamblia. Total microbiota in these samples was analysed by IS pro. IS pro is a high throughput molecular fingerprinting method which enables a fast and automated identification of the intestinal microbiota. It is based on length variation of the 16S 23S ribosomal DNA (rDNA) interspace (IS) region combined with phylum specific sequence variation of the 16S rDNA and provides relative quantification of all members of the most prominent bacterial phyla in the human intestine, including Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria. Data were analysed with the Spotfire software package (TIBCO, Palo Alto, USA) in combination with in house developed automated data analysis tools. Results: In all bacterial diarrheal samples we found relatively low abundances of the associated pathogens. Furthermore, we found a significant increase in Escherichia coli abundance for both bacterial and viral diarrheal samples as compared to healthy control samples. Strikingly, we found a significant increase in Bacteroidetes and a total disappearance of E. coli in all samples with G. lamblia infection. We were able to confirm this result with qPCR.
Conclusion: In conclusion, intestinal pathogens seem to have a varying effect on intestinal microbiota. Most outspoken effects seem to be in the facultatively anaerobic E. coli population, with a dramatic increase in bacterial and viral gastroenteritis and a total disappearance in G. lamblia infection. Further investigation into the causative mechanisms behind these findings may provide important new insights into infectious gastroenteritis.

Rectal swabs as feasible and reproducible sampling method of the intestinal microbiota in a clinical setting

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Objectives Recently, the gut microbiota has become an interesting potential target for clinical diagnostics. Currently, the most commonly used sample types for its analysis are faeces and mucosal biopsies. However, as sampling method, storage and processing of samples have been shown to affect microbiota analysis, these sample types have limitations in respectively standardisation and accessibility. An ideal sample type should be easily obtained in a standardised fashion with no preceding perturbation of the microbiota. Rectal swabs satisfy these criteria, but little is known about microbiota analysis on these sample types. In this study we investigated the applicability of rectal swabs for gut microbiota profiling in a clinical routine setting. We analysed optimal storage and processing of rectal swabs for clinical routine, reproducibility of profiles from rectal swabs and similarity to microbial profiles from fecal and mucosal samples. Methods Rectal swabs, mucosal biopsies, mucosal washings and fecal samples from 38 subjects were prospectively collected and analysed by IS pro, a high throughput molecular fingerprinting method. Two rectal swabs were stored in RTF buffer at room temperature for two hours before freezing at 20°C and one was immediately snap frozen. These samples were used to evaluate reproducibility of rectal swabs and effect of storage at room temperature. IS profiles from rectal swabs were further compared to mucosal and fecal samples. All data analysis was performed with in house developed software tools in combination with the Spotfire software package (TIBCO, Palo Alto, USA). Results IS profiles from the two rectal swabs stored in RTF buffer at room temperature were highly similar (estimated correlation coefficients of IS profiles >90%) and were equally similar to the snap frozen rectal swab. Correlation of rectal swabs to feces was low (estimated correlation coefficients of IS profiles 40 60%) and correlations to mucosal samples were slightly higher (50 70%). Correlations of fecal samples to mucosal samples were low (40 60%).
Conclusion We find that rectal swabs give highly reproducible microbiota profiles that resemble mucosal adherent microbiota more closely than feces. Storage of swabs in RTF buffer of up to two hours at room temperature does not affect the results of subsequent microbiota analysis, making reproducible routine sampling in a clinical setting feasible.

Diagnostic value of multiple auto(antibodies) and carbohydrate antigen 19.9 in disciriminating between autoimmune pancreatitis, malignancy and other disorders

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Background: Autoimmune pancreatitis (AIP) is a benign disease that may clinically mimic pancreatic or cholangiocarcinoma and occasionally other conditions including chronic pancreatitis and primary sclerosing cholangitis (PSC). There is no single diagnostic test reliably differentiating AIP from other disorders. A number of serological markers (IgG4, total IgG or the presence of other autoantibodies like antinuclear antibody/ANA, rheumatoid factor/RF, anti carbo anhydrase II/ACA II and antilactoferrin/ALF) have been proposed as useful diagnostic tests. However, most of these tests lack sufficient validation. Objective To determine the diagnostic value of multiple tests (total IgG, IgG subclasses, IgE, ANA, RF, pANCA, ENA (aSSa and aSSb), ACA II, ALF, anti elastase (AE) and tumour marker Ca 19.9 in a group of western AIP patients, various pancreatobiliary diseases and Sjögren's syndrome (SS). Methods Sera were obtained from patients with AIP (n=33), pancreatic carcinoma (n=53), cholangiocarcinoma (n=32), chronic pancreatitis (n=30), primary sclerosing cholangitis (n=30) and Sjögren's syndrome (n=31). Frequencies of positive tests were determined in each group. One way analysis and pairwise comparisons with Bonferroni correction for multiple testing were performed to detect significant differences between groups. ROC curves were constructed to assess optimal cut off levels. Logistic regression was performed to detect combinations of tests that predict AIP. Results: Only IgG4, IgG3, Ca 19.9, IgE, IgG and IgG1 significantly differentiate between AIP and malignancy, with AUC's of 0.89, 0.76, 0.76, 0.75, 0.74 and 0.70 respectively. The optimal cut of levels are: IgG4 >2.8 g/l, IgG3 >0.37 g/l, Ca 19.9 <70 U/ml, IgE>155 kU/l, IgG >10.6 g/l and IgG1>6.8 g/l. None of the autoantibodies was found to be discriminative. Combination of IgG4, IgG3 and Ca 19.9 predicts probability of AIP with an AUC of 0.93 ($p<0.001$, $p=0.035$, and $p<0.001$). Conclusions IgG4 is the best single test to differentiate between AIP and malignancy, with an optimal cut off level of 2.8 g/l (twice the upper limit of normal). Combining IgG4, IgG3 and Ca 19.9 can be used to reliably predict a diagnosis of AIP. Testing of autoantibodies does not appear to be useful.

The Reflux Finding Score for Infants (RFS I): Inter and intraobserver variability

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Larynxedema is encountered frequently in infants with laryngomalacia. It is hypothesized that larynxedema is caused by gastroesophageal reflux (GER). In adults, the Reflux Finding Score (RFS) is a validated tool to assess larynx edema. Anatomy and the size of the larynx differ significantly in infants compared to adults. Aim: To test the reliability of assessing reflux associated edema in infants when evaluated through flexible laryngoscopy (FL) with the use of an adapted RFS for infants (RFS I).A pre validation study was performed to assess the visibility of anatomic landmarks in the infant larynx. Items for the RFS I were included based on inter and intraobserver variability of three ENT specialists and a review process of expert opinions. Laryngeal edema, erythema or hyperemia, vocal cord visibility and endolaryngeal mucus were subsequently included to form the RFS I. Forty infants (3 18 months) were selected from a database of FL procedures. Twenty infants with reported evidence of larynx edema and twenty infants with no reported pathologic findings during FL were selected. Next, 3 pediatric othorhinolaryngologists, 2 ENT doctors and 2 gastroenterology fellows (group 1, 2 and 3 respectively), from 2 different centers were presented an educational tutorial that explained the scoring items. Next, the video clips were presented in a randomized order, blinded for the clinical profile and findings during initial FL. To ensure intra rater consistency, all reviewers performed a second rating of the video clips at least 2 days after their first view. Cohen's kappa (κ) was calculated for categorical data and for analysis of >2 raters Fleiss' kappa (κ) was used, for ordinal data the intraclass correlation coefficient (ICC) was used.Of the 40 infants, (median age: 4 (0 16) months), age and gender did not differ significantly between the two groups. Overall interobserver agreement was moderate (ICC=0.45). Intraobserver agreement ranged from moderate to excellent agreement (ICC=0.50 0.87). A ROC curve of group 1 showed an AUC of 0.77, 0.65 and 0.59 respectively. With a cutoff value of <4 for the RFS I, sensitivity and specificity were respectively 95% and 26.3%, 60% and 36.8%, 65% and 31.6%.
Conclusion: Inter and intraobserver variability of the RFS I is moderate. GER related larynxedema in infants, when assessed through FL, should be used with caution in research settings and cannot guide clinical practice. Other diagnostic tools, such as rigid laryngotracheoscopy should be considered and further investigated as a valid approach to detect larynx edema in infants.

The value of Golgi protein 73 as a marker to differentiate between solid benign and malignant liver tumours

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Introduction: In a primary focal solid liver lesion a good diagnose is essential because the differential diagnosis includes benign liver tumours like Hepatocellular adenoma (HCA) and Focal Nodular Hyperplasia (FNH), as well as Hepatocellular Carinoma (HCC). These tumours could be differentiated with molecular markers. A new promising marker could be Golgi Protein 73 (GP73). This marker is described in several studies but they only included cirrhotic patients and/or healthy persons as control groups. The aim of our study is to determine the predictive value of GP73 in the differentiation between solid benign and malignant tumours of the liver. Materials and methods: A total of 252 patients were included in this study with among them 84 patients with an HCC, 84 patients with an HCA and 84 with FNH. From each patient a blood sample was collected in the out patient clinic. In these samples we measured GP 73 levels with a quantitative ELISA assay. The levels of GP73 in the HCC patients were compared to levels of GP73 in patients with benign liver tumours. The ROC (received operating curve), sensitivity and specificity of GP73 were calculated and compared with alpha fetoprotein (AFP). Results: The GP 73 area under ROC was 0.701.The sensitivity was 60% and the specificity of 77% to differentiate HCC patients from patients with a HCA and FNH. The AFP area under the ROC was 0.912 with a sensitivity of 65% and specificity 96%.
Conclusion: Although literature suggests GP73 is a valuable serum marker in patients with HCC and superior to AFP, GP73 does not seem useful to discriminate between solid liver lesions either malignant or benign. Therefore, GP73 should not be used as a diagnostic marker if there is a solid tumor in the liver of unknown origin as GP73 could also be increased in benign liver tumours.

Human small intestinal barrier function and tight junction integrity during ischemia reperfusion

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The small intestine is lined with epithelial cells interconnected by tight junctions (TJ) to prevent exposure of host interior to potentially harmful luminal content such as microbes. Intestinal ischemia and reperfusion (IR) is associated with damage to this barrier. This can lead to bacterial translocation, systemic inflammation and eventually multiple organ failure. Surprisingly, previous studies showed that human small intestine is able to morphologically restore IR induced damage after 30 minutes of ischemia followed by 120 minutes of reperfusion. However, it is unknown if the barrier is also functionally restored within this time frame. In this study, we therefore aimed to assess functional barrier integrity during intestinal IR by means of a dual sugar test and relate outcome with TJ status.Intestinal IR was studied using a human experimental model. In 10 patients undergoing pancreaticoduodenectomy an isolated part of jejunum, to be removed for surgical reasons, was subjected to 30 minutes of ischemia (30I) followed by 30 (30R) and 120 minutes of reperfusion (120R). Before induction of ischemia, the sugars lactulose and rhamnose were injected into the lumen of the isolated bowel segment to assess intestinal permeability. A sham procedure without IR was performed in 3 patients. Arterial (A) and venous (V) blood was sampled from the radial artery and the venule draining the isolated jejunum, respectively, before (control) and during IR/sham procedure. Plasma sugar concentrations were measured using HPLC mass spectrometry and used for calculating AV concentration differences and lactulose/rhamnose (L/R) ratios to assess intestinal permeability. Intestinal tissue was sampled and stained for ZO 1/occludin and analyzed by electron microscopy to visualize TJs. Results were analyzed using Mann Whitney U test. Data are presented as mean±SEM. Plasma L/R ratio increased significantly at 30I30R compared to control (0.75±0.10 vs 0.20±0.09, P<.05), indicating increased intestinal permeability. At 30I120R the ratio normalized to 0.17±0.06 which was not significantly different from control or sham. ZO 1/occludin staining showed continuous staining in control tissue, while at 30I distortion of staining was observed, indicating TJ loss. An intact lining of ZO 1/occludin was observed again at 120R. Electron microscopy analysis revealed disrupted TJs after 30I, which were restored after 120R.In conclusion we provide evidence that the human small intestinal barrier is damaged after 30I followed by 30R and that morphological and functional recovery of this barrier occurs within 120R, highlighting the unique ability of the human gut to withstand short ischemic events.

Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile infection, results of a randomized controlled trial

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Background: Recurrent Clostridium difficile infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent C. difficile infection. Methods: We randomly assigned patients with recurrent C. difficile infection to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with C. difficile infection without relapse after 10 weeks. Results: The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of C. difficile–associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of C. difficile infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage ($P<0.001$ for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, with an increase in Bacteroidetes species and clostridium clusters IV and XIVa and a decrease in Proteobacteria species.
Conclusions: The infusion of donor feces was significantly more effective for the treatment of recurrent C. difficile infection than the use of vancomycin. Funded by the Netherlands Organization for Health Research and Development and the Netherlands Organization for Scientific Research; Netherlands Trial Register number, NTR1177

Prucalopride decreases esophageal acid exposure and accelerates gastric emptying in healthy subjects

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Background: The 5 HT4 receptor agonist prucalopride is a prokinetic drug that affects colon motility and is effective for the treatment of chronic constipation. Animal data and in vitro studies suggest that the drug also has an effect on gastric and esophageal motor function. We aimed to assess the effect of prucalopride on gastric emptying, esophageal motility and gastroesophageal reflux in man. Methods: In this double blind, placebo controlled, randomized, crossover study we included 21 healthy volunteers who received 4 mg prucalopride or placebo per day for 6 days. At day 5 subjects underwent high resolution manometry (HRM) followed by 120 minutes combined HRM pH impedance monitoring after a standardized meal in order to study reflux mechanisms and the effect on transient lower esophageal sphincter relaxation (TLESR). The latter was followed by ambulatory 24 hr pH impedance monitoring. The next day gastric emptying for solids was assessed scintigraphically. Results: HRM showed that esophageal motility as well as basal pressure of the lower esophageal sphincter were not affected by prucalopride. The 24 hr impedance pH measurements revealed that prucalopride significantly decreased (median (IQR)) total acid exposure time (AET) (3.4 (2.5 5.6) vs 1.7 (0.8 3.5) %, $p<0.05$) and upright AET (4.8 (3.5 7.6) vs 2.6 (1.4 4.3) %, $p<0.05$). The total number of reflux events was not affected by prucalopride, however, the number of reflux events extending to the proximal esophagus was significantly reduced by prucalopride (15.5 (9.8 25.5) vs 10.5 (5.3 17.5), $p<0.05$) as well as the proportion of reflux episodes reaching the proximal esophagus (29 (18 43) vs 21 (12 31) %, $p<0.05$). Furthermore, prucalopride significantly improved acid clearance time (77.5 (47.8 108.8) vs 44.0 (30.0 67.8) s, $p<0.05$). During the mechanistic 120 min study, prucalopride did not affect the number of TLESRs or their association with reflux events. Prucalopride increased gastric emptying (T1/2 (49.8 (37.7 55.0) vs 32.7 (27.9 44.6) min, $p<0.05$), residue after 120 min (8.8 (4.4 14.8) vs 2.7 (1.3 5.4) %, $p<0.05$).
Conclusion: Prucalopride accelerates gastric emptying and reduces esophageal acid exposure in healthy volunteers.

A multicenter retrospective head to head comparison of adalimumab and infliximab for Crohn's disease

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Although it is generally assumed that the efficacy of infliximab (IFX) and adalimumab (ADA) for the treatment of Crohn's disease (CD) is approximately equivalent, no head to head comparisons have been published. The aim of the present study is to compare the efficacy and safety of IFX and ADA in carefully matched cohorts of CD patients. Patients with CD treated with anti TNFα were identified from databases of six hospitals in the Netherlands. Anti TNFα naive patients starting on IFX or ADA after 2006 and with a follow up of at least one year were selected. Patients were matched for indication of anti TNFα therapy, duration of disease, age at base and Montreal classification. Patients were considered to have a steroid free clinical response if one of the following criteria was not met: (1) hospitalization due to exacerbations or CD related surgery, (2) stopping of anti TNFα because of primary or secondary loss of response or due to side effects and (3) need for or dependency on steroids. A total of 200 patients, 100 per arm, were studied (55% female, mean age at base 36.6±12.5 yrs, mean duration of disease 10.2±9.5 yrs). In 77% patients, luminal activity was the indication for initiation of anti TNFα therapy. Base characteristics for ADA and IFX treated patients showed no significant differences. Most patients (96.5%) were treated in tertiary referral hospitals. After one year; response rates were 62 and 65% for ADA and IFX, respectively (ns). After 2 years, follow up data of 151 patients were available (64 and 87 in the ADA and IFX group,respectively). Of these, 41% (ADA) and 49% (IFX) still showed a steroid free clinical response. Kaplan Meier curves of IFX and ADA demonstrated identical decreases of response rates. Comparison of anti TNFα therapy with and without co medication (Azathioprine, Methotrexate, Mercaptopurine or Tioguanine) showed higher response rates in favor of patients treated with co medication, although this was only significant among patients that received IFX (p=0.03). In 8.5% of cases, opportunistic infections were encountered; 8% and 9% for ADA and IFX, respectively (p=NS).
In conclusion, efficacy of ADA and IFX treatment in anti TNFα naïve patients with CD is comparable after 1 and 2 years of follow up with regard to steroid free clinical response rates, side effects and opportunistic infections. Both IFX and ADA seem to be more effective when co medication is administered, although not statistically significant in case of ADA.

Estrogens promote development of colitis associated cancer

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Background and Aim: In patients with inflammatory bowel diseases the risk of colorectal cancer (CRC) is up to 6 fold increased compared to the general population. The sequence of mutations that drives colitis associated colorectal carcinogenesis is distinct from the sporadic adenoma to carcinoma sequence and factors that influence its initiation and progression are poorly defined. The Women's Health Initiative studies have clearly established that female hormones protect against sporadically occurring CRC. Recently, it was shown that postmenopausal hormonal replacement increases the risk for developing inflammatory bowel disease. We therefore set out to determine the influence of female hormones on colitis associated colorectal carcinogenesis. Methods: We studied colitis associated cancer using a model that combines treatment with dextran sodium sulphate (DSS) and azoxymethane (AOM). Female mice were subjected to ovariec–tomies or sham operations and supplemented with placebo, estradiol (E2), the progestin medroxyprogesterone acetate (MPA) or a combination of both. We used estrogen receptor (ER) α and β mutant mice to examine the role of these receptors in colitis associated cancer development. Results: Females that had undergone ovariectomy were markedly protected from tumor development compared to sham operated mice (7.0 vs. 12.0 polyps per colon, $P < 0.001$). Hormone replacement with MPA alone did not affect tumorigenesis in ovariectomized mice. Mice that received E2 showed a dramatic increase in polyp development compared to placebo treated mice (16.0 vs. 1.5 polyps per colon, $P < 0.001$). Besides increased numbers of polyps, E2 also strongly promoted tumor progression with all E2 treated animals developing at least one invasive adenocarcinoma whereas placebo treated animals developed adenomas only. E2 treated animals showed an aggravated response to DSS with increased production of Il 6 and enhanced epithelial proliferation 5 weeks after the last cycle of DSS. Using estrogen receptor (Er) mutant mice we find that protumorigenic effect of estrogen depends on both Erα and Erβ.

Conclusion: Female hormones promote colitis associated tumorigenesis. We identify estradiol as the factor responsible for this effect. DSS induced colitis as well as colitis associated tumors are aggravated by estradiol. We find that tumorigenesis is influenced by both estrogen receptors α and β. Our findings suggest that estrogens promote inflammation associated cancer development by impairing the mucosal response to inflammatory damage.

Defective CSF2RB signaling in Crohn's disease patients bearing the NCF4 risk allele

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Introduction: At least 100 risk loci associated with Crohn's disease (CD) have been identified, many of which are associated with innate immunity. One of the single nucleotide polymorphisms shown to confer risk of CD development is a T to C conversion in the NADPH oxidase gene NCF4 (rs4821544) This protein plays a pivotal role in the production of reactive oxygen species (ROS) by granulocytes (PMN), essential for bactericical activity. We previously showed that GMCSF primed ROS production is impaired in rs4821544 carrying CD patients. Interestingly, the GMCSF-receptor β gene (CSF2RB) lies adjacent to the NCF4 gene. Here, we assessed CSF2RB function between CD patients bearing the NCF4 risk and wildtype alleles. Materials and methods: PMN were freshly isolated from risk allele rs4821544 and wild type allele carrying patients, simultaneously. Expression of CSF2RB was determined by flow-cytometry and confirmed by qPCR. ROS production upon stimulation of cells with fMLP with or without prior priming with GMCSF or GCSF was measured by flowcytometry. Uptake and killing of E. Coli were measured using fluorescence spectophotometry. CSF2RB signaling was studied after stimulation with GMCSF and IL5.
Results: Membrane expression of CSF2RB is similar between patients bearing either T or C alleles (n=10; 323±40 and 323±54 MFI). GMCSF-primed ROS production was greatly diminished in C allele patients compared to T allele patients (n=10, 221±41 MFI vs 464±52 MFI, p=0.002), wereas GCSF-primed ROS production was unaffected (210±30 vs 225±20 MFI, p=0.79). indicating a specific GMCSF receptor signaling defect. E.Coli uptake was not different, whereas a trend towards diminished killing was observed in C allele patients (171±28 vs 280±86 CFU). In C-allele patients, GMCSF stimulation induced less activation of STAT3 (n=5, 1.8±0.8 vs 3.5±1.1 vs); AKT (11±5 vs 23±13) and ERK (30±20 vs 40±10) in C allele carriers. IL5 induced lower STAT5 (n=4, 0.2± 0.1 vs 0.5±0.2) and AKT signaling (0.03±0.06 vs 0.7±0.04).
Conclusion: We show a specific defect in CSFR2B signaling in patients carrying the NCF4 risk allele. The CSFR2B receptor is used by both GMCSF and IL5, and both cytokines induce reduced signaling in C-allele patients. In contrast, priming of PMN by GCSF, which signals through a different receptor, was normal. Thus, the NCF4 risk allele confers a defect in CSFR2B signaling, and may identify a subset of CD patients whose inflammation is influenced by impaired innate immunity induced by neutrophils. GM-CSF treatment, which is beneficial for some patients, may be limited by NCF4 genetic back-ground of patients.

JAK inhibitor tofacitinib interferes with interferon alpha mediated inhibition of hepatitis C replication

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Background: End stage liver disease caused by chronic hepatitis C infection is a leading indication for liver transplantation. After transplantation however, reinfection of the graft occurs universally, leading to accelerated fibrosis and early development of cirrhosis. The use of immunosuppressive medication after transplantation may contribute to the aggravated course of infection and increased resistance to antiviral therapy. Therefore, there is a need for new immunosuppressive agents. Tofacitinib is a new immune-suppressant that was developed as a selective inhibitor of the Janus kinase 3 (JAK3) but may inhibit other members of the JAK family. Therefore, the aim of our research is to investigate the effect of tofacitinib on HCV replication and JAK1 mediated interferon-α (IFN-α) signalling.Methods: As a model for HCV replication we used a Huh7 hepatoma cell line, stably transfected with the non-structural coding sequence of HCV coupled to a luciferase reporter (Huh7-ET). The amount of luciferase in these cells is a direct representation of HCV replication. A Huh7 cell stably transfected with a luciferase gene controlled by an interferon response element (Huh7-ISRE-luc) was used to investigate effects of tofacitinib on IFN-α signal transduction. Results: In Huh7-ISRE-luc cells, tofacitinib inhibited IFN-α stimulated gene expression in a dose dependent manner. The highest dose of tofacitinib (1000 ng/ml) completely inhibited IFN-α stimulated gene expression and 100 ng/ml tofacitinib reduced IFN-α activity by 50%. With 10 U/ml IFN-α a complete inhibition of HCV replication was observed. This IFN-α mediated inhibition of HCV was completely abrogated by tofacitinib in a dose dependent manner.
Conclusion: Although tofacitinib was developed as a specific inhibitor of JAK3, with a reported 100-fold less potency for JAK1, we found that tofacitinib effectively inhibits IFN-α regulated gene expression, and interferes with IFN-α mediated inhibition of HCV replication. This observation explains the higher incidence of viral infections found in patients that are treated with tofacitinib.

Functional consequences of a novel IL-10 receptor alpha mutation on innate and adaptive immunity in early-onset inflammatory bowel disease

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Inflammatory bowel disease (IBD) is driven by aberrant T-cell responses to intestinal microbiota. Although interleukin-10 (IL-10) is known to be crucial for maintaining intestinal immune homeostasis, its mechanisms of action in the human intestine are not well studied. Here, we describe a now 10-year old IBD patient with a novel homozygous frame shift mutation in the IL-10 receptor alpha chain, who developed severe early-onset colitis and fistulising perianal disease in the first months of life. In vitro studies showed that IL-10 suppression of lipopolysaccharide (LPS)-mediated TNFα production was defective in PBMCs. Additionally, deficient STAT3 phosphorylation after IL-10 stimulation confirmed the impaired IL-10-mediated signalling in patient PBMCs. Despite normal co-stimulatory molecule expression, monocyte-derived dendritic cells released enhanced amounts of TNFα and IL-6 upon LPS stimulation. During treatment, normal frequencies of Foxp3+ regulatory T cells, T helper 1 (Th1) and Th17 cells were found in patient peripheral blood. However, IL-10 failed to control IFNγ and IL-17 production by activated CD4+ T cells in vitro. In agreement, lesional intestinal tissue taken at onset of disease contained high numbers of IL-17+ and Tbet+ (Th1) cells. Disease remission is currently achieved with thalidomide, intravenous immunoglobulin (IVIG) and colchicine. Interestingly, in vitro studies showed that IVIG efficiently suppressed anti-CD3-driven IL-17 and IFNγ release while thalidomide inhibited LPS-mediated TNF production by PBMCs.

Taken together; our study describes the functional consequences of a novel IL-10 receptor mutation and reveals that IL-10 controls both antigen presenting cells and effector T cells in human intestinal immune responses.

First multi-ethnic genetic analyses in inflammatory bowel disease show transferability of loci and population specific variants associated in non-Caucasian populations

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Genome wide association studies (GWAS) have been extremely succesful in inflammatory bowel diseases (IBD), uncovering 163 genetic risk loci. There has been a huge bias towards the Caucasian population in genetic studies, only 4% of all GWAS were performed in non-Caucasian populations. Due to evolutionary distinct development these populations have a different genomic structure and possibly different disease associated variants or genes. We can also use this to narrow down the association signal and identify causal genes within the associated loci by trans-ethnic finemapping. This study focuses on two unique cohorts from the Punjabi region in north India and from Iran. We used a custom-made genotyping platform (Immunochip), containing 200,000 single nucleotide polymorphisms (SNPs), densely covering loci associated with autoimmune diseases, including IBD to genotype our two unique non-CEU IBD cohorts. The north Indian cohort consisted of 868 ulcerative colitis and 905 matched controls. The Iranian cohort holds 594 IBD cases and 686 matched controls. We performed principal component analysis to investigate population structure within and between cohorts. As a first step in this project we performed basic association analyses per ethnicity by doing logistic regression analysis.PCA analyses showed that both the north Indian and Iranian cohorts cluster separately between European and East Asian populations as expected. We were able to replicate nine IBD-loci in the north Indian cohort, including the HLA, REL and CARD9 loci. Furthermore we found a suggestive novel association ($p < 10^{-5}$) for a locus harbouring IL12RB1, which is part the IL23 receptor. In the Iranian cohort we were able to replicate 3 loci, the HLA, TXK and IRF1 loci.

Concluding, in this first analysis we show the transferability of multiple IBD loci in a north Indian and an Iranian cohort. In addition to these findings, we are currently perfoming basic association analyses in another independent set of ~3,000 East Asian IBD cases and ~3000 matched controls from Japan, Korea and Hong Kong China. We will compare our results with those generated in ~75,000 Caucasian cases and controls. Next we will perform a meta-analysis of all non-Caucasian samples to pinpoint the exact position of the association signal and use the different genomic structures in these populations to finemap the loci and identify causal genes and variants.

Low molecular weight protein tyrosine phosphatase (LMW-PTP) is upregulated in primary colorectal cancer and affects cancer signaling pathways

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Background and aim: Cancer cell functions are tightly regulated by protein phosphorylation and dephosphorylation. Enhanced kinase activation and phosphorylation is often observed in colorectal cancer (CRC). Whereas kinases are seen as potential oncogenes, dephosphorylation of proteins by phosphatases is commonly assumed to be tumor suppressive. However, some phosphatases may also stimulate tumor growth and invasion. One of these is low molecular weight protein tyrosine phosphatase (LMW-PTP), overexpression of which in cell lines is sufficient for cellular transformation. The aim of this study was to investigate the expression levels of LMW-PTP in primary CRC specimens, and elucidate its role and signaling targets in CRC cells. Methods: LMW-PTP expression was analysed on microsections from biopsies of low grade dysplasia (LGD; n=9), high grade dysplasia (HGD; n=7), and adenocarcinoma (AC; n=12) by immunohistochemistry. Normal colon tissue (n=2), active ulcerative colitis (n=6) served as controls. This staining was subsequently performed on a tissue microarray (TMA) of 72 patients with colorectal adenoma (N=47) and/or carcinoma (N=164) and their corresponding normal tissue (N=63). To investigate downstream targets of LMW-PTP, we manipulated the LMW-PTP expression in vitro by lentiviral transduction of HCT116 and Caco-2 cells with siRNA against LMW-PTP. Results: In our initial screen LMW-PTP expression in intestinal epithelial cells (IEC) was limited to 9% of IEC in non-cancerous tissues. In contrast, expression of LMW-PTP significantly increased with subsequent levels of dysplasia (42%, 80% and 100% positive IEC in LGD, HGD and AC respectively). Staining of the TMA confirmed these observations: the mean % positive IEC was 27±3% in normal tissues, 64±4% in adenoma and 90±3% in carcinoma ($p<0.001$). There was a significant difference between different cancer-stages within patients (N=15, paired testing; $p<0.001$), however, Dukes stage or patient survival did not correlate with LMW-PTP expression. Knocking down LMW-PTP in CRC cells reduced phosphorylation of the EGF-receptor and β-catenin in vitro by approximately 50%.
Conclusion: LMW-PTP expression is drastically upregulated in epithelial dysplasia and CRC. During transformation of IECs, LMW-PTP expression increases, suggesting a role for LMW-PTP in the pathogenesis of CRC. As LMW-PTP knockdown decreases EGFR and β-catenin phosphorylation, overexpression of LMW-PTP in CRC samples may contribute to the enhanced EGF and β-catenin signaling, known to play a role in CRC development. In conclusion, LMW-PTP is overexpressed in CRC, may function as an oncogene, and represent a compelling target for future therapy.

Hyperactivation of the endoglin/TGF-β pathway plays a role in CRC invasion and metastasis

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The involvement of the tumor microenvironment in colorectal cancer (CRC) progression is becoming more and more clear. Especially the interaction between epithelial tumor cells and cancer-associated fibroblasts (CAFs) seems to be important. In this study we evaluated how epithelial cancer cells functionally interact with CAFs, focusing on the cancer progression-associated transforming growth factor-β (TGF-β) pathway. Our results show strong activation of the TGF-β pathway in the CAFs of 100 CRC patients. Activation of this pathway in epithelial cancer cells was associated with decreased patient survival. Next, we evaluated the interaction between epithelial tumor cells and CAFs in vitro. Our data show that primary CAFs are responsive to TGF-β by enhanced secretion of invasion-related proteases, like matrix metalloproteases (MMPs). The interaction with epithelial cancer cells hyperactivated the TGF-β pathway in these CAFs. Co-culture with epithelial tumor cell derived medium increased and prolonged Smad phosphorylation (downstream in signaling cascade), MMP expression and TGF-β secretion. To further evaluate this pathway we analyzed the expression of the TGF-β co-receptor endoglin. In addition to being present on endothelial cells, endoglin was also highly expressed by CAFs, specifically at invasive areas in human CRC tissue samples. CAFs from CRC expressed high levels of endoglin in vitro. Additional experiments showed that endoglin plays an important role in determining the migratory capacity of CAFs in vitro. This observation is further strengthened by the use of a neutralizing antibody against endoglin, which inhibits migration of CAFs in 3-dimensional invasion models. Moreover, preliminary data from an in vivo experiment in a breast cancer model suggest an important role for endoglin during cancer progression. These data under the importance of the endoglin/TGF-β pathway in the interaction between epithelial cancer cells and CAFS, and its role in CRC progression and metastasis.

Loss of Bone Morphogenetic Protein Receptor IA predicts poor survival in patients with pancreatic cancer and is responsible for invasiveness and proliferation of cancer cells

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Introduction: The expression of SMAD4, the central component of Transforming Growth Factor beta (TGF-β) and Bone Morphogenic Protein (BMP) signalling pathways, is lost in 50% of the pancreatic cancers and is associated with a poor survival. Although the TGF-β pathway has been extensively studied and characterized in pancreatic cancer, very limited data are available about BMP signaling, a well-known tumour suppressor pathway. BMP signalling can be lost not only at the level of SMAD4 but also at the level of BMPReceptors (BMPR) as has been described in colorectal cancer. We therefore set out to investigate the role of BMP signalling in pancreatic cancer by performing analysis of BMP signalling components expression, subsequently correlating those with the clinical outcome of patients, and by manipulating the activity of BMP signalling in vitro. Methods: We performed an immunohistochemical analysis of the expression BMPReceptors and SMADs in a tissue microarray of 41 patients with pancreatic ductal adenocarcinoma (PDAC) and correlated this to patients' survival. We also compared the expression levels of these components in 51 primary pancreatic tumours with 17 metastases. shRNA against SMAD4 and a plasmid encoding SMAD4 was used to investigate the effect of SMAD4 loss in vitro. The BMPReceptor expression was manipulated using siRNA against in a panel of pancreatic cancer cell lines and effects were analyzed using proliferation and invasion assays. Results: Loss of SMAD4 in patients with PDAC is associated with significantly worse survival (p=0.025). Moreover, SMAD4 loss is more frequent in the metastases samples compared to the primary tumours (65% vs. 47%). Loss of SMAD4 induces transformation of cancer cells into more aggressive mesenchymal cell type with properties of the cancer stem cells, which proliferate slower and are more resistant to chemotherapy. Importantly, in a group of patients with intact positive SMAD4 expression loss of BMPR1a correlates significantly with a poor prognosis (p=0.02). Activation of BMP signalling in SMAD4 positive cancer cells leads to reduced proliferation, migration and invasion. The importance of BMP Receptor loss is confirmed by showing an increase in proliferation and invasion of pancreatic cancer cells after siRNA mediated knockdown of the BMPReceptors or opposite effect after restitution of BMPR.
Conclusion: Loss of BMPR1a and SMAD4 results in poor survival in patients with pancreatic cancers. Inactivation of the BMP pathway increases aggressive tumourigenic properties of pancreatic cancer cells, while activation of the BMP pathway in pancreatic cancer reduces invasive metastatic phenotype of cells. Our data suggest that the BMP pathway can be an attractive target for future therapeutic interventions.

Abrogation of tumor-associated immunosuppression by targeting tumor-infiltrating regulatory T-cells restores impaired T-cell responses in patients with liver cancer

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Growing evidence shows that regulatory T cells (Treg) hamper the development of effective anti-tumor immunity in patients with cancer, and present a major hurdle for tumor immunotherapy. We recently described accumulation of activated CD4+FoxP3+ Treg at the tumor site in patients with liver cancer (hepatocellular carcinoma or metastasized colorectal cancer). These tumor-infiltrating Treg are potent suppressors of the local anti-tumor T cell responses, and they are characterized by the expression of higher levels of CTLA-4 and GITR than Treg in normal liver tissue or blood from the same patients. Now we show that treatment with a soluble form of the natural ligand of GITR (GITRL), or with blocking antibodies to CTLA-4, reduces the suppression mediated by tumor-derived Treg in ex vivo assays, restoring proliferation and cytokine production by effector T cells. These results suggest that modulation of intra-tumoral Treg function by either GITR-ligation or blocking CTLA-4 may be a promising strategy for alleviation of intra-tumoral immunosuppression, thereby contributing to immunotherapy induced effective immune responses in liver cancer patients.

Perioperative selective decontamination of the digestive tract (SDD) decreases tumor cell adhesion in the liver post-operatively

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Surgical resection of the primary tumor provides the best chance of cure for patients with colorectal cancer (CRC). However, we previously demonstrated that abdominal surgery paradoxically led to enhanced adhesion of tumor cells in the liver vasculature, which can grow out into metastases. Furthermore, previous studies demonstrated that patients with anastomotic leakage after resection of the tumor had poorer long term survival. Moreover, we showed in a rat model that colectomy resulted in bacterial translocation, suggesting that bacterial contamination due to resection of primary CRC may have a negative impact on metastases development and long-term patient outcome.Therefore, the aim of this study was to investigate the impact of selective decontamination of the digestive tract (SDD) prior to colectomy on surgery-induced liver metastases outgrowth. SDD is an infection prophylaxis regimen consisting of polymyxine B sulfate, tobramycin, and amphotericin B to eradicate potential pathogenic aerobic gram-negative bacteria from the gastrointestinal tract, while leaving the normal anaerobobic flora undisturbed. The study was performed in a rat colon carcinoma model and SDD prophylaxis was given 5 days pre-operative in drinking water. Rectal swabs were taken to evaluate the effect of SDD on gram-negative bacterial load. Rats underwent a sham operation (laparotomy), partial colectomy, or anaesthesia alone, after which fluorescently-labeled tumor cells were injected into the portal circulation. All rats were sacrificed 2 hours post-operatively, liver samples were taken, and the number of adhered tumor cells was determined with fluorescence microscopy. Pre-operative SDD decreased the amount of gram negative bacterial load in the gastrointestinal tract. Endothelial continuity was investigated by analysis of the tight junction molecule Claudin-5. Liver vessel integrity in rats with SDD intake, was less disrupted compared to the rats without SDD. This indicates that SDD prophylaxis prevents loss of cell-cell contact after abdominal surgery, preventing exposure of the extracellular matrix with adhesion molecules. SDD intake did not decrease the number of adhered tumor cells in the liver in the control and laparotomy groups. Importantly, tumor cell adhesion was significantly decreased in rats that underwent a partial colectomy after SDD intake.
In conclusion, our results support that exposure to bacterial products after colectomy contributes to development of surgery-induced liver metastases, which can be reduced by a SDD antibiotic regime pre-operatively. We therefore anticipate that SDD of patients undergoing CRC resection will significantly improve their prognosis.

Aurora kinase A (AURKA) expression in colorectal cancer liver metastasis is associated with poor prognosis

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Approximately half of all colorectal cancer (CRC) patients die as a consequence of metastases. Hemihepatectomy, occasionally in combination with radiofrequency ablation (RFA), is the only curative treatment available for patients with CRC liver metastases (CRCLM). Patient eligibility is based on established prognostic clinicopathological variables. Futile surgery has been reduced by patient selection using ^{18}FDG positron emission tomography (PET) molecular imaging. However, 70% of patients still die within 5 years, indicating that better prognostic markers are needed. We recently demonstrated that aurora kinase A (AURKA) protein expression is associated with 20q amplicon-driven adenoma-to-carcinoma progression and disease recurrence in stage III CRC patients. This study aimed to investigate the prognostic value of AURKA protein expression in liver metastases of CRC patients who underwent hemihepatectomy with curative intent.Tissue microarrays (TMAs) were generated from formalin-fixed paraffin-embedded CRCLM of 507 patients who underwent hemihepatectomy in the Netherlands between 1990 and 2010. Matched primary CRC tissue was collected of 234 patients. TMAs were stained for AURKA by immunohistochemistry, nuclear expression of neoplastic cells was assessed and subsequently associated with patient overall survival (OS) in a training and validation set.High AURKA expression in CRCLM was associated with poor OS (HRR 1.68; 95%CI 1.04-2.73; P=.03), also after correction for established prognostic clinicopathological variables (HRR 1.77; 95%CI 1.02-3.08; P=.04). Furthermore, AURKA expression in liver metastases was correlated to its expression in corresponding primary CRC (P=.0002).To conclude, AURKA protein expression is a molecular biomarker with prognostic value for CRC patients with liver metastasis.

Right versus left-sided ischemic colitis: different presentation and worse prognosis; a study in a cohort of 474 patients

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Ischemic colitis runs mostly a benign course but can also lead to severe symptoms and even death. Based on recent studies, a more insidious disease and poor outcome seems associated with right colon involvement. We aimed to establish the difference in presentation, risk factors and outcome between right-sided and left-sided ischemic colitis. A retrospective study was undertaken in two large regional medical centers. Patients that presented with ischemic colitis between January 2000 and December 2011 were identified by a search in the hospital information system, endoscopy and pathology database. We included patients with 1)biopsy proven or compatible ischemic colitis and/or 2) with endoscopically and/or peroperative findings that were in combination with clinical presentation compatible with ischemic colitis. Basic patient characteristics, findings at presentation, radiology reports concerning main splanchnic stenoses, treatment and outcome were recorded. A distinction was made between right-sided and left-sided ischemic colitis (RIC, lesions proximal to the hepatic flexure; LIC, lesions distal of the hepatic flexure).474 patients with ischemic colitis were included, mean age 70 years (SD 12.6), 49.8% female. Diagnosis was made by endoscopy (79.5%) and laparotomy (20.5%). 67.1% had biopsy proven ischemic colitis and 28.5% biopsy compatible ischemic colitis. RIC was found in 30.6% and LIC in 69.4%. The cause of ischemic colitis was more often idiopathic with left-sided localization (37.7% vs. 15.2; p<0.001). In RIC we found more main splanchnic artery stenoses compared to LIC (35.2% vs. 17.6%; p<0.001). The prevalence of low-flow states however did not differ in both groups; 31% in LIC and 33.1% in RIC (p=0.651). Other reported causes were preceding surgery for example aortic surgery, bacterial pathogens, and secondary to other colonic pathology; for these groups we found no significant differences between RIC and LIC. Abdominal pain was present in both RIC and LIC (75.6% vs. 79.4%, p=0.4). Rectal bleeding was remarkably predominant in LIC (86.9% vs. 46.5%; p<0.001). In RIC more nausea/vomiting (60.4% vs. 45.7%; p=0.004), weight loss (51.1% vs. 25.2%; p<0.002), ileus (33.3% vs. 12.7%; p<0.001) and peritoneal signs (26.3% vs. 4.6%; p<0.001) were observed. The outcome of RIC was worse for hospital stay (median 14 vs. 8 days; p<0.001), need for surgery (61.4% vs. 23.7%; p<0.001) and in-hospital mortality (31% vs. 16.1%; p<0.001).

In conclusion, RIC and LIC are different disease entities. Right-sided ischemic colitis has a different presentation, more underlying main splanchnic artery stenoses, and a higher in-hospital mortality.

Follow-up endoscopy for benign appearing gastric ulcers has no additive value in detecting malignancy

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Background and Aims: Current guidelines recommend follow-up gastroscopy of all gastric ulcers to ensure healing, due to the potential for malignancy. This retrospective study aimed to determine the diagnostic efficiency of endoscopic surveillance for gastric ulcers with a benign appearance and negative histology at first endoscopy.Methods: All cases of gastric ulcers diagnosed at our hospital between September 2005 and November 2011 were reviewed. The cases were selected by using ENDOBASE, searching on the terms 'gastric ulcer' and 'gastric tumour'. Noted was whether the endoscopic report contained an explicit suspicion of malignancy. Three potential malignant characteristics of the ulcer(s) i.e. a dirty base, elevated or irregular border of the ulcer were also noted. Appearance as described in the report was evaluated in combination with histology of the first endoscopy. Results: During the 6 year period 341 cases with a gastric ulcer were diagnosed; 191 (56%) benign ulcers, 107 (31%) malignant ulcers and 43 (13%) ulcers were unclassified (histology was negative and the patient either died (20) within a year or was lost to follow up (23)). The mean age of the population was 71 years. In 215 patients the ulcer was classified as benign appearing at the first endoscopy. However, in 5 of these patients the ulcer was malignant. In all of these 5 neoplasms the index gastroscopy revealed a non-benign histology. Therefore, the sensitivity of suspicion in combination with histology at the first endoscopy is 100%. In 125 patients the ulcer (37%) was explicitly labeled as potentially malignant in the report of the first endoscopy. Of these ulcers, 102 (82%) were indeed malignant as confirmed by histology, 17 (14%) were benign and 6 (5%) were unclassified. The sensitivity of the 3 potential characterisics were as follows: dirty base 87%, elevated border 74%, irregular border 82%. Their specificity is 89%, 96% and 95%, respectively.In total 567 gastroscopies were performed, of which 387 were follow-up endoscopies. By not monitoring ulcers considered both benign in appearance and in histology, 167 gastroscopies would not have been performed, resulting in a dec of 43% of follow-up endoscopies.
Conclusion: Surveillance endoscopy of gastric ulcers considered benign by appearance and with benign histology has no additive value in detecting unsuspected malignancy. Abandoning the current guidelines in case of these ulcers would also save a lot of distress to the patients and would reduce hospital costs.

The impact of sexual abuse in the Gastroenterology practice A multicentered cross-sectional study among colonoscopy patients

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Estimates of the prevalence rates of sexual abuse (SA) within the general population range from 13.5% to 27% in women and from 2.5% to 16% in men. SA has been linked to strong and persistent effects on GI health, particularly to functional GI disorders; furthermore it is linked to pelvic floor dysfunction (PFD). Inquiring into SA can therefore be of importance in patients presenting with gastrointestinal complaints. In particular, before performing a colonoscopy it may be relevant to be informed about SA, since colonoscopic procedures can provoke intense emotional reactions in those patients. With this study we aimed to find the prevalence of SA and pelvic floor related complaints in a cross-sectional population of patients which recently underwent colonoscopy. In addition, we aimed to obtain patients' vision regarding doctors' inquiry about delicate subjects such as SA and pelvic floor complaints. With a distress thermometer, differences in experience between patients with and without SA during the colonoscopy were measured. An anonymous questionnaire was sent to 1171 patients (from 3 different centers) that underwent colonoscopy and had stated their willingness to participate in the study. The questionnaire was completed by 782 patients (response rate 66.8%). The prevalence of SA was 3.9% in male- and 9.3% in female patients. Sexual abused patients reported significantly more distress during colonoscopy on a 0 to 10 VAS-scale. Mean ratings were 8.4 in patients with a SA experience versus 3.9 in patient that did not report SA ($p < 0.001$). To the majority of respondents (74.2%) a question about SA in an intake questionnaire at first consultation with the gastroenterologist would not appear strange. Furthermore, patients with a SA history reported more complaints of micturition ($p<0.001$) and sexual dysfunction ($p<0.001$); and more often had complaints in two, or all three of the pelvic floor domains (complaints of micturition, defecation and/or sexual function; $p=<0.001$ resp. $p=<0.001$).
Conclusion: SA is very prevalent in patients presenting to the gastroenterologist and these patients experience significant more distress during the colonoscopic procedure. An intake questionnaire could be a useful tool to obtain information about SA and could guide more individualized patient care in the gastroenterology practice.

Long-term quality of life and sexual function after ileal pouch-anal anastomosis in adults with ulcerative colitis or familial adenomatous polyposis

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Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the preferred surgical intervention in therapy-resistant ulcerative colitis (UC) or familial adenomatous polyposis (FAP). Short-term advantages of IPAA such as body image and cosmesis have been well investigated. Data regarding long-term quality of life (QoL) and sexual dysfunction are scarce, although these factors are important for patient satisfaction after extensive surgery. We assessed QoL and sexual function in adults more than one year after IPAA. Seventy-one IPAA patients operated between January 1985 and December 2009 because of UC or FAP were invited. QoL was scored using the Short-Form 36 (SF-36) health survey. Eight subscales of SF-36 (physical functioning, role limitations due to physical health (role-physical), role limitations due to emotional health (role-emotional), vitality, mental health, social functioning, pain, general health) were used to aggregate the Physical (PCS) and Mental (MCS) Component Summary scores. Findings were compared to historical data from a Dutch adult population and to UC patients in the population-based IBD-SL cohort. Gender-specific sexual dysfunction was assessed using the International Index of Erectile Dysfunction (IIEF <43 (range 5-75)) or the Female Sexual Function Index (FSFI <26 (range 2-36)). Medical records were reviewed for patient characteristics. Fifty-six patients (53 UC, 3 FAP) participated in this study (response rate 78.9%). Mean (SD) age was 47.4 (11.8) years and mean post-surgery follow-up was 10.8 (6.4) years. Open surgical procedures were performed in 43 patients (78.2%). Twenty-one (42.9%) patients were given a protective ileostomy. The mean (SD) QoL scores, 48.4 (9.7) for PCS and 50.1 (10.1) for MCS, respectively, did not differ significantly from the scores of UC patients or the Dutch population. IPAA patients scored lower on general health than the Dutch population (57.8 vs. 70.7, P<0.001) and had less pain than UC patients (80.6 vs. 72.4, P=0.009). Furthermore, sexual dysfunction was common after IPAA, with prevalence rates of 50.0% among women and 43.5% among men.

Conclusions: Long-term QoL in IPAA patients is comparable to other UC patients and the Dutch general population, judging from the overall SF-36 scores. Sexual dysfunction is not scored in most tools assessing quality of life. The prevalence of sexual dysfunction was high in both sexes. Data on long-term sexual functioning after IPAA are limited. Since IPAA is frequently performed in young people, further research to improve the treatment strategies is necessary to decrease the risk for sexual dysfunction in the future.

Towards non-invasive diagnosis and monitoring of celiac disease: a prospective study to the usefulness of I-FABP

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A non-invasive marker for evaluation of mucosal damage in celiac disease (CD) patients at diagnosis, on a gluten-free diet (GFD) and during gluten challenge (GC) would be useful in clinical practice and research purposes. Our retrospective studies showed the differentiating potential of intestinal fatty acid binding protein (I-FABP), a sensitive marker for enterocyte damage, in patients with positive CD autoantibodies (IgA-tTG) with and without celiac disease (CD). This study evaluates the usefulness of plasma I-FABP in diagnosing CD in children with positive IgA-tTG titers, for monitoring disease activity in patients on a GFD and for evaluating disease activity in adults during GC. In a prospective, multicentre study all children presenting with positive CD autoantibodies between 2010 and 2012 were included. Patients fulfilling the ESPGHAN criteria for CD (villous atrophy and/or IgA-tTG >10x cut-off level) started a GFD. Plasma I-FABP and IgA-tTG were determined at presentation and after 3, 6, 12 and 26 weeks of GFD in 61 children. The control group consisted of 90 children with a clinical suspicion of CD but normal CD autoantibody titers. Moreover, 20 adult CD patients in clinical remission underwent a two-week gluten challenge. Study visits occurred at -14, 0, 3, 14 and 28 days after starting GC. Plasma I-FABP levels were significantly elevated at presentation in children with CD (775 pg/ml, IQR 438-1354 pg/ml) compared to the control group (207 pg/ml, IQR 123-288 pg/ml, $p<0.001$) and correlated with Marsh grade ($R=0.37$, $p<0.05$, $n=61$). The positive and negative predictive values of I-FABP for CD were 95.2% and 77.0%, respectively. I-FABP levels decreased significantly to 444 (n=18), 378 (n=57), 258 (n=50) en 221 (n=52) pg/ml after 3, 6, 12 and 26 weeks GFD, respectively. Median IgA-tTG titers did not normalize in 26 months of GFD and recovery was significantly slower. Adult CD patients on a GC showed a significant increase in I-FABP levels from base to day 14, and a decrease after withdrawal of gluten, while autoantibody titers increased slightly from base to day 14 but markedly by day 28, when gluten was already eliminated. I-FABP levels correlated significantly with intraepithelial lymphocyte count, while no significant correlation between I-FABP levels, autoantibodies, villous atrophy or symptoms was found.

Conclusion: An elevated I-FABP level confirms the diagnosis of CD in 91.7% of all children with positive autoantibody titers. I-FABP analysis could reduce the need for a duodenal biopsy with almost 75%. I-FABP levels increase and decrease much faster after gluten introduction and gluten withdrawal in CD patients, respectively, as compared to the currently used autoantibodies. Plasma I-FABP is a reliable additional marker for CD diagnosis and might provide insight in intestinal damage in CD children on a GFD and adults on a GC.

Differential IL-13 production by lamina propria derived leucocytes in uncomplicated and refractory celiac disease

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Celiac disease (CD) is a gluten-sensitive autoimmune enteropathy with a prevalence of ca. one percent. A small fraction of CD patients does not recover despite strict exclusion of gluten from the diet. After exclusion of other enteropathies refractory celiac disease (RCD) is diagnosed in these patients. While in CD the immunopathology has been extensively studied, less is known in RCD where the inflammation is not gluten-driven. In order to explore potential mediators of RCD we measured IL-5, IL-10, IL-13, IL-17, INFγ and TNFα. Furthermore, we investigated whether the well-investigated cytokine IL-15, could be used as a diagnostic marker for RCD-II. Consecutive CD patients were divided into active CD (ACD), gluten-free diet (GFD) and RCD type II (RCD-II). ACD patients were recently diagnosed untreated CD patients, GFD patients were CD patients that recovered histologically and serologically on a gluten-free diet and RCD-II patients were defined by the presence of 20% or more aberrant intra-epithelial lymphocytes (IEL) (surface CD3-negative, but intracellular CD3-positive). The cytokines IL-5, IL-10, IL-13, IL-17a, INFγ and TNFα were measured in supernatants of 24h-cultured lamina propria CD45+ leucocytes (LPL) and IEL stimulated with PMA, ionomycin and/or LPS. IL-15 was measured from cell lysates of unstimulated LPL and IEL by ELISA and on live cells by FACS. IL-13 production was significantly higher in RCD-II patients as compared to ACD patients ($p=0.03$). IL-13 levels were also significantly increased in GFD patients compared to ACD patients ($p=0.004$). To a lesser extent this also was true for TNFα, which was significantly increased in GFD patients compared to ACD patients ($p=0.02$); in RCD-II TNFα levels were also higher than in ACD but the difference was not significant. A strong and significant correlation of TNFa and IL-13 was found ($r=0.67$, $p=0.001$). IL-15, thought to originate mainly from epithelial cells, was found in relatively large amounts associated with intra-epithelial lymphocytes. These data indicate that IL-13 and probably TNFα are differentially expressed in ACD and RCD. IL-15 may locate to T-lymphocytes rather than to epithelial cells, but is not specific enough for RCD-II to serve as a diagnostic marker.

Gastroenterologist's gut feeling versus Blatchford risk score to predict the need for a medical intervention in suspected upper GI bleeding: results of a multicenter prospective cohort study

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The Blatchford score (BS) has been developed to estimate the need for an intervention in patients with upper GI bleeding. The implementation rate of this risk score in clinical practice is low however, which is in part due to the belief that the score does not add to clinical judgement (gut feeling). Therefore we aimed to compare the gut feeling of a gastroenterologist with the BS in predicting the need for a medical intervention such as therapeutic endoscopy or blood transfusion in patients presenting with suspected upper GI bleeding. We prospectively evaluated the gut feeling of consultant gastroenterologists by asking them to predict the need for a therapeutic intervention or blood transfusion in patients presenting in the hospital with suspected upper GI bleeding. Gastroenterologists could choose between low (<1%), medium (1-10%) or high risk (>10%) for the need for a medical intervention. The gut feeling was compared with a risk score for predicting the need for an intervention (i.e. the BS). We included 926 patients with suspected upper GI bleeding of which 611 patients (66%) received a medical intervention. Based on the gut feeling of the gastroenterologists 634 patients were classified as medium (between 1-10%: 31.2%) or high risk (>10%: 37.3%) for the need for an intervention. Out of these 634 patients with a predicted risk for an intervention > 1%, 79.5% needed an intervention. Out of 796 patients with a BS > 2 points (> 1% predicted risk for an intervention), 74.1% needed an intervention. The gut feeling for the need of an intervention, classifying patients in medium and high risk, was associated with the need for an intervention (odds ratio [OR] of 3.6, 95% confidence interval [CI] 2.6-5.1 for medium risk patients and OR 16.0 95%CI 10.3-24.7 for high risk patients). Also, after correcting for the BS, the gut feeling was still independently associated with the outcome. However, comparing the area under the curve of the gut feeling with the BS, the BS had a better predictive power than the gut feeling of the gastroenterologists (AUC 0.85 versus 0.77, respectively). Combining the gut feeling with the BS improved the predictive power to 0.87.

Conclusion: The gut feeling of gastroenterologists was an independent predictor for the need for a medical intervention in patients presenting with suspected upper GI bleeding. While the predictive power of the BS was better than the gut feeling, the combination of both the gut feeling and BS yielded the best predictive power, demonstrating that a gastroenterologist's gut feeling should also play a role in the decision to perform an emergency upper endoscopy.

The simplified Forrest classification for the prediction of rebleeding of peptic ulcer bleeds: results of a prospective cohort study

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In 1974, the Forrest classification was introduced to estimate the risk for rebleeding in peptic ulcer bleeds, and this classification has been adopted in many clinical guidelines. However, the etiology and treatment of peptic ulcer bleeds has changed considerably over the last decades and with this the predictive power of the Forrest classification may also have changed. The aim of this study was to assess the value of the Forrest classification in predicting rebleeding of peptic ulcer bleeds. We prospectively collected data from patients with symptoms suggestive of upper gastrointestinal bleeding (UGIB) presenting to the emergency room of 8 participating hospitals. All peptic ulcer bleeds were categorized according to the Forrest classification : Ia Spurting hemorrhages, Ib Oozing hemorrhages, IIa Visible vessel, IIb Adherent clot, IIc Hematin on ulcer base, III Clean base ulcer. The primary outcome was rebleeding rate within 30 days. Out of 926 patients presenting with suspected UGIB, 431 peptic ulcer bleeds were identified (54% gastric ulcers,46% duodenal ulcers). The Forrest classification was recorded in 397 cases (92%). In total 74 patients (18.6%) developed a rebleeding. Rebleeding rates were highest for Forrest Ia peptic ulcer bleeds (58.8%), but comparable for Forrest Ib, IIa and IIb ulcers (26.0%, 21.2% and 31.2% respectively). Forrest IIc and III showed lower rates for rebleeding (15.6% and 6.5% respectively). We found that patients with Forrest Ia ulcers are at very high risk (Odds ratio [OR] 17.0; 95% Confidence Interval [CI] 5.3-54.3) for rebleeding. And a stepwise increased rebleeding risk of patients with Forrest Ib, IIa, IIb and IIc (OR 4.2; 95% [CI] 1.8-9.6 for Forrest Ib, OR 3.2; 95% CI 1.4-7.3 for Forrest IIa, OR 5.4; 95% [CI] 2.0-14.5 for Forrest IIb and OR 1.6 95% [CI] 0.6-4.4 for Forrest IIc) compared to Forrest III ulcers. The association between the Forrest classification and rebleeding was higher in gastric ulcers compared to duodenal ulcers.
Conclusion: The Forrest classification is still a clinically useful tool to identify patients who are at increased risk of rebleeding, with the highest prognostic significance for gastric ulcers. Based on our results, we suggest to simplify the Forrest classification into three categories, with patients with a Forrest III ulcer being classified at a low risk, patients with oozing hemorrhages or ulcers with stigmata of recent hemorrhage (Forrest Ib-IIc Forrest) at an increased risk and patients with spurting hemorrhages (Forrest Ia) at a high risk of rebleeding.

Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily clinical practice?

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Two strategies for prevention of upper gastrointestinal (UGI) events for non-selective (ns)NSAID users are replacement of the nsNSAID by a cyclo-oxygenase-2-selective inhibitor (coxib) or coprescription of a gastroprotective agent (GPA). Most clinical trials did not show superiority for one preventive strategy over the other, however extrapolation of these results to clinical practice is limited due to selective inclusion of either high- or low-risk patients. Thus, which preventive strategy is superior in avoiding NSAID-related UGI events in daily clinical practice is still unknown.

The aim of this study was to identify the risk of UGI events with these preventive strategies in certain subgroups. A nested case-control study was conducted using three European primary care databases (United Kingdom, the Netherlands, Italy). We selected a cohort including all incident nsNSAID+GPA (≥ 80% adherence to coprescribed GPA;≥ 80% adh) and coxib users (without GPA use) aged ≥50 years. Cases with an UGI event (i.e. symptomatic UGI ulcer or bleeding (UGIB)) were matched to cohort members without an UGI event on age, sex, number of UGI risk factors (i.e. UGI event history, age ≥65 years, concomitant use of anticoagulants, antiplatelets, or glucocorticoids) and calendar time. Odds ratios (ORs) with 95% CI were calculated using conditional logistic regression on data pooled on patientlevel, while adjusting for potential confounders, including NSAID dose and duration. Within the NSAID cohort (n=617,220), 398 UGI event (UK: 307, NL: 17 and IT: 74) and 225 UGIB (UK: 194, NL: 14 and IT: 225) cases were identified. The risk of UGI events was equal for coxib and nsNSAID+GPA (≥ 80% adh) users (OR: 1.0; 95%CI: 0.8-1.4) as was seen for UGIB (OR: 1.1; 95%CI: 0.8-1.7). In the subgroups, in concurrent glucocorticoid users the risk of UGI events was significantly elevated for nsNSAID+GPA (≥80% adh) compared to coxib use (OR: 9.0; 95%CI: 1.6-50.5). In non-antiplatelet users, a non-significant increased risk both for UGI events and UGIB was observed for nsNSAID+GPA (≥80% adh), whereas coxibs users had a non-significant increased risk with concurrent antiplatelet use.

In conclusion, the risk of UGI events and UGI bleeding was similar in nsNSAID+GPA (≥80% adh) and coxib users. With concurrent antiplatelet use, coxib users are at increased risk of developing UGI events, whereas in patients concurrently using glucocorticoids a significant increased risk for UGI events for nsNSAID+GPA use was observed. Future studies on this topic are needed, as use of steroids is a risk factor that, according to guidelines, often will initiate GPA therapy in NSAID-treated patients.

Long-term outcome of treatment with temperature-controlled radiofrequency energy (SECCA) in patients with faecal incontinence

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Introduction: Controlled delivery of radio frequent energy (SECCA) has been suggested as treatment for faecal incontinence (FI). The supposed mechanism of action of SECCA is shrinkage and remodelling of the mechanical properties of the anorectum. Smooth muscle cell alteration mediated by heath shock protein and activation of interstitial cells of Cajal are alleged pathways which improve internal anal sphincter function and increase basal pressure, improving continence. Objective: To evaluate the short- and long-term efficacy of SECCA treatment for (FI). Materials and Methods: Between 2005 and 2010, 31 patients who failed conservative management for FI received SECCA at our outpatient clinic. FI was scored using the Vaizey scores (VS) of all available patients at baseline, 6 months, 1 yr, 3 yrs, 5 yrs and 7 yrs. Anal sonography and anal manometry was performed at 3 months and compared with baseline. Using decreases in VS patients were assessed as improved (≥ 50% drop), slightly improved (≥ 20-<50% drop) or not improved (<20%) when compared with the pre-treatment VS. Response to Secca was measured at 6 months as improved or slightly improved. Regarding long-term results, 7 respectively 10 patients were not yet available for 5 and 7 yr follow up. Results: All 31 patients, (mean age 61 yrs, 30 females) received Secca treatment. Mean length of FI was 10 yrs. Twenty-one patients (68%) had an anal sphincter defect; 12 external anal sphincter (EAS) defects (39%), 2 internal anal sphincter (IAS) defects (6%) and 7 (29%) IAS and EAS sphincter defects. At follow-up of 6 months, 1 yr, 3, 5 and 7 yrs, mean VS was 18 (SD 3), 14 (SD 4), 14 (SD 4), 14 (SD 4), 13 (SD 6) and 14 (SD 6) respectively, (P<001). At follow-up of 6 months, 1yr, 3, 5 and 7 yrs, 5/31, 3/31, 2/31, 2/23 and 2/13 patients were improved, 12/31, 10/31, 7/31, 4/23 and 2/13 were slightly improved and 14/31, 18/31, 22/31, 17/23 and 9/13 showed no improvement. In the (slightly) improved, mean VS stayed decreased up to 3 yrs (P<0,001), up to 5 yrs (P=0,002), up to 7 yrs (P=0, 06) and rectoanal inhibitory reflex (RAIR) increased (20 to 33 ml), P=0,003. One patient died due to metastatic melanoma. No predictive factors for success could be demonstrated.
Conclusion: SECCA is a safe, minimally invasive procedure for FI. Initial (slight) improvement of 55% after 6 months decreased to 30% after 3 years and remained constant up to 7 years. Besides a higher threshold for evoking RAIR, no improvement of anal pressures or anorectal function became apparent. Since other treatments for FI such as sacral nerve stimulation are encouraging, comparative studies investigating cost-efficiency are recommended.

Feacal incontinence, sexual complaints, and anorectal function in patients with a third degree anal sphincter rupture: long term follow-up

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Introduction and aim of the study: Anal incontinence (AI) affects activities of daily life and can have a devastating effect on the physical and emotional well being. The primary cause of AI in women is vaginal delivery. Its true prevalence is underestimated in most epidemiological studies, probably because women may feel unable to discuss the symptoms they experience and avoid seeking medical advice. With this study we aim to evaluate the long-term alteration of anorectal function in women after primary surgical repair of a third degree obstetrical anal sphincter injury (OASI) in relation to clinical outcome. Patients and methods: All women who suffered a third degree (OASI) between 1998 and 2008 in our hospital were sent for anorectal function evaluation (AFE) consisting of anal manometry and anal endosonography three months post partum. These women were invited to participate in the present study by sending them questionnaires regarding complaints of AI (Vaizey/Wexner), urine incontinence (UI) (ICIQ), sexual complaints using the female sexual function index (FSFI) and quality of life (QOL) (SF-36) and were asked to undergo additional AFE. Results: Sixty-six women underwent AFE. With an OASI follow-up time of 5.0 years (2,4-11, 4), 40 women (61%), mean age 37, 5, were available for follow up regarding complaints of AI and UI. Prevalence of AI was; 63% (flatus), 50% (liquid stool) and 20% (solid stool). Incontinence for urine was present in 48% of women. Of the 40 responding women, 32 (80%) also returned questionnaires regarding experienced sexual function and QOL. QOL was lower in women with larger OASI. Overall sexual function was diminished (total FSFI of 23) compared to the FSFI sexual dysfunction cut-off value of 26, 5. Compared to controls, all FSFI subscales were lowest in women with larger OASI, ($p<0,001$). Sixteen women (20%) underwent additional AFE; 10 had an external anal sphincter (EAS) defect and six had a defect of both the internal anal sphincter (IAS) and EAS. Maximal basal pressure (MBP) and maximal squeezing pressure (MSP) decreased most in women with combined EAS and IAS involvement, MBP: 39,mmHg to 25 mmHg, MSP: 53 mmHg to 40 mmHg, $p<0, 05$.
Conclusion: Women with a combined EAS and IAS defect had the lowest anal pressures, experienced lower QOL and had the most severe complaints. Special attention should be paid regarding prevention, proper OASI classification and suturing external and IAS in these women, since anorectal function will deteriorate the most and sexual dysfunction is more prominent.

Improvement of plasma parameters linked to nonalcoholic fatty liver disease after weight loss induced by proximal small intestinal exclusion by duodenal-jejunal bypass liner

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The rising prevalence of obesity is accompanied with an increase in people suffering from obesity-related comorbidities, such as type 2 diabetes (T2DM) and non-alcoholic fatty liver disease (NAFLD). While the early stage of NAFLD, hepatic steatosis, is considered benign, progression to nonalcoholic steatohepatitis and even liver failure often occurs. Bariatric surgery has been shown to improve obesity, T2DM, and NAFLD. However, traditional bariatric techniques are invasive. Recently, a non-surgical bariatric device, the duodenal-jejunal bypass liner (DJBL), has been developed. Previous studies with this device have revealed positive effects on obesity and T2DM. We here investigated the effect of DJBL treatment on plasma parameters that reflect NAFLD. Seventeen subjects with obesity and T2DM received the DJBL for 24 weeks. At base and at 3 and 6 months post-implantation of the DJBL, plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (γ-GT), albumin, caspase-cleaved cytokeratin-18 (CK-18), and liver fatty acid-binding protein (L-FABP) were determined. At baseline, patients had a BMI of 37.0±1.3kg/m^2. Mean plasma levels of AST, ALT, and γ-GT were elevated (AST: 35±4IU/L, ALT: 54±5IU/L, and γ-GT: 66±14IU/L, respectively). CK-18 and L-FABP concentrations were 214.4±35.6U/L and 29.3±2.6ng/mL respectively. Three months after DJBL placement, BMI had decreased to 33.6±1.2kg/m^2 ($p<0.05$). Plasma levels of AST, ALT, γ-GT, CK-18, and L-FABP had also decreased (AST: 28±3IU/L, ALT: 32±2IU/L, γ-GT: 44±7IU/L, CK-18: 140.6±16.3U/L, and L-FABP: 18.2±1.5ng/mL, $p<0.05$ for all except AST: p=ns). A further decrease of AST, ALT, and γ-GT was observed at 6 months post-DJBL-implantation (AST: 23±2IU/L, ALT: 28±2IU/L, and γ-GT: 35±5IU/L, $p<0.05$). At that time, mean BMI had decreased to 32.9±1.2kg/m^2 ($p<0.05$). No further change in CK-18 and L-FABP was observed (CK-18: 149.2±23.1U/L, L-FABP: 20.2±1.6ng/mL, p=ns), Plasma albumin levels of all patients were within the normal range at all time points. In conclusion, DJBL treatment improves established clinical plasma liver parameters. Additionally, a decrease in plasma levels of CK-18 and L-FABP reflecting decreased liver injury was observed. These data might indicate that proximal small intestinal exclusion by DJBL positively affects NAFLD in obese patients with T2DM.

A subgroup of achalasia patients with manometrically normal LES relaxation can be identified by measurements of esophagogastric junction distensibility

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Esophageal manometry is the gold standard for diagnosing achalasia. Typical findings are aperistalsis and incomplete relaxation of the LES (integrated relaxation pressure (IRP) >15 mmHg). However, in a subgroup of patients with typical symptoms of achalasia, stasis on barium esophagogram and aperistalsis on manometry, LES relaxation is not impaired. The aim of our study was to further characterize these patients using distensibility measurements of the esophagogastric junction (EGJ) and to study the effect of treatment. Consecutive patients with typical symptoms of achalasia, no abnormalities on upper endoscopy, significant stasis on barium esophagogram, aperistalsis but normal IRP were included. Distensibility of the EGJ was measured using impedance planimetry (EndoFLIP). Distensibility was defined as the minimal cross-sectional area of the EGJ divided by balloon pressure at volumes of 20, 30, 40 and 50 ml (mm^2/mmHg) and was compared to previously established data of 15 healthy controls. The cut-off for normality was determined at the lower 90^{th} percentile of the EGJ distensibility at 50 ml in these controls. Symptom severity was assessed using the Eckardt score. Measurements of EGJ distensibility and Eckardt score were repeated >3 months after treatment. We included 9 patients (5 male; age 21-59 years) with typical symptoms of achalasia, Eckardt score 6 (5-7) (median (IQR)). On esophageal manometry failed contractions were observed in 5 patients, panesophageal pressurization in 3 patients and spastic contractions in 1 patient. The median IRP was 9.3 mmHg (3.7-11.95), base LES pressure was 8.6 mmHg (4.5-11.9). Distensibility of the EGJ was significantly reduced in patients compared to controls at all balloon volumes: 20 ml (1.97±0.16 vs 2.46±0.54 mm^2/mmHg, P <.05 (mean±SEM)), 30 ml (1.81±0.08 vs 2.67±0.36 mm^2/mmHg, P <.0001), 40 ml (1.08±0.12 vs 5.02±0.58 mm^2/mmHg, P <.0001) and 50 ml (1.08±0.11 vs 6.28±0.65 mm^2/mmHg, P <.0001). All patients exhibited EGJ distensibility below the cut-off value set for normality (2.9 mm^2/mmHg). Treatment was performed in 6 patients (4 pneumodilation, 2 Heller myotomy). Post-treatment, in all of these patients symptomatic improvement was seen (Eckardt 2 (1-2)) and a substantial increase in EGJ distensibility to a value within the normal range (5.32±0.9 mm^2/mmHg) was observed.

Conclusions: A subgroup of patients with typical symptoms of achalasia, significant esophageal stasis, aperistalsis but no impaired LES relaxation on esophageal manometry can have impaired EGJ distensibility at impedance planimetry. These patients can be regarded as having achalasia and respond favorably to achalasia treatment.

Does post-procedure Esophagogastric Junction (EGJ) Distensibility predict treatment success in newly diagnosed achalasia patients?

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Although initial treatment success rates with pneumatic dilation in achalasia are high, recurrences may occur in more than 50% of patients. Identification of patients in need of re-treatment may be difficult as they are accustomed to a certain level of discomfort. LES pressure ≥10mmHg is considered as an indication for additional therapy but several studies reported a significant proportion of patients with persistent symptoms and low or absent LES pressure. We aimed to study whether post-procedure assessment of esophagogastric junction (EGJ) distensibility can predict treatment success in newly diagnosed achalasia patients. Eighteen newly diagnosed achalasia patients (10 male, mean age 47.9, range 19-75) underwent 2 pneumatic dilations (PD) with 30- and 35mm balloons separated by 1 week. Before and after the 30mm dilation, EGJ distensibility was measured using an endoscopic functional luminal imaging probe (EndoFLIP). Using an EndoFLIP probe with an inflatable bag, EGJ distensibility (cross-sectional area of the diaphragmatic hiatus (CSA)/pressure within bag during distensions; mm^2/mmHg) was measured with 40 and 50ml distensions. After 3 months patients were assessed by esophageal manometry and with validated symptom questionnaires to determine the Eckardt score, with a score <4 indicating treatment success. Mean post-procedure EGJ distensibility increased at the 40 and 50ml distention volumes (40ml: from 1.0±0.1 to 2.9±0.4, p<0.001; 50ml: from 1.2±0.2 to 4.3±0.6, p<0.001). According to the Eckardt score at 3 months after treatment, 14 out of 18 achalasia patients (77.8%) were considered as having treatment success; treatment failures (n=4) underwent an additional PD with the 40mm balloon. Post-procedure EGJ distensibility of successfully treated patients at 40 and 50ml distention volumes were not significantly higher than in treatment failures (40ml: 3.1±0.5 vs. 2.6±1.2, p=0.69; 50ml: 4.7±0.7 vs. 2.8±1.2, p=0.20). At 3 months after treatment, LES pressure of successfully treated patients was lower than in treatment failures (11±1 vs. 36±12, p=0.13) and a good correlation was found between LES pressure and symptom scores (r=0.88, p<0.001). Post-procedure EGJ distensibility at 40 and 50ml distention volumes correlated poorly with symptom scores at 3 months (40ml: r=-0.10, p=0.70; 50ml: r=-0.26, p=0.37) and modestly with LES-pressure (40ml: r=-0.32, p=0.24; 50ml: r=-0.55, p=0.05).
Conclusion: Post-procedure Esophagogastric Junction (EGJ) Distensibility of newly diagnosed achalasia patients improves after pneumatic dilation but is not associated with treatment success after 3 months as compared with symptom scores and LES pressure.

Acid suppression restores impaired esophageal mucosal integrity in patients with esophageal eosinophilia

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Gastroesophageal reflux and allergies are both thought to play a role in the pathophysiology of eosinophilic esophagitis (EoE). It has been suggested that acid-induced esophageal mucosal damage promotes transepithelial allergen flux. Anecdotal evidence suggests that patients with typical signs and symptoms of EoE benefit from acid-suppressive therapy. The aim of our study was to evaluate esophageal mucosal integrity in patients with significant esophageal eosinophilia (SEE) and to study the effects of acid-suppressive therapy with PPI on symptoms, endoscopic signs, mucosal integrity, dilation of epithelial intercellular spaces (DIS), and peak eosinophilia and mastocytosis. We included 11 adults with SEE (>15 eosinophils/hpf) and predominant symptoms of dysphagia and typical endoscopic signs of EoE, and 11 controls. All subjects underwent endoscopy at baseline; in SEE patients endoscopy was repeated after 8 weeks of esomeprazole 40 mg BID. Esophageal mucosal integrity was measured during endoscopy with a through-the-scope electrical tissue impedance spectroscopy probe (ETIS) at 5 cm proximal of the LES. At the same location, we obtained 2 biopsies for electron microscopic analysis of DIS and 4 biopsies for mucosal integrity experiments in Ussing chambers. In the Ussing chambers, we measured transepithelial electrical resistance (TER) and transmucosal flux of small molecules (40 kDa) during 1 hr. In SEE patients, we additionally scored eosinophilia and mastocytosis in esophageal biopsies as well as symptoms and endoscopic signs of EoE at each endoscopy. In SEE patients compared to HC, both structural (DIS 41 vs 16%) and in vivo and in vitro functional measurements (ETIS 2022 vs 7707 Ωm; TER 42.7 vs 116.7 Ω/cm^2; molecule flux 2428 vs 345 nmol/cm^2/h) of mucosal integrity showed significant impairment (all $p < .01$). After acid-suppressive therapy, mucosal integrity was significantly improved in patients with SEE (DIS 33%; ETIS 5713 Ωm; TER 60.8 Ω/cm^2; molecule flux 1476 nmol/cm^2/h; all $p < .05$), but still did not reach the levels seen in controls. Esophageal peak eosinophilia (55.0/hpf) and mastocytosis (25.8/hpf) also decreased after acid-suppressive therapy (to 25.6 resp. 18.9/hpf), as well as symptoms and endoscopic signs of EoE.
Conclusion: Patients with SEE have an impaired esophageal mucosal integrity, which is partially restored after acid-suppressive therapy. The observed reduction of transmucosal flux of molecules with a similar size as food allergens after acid-suppressive therapy supports the hypothesis that acid-induced mucosal damage facilitates transepithelial food allergen flux, which results in esophageal eosinophilia.

First results of the BaroSense ACE stapler procedure for the treatment of morbid obesity: effect on food intake and satiety

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Conventional bariatric surgery is a very effective therapy for weight loss but has several risks and limitations. Recently alternative non-incisional endoscopic procedures have been introduced such as the BaroSense Articulating Circular Endoscopic (ACE™) Stapler technique. This trans-oral procedure intends to reduce the capacity of the stomach to expand by endoscopically creating plications in the region of the fundus and greater curvature. In this first explorative study we tried to provide more information about the potential efficacy and mechanism of weight loss of the BaroSense ACE stapler procedure. Methods: This prospective study was performed in 10 morbidly obese patients (4 women, mean age 41±10 years, mean BMI 39.6±2.8 kg/m2) who underwent the BaroSense ACE stapler. Patients were studied prior to and one month after the operation. All procedures went without any complications and patients were discharged one day after the operation. Gastric emptying (by 13C octanoic acid breath test) and satiety (VAS) were measured at different time points before and after the intake of a standardized, fixed breakfast meal (t=0, breakfast consisted of 200kcal and 100mg 13C octanoic acid was added). Food intake was assessed by offering an ad libitum meal at t=240 min. Comparisons of gastric emptying half time and food intake were analyzed using paired samples t-tests whereas all VAS scores were examined by using the repeated measures ANOVA. All results are expressed as mean±S.E.M.Results: The included patients showed loss of 19.9±5.7% excess BMI one month postoperatively. Patients did not report any gastrointestinal complaints, but satiety AUC was significantly increased 1 month after the procedure compared to before (AUC 68.8±8.9 and 48.1±9.4 $p<0.02$). Ad libitum food intake decreased significantly from 842.8±45.9 to 441.8±100.1 kcal (preop vs postop, $p<0.01$). No differences were observed in gastric emptying half time (141.3±5.9 versus 138.7±12.3 minutes, $p>0.05$)Conclusion: Our data indicate that endoscopic reduction of the stomach volume by the BaroSense ACE stapler procedure results in significant weight loss, increase in satiety and a decrease in food intake one month postoperatively. Although capacity of the stomach for relaxation is impaired, gastric emptying of a standard and fixed test meal was not affected. These first explorative data indicate that the BaroSense ACE stapler is a potentially very promising technique that effectively reduces food intake and affects satiety but does not interfere with gastric emptying. Inclusion of larger numbers of patients and more prolonged follow up of BaroSense ACE stapler procedures is needed.

Neuronal modulation of intestinal inflammation during Postoperative ileus

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Background: The cholinergic anti-inflammatory pathway is a neuronal circuitry by which the vagus nerve regulates inflammation. In diverse inflammatory settings, the spleen was identified as the major mediator of the vagal immune-suppressive effect. We decided to elucidate the neuronal circuitry involved in the vagal modulation of the intestinal inflammation in a murine model of Postoperative ileus (POI). Therefore, we investigate the respective role of the vagal innervation of the small intestine and the spleen in the modulation of intestinal inflammation and its motility. Methods: Selective vagal denervation of the intestine (Ix) or complete denervation of the spleen (Sx) was performed in mice 2 weeks prior to Intestinal Manipulation (IM). Gastrointestinal transit was measured using a non-absorbable tracer and the spleen and intestine were collected for analysis 24h, 72h and 120h post-IM. For statistical analysis, two-way ANOVA tests were performed followed by an unpaired t test when appropriate. Results are expressed as mean ± SEM. Results: Vagal intestinal denervation induced an increase in the transcript level of pro-inflammatory cytokines such as IL-6 (5.9 ± 1.9 vs 21.5 ± 7.0; $p<0.05$), and IL-1b (8.0 ± 1.5 vs 27.4 ± 8.4; $p<0.05$). This increased inflammation did not lead to enhanced delay in the intestinal transit 24h after IM or affect the recovery phase (72h and 120h after IM).Interestingly, intestinal inflammation triggered a massive decrease in the number of splenocytes (26%). This splenic response, observed only at 24h after IM, was abolished by pretreatment with CYM-5442, a S1P receptor 1 agonist. This active departure of splenic cells was partly affected by surgical denervation of the spleen suggesting the spleen is part of the vagal neuronal circuitry that modulates intestinal inflammation. Interestingly, preliminary data indicate that denervation of the spleen delayed the recovery of the intestinal transit compared to that of intact mice, 5 days after IM.

Conclusion: In this study, we demonstrated that removal of the vagal innervation enhanced intestinal inflammation, confirming that the vagal anti-inflammatory pathway directly modifies the intestinal immune system. In addition, we demonstrated that the spleen responds to the local manipulation-induced intestinal inflammation by an active departure of cells, a response that is partially controlled by the splenic innervation. The exact physiological significance of the latter however remains to be determined.

The effect of chewing gum before and directly after surgery on postoperative ileus in colorectal surgery; a randomized controlled trial

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The aim of this study is to investigate the effect of sham feeding just before and directly after colorectal surgery on postoperative ileus, surgical complications and length of hospital stay. Mechanical stimulation of the autonomic nervous system has been shown to ameliorate postoperative ileus in an experimental model. Interestingly, this protective neuro-immune mechanism can also be stimulated by enteral nutrition in a physiological way when given just before and directly after the inciting event. Timing of the intervention is essential, however anaesthesiology guidelines advocate a pre-operative fast. Therefore we investigated the hypothesis whether activation of the autonomic nervous system through sham feeding via chewing gum reduces postoperative ileus following colorectal surgery. In this dual center, placebo-controlled randomized trial a total of 120 patients were randomized for chewing gum just before and directly after surgery (58 patients) or received a dermal patch placebo (62 patients). Time to first flatus and first defaecation were assessed and gastric emptying following a standardized meal was measured by ultrasonography of the gastric antrum on the second postoperative day. Furthermore, surgical complications as classified by Clavien-Dindo were registered as well as length of stay. Time to first flatus and first defaecation was significantly reduced in patients chewing gum compared with the control group (P = 0.006 and P = 0.04 respectively). Moreover, gastric emptying, expressed as rate of change in antral area (in percentages) was significantly increased in the group receiving chewing gum (n = 42, median 25%, interquartile range (IQR) 7% to 44%) compared with the control group (n = 44, median 10%, IQR -2% to 27%; P = 0.004). Furthermore, there were more reinterventions under general anaesthesia (Clavien-Dindo Grade III-b complications) in the placebo group (n = 9) compared with the chewing gum group (n = 2; P = 0.048). Finally, length of stay was shorter in patients that received chewing gum just before and directly after colorectal surgery (mean of 8.5 days, standard deviation (SD) 0.6) compared with the placebo control group (mean of 11 days, SD 1.8), however this did not reach statistical significance (P = 0.055). These results show that chewing gum just before and directly after colorectal surgery reduces postoperative ileus, reduces the number of reinterventions under general anaesthesia and may shorten length of hospital stay. Chewing gum just before and directly after surgery is a simple and safe intervention to reduce postoperative complications and enhance recovery following colorectal surgery.

Effect of a multispecies probiotic on visceroperception in hypersensitive IBS patients

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Introduction: Pathophysiology of Irritable bowel syndrome (IBS) is multifactorial. Various treatment modalities have not been very successful. Recent interest has focused on probiotics but studies with probiotics showed only modest positive results, which might be related to the heterogeneous character of IBS. We hypothesized that focusing on a subgroup of patients with one common pathophysiological mechanism may improve treatment efficacy. Aim of the present study was to assess the effect of a multispecies probiotics vs. placebo on visceroperception in a group of IBS patients with visceral hypersensitivity.Methods: A randomized, placebo-controlled, double blind trial was performed. Eligible patients with IBS according to the Rome III criteria underwent a rectal barostat. Accordingly, patients with visceral hypersensitivity were randomized to receive either a multispecies probiotics (5x109 CFU/daily) or placebo for 6 weeks. The probiotic strains were selected by their anti-nociceptive and anti-inflammatory potential and beneficial effects on intestinal permeability. At the end of the intervention, again a rectal barostat was performed. Two-week symptom diaries were completed before and at the end of intervention. Seventeen patients per group were required to demonstrate a significant effect (i.e. pain threshold increase of 7mmHg) of probiotic treatment versus placebo on visceroperception. Data was tested for normality and presented by intention-to-treat analysis (ITT). Results: Of the 40 IBS patients that started (probiotic: n=21), 35 patients completed the trial (probiotic: n=19). Mean age (±SEM) did not differ between the probiotic and placebo group (40.0±2.2yr vs. 41.1±4.1yr P=0.93), nor did the distribution of sexes (male sex n=7 vs. n=8 in probiotic vs. placebo respectively; P=0.74). The percentage of patients with visceral hypersensitivity decreased significantly in the probiotic (23.5%) and placebo group (28.6%), but did not differ between the groups (P=0.24). Improvement in mean symptom composite score (MSS) did neither differ between probiotic versus placebo (-0.66 [-3.77–1.64] vs. -1.36 [-7.42–1.43]; P=0.16). Looking at individual symptoms, flatulence improved significantly in the placebo but not in the probiotic group (-0.59 [-1.95–0.67] vs. -0.07 [-1.03–0.72]; P<0.01). No such difference was found for the other symptoms nor between the groups. The per protocol analysis did not differ from ITT.Conclusion: The present study could not demonstrate a reduction in visceroperception nor in symptom scores in IBS patients characterized by visceral hypersensitivity after 6 weeks of treatment with a multispecies probiotic when compared to placebo.

Does colonic transit time predict the result of colonic manometry in patients with chronic obstipation?

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Chronic constipation is divided into subgroups of which slow transit constipation is supposed to result from changes in colonic motility. Nowadays colonic motility can be evaluated using 24-hour ambulatory colonic manometry. However, availability of colonic manometry is limited , the procedure is invasive, time consuming and uncomfortable for patients. On the other hand, colonic manometry may help to select patients for medical or surgical therapies. First, it will be helpful to know which patients will benefit from undergoing colonic manometry. Aim of this study was to compare data of colonic transit time (CTT) with those of colon manometry (CM) findings in patients with severe and invalidating chronic constipation. Methods: A total of 51 patients (45 women, 44.0±12.5 years) with severe chronic constipation underwent CTT and CM in our tertiary referral centers between 2003-2012. Data from CTT and CM obtained in 12 healthy subjects (10 women, 39.8±11.2 years) served as control values. CTT was measured with follow up to 4 days after ingestion of one pallet of radio-opaque markers. Subjects underwent 24-hr ambulatory colonic manometry with a 6 solid-state pressure sensor catheter that was endoscopically positioned with the tip in the ascending colon and clipped to the mucosa. In CM we focussed on High Amplitude Peristaltic Contractions (HAPCs). CM was defined as normal when at least three HAPC propagating over at least 3 sensors, with an amplitude of ≥80 mmHg) were identified. All results are expressed as mean±S.E.M and were compared using chi square and independent-samples T-test. Results: Of the 51 patients, 40 had delayed CTT and 11 normal CTT. All 11 patients with normal CTT also had a normal CM. However, patients with delayed CTT had in 57.5% (23/40) an abnormal CM. Patients with delayed transit showed significantly less HAPC's compared to patients with normal transit and to controls (2.31±0.41 versus 4.7±0.41 versus 5.25±0.87per 24 hrs; $p<0.05$ and $p<0.005$ respectively). In patients with normal CTT, HAPC's propagated more frequently over 5 -6 sensors whereas the majority of HAPCs in patients with slow transit propagated over only 3 sensors.
Conclusion: In this population of patients with severe chronic constipation a normal CTT predicts that colonic manometry will be in the normal range with respect to HAPC's and has no additional diagnostic value whereas in case of delayed CTT colonic manometry is abnormal in more than 50% of patients. Easy to perform colonic transit studies help to predict the presence of an underlying motility disorder in chronic constipation.

Brain processing of rectal sensation in children with chronic functional constipation

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Background and Hypothesis: The pathophysiologic mechanisms underlying chronic defecation disorders in children without obvious organic etiology are poorly understood. Children with functional constipation (FC) often report loss of defecatory urge sensation. However, a clear relation between lack of sensation and anorectal parameters has never been identified. Functional magnetic resonance imaging studies (fMRI) have been used to unravel the brain processing of visceral sensation in adults with functional gastrointestinal disorders. However, fMRI in combination with rectal distension has never been performed in the pediatric patients with constipation. The hypothesis of this study is that cerebral activity in response to rectal distension in children with chronic constipation is impaired.Patients and Methods: 10 patients between 12-18 years old (6 male, median age 14.5 years), who suffered for at least 2 years from FC defined by the ROME III criteria. All patients underwent colonic transit time measurement and rectal barostat. A stepwise pressure-controlled intermittent distension protocol was performed to determine rectal sensation. The rectal pressure at which urge to defecate was felt was used, during acquisition of blood oxygenation level-dependent (BOLD) fMRI. Subjects received two sessions of 5 stimulations consisting of repetitions of 30 seconds of rectal stimulation followed by 30 seconds of rest. Functional and structural images were acquired on a 3Tesla MRI scanner equipped with an 8-channel SENSE head receive coil. A T2*-weighted echo planar imaging (EPI) sequence was acquired with the following parameters: TR/TE=3000/30 ms, slice thickness = 3.0 mm, voxel size = 1.72 x 1.72 x 3 mm, with 40 axial slices, in ascending mode covering the whole brain. In addition, a structural T1-weighted 3D anatomical image of the whole brain was obtained. Whole brain fMRI BOLD signal differences between rectal stimulation and non-stimulation sessions were analyzed using SPM8 implemented in Matlab version 7.14, thresholded at $p<0.01$. Results: All patients had a delayed colonic transit time (> 62 hours, median 100.8 hrs). Sensation of urge to defecate was reported at a median pressure of 28.5 mmHg (range 18-33 mmHg). There were no significant activated brain areas associated with sensation of urge to defecate during rectal distension.
Conclusion: Our preliminary results suggest that there is no responsiveness of the central nervous system of the defecatory urge sensation in hyposensitive children with severe functional constipation. In future research it is important to compare these results with a healthy pediatric control group and to specify regions of interest for a more detailed analysis.

Assessment of ERCP performance in novice trainees

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Introduction: Measures for ERCP competence during training are poorly defined. Currently, various guidelines state to base competence on a minimum number ERCP procedures, ranging between 100-150. This arbitrary number is lacking any scientific support and needs to be reconsidered. In this process, there is a general awareness that procedural competence certification should be based on objective performance criteria, rather than threshold numbers. Continuous self-assessment using a Rotterdam Assessment Form for ERCP (RAF-E) has shown to be useful in gaining insight in performance of novice trainees. The aim of this study was to express competence development as a learning curve for different types of procedures and to assess the performance of residents starting with ERCP training. Methods: Trainees in ERCP in two tertiary referral centers were invited to participate. All procedures were appraised using RAF-E. The indication for each ERCP was classified as well as presence of a virgin papilla. Complexity was graded on a 3-point scale, derived from Schutz's classification. [Schutz et al. Gastrointest Endosc 2000;51:535-9]. The primary outcome parameter was common bile duct (CBD) cannulation success rate in patient populations with different grades of procedure complexity. Results: Eighteen trainees from two tertiary medical centers in the Netherlands were included in this study. 1436 ERCPs were assessed through RAF-E. Overall unassisted CBD cannulation success rate was 62.8%. 520 (36.2%) patients had a virgin papilla; a successful cannulation of the CBD was achieved in 41.7% of these cases. We took a closer look at the first 100 procedures after the start of ERCP training, since that number is the threshold for certification in the Netherlands. 1132 procedures were in this range. Overall CBD cannulation success rate in this group was 51.6%. Cannulation success in patients with a virgin papilla (n=450) improved from 26.8% in the first 20 procedures to 45.8% in procedures 80-100 ($p=0.02$). Difficulty 1 procedures (n=743) accounted for an overall CBD cannulation success rate of 57.3% and improved from 47.1% in the first 20 ERCPs to 73.4% in ERCPs 80-100 ($p<0.001$). Performance can be plotted as a learning curve.
Conclusions: Learning curves of trainees are a valuable means to assess competence in ERCP. Differences in learning curves for specific types of procedures can be shown with RAF-E. A threshold number of 100 procedures for certification in ERCP is inadequate. Competence should be based on actual performance, such as successful cannulation, instead of pure minimum numbers.

Optical diagnosis of colorectal polyps using HD i-scan is feasible and correctly predicts surveillance intervals

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Optical diagnosis of small colorectal polyps holds promise to improve cost-efficiency of colonoscopy. Nevertheless, at least 90% negative predictive value (NPV) for adenomas and agreement with the pathology-based surveillance intervals should be attained for a safe implementation in the community practice. In this study, we review our experience regarding the feasibility and safety of optical diagnosis using high-definition (HD) i-scan. Methods: We firstly familiarized our endoscopists with regard to optical diagnosis of colorectal polyps, using a short didactic training session (still images) and individual feedback. Subsequently, we embarked in a prospective study of consecutive patients undergoing colonoscopy having at least 1 small (<10 mm) colorectal polyp. Four endoscopists with different levels of experience and who each evaluated at least 25 colorectal polyps by HD i-scan participated. All small colorectal polyps were examined using HD white-light followed by HD i-scan, then classified into adenomatous or non-adenomatous with a high-or low level of confidence, and subsequently removed and sent for histopathologic examination. Distal colon was defined as rectosigmoid whereas proximal colon was defined as proximal to the rectosigmoid. Sensitivity, specificity, positive, NPV and accuracy for prediction of histopathology were calculated. The agreement between surveillance recommendations that would follow optical diagnosis for small colorectal polyps combined with histopathology assessment of the remaining polyps versus histopathology assessment alone was calculated. Results: A total of 309 small colorectal polyps from 93 patients were examined. Of them, 295 (95.5%) were predicted with high-confidence and hence, included in the final analyses. Of these, 110 (37.3%) were distally located of which 33 (30%) were adenomatous and 77 (70%) non-adenomatous. The NPV for adenoma histology of all small colonic polyps was 87%, small proximal colonic polyps 76% and 97% for small distal polyps. In addition, the agreement between surveillance recommendations by formal histopathology versus HD i-scan analysis of all small colonic polyps was 81% and increased to 94% for small distal polyps only. Of note, the 6% disagreement reflects patients receiving surveillance earlier than recommended by histopathology alone.
Conclusion: Our data indicate that optical diagnosis of small distal polyps using HD i-scan is already feasible in the routine practice, with a negative predictive value of 97% and 94% agreement of surveillance recommendations. However, prediction of histology in proximal polyps is only moderate, emphasizing the need for continuous training.

Computer-Aided Delineation of Early Neoplasia in Barrett's Esophagus using High Definition Endoscopic Images

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Adenocarcinoma of the esophagus is the fastest rising type of cancer in the Western world. The recent development of High Definition (HD) endoscopy has enabled the specialist physician to identify Barrett's cancer at an early stage. Nevertheless, it still requires considerable effort, training and expertise to be able to recognize these irregularities associated with early cancer. As a first step towards a Computer-Aided Detection (CAD) system that aids the physician in finding these early stages of cancer, we propose an algorithm that is able to automatically detect early Barrett's cancer, using HD endoscopic images. Since early Barrett's cancer is characterized by different color and texture patterns, we employ features for capturing color and texture information. For our system, we have selected the Color Histogram (CH) and Gabor features and we compare with other well-known color and texture features. The system employs tile-based processing, which enables the delineation of regions containing early cancer. For classification of these tiles, we employ the widely used Support Vector Machine (SVM) and evaluate its performance using different parameters and kernel functions.
For clinical evaluation of the proposed algorithm, we selected a total of 103 images of 30 patients and let an expert physician delineate the early cancer. We split the images into square tiles of different dimensions, ranging from 25×25 to 250×250 pixels. Using the delineations of the expert, we split the tiles into two classes, one with the tiles containing early cancer and another one with the tiles containing non-dysplastic Barrett's tissue. This was done for each tile size separately. We used the tiles of 21 patients for training and testing a classifier, where we ensured that no patient was in both the training and the test set. The images of the other 9 patients were used for evaluation of the automatic delineations. The proposed system achieves a classification accuracy 94.2% on these tiles of normal and of tumorous tissue and reaches an Area Under the Curve (AUC) of 0.986. Figure 1 shows the delineations of an expert gastroenterologist versus the delineations made by the algorithm. Our experiments and clinical validation of the results show that our approach is promising for a computer-aided detection system that helps the endoscopist in finding early stage Barrett's cancer. Further research and clinical validation is needed for the development of a system for real-time video analysis of endoscopic images.

Preoperative Esophagogastric Junction (EGJ) Distensibility predicts treatment outcome after endoscopic fundoplication in GERD patients

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Increased esophagogastric junction (EGJ) distensibility is considered a key factor in GERD permitting increased volumes of reflux across the EGJ. It has been suggested that stratification of GERD patients according to EGJ distensibility could identify those responsive to endoluminal or surgical therapies. Our aim therefore was to study whether preoperative assessment of EGJ distensibility can predict treatment outcome after endoscopic fundoplication in GERD patients. Forty-two GERD patients with symptoms refractory to medication (26 males; mean age 45, range: 20-68 yrs), abnormal acid exposure time and hiatal hernia ≤2cm underwent EGJ distensibility measurement before and after endoscopic fundoplication. Ambulatory 24hr pH-impedance monitoring and symptom assessment by a disease-specific quality of life questionnaire (GERD-HRQL) were performed at base and 6 months follow up. Using an EndoFLIP probe with an inflatable bag, EGJ distensibility (cross-sectional area of the diaphragmatic hiatus (CSA)/pressure within bag during distensions; mm^2/mmHg) was measured with 20 and 30ml distensions. Analysis of 24hr pH-impedance measurements included acid exposure time (%), number of liquid, acid and proximal reflux episodes. Patients with normalized acid exposure time (pH<4 ≤4.0%) at 6 months were considered as responders. Acid exposure time was reduced after endoscopic fundoplication from 10.8±1.1% to 5.9±0.8% ($p<0.001$) and normalized in 58% of the patients at 6 months (responders). Mean postoperative EGJ distensibility decreased at the 20 and 30ml distention volume (20ml: from 1.9±0.2 to 1.4±0.1, $p=0.005$; 30ml: from 2.3±0.3 to 1.8±0.2, $p=0.03$). Mean preoperative EGJ distensibility was lower in responders than in non-responders at the 20 and 30ml distention volume (1.5±0.1 vs. 2.5±0.6, $p=0.02$ and 1.7±0.2 vs. 3.3±0.7, $p=0.07$). A positive correlation was found between preoperative EGJ distensibility and postoperative acid exposure time ($r=0.50$, $p=0.002$) and number of liquid, acid and proximal reflux episodes at 6 months after treatment (liquid: $r=0.46$, $p=0.006$; acid: $r=0.53$, $p=0.001$; proximal: $r=0.48$, $p=0.003$). Postoperative GERD-HRQL scores did not correlate with preoperative EGJ distensibility.

Conclusions: Low preoperative Esophagogastric Junction (EGJ) Distensibility is associated with a better response to endoscopic fundoplication in GERD patients and correlates with postoperative acid exposure time and number of reflux episodes. EGJ distensibility may be helpful in selecting patients for antireflux procedures.

An endoscopic grasp-and-traction device is helpful for gastric endoscopic submucosal dissection in the forward, but not in the retroflex approach: an ex-vivo comparative study on the usefulness of Endolifter®

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Endoscopic submucosal dissection (ESD) is a demanding technique with a higher complication rate compared to conventional endoscopic resection techniques. The Endolifter (EL; Olympus Medical Systems Corp., Tokyo, Japan) has been developed to grasp and pull up the partly dissected mucosa, thereby simplifying the ESD procedure, especially in the phase of submucosal dissection. The aim was to investigate whether this promising tool could indeed accelerate endoscopic submucosal dissection in an ex vivo porcine model. Sixty-four ESDs were performed in a total of 16 isolated porcine stomachs with the Dual knife (Olympus) or the Hook knife (Olympus) by 2 endoscopists (1 less experienced in ESD, 1 expert). Each stomach included 4 artificial lesions in the gastric corpus, 3 cm in diameter each. Two lesions were located at the posterior wall for a forward approach (group F) and 2 at the lesser curvature for a retroflex approach (group R). In both groups, 1 lesion was dissected with and 1 without the use of EL. The order of ESD for the 4 conditions was randomly assigned. After creating a submucosal cushion, a circumferential mucosal incision was made along the markings, followed by a submucosal dissection with or without the EL. The surface size (cm^2) of all resection specimens was assessed, and “time needed for dissection” was calculated in min/cm2. Three determinants (“use of EL”, “endoscopist”, and “study period [divided into 4 quarters per endoscopist]”) on the “time needed for dissection” were analyzed by a multivariate analysis in a logistic regression model, separating the “time needed for dissection” at a median, thereby composing 2 categories (Fast/Slow). En bloc resection rate was 98.4% (63/64 cases). Perforation occurred in 1 case (1.6%). Total submucosal dissection time (min [range]) was 5.9 [1.4-35.0], and the resected area (cm2 [range]) was 7.10 [3.77-16.61]. The median time needed for dissection (min/cm2 [range]) was 0.77 [0.23-4.69]. In a multivariate analysis, in group F “use of EL” and “endoscopist” were independent predictors for Fast (odds ratio [95%CI]; 9.14 [1.35-104.82] and 11.50 [1.99-109.75] , respectively), whereas in group R “study period” was an independent predictor for Fast (odds ratio [95%CI]; 8.69 [0.72-234.79] in the 2nd, 11.56 [1.31-265.87] in the 3rd, and 19.34 [1.68-553.79] in the 4th quarter as 1 in the 1st quarter). Conclusion: In gastric ESD, Endolifter may be of help to save time during submucosal dissection in a forward, but not in a retroflex approach.

A large International Multicenter Experience with an Over-The-Scope Clipping Device for Endoscopic Management of Gastrointestinal Perforations, Fistulae, and Leaks in 188 Patients

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Technological advances have increased success of endoscopic closure of gastrointestinal (GI) perforations, fistulae, and anastomotic leaks. Conventional treatment of these defects is surgical and associated with significant morbidity and mortality. The over-the-scope clip (OTSC) provides more durable closure than standard clips because of its ability to grasp larger amounts of tissue. In addition, full-thickness closure is achievable due to greater compressive force. However, only case reports and small case series have reported on outcomes of OTSC closure of GI defects. Aims: To describe a large international multi-center experience with OTSC for the management of GI perforations, fistulae, and anastomotic leaks. Methods: A retrospective chart review of patients who underwent OTSC placement for the management of GI defects between May 2006 and November 2012 was performed. Fistulae were defined as abnormal communications between two epithelialized surfaces and leaks as loss of integrity of anastomoses. Data abstraction for patient demographics, clinical history, prior therapy, procedural details, adverse events (AE), and follow-up was obtained. Clinical success was determined by lack of contrast extravasation or evidence of output through the defect. Results: A total of 188 patients (mean age 59yrs, range 19-92, 101 females) underwent OTSC placement at 16 international centers with a mean follow-up of 266 days (range 1-5,324 days). The most common indication for OTSC was closure of fistulae (n=108, 57.4%), followed by perforation (n=48, 25.5%), and leaks (n=32, 17.1%). The most common location for OTSC use was in upper GI tract with a mean defect size of 7.7mm, 10.6mm and 8.5mm for fistulae, perforations, and leaks, respectively. Technical success was achieved in 94.7% of cases. Immediate clinical success was achieved in 163 (86.7%) cases (fistulae 89, 82.4%; perforations 45, 93.8%; leaks 29, 90.6%), long term clinical success without need for further interventions was noted in 118 (63.4%) of these patients (fistulae 49, 46.2%; perforations 43, 89.6%; leaks 26, 81.3%; fistulae vs. other, $p<0.0001$). Surgery was warranted in 18 (9.6%) cases only, with remainder of cases successfully managed with further endoscopic therapy (OTSC, standard clips, stents). There were no adverse events directly related to OTSC placement. One patient died after failed closure of colonic perforation despite subsequent surgical intervention.
Conclusion: Use of OTSC in the management of GI defects was safe and efficacious. While long-term success without need for further intervention was achieved in majority of patients with perforations and leaks, this was attained in less than half of patients with fistulae.

Placement of a fully covered metal stent (AXIOS) for EUS-guided drainage of peripancreactic fluid collections; a prospective European cohort study

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Endoscopic ultrasonography (EUS)-guided transmural drainage with placement of double-pigtail plastic stents is an important treatment for symptomatic peripancreatic fluid collections (PFC). The limitation of small-diameter plastic stents (7/10F) is the high risk of stent occlusion, especially in PFCs containing necrotic debris. Stent occlusion may result in infection and delayed PFC resolution. A novel large-diameter (10/15mm) fully-covered self- expanding metal stent, the AXIOS stent, has been developed to overcome these limitations. We evaluated technical and clinical success, stent migration and safety of EUS-guided PFC drainage using the AXIOS stent. From May 2011 until November 2012 patients who underwent EUS-guided drainage of PFCs with the AXIOS stent in 16 European medical centers were prospectively enrolled in a web-based database. In total, 62 patients (39 men, median age 54 (range 22 - 88) years) were included. PFCs were classified as walled-of pancreatic necrosis (n=47) or pancreatic pseudocyst (n=15) and almost half of the PFCs were infected (n=29; 47%). The median diameter of the PFC was 90 mm (range 40-230). A transgastric approach was used in the 59 patients (94%) and in 3 patients (6%) a transduodenal drainage was performed. Stent placement was technically successful in 61 patients (98%) while in 1 patient the entire stent was deployed inside the PFC and was removed during a subsequent endoscopy. Resolution of the PFC was achieved in 51 patients (82%) after a median of 29 days (range 1-136) days. In 5 patients (8%), the PFC has not yet been resolved, 3 patients (5%) required surgery because of severe sepsis, 1 patient (2%) died due to an unrelated cause before resolution and 2 patients (3%) were lost to follow up. Stent removal was successfully performed in 43 patients (70%) after a median of 32 days (range 2-178), 13 stents (21%) are still in situ, 4 stents (6%) dislodged during endoscopic transmural necrosectomy and 2 stents (3%) migrated to the GI-tract without complications. Stent removal was rated as easy in 42 patients (98%), but in 1 patient hyperplastic tissue ingrowth made removal difficult. In total, 13 major complications were reported in 12 patients (19%), including stent dislodgement (n=4), infection of the PFC (n=4), stent migration (n=2), bleeding (n=1), retroperitoneal abscess (n=1) and abdominal pain after stent removal (n=1). We concluded that placement and removal of the AXIOS stent is technically feasible for drainage of PFCs with an acceptable complication rate. Clinical success seems promising but further studies with longer follow-up and a direct comparison with plastic stents are needed.

A fully covered self-expandable metal stent, Niti-S, for benign biliary strictures: a prospective multi-center follow-up study

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Treatment of benign biliary stricture (BBS) generally consists of sequential placement of multiple plastic stents. A major drawback of this approach is the need for frequent stent exchange. Fully covered self-expandable metal stents (FCSEMS) are increasingly being used as an alternative because of their larger diameter; however, there is a risk of stent migration due to a lower anchoring capacity. The Niti-S is a fully covered SEMS with flared ends to prevent migration. We evaluated technical and clinical success and safety of temporary Niti-S placement in patients with BBS. From Aug. 2010 to Nov. 2012, consecutive patients with BBS were included and underwent Niti-S placement for 3 months. Patients were prospectively followed for up to 1 year. Thirty-two patients were included (21 men, median age 56 years (range 19-85)). Etiology of the stricture included chronic pancreatitis (n=19), post-surgical stricture formation (n=6), papillary stenosis (n=4) or another cause (n=3). Twenty-six patients (81%) were previously treated with plastic stent placement. Stent placement was technically successful in 31 patients (97%) while in 1 patient the stent did not dilate the complete stricture due to inward migration and a plastic stent was placed through the Niti-S. Stent removal was performed in 29 patients after a median of 91 days (IQR 90-98), complete stent migration was observed in 7 of those patients (24%) and partial migration in 2 patients (7%). The stent is still in situ in 2 patients (follow-up < 3 months) and 1 patient died due to an unrelated cause before removal. Stricture resolution was observed in 22 of 29 patients (76%). A persisting stricture was seen in 7 patients (24%), of which 4 occurred in patients with stent migration, 2 after early stent removal for cholangitis and persistent pain and 1 stricture was found to be malignant. Seventeen patients (77%) are still without obstructive symptoms after a median of 243 days (range 7-313) after stent removal, whereas stricture recurrence was observed in 4 patients (18%) after a median of 182 days (range 3-313). One patient (5%) developed a malignant stricture. In total, 11 complications occurred in 10 patients (31%), including cholangitis (n=4), post-ERCP pancreatitis (n=1), flare up of chronic pancreatitis (n=2), cholecystitis (n=1), portal vein thrombosis (n=1), transient fever of unknown origin (n=1) and pain requiring SEMS removal (n=1). Resolution of BBS is achieved in all patients after a Niti-S stent dwell time of 3 months. Since the major cause of a persisting stricture is stent migration, we conclude that further improvement in stent design is needed to reduce the risk of migration.

Self-expandable metal stents as definite treatment for esophageal variceal bleeding

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Acute esophageal variceal bleeding (EVB) is a life-threatening condition. Standard pharmacological therapy in combination with endoscopic variceal band ligation (VBL) fails to control bleeding in 10-20% of patients. The use of self-expandable metal stents (SEMS) has occasionally been described for the treatment of uncontrollable EVB as a bridge to an alternative treatment, in particular transjugular intrahepatic portosystemic shunt (TIPS). It is currently not known if SEMS can serve for more than temporary hemostasis. We therefore aimed to assess initial and sustained hemostasis and long-term patency of SEMS used for EVB. We analyzed all patients who received a SEMS between February 2012 and October 2012 for acute EVB failing VBL. Data on sex, age, procedural details, rebleeding and clinical course were collected prospectively, anonymized, and analyzed. Endoscopic interventions were exclusively performed by endoscopists experienced in therapeutic hemostatic interventions. VBL using a 6-Shooter Multi-band Ligator® (Cook Medical, Winston-Salem, North Carolina, USA) was the principal modality to obtain hemostasis. Insertion of the SEMS (Sx-Ella Danis, fully covered, Ø 30/25/30 x 135 mm, ELLA-CS, Hradec Králové, Czech Republic) was considered if endoscopic hemostasis failed and if the patient was not considered candidate for TIPS at that moment. Five patients (M/F 3/2; median age 58 (range 48-78)) received a SEMS for uncontrollable EVB. None of them was candidate for TIPS at time of bleeding due to severe comorbid illnesses (i.e. sepsis, metastasized cancer). Successful initial hemostasis was achieved with SEMS in all five patients, and sustained hemostasis in four of them (80%). One patient experienced a rebleeding 7 days after SEMS placement, which was considered due to suboptimal wall pressure of the SEMS at the level of the gastroesophageal junction. Stents were removed in 2 patients after >14 days and remained in situ till death in the 3 other patients (range 6-214 days). No SEMS-related complications occurred during follow-up.
Conclusions: SEMS can be a definite treatment for uncontrollable esophageal variceal bleeding in patients with a limited life expectancy and those (currently) unsuitable for TIPS. Inclusion of such patients in future trials on the applicability of SEMS for variceal bleeding is recommended to increase the generalizability of results.

Incidence and management of late postpancreatectomy hemorrhage

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Mortality after pylorus preserving or classic pancreatoduodenectomy (PPPD) has reduced dramatically over the past decades in high volume centers, but late postpancreatectomy hemorrhage (PPH), generally in combination with anastomotic leakage, is still an important cause of postoperative mortality. The aim of this present study was to analyze the incidence and management of late PPH after PPPD. This study included a consecutive group of patients who underwent PPPD from 1992-2012. Patients with late PPH (> 24 hours after index operation) were divided into two cohorts, cohort 1: 1992-2000 and cohort 2: 2001-2012. PPH was defined as clinically relevant PPH grade B or C, according to the ISGPS criteria. Management of PPH, success of primary treatment strategy and mortality were analyzed. The study group contained 1035 patients, late PPH was reported in 46 patients, 17 patients (4.6%) in cohort 1 and 29 patients (4.3%) in the second cohort. Sixty three per cent of patients with PPH (n=29) also suffered from anastomotic leakage. Overall mortality of the study group was 1.9% (20/1035), mortality in patients with late PPH was 13% (6/46). Mortality in patients with PPH and anastomotic leakage was 17.2% (5/29). In the first cohort embolization was the primary treatment strategy in 4 patients (24%); this was successful in 1 patient. Surgery was the primary treatment strategy in 3 patients, all PPH grade C. In the second cohort embolization was the primary treatment strategy in 19 patients (66%); this was successful in 13 patients (68%). Surgery was the primary treatment strategy in 3 patients, all PPH grade C. In all patients who were treated unsuccessfully by embolization subsequent re-laparotomy was performed. Mortality did not differ between both cohorts or between the treatment strategies.
Conclusion: Incidence of late PPH has not changed. Mortality is high, 13%, in particular in patients who develop both PPH and anastomotic leakage, 17.2%. Primary treatment strategy however has shifted towards embolization by stenting or coiling. Success rate of this treatment strategy has increased.

Long-term survival after palliative resection and bypass procedure in patients with periampullary adenocarcinoma

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Despite all efforts, patients with periampullary adenocarcinoma still have a dismal prognosis. When patients are candidates for surgical exploration, an R0 resection is always pursued. A positive resection margin is known to have a significant negative impact on long-term survival. However, some discrepancy exists on the overall survival benefit of patients after an R1 resection compared to patients with advanced un-resectable disease. The aim of this study was to analyze this survival benefit of patients undergoing an R1 resection compared to patients with advanced unresectable disease, found during surgical exploration. The study population consisted of all patients who underwent surgical exploration between 1992 and 2012 for a pathology proven periampullary adenocarcinoma. Clinicopathological data of all patients was analyzed; overall survival between patients with an R0 and R1 resection and patients with advanced unresectable disease with and without metastasis was compared. In total 1239 patients underwent surgical exploration, a resection (pylorus preserving pancreato-duodenectomy or classic whipple procedure) was performed in 760 patients (61%). In 32% of the resected patients (n=246) pathology reported a positive resection margin (R1 resection). Overall survival of patients who underwent an R0 resection was better compared to patients who underwent an R1 resection, 37.1 vs. 16.9 months respectively ($P<0.001$). The remaining 479 patients (39%) underwent bypass surgery due to advanced disease. Overall survival was 7.7 months, significantly worse than patients undergoing an R1 resection ($P<0.001$). Patients undergoing bypass surgery due to locally advanced disease without metastases had a better survival compared to patients with metastases, 9.5 vs. 5.6 months respectively ($P=0.035$).
Conclusion: Patients undergoing surgery for periampullary adenocarcinoma in which a positive resection margin is reported still have a better overall survival compared to patients who are found to be unresectable during surgical exploration.

Near-infrared fluorescence-guided resection of otherwise undetectable hepatic colorectal metastases using indocyanine green

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A fundamental principle of oncologic surgery is the complete resection of malignant cells. However, conventional techniques lack sensitivity and/or resolution to find small tumors. This is especially important in colorectal cancer, where hepatic metastasectomy may improve survival. Near-infrared fluorescence imaging has been advocated to intraoperatively detect liver metastases using the fluorescent dye indocyanine green (ICG). To assess optimal timing and dose, we intravenously injected ICG, at doses of 10 or 20 mg, 24 h or 48 h preoperatively, into 4 groups of 4 consecutive patients undergoing liver resection for colorectal cancer metastases. Subsequently, 20 patients were administered the optimal dose of ICG at the optimal time before resection. We compared real-time intraoperative NIR fluorescence imaging using the Mini-FLARE imaging system to conventional preoperative imaging by computed tomography (CT), intraoperative ultrasound (IOUS), and intraoperative palpation. In all patients (N = 36), ICG fluorescence was seen as a rim around the tumor, located microscopically in the transition zone between tumor and normal liver tissue. No significant differences in tumor-to-liver ratio (TLR) between time-points or doses were found in the first 16 patients. Therefore, the subsequent 20 patients were administered 10 mg of ICG 24 hours prior to surgery, which is safe and desirable from a logistical point of view. In 5 out of 36 patients (14%), additional small and superficially located metastases were identified using NIR fluorescence only, which were not otherwise detected using preoperative CT, IOUS, visualization, or palpation. NIR fluorescence also distinguished benign liver lesions from metastases. However, all metastases that were located deeper than 8 mm, could not be detected using NIR fluorescence.
Conclusions: This study suggests that NIR fluorescence imaging is complementary to conventional imaging for hepatic metastasectomies to identify small superficial lesions.

Hepatocyte and cholangiocyte-derived microRNAs in serum as early markers for ischemia & reperfusion injury in pigs

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Ischemia and reperfusion injury (IRI) of the liver graft is an important factor determining long-term transplantation success. At different stages of graft procurement, transportation and directly post-engraftment, ischemic injury of the graft can occur. Due to a lack of biomarkers however, it remains difficult to assess graft quality and the degree of ischemic injury during liver transplantation. Recently, hepatocyte and cholangiocyte-derived microRNAs (HDmiRs and CDmiRs) have been identified as sensitive markers for liver injury in patients' serum after liver transplantation. The aim of this study was to investigate whether HDmiRs and CDmiRs in serum can accurately assess the amount of hepatic IRI in a porcine model. Ten female Yorkshire pigs were subjected to hepatic IRI using a total vascular exclusion model by clamping the hepatic artery, portal vein and hepatic veins for 45 minutes. Two vascular probes continuously monitored the absence of blood flow during ischemia. Serum and liver biopsies were collected prior to ischemia and up to 90 minutes after reperfusion. Samples were tested for levels of AST, ALT, gamma-GT, total bilirubin and LDH. Through real-time qPCR serum and biopsy samples were analysed for HDmiR-122 & HDmiR-148a, and CDmiR-30e & CDmiR-222. As control miRNAs in serum, the muscle-derived miR-133a and blood-derived miR-191 were analysed.Both HDmiRs and CDmiRs were detectable in porcine serum and liver biopsies. Of the conventional injury markers, only AST elevated in serum with a maximum of three-fold after reperfusion (64 ± 30 U/L at base vs. 64 ± 10 U/L at reperfusion and 135 ± 50 at 60 minutes after reperfusion, P=0.012). In contrast to this, serum HDmiR- and CDmiR-levels were already significantly higher at time of reperfusion (1.0 vs 4.9 ± 3.7 fold change, P=0.02) and their levels remained elevated longer after reperfusion compared to AST, reaching up to 90-fold (32.7 ± 29.9 fold change). Consistent with increased miRNA levels in serum, a decreased expression of three out of four miRNAs was observed in liver biopsies, of which CDmiR-222 was the most pronounced (43.5 ± 12.3 copies at base vs 27.6 ± 17.2 copies post reperfusion, P=0.016). Levels of control miRNAs in serum, namely miR-191 and miR-133a,neither showed significant changes after ischemia/reperfusion, suggesting changes in HDmiRs and CDmiRs are specific.

Conclusion In this study we demonstrate that microRNAs are an early and sensitive serum marker for hepatic IRI in pigs. To further investigate the correlation between miRNA release in serum and liver injury, paired biopsies will be analysed on liver and bile duct histology.

Efficacy of absorbable embolization materials for portal vein embolization to induce liver regeneration in a rabbit model

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Unilateral portal vein embolization (PVE) is used to increase future remnant liver volume in patients requiring extended resections. Reversible PVE is of interest when generating sufficient hypertrophy while preserving the embolized liver lobe. We aimed to evaluate the hypertrophy response following PVE using three absorbable embolization materials in rabbits. PVE of 80% of total liver volume was performed in rabbits using gelatin sponge (GS,n=5) or fibrin glue with aprotinin (FG+aprot,n=4) or without aprotinin (FG-aprot,n=5). Aprotinin inhibits fribrinolysis and thereby delays absorption of FG. The rabbits were sacrified after 7days. CT volumetry of non-embolized lobe (NELVol), liver damage parameters, liver-to-body weight ratio of NEL, hepatocellular proliferation rate and histology were evaluated. Data were compared with a previous series using a permanent embolization material, i.e. polyvinyl alcohol (PVAc). Post-PVE portography showed complete occlusion of the embolized portal vein branch in all rabbits. GS and FG-aprot were completely absorbed within 7 days and resulted in a significantly lesser hypertrophy response compared to PVAc (p=0.002). The increase rates of NELvol in the GS, FG+aprot, FG-aprot and the PVAc groups were -7,9±8,9%, 60,21±,65,99%, 8,56 ± 28,40% and 79.8 ± 18,76%, respectively. Hypertrophy response in FG+aprot was greater compared to FG-aprot (p=0,05). CT volumetry data were supported by liver-to-body weight ratio. Significantly more proliferating hepatocytes were found in the hypertrophic, caudal lobe of FG+aprot and GS groups compared to the atrophic, left lateral lobe. At sacrifice, the embolized portal vein branches in the FG+aprot were still occluded.
Conclusions: PVE using gelatin sponge resulted in significantly less hypertrophy response compared to PVAc. FG+aprot resulted in significantly greater hypertrophy response than FG-aprot, comparable to PVAc. Aprotinin might be useful in regulating the absorption time of the embolization material. Longer observation time is required to assess absorption of FG+aprot.

Risk factors for bleeding in hepatocellular adenoma

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Hepatocellular adenoma (HCA) is a benign hepatic lesion known with sometimes severe bleeding complications, but the risk for bleeding is still ill defined. We aimed to assess risk factors for bleeding in patients diagnosed with HCA and during follow-up. Methods: Patients with HCA were prospectively included from January 2008 until July 2012. Case characteristics were noted; including body-mass-index (BMI), oral contraceptive use, and pregnancy. All patients underwent dynamic MR and/or CT imaging at presentation and during follow-up. Lesion characteristics on (follow-up) imaging were noted, and bleeding was graded as intratumoral (Grade I), intrahepatic (Grade II), and extrahepatic (Grade III). Standard of reference for diagnosis was histopathology, or dynamic MR and/or CT imaging. Results: In 45 patients included (mean age 40 years; 22-60 years, female/male 44:1), a total of 201 lesions were evaluated. Bleeding was seen in 29/45 (64%) patients and in 46/201 (23%) lesions with a mean size of 43mm (6-160mm). Lesions >35mm showed a higher rate of bleeding compared to lesions <35mm. Lesions in segment 2-3 showed more bleeding compared to lesions located elsewhere (11/31; 35% versus 30/164; 18%: P = .05). Exofytic lesions showed a higher incidence of bleeding (17/25; 68%: P <.001) compared to intrahepatic (10/85; 12%) and subcapsular lesions (19/91; 21%). When lesions exhibited peripheral or central arteries, the lesions were more likely to show bleeding (10/12;P<.001). Patients with BMI>25 showed an increased risk for high grade bleeding Grade II and III (13/35 versus 1/11; P =.03). Bleeding occurred more often in steatotic compared to inflammatory HCA (4/7; 57% versus 11/31; 35%: P =.018). Conclusion: Risk factors for bleeding of HCA include size >35mm, BMI (>25), presence of lesional arteries, location in the left lateral liver, exofytic growth, and steatotic HCA.

Is oesophagogastroduodenscopy prior to Roux-en-Y gastric bypass surgery mandatory?

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Background and study aims: Roux-Y Gastric Bypass is one of the most frequently used techniques in bariatric surgery for morbidly obese patients. Postoperative anatomy is altered by exclusion of the stomach which makes this organ inaccessible for future Esophagogastroduodenoscopy (EGD). There is no definite consensus about preoperative assessment of the stomach. Some institutions choose to investigate the future remnant stomach by EGD, others do not. Aim of the present study is to quantify the yield of preoperative EGD in our institution. Methods: Patients, who were planned for laparoscopic Roux-Y Gastric Bypass (LRYGB) from December 2007 until August 2012, were screened by EGD in advance. These files were retrospectively reviewed for results of the EGD. In addition the files were searched for comorbidities, medication and other patient characteristic. All these data were analyzed. Results: 664 patients (136 male, 526 female, median age 44.2 years, average BMI 45.6) underwent preoperative EGD. In 341 cases no abnormalities were found (A), 115 patients had findings that did not have consequences (B1), 112 (of 417) patients needed HP eradication therapy (B2), 87 patients needed preoperative treatment by proton pump inhibitors (B3), and 6 patients needed follow up EGD before the surgery (C). For one patient the operation was cancelled because preoperative EGD showed Barrett's esophagus with carcinoma (D). When all abnormalities are taken into account, baselines show a significant difference for age, gender, hypertension and alcohol. Regarding the treatment consequences, the number needed to treat to find one serious abnormality (postponing/ follow up EGD or cancel operation) is 94,5.
Conclusion: Based on our results and the results in the literature we state that standard preoperative assessment by EGD is questionable. The number needed to treat for abnormalities with treatment consequences is high. Undergoing EGD for patients without sedation is not to be taken lightly and also the economic burden of performing EGD in all patients is noteworthy.

The role of hospital of diagnosis in offering curative surgery and the impact on survival in resectable oesophageal cancer

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Background: According to the Dutch guidelines the preferred treatment for resectable oesophageal cancer is surgery with or without neoadjuvant chemoradiation. Due to centralisation, treatment of curable oesophageal cancer in the Netherland is reserved to regional referral centres. However, the decision to refer patients for potential curative treatment is made in the referring hospital. The objective was to determine the influence of hospital of diagnosis on the decision to propose surgery or curative intent treatment and the influence on overall survival in patients with resectable oesophageal cancer.
Material and method: All patients with resectable oesophageal cancer (T1-3, N0-3, M0-1A) diagnosed in 2003-2010 (n=849) were selected from the population based Eindhoven Cancer Registry, an area with two referral centres and eight referring hospitals. Logistic regression analysis was conducted to examine the effect of hospital of diagnosis on surgery, adjusted for gender, age, comorbidity, T stage, histology, tumour location, and socioeconomic status (SES). Furthermore, the effect of hospital of diagnosis on overall survival was examined using multivariate Cox regression analysis.
Results: A notable difference in patients proposed for potentially curative surgery was observed ranging from 33% to 67% (p=0.002) between hospitals of diagnosis. No significant differences with regard to age, comorbidity, histology, and tumour location were observed, although T-stage and SES were significantly different between hospitals. Multivariate logistic analysis showed that patients in half of the hospitals were offered significantly less often for curative surgery. Furthermore, patients diagnosed in eight hospitals were less likely to receive curative intent treatment. In three hospitals resectable oesophageal cancer patients had a significant worse overall survival. Conclusion: Hospital of diagnosis plays a significant role in offering potentially curative surgery to patients with resectable oesophageal cancer, with an independent effect on overall survival. This study shows that all patients diagnosed with resectable oesophageal cancer should be discussed within a regional multidisciplinary panel.

PET-CT after neoadjuvant chemoradiotherapy can prevent non-curative surgical interventions in esophageal cancer patients

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Esophageal cancer is notorious for its rapid dissemination. Accurate staging at the time of diagnosis is essential to identify patients eligible for curative treatment. For the majority of these patients the preferred strategy consists of neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy. Given the aggressive nature of esophageal tumours, it is conceivable that in a significant portion of patients treated with nCRT, dissemination becomes manifest during this preoperative course. Since metastatic disease is a contraindication for esophagectomy, we added a post- neo-adjuvant therapy PET-CT to the standard work-up of patients with potentially resectable esophageal carcinoma at initial presentation. The aim of this study was to determine the value and diagnostic accuracy of PET-CT after nCRT in identifying patients with metastases preoperatively. From January 2011 until September 2012 all consecutive esophageal cancer patients deemed eligible for a curative approach with nCRT and surgical resection underwent a PET-CT after completion of nCRT (median interval 18 days). Staging at initial presentation consisted of endoscopy with biopsy, endoscopic ultrasonography, external ultrasonography of the neck and a thoracoabdominal CT scan. A PET scan was not part of the initial staging. Neoadjuvant therapy consisted of 5 cycles of carboplatin AUC 2, paclitaxel 50 mg/m2 and concurrent radiotherapy (41.4 Gy in 4.5 weeks). If abnormalities on PET-CT were suspect of metastases, histologic proof was acquired. During the study period a total number of 280 new esophageal cancer patients were analysed at the outpatient clinic. Of these patients 148 underwent a PET-CT after nCRT. The remaining 132 patients were considered ineligible for curative esophagectomy at initial presentation due to comorbidity, unresectable tumours or distant metastases (94 cases), refused to undergo surgery (12), were operated without nCRT (13) or did not complete nCRT in our centre (13). In 29 patients (19.6%) PET-CT showed abnormalities suspicious for dissemination requiring additional imaging and/or biopsy, resulting in 16 cases of proven metastasis (10.8%) and a false-positive rate of 8.8%. Of the patients without proven metastatic disease 116 patients have been operated at this time. In 4 of these 116 cases distant metastases were detected intraoperatively, leading to a false-negative rate of 3.4%. Conclusion: In 10.8 percent of esophageal cancer patients distant metastases are seen on PET-CT after neoadjuvant chemoradiotherapy. To avoid non-curative resections we advocate post-neoadjuvant therapy PET-CT as part of the standard work-up of candidates for surgery.

How to treat an appendicular mass: operatively or conservatively?

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Whereas there is large consensus how to effectively treat an acute appendicitis namely byperforming an appendectomy, the most suitable treatment for an appendicular mass remains subject to considerable debate. This study compares treatment outcome of patients with an appendicular mass who were treated conservatively and/or operatively.
In a five-year period (2007-2011) we included 119 patients with an appendicular mass. Eighty-five patients (71.4%) were treated conservatively and 34 patients (28.6%) were treated operatively. In the conservative group 56 patients (65.9%) experienced one or more recurrences for which 14 patients (16.4%) required radiological abscess drainage and 24 patients (28.2%) required an operation. In the operative group none of the patients experienced a recurrence. In the conservative group the average length of stay was 13.6 days and the rate of re-admission was 44.8%. In the operative group the average length of stay was 9.2 days and the rate of re-admission was 5.9%. Considering follow-up study to rule out bowel malignancy: in the conservative group no colonoscopy was realized in 31 patients (36.5%); in the operative group this applied to two patients (5.6%). Nine patients (7.6%) appeared to have a malignant tumour: two in the conservative group and seven in the operative group.
Conclusion: the high recurrence and intervention rate in the conservative group and the large percentage of these patients that do not receive adequate follow-up while the incidence of bowel malignancies is 7.6% support an operative management of appendicular mass.

Complications after laparoscopic cholecystectomy: did we reach critical view of safety. A video evaluation study

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Achieving the critical view of safety (CVS) before transection of the cystic artery and cystic duct is one of the most important ways to reduce biliary duct injury in laparoscopic cholecystectomy. We conducted a study to determine whether the requirements of CVS were obtained on video of patients with a complicated laparoscopic cholecystectomy.All consecutive patients, who had undergone a completed laparoscopic cholecystectomy for symptomatic gallstone disease between 2009 and 2011, were included. The videos of the operations of all patients with complications were reviewed and rated by two researchers and two gastro-intestinal surgeons independently. The reviewers answered consecutive questions about the items of CVS.Eleven hundred and eight consecutive patients who had undergone a laparoscopic cholecystectomy were analyzed. Eighty-nine of the 1108 (8.6%) patients developed complications, 28 were male and 70 were female, with a mean age of 51 years. Sixty-six surgical videos were available for analysis. Nineteen patients (1.7%) had bile duct injuries. Six patients (0.6%) had a major bile duct injury, type B, D or E injury. According to the operative note of the 65 patients, in 80% CVS was reached. However, according to the reviewers of the videos in only 10.8% CVS was reached. In 89.2% more than one item of CVS was not reached. In case of biliary injuries, in none of the patients CVS was reached.
Conclusion: We conclude that in laparoscopic cholecystectomy with a complicated course, CVS is reached in only few cases. Evaluating surgical videos of complicated laparoscopic cholecystectomy cases is important because it gives insight in the cause of complications and can and should be used to improve the technique.

Longer disease-free survival following colorectal cancer when operation is performed by a high-volume surgeon

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Introduction: Recently studies have shown that patients undergoing surgery for colorectal cancer by a high-volume surgeon have an improved outcome with regards to complications, hospital stay and post-operative mortality. To date, not much attention has been given on the effect this will have with regards to disease-free and overall survival. Therefore we conducted this study to investigate the impact of a high-volume surgeon on the survival of patients operated in our hospital. Methods: We conducted a retrospective analysis of our prospectively collected colorectal cancer database including patients who underwent a resection between 2004 and 2011. Patients were divided into two groups based on the surgeon who performed the procedure: a high-volume surgeon (>25 cases/year) or a low-volume surgeon (<25 cases/year). Pre-, intra- and post-operative data were collected as well as the recurrence and survival data. Results: A total of 774 patients underwent a colorectal resection for a malignancy by 14 low-volume surgeons, who operated 453 patients, and 3 high-volume surgeons, who operated 321 patients. Groups showed an equal distribution for the pre-operative characteristics. After adjusting for all covariates in a multivariate analysis, after a median follow-up of four years a resection performed by a high-volume surgeon proved to be an independent prognostic factor for the disease-free survival (hazard ratio [HR], 0.739; 95% CI, 0.56-.099; P=0.039). Although the overall survival did show a significant difference in the univariate analysis (HR, 0.495; 95% CI, 0.35-0.69; P<0.001) it failed to reach statistical significance in the multivariate analysis (HR, 0.731; 95% CI, 0.71-1.68; P=0.088)
Conclusions: The current study shows that an increased volume of colorectal cases performed by an individual surgeon is associated with a longer disease-free survival. Although overall survival only showed a statistical significant difference in the univariate analysis and failed to do so in the multivariate analysis, it is expected that after a longer follow-up period this will also reach statistical significance.

Resection of the primary tumor in the treatment of synchronous peritoneal carcinomatosis from colorectal cancer with hyperthermic intraperitoneal chemotherapy

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Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly applied as a standard treatment in patients with synchronous peritoneal carcinomatosis (PC) from colorectal cancer (CRC). Synchronous PC is often diagnosed at laparoscopy or laparotomy scheduled to resect the primary tumor. CRS and HIPEC is a complex multimodality procedure, which is generally performed in specialized referral centers after prior resection. This study compares the clinical outcome of CRS and HIPEC procedures in CRC patients with synchronous PC in whom the primary tumor was previously resected to patients in which the primary tumor was resected in the same procedure as the CRS and HIPEC. In total 72 patients (44 males; median age 60 years) with synchronous PC from CRC who underwent CRS and HIPEC between march 2005 and January 2012 were selected. Relevant clinicopathologic data were retrospectively retrieved from patient charts with special interest in bowel continuity, ostomy formation and postoperative complications. In twenty patients (27.8%) the primary tumor was resected at the HIPEC procedure; fifteen of these patients had non-resective prior surgery, e.g. formation of a deviating ostomy. In the other 52 patients (72.2%) the primary tumor was resected prior to the HIPEC procedure, with the creation of 37 anastomoses (71.1%). During CRS and HIPEC 22 (59.5%) of these anastomoses were resected. In 12 (54.5%) histopathological assessment of the anastomoses revealed malignancy. The median duration between the first operation and HIPEC procedure was 37 days (range 8 – 85) in patients with non-resective preceding surgery, which was significantly shorter ($P<0.001$) compared to patients whom already underwent a resection; median 93 days (range 42 – 175). Complication rates and long-term results were not statistically different between both groups. Anastomotic leakage rates seemed higher in patients with a resection of a previous anastomosis compared to the rest of the patients (31.8% vs. 14.7%). Twenty patients ended with a colostomy after CRS and HIPEC, 10 of these patients had complete bowel continuity after previous resection. In conclusion, referral before resecting the primary tumor may prevent extended bowel resections and permanent colostomy. Therefore, it is important to consider CRS and HIPEC in patients with synchronous PC from CRC.

Cyclooxygenase-2 (cox-2) is essential for colorectal anastomotic healing

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Anastomotic leakage is a frequent complication after colorectal surgery (incidence 8% in the Netherlands), associated with high short-term mortality rates of up to 40%. Cyclooxygenase-2 (cox-2) inhibitors have been associated with increased risk for anastomotic leakage. Cox-2 is known to be a key enzyme in gastrointestinal inflammation, proliferation and angiogenesis. It is however unknown whether cox-2 plays a pivotal role in the healing of colorectal anastomoses and by which mechanisms. In this study, it is investigated whether cox-2 depletion is associated with impaired anastomotic healing.Twenty male and 21 female mice of different cox-2 genotypes were subjected to a model of colonic anastomotic leakage. Twelve were cox-$2^{-/-}$, 17 were cox-$2^{+/-}$, and 12 had the wildtype cox-2 gene. Differences in anastomotic healing between the genotypes were analyzed. Endpoints for anastomotic healing were incidence of anastomotic leakage, and bursting pressure (BP).Of cox-$2^{-/-}$ mice, 92% developed anastomotic leakage, compared to 41% of a cox-$2^{+/-}$ mice, and 25% of wildtypes. This difference was significant between cox-2 knockouts and wildtypes (p=0.003). Furthermore, the incidence of anastomotic leakage was significantly different between males (70%) and females (33%), p=0.03. With multivariate logistic regression analysis, genotype came out to be the independent predictor of anastomotic leakage. Bursting pressures were not significantly different between groups based on genotype, nor between mice without anastomotic leakage and mice with anastomotic leakage. Cox-2 seems to be essential for the healing of colorectal anastomoses in this experimental murine model of anastomotic leakage.

The Accuracy of Computed Tomography in Detecting Anastomotic Leakage After Colorectal Surgery

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Background: It is essential to identify anastomotic leakage (AL) after colorectal surgery as soon as possible, to minimize morbidity and mortality. Computed Tomography (CT) is held standard in this diagnostic process. This study investigates the accuracy of CT in detecting AL. Methods: A total of 395 consecutive colorectal cancer patients underwent a resection with primary anastomosis between January 2006 and December 2010. Clinical data of these patients were retrospectively collected. We analyzed the outcome in all patients who received a CT-scan within 14 days postoperatively for the clinical suspicion of AL. Results: Of the 395 patients, 59 (15%) underwent a CT-scan because of a suspicion of AL. Of these 59 patients, 17 (29%) had proven AL during relaparotomy. CT scan showed AL in 11 patients (true positive 65 %) and missed it in 6 (false negative 14 %). The positive predictive value (PPV) and negative predictive value (NPV) of the CT-scan in detecting AL were 0.65 and 0.86 respectively.
Conclusion: CT-scan has it limitations in detecting AL after colorectal surgery. Awareness of these shortcomings is of great importance to minimize delay in treatment.

Early closure of anastomotic leakage after ileal pouch-anal anastomosis: a novel solution to an old problem

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A restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is performed in patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP). Anastomotic leakage after IPAA can occur in up to 10% of patients. Leakage interferes with stoma reversal, might compromise pouch function later on, and might result in a chronic presacral sinus precluding stoma closure. Vacuum assisted closure has been reported to be effective to close anastomotic sinuses at the expense of high material costs and time. Early closure of the anastomotic dehiscense after vacuum assisted cleansing of the presacral cavity might overcome the drawbacks of vacuum assisted therapy. A vacuum assisted early closure is proposed and compared to a historical control of patients with leakage of the ileoanal anastomosis. Ten patients undergoing early closure of the anastomotic leakage between April 2010 and September 2012 were prospectively followed and compared with a consecutive cohort of 19 patients that were treated with spontaneous closure between 2003 and 2009. Patients undergoing early closure were treated with an open-pored polyurethane endo-sponge. One or more sponges were placed in the abscess cavity and connected to a low-vacuum suction bottle for a maximum of four days after which the endo-sponge was changed or removed. When the abscess cavity was considered eligible for closure the anastomotic defect was transanally sutured with polydioxane (PDS) sutures. In patients in the spontaneous closure group a diverting loop ileostomy was created and drainage of the abscess cavity was performed. Closure was defined as closure confirmed by radiologic imaging or endoscopy. All study participants were treated in concordance of the declaration of Helsinki. Closure of the anastomotic defect was successful in all 29 patients. In 8 of 10 early closure patients, an ileostomy was created before start of treatment. Two patients were diverted after a first period of VAC treatment; thereafter a second period of Endosponge treatment was performed. The endo-sponge was placed after a median of 2.5 days (interquartile range (iqr) 0-21 days) from diagnosis of leakage. Endo-sponge treatment was continued for a median of 13 days (iqr 10.3-15.3 days), with a median of 3 (iqr 3-4) endo-sponge changes. Closure of the defect was achieved in a median of 16 days (iqr 11.8-46.3 days) in the early closure group vs 85 days (iqr 53-238 days) in the spontaneous closure group after diagnosis of the leakage (p=0.001). Early closure of anastomotic leakage after IPAA with the use of a endo-sponge resulted in an earlier closure of the anastomotic defect and is a very promising concept solving this difficult problem.

Plasma markers for anastomotic leakage after colorectal surgery

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Anastomotic leakage is a frequent complication after colorectal surgery (incidence 8% in the Netherlands), associated with high short-term mortality rates of up to 40%. Moreover, anastomotic leakage negatively impacts cancer specific survival rates. Early re-intervention is critical to reduce mortality. As early clinical and radiological of anastomotic leakage are often non-specific, there is an urgent need for accurate biomarkers. Markers of inflammation and gut damage may be suitable, as these are hallmarks of anastomotic leakage. The aim of this study was to find biomarkers that accurately detect anastomotic leakage at an early time-point.In 50 patients (6 with anastomotic leakage (AL), confirmed by laparotomy or extraluminal contrast on CT) undergoing scheduled colorectal surgery with primary anastomosis, plasma samples were collected preoperatively, and daily after surgery until discharge from the hospital. The inflammatory markers C-reactive protein (CRP), calprotectin, and IL-6; and the markers of gut damage intestinal fatty acid binding protein (I-FABP), liver fatty acid binding protein (L-FABP), and ileal lipid binding protein (ILBP) were measured by ELISA. Diagnostic accuracy of single markers or combinations of markers was analyzed by ROC curve analysis.CRP at postoperative day (POD) 3 predicted AL with sensitivity, 80%; specificity, 75%; positive likelihood ratio (LR+), 3.20 (95% confidence interval (CI), 1.10 – 9.35); negative likelihood ratio (LR-), 0.27 (95% CI, 0.04 – 1.61); p=0.03. IL-6 at POD 3 yielded comparable results, and calprotectin on POD 3 predicted AL with sensitivity, 100%; specificity, 75%; LR+ 4.00 (95% CI, 1.35 – 8.59); LR-, 0.00 (95% CI, 0.01 – 1.67); p=0.02. I-FABP levels at POD 3 predicted AL with sensitivity, 83%; specificity, 81%; LR+, 4.37 (95% CI, 1.85 – 10); LR-, 0.21 (95% CI, 0.04 – 1.25); p=0.03. L-FABP and ILBP levels were not statistically different between groups. Combination of calprotectin and I-FABP levels on POD 3 yielded highest accuracy: sensitivity, 100%; specificity, 91%; LR+, 11 (95% CI, 1.61 – 34); LR-, 0.00 (95% CI, 0.01 – 1.37); p=0.002. The inflammatory markers CRP, IL-6 and calprotectin predict anastomotic leakage with reasonable accuracy on day 3 following colorectal surgery. When combining with I-FABP, a marker of intestinal epithelial damage, accuracy increases drastically. This pleads for implementation of these markers in daily practice.

Surgical treatment for complex perianal fistulas combined with platelet rich plasma. Long-term results

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In the long-term, the results of surgical closure of high cryptoglandular perianal fistulas (HCPF) are disappointing. Goal of this study is improving the long-term results of surgical treatment for HCPF, combining the mucosal advancement flap with platelet-rich plasma. All patients presenting with HCPF, defined as fistulas involving the middle or upper third of the anal sphincter complex, were included. Patients with inflammatory bowel diseases, low platelet levels or other bleeding disorders, haematological or local malignancies, and pregnant patients were excluded.First, all patients were treated with a seton. After at least two to three months, later if inflammatory activity was still present, the patients were treated with a mucosa advancement flap (MAF). The external fistula opening was excised and left open. A debridement of the fistula tract is performed. Platelet-rich plasma (PRP), centrifuged from 55mL of the patient's blood, is introduced in the external opening and left behind in the fistula tract. No activating agent is added. Treatment failure was defined as absent closure of the fistula within 3 months. We operated 25 patients between 2006 and 2012. All patients were treated according to protocol. One patient (4.0%) was lost to follow-up after four months. The median follow-up period was 27 months. The recurrence rate was 16% (four out of 25 patients). Of the four patients with a recurrence, two (8.0%) were treated with a MAF and PRP again and both healed. One (4.0%) patient refused another treatment, but agreed to stay in follow-up. One patient (4.0%) requested a colostomy, resulting in closure of the fistula afterwards. In one patient (4.0%) the treatment was complicated by a perianal abscess, which was drained twice. This was one of the patients with a recurrence. No other complications were seen. Incontinence numbers were low with a median Vaizey score of 3.0 out of a maximum of 24. The median maximum and minimum Visual Analogue pain Scores (VAS) were both 0. SF-36 mean scale scores were comparable to the general Dutch population.
Conclusion: The long-term outcome results of patients with HCPF treated with a seton followed by MAF and PRP, show low recurrence, complication and incontinence rates. Therefore, this technique seems to be a valid option for the treatment of HCPF. Larger and randomised controlled studies are needed to further explore this surgical technique.

Lipid raft modulation in rat visceral hypersensitivity: proof of principal study

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The activation signals of many receptors are regulated in membrane microdomains, or lipid rafts, that serve as stable, efficient signaling platforms for ligand-engaged receptors. Previously, we have identified two possible targets for treating visceral hypersensitivity, relevant for irritable bowel syndrome (IBS), in our maternal separation (MS) model; mast cell activation and activation of TRPV1 channels. In this proof of principle study we used the prototype raft modulator Miltefosine to establish whether lipid raft modulation should be considered as a treatment option for visceral hypersensitivity.Adult MS and nonhandled (NH) rats were subjected to 1hr water avoidance stress (WA). The visceromotor response (VMR) to colorectal distension was measured pre- and post-WA and after 7 days of Miltefosine treatment (0.1, 1 and 10 mg/kg daily through oral gavage) or vehicle. In addition, separate groups of NH rats were treated with Miltefosine (10 mg/kg daily through oral gavage) or vehicle. Rats were then rectally infused with 100µL 0.1% capsaicin. VMR to colorectal distension was measured before treatment with Miltefosine or vehicle, and pre- and post-capsaicin infusion. In both experiments, response to distension (1, 1.5 and 2ml) was expressed as area-under-the-curve (AUC, volume-vs-response). Lastly, we used TRPV1-transfected SH-SY5Y and WT cells to evaluate the TRPV1 modulating capacity of Miltefosine in Ca^{2+}-mobilization assays.WA lead to increased VMR to distension in MS vehicle-treated rats (pre-WA vs post-WA AUC; 76 vs 101, P=0.021) but not in NH rats. Treatment with 1 and 10 mg/kg Miltefosine reversed post-WA hypersensitivity (pre-WA vs post-treatment AUC; 67 vs 72, P= 0.093 and 72 vs 72, P= 0.953 respectively), whereas rats treated with 0.1 mg/kg or vehicle remained hypersensitive. Capsaicin-induced hypersensitivity was observed in vehicle-treated NH rats but not in Miltefosine-treated rats (pre- vs post-capsaicin AUC; 77 vs 111, P= 0.002 and 75 vs 93, P= 0.055 respectively). These findings were confirmed in vitro, where Miltefosine dose-dependently inhibited capsaicin-induced Ca^{2+} mobilization. Conclusion: Showing beneficial effects on modulating both capsaicin-induced (TRPV1-dependent) and established stress-induced (TRPV1- and mast cell-dependent) visceral hypersensitivity, our results provide strong evidence for the concept of lipid raft modulation to reduce visceral hypersensitivity in IBS.

The microbiota in mouse colon is causal for dietary heme-induced epithelial hyperproliferation and hyperplasia

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Colorectal cancer risk is associated with diets high in red meat. Heme, the iron porphyrin pigment of red meat, induces oxidative and cytotoxic stress in the colonic lumen injuring the surface epithelium. Compensatory hyperproliferation and inhibition of apoptosis lead to hyperplasia, which may develop into colon cancer. The aim of this study was to investigate whether colonic bacteria play a role in heme-induced hyperproliferation and hyperplasia. C57Bl6/J mice received a Westernized control diet (40 energy% fat, low calcium (30 µmol/g)), with or without 0.5 µmol/g heme for 2 weeks. The microbial composition was analyzed by 16S rRNA phylogenetic arrays. Mucosal responses were investigated by whole genome microarrays.The heme diet changed the microbial composition, with a major decrease in Firmicutes and increases in Bacteroidetes, Proteobacteria and Verrucomicrobia. The mucin degrading bacteria Akkermansia (Verrucomicrobia) and Prevotella (Bacteroidetes) were drastically increased by heme. No inflammation or changes in epithelial microbe sensing were observed, as evidenced by the absence of infiltrates. Moreover, gene expression levels of macrophage (e.g CD14, F4/80) and neutrophil markers (e.g. Mpo, Emr4) and of downstream targets of Toll-like receptors (such as TNFα, Il-1β, Il-6, Il-12) were not changed. Whether bacteria play a causal role in heme-induced hyperproliferation and hyperplasia was studied using broad-spectrum antibiotics (Abx) in the drinking-water. Heme induced luminal oxidative and cytotoxic stress in heme and heme + Abx fed mice, so there was no major role for bacteria in the formation of reactive oxygen species and the cytotoxic heme metabolite. Heme induced hyperproliferation and hyperplasia, but this was blocked completely by Abx. Transcriptome analysis showed that Abx blocked the heme-induced differential expression of oncogenes, tumor suppressors and cell turnover genes. Moreover, Abx blocked the mucosal sensing of luminal cytotoxicity, indicating that Abx fortified the mucus barrier. Abx eliminated Akkermansia, Prevotella and sulfate reducing bacteria (SRBs) producing sulfide. We show that sulfide reduces disulfide bonds very potently in vitro, suggesting that SRB-generated sulfide may denature mucins and increase mucus barrier permeability.This study shows that heme changes the microbial composition of mouse colon by increasing the relative abundance of mucin degrading bacteria. These bacteria can break the mucus barrier, thereby decreasing the mucosal protection against luminal irritants, such as the cytotoxic heme metabolite, and increasing the risk of colon cancer.

Activation of snail via reactive oxygen species mediates acetaldehyde-induced disruption of tight junctions in Caco-2 cell monolayer

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Background: Exposure to acetaldehyde is associated with intestinal barrier dysfunction and risk of malignant transformation in the gastro-intestinal tract. Epithelial-mesenchymal transition (EMT) is a developmental program shown to play a role in loss of epithelial integrity, cancer progression and metastases. EMT is induced by its transcription factor Snail, which downregulates E-cadherin expression. Recently, activation of EMT Snail has been found to mediate ethanol-induced intestinal barrier disruption. As acetaldehyde has an even higher potency to induce barrier dysfunction and is mutagenic, we hypothesized that acetaldehyde disrupts intestinal epithelial integrity by inducing oxidant-dependent Snail activation.Aims: To investigate the role of oxidative stress and Snail activation in acetaldehyde induced barrier disruption in an in vitro model of intestinal permeability.
Methods: Caco-2 monolayers were exposed from the luminal side to 25 μM acetaldehyde +/- 100 μM L-cysteine to inhibit ROS generation. Intestinal epithelial permeability, localization and expression of ZO-1, occludin, E-cadherin, β-Catenin were examined using TEER and FITC-D4 flux, immunofluorescence and ELISA, respectively. ROS generation and Snail activation were assessed by ELISA and immunofluorescence. Involvement of Snail was further addressed by inhibiting Snail using small interfering RNA (siRNA). Results: Exposure to acetaldehyde 25 μM significantly increased the paracellular permeability (60% decrease in TEER and 34% increase in FITC-D4 flux vs. medium only-treated controls, both P <0.0001) in association with redistribution and decrease of tight junction (TJ) and adherens junction (AJ) protein levels. Acetaldehyde increased ROS generation by 40% and Snail phosphorylation by 30% (both P < 0.0001 vs. medium only-treated controls). These effects were attenuated by L-Cysteine (P < 0.0001 vs. acetaldehyde only-treated monolayers). Knock down of Snail by siRNA significantly attenuated acetaldehyde-induced changes and decrease in TJ and AJ proteins, improved TEER and decreased FITC-D4 permeation (all P < 0.05 vs. non-specific Snail-transfected cells).
Conclusions: Our data demonstrate that oxidative stress-mediated Snail phosphorylation is likely a novel mechanism contributing to the deleterious effects of acetaldehyde on intestinal barrier function. Identification of mechanisms involved in acetaldehyde-induced intestinal barrier dysfunction may provide new therapeutic targets for prevention of alcohol-related gut leakiness with subsequent development of liver disease and colon carcinogenesis.

Novel treatment options to improve protein folding and enhance pre-mRNA splicing in ATP8B1 deficiency

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Although individually rare, genetic diseases resulting from missense or splice site mutations affect millions of people worldwide. Tailored solutions for individual patients or patients with the same mutation are unlikely to be developed, due to the significant investments required for this. Compounds that affect the cellular splicing machinery might be useful to improve pre-mRNA splicing in a much larger group of patients. Similarly, compounds that stimulate the cellular protein homeostasis (proteostasis) machinery (proteostasis regulators) are likely to improve protein folding in a potentially very large group of patients. ATP8B1 deficiency is a severe hereditary disease characterized by intrahepatic cholestasis. The exact pathogenesis of the disease is elusive, and no effective pharmacological therapy is currently available. Many of the genetic defects in ATP8B1 are predicted to affect mRNA splicing and the most common missense mutation (p.I661T) leads to ATP8B1 protein misfolding. We investigated the potential of 13 proteostasis regulators to restore ATP8B1 plasma membrane expression by cell surface biotinylation in U2OS cells expressing wild-type ATP8B1 or the most common mutant ATP8B1 p.I661T. The splicing effect of 15 predicted splice-site mutations in ATP8B1 was determined by RT-PCR using 9 minigenes. Three of the 15 ATP8B1 mutations resulted in partial correct exon inclusion, in with the relatively mild BRIC phenotype of the patients with these mutations. All other ATP8B1 splice-site mutations resulted in complete exon skipping, or did not yield detectable RT-PCR products. Initial results with natural compounds that affect cellular splicing show improved exon inclusion for BRIC mutations. Furthermore, six proteostasis regulators caused a significant upregulation of ATP8B1 protein plasma membrane expression, 3 compounds resulted in a minor increase and 3 were ineffective. One regulator was excluded for further analysis due to excessive toxicity. In conclusion, proteostasis regulators may provide novel therapeutic options for protein misfolding diseases including ATP8B1 deficiency. PFIC1 mutations lead to very low efficiency of exon-inclusion, whereas in BRIC1 residual correctly spliced ATP8B1 mRNA is detectable. Currently splicing-modulating compounds are tested in vitro and proteostasis regulators are tested functionally using hepatocyte-like cells differentiated using induced pluripotent stem cells derived from a patient homozygous for the p.I661T mutation in ATP8B1.

27-Hydroxycholesterol: a potential treatment for non-alcoholic steatohepatitis in mice

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Non-alcoholic steatohepatitis (NASH) is characterized by hepatic steatosis in combination with inflammation. While steatosis itself is considered benign and reversible, the presence of inflammation can lead to further liver damage. We recently demonstrated a clear association between hepatic inflammation and lysosomal cholesterol accumulation inside Kupffer cells (KCs). 27-hydroxycholesterol (27HC), a derivative of cholesterol formed by CYP27A1, has been shown in vitro to mobilize cholesterol from the lysosomes to the cytoplasm. Here, we hypothesized that 27HC can redirect the intracellular cholesterol distribution in vivo, thereby influencing hepatic inflammation. To investigate the role of CYP27A1 in NASH, irradiated low density lipoprotein receptor knockout (Ldlr-/-) mice were transplanted (tp) with Cyp27a1-/- and wild-type (Wt) bone marrow. After 9 weeks recovery, mice were fed either regular chow or a high-fat, high-cholesterol (HFC) diet for 3 months. To examine whether exogenous 27HC influences intracellular cholesterol distribution and hepatic inflammation, 27HC was administered to Ldlr-/- mice that received regular chow or an HFC diet for 3 weeks.
Electron microscopy analysis of KCs revealed more lysosomal cholesterol accumulation in Cyp27a1-/--tp mice than in Wt-tp mice after HFC feeding. Liver histology and gene expression showed increased inflammation and liver damage in HFC-fed Cyp27a1-/--tp mice. In with these data, administration of 27HC to Ldlr-/- mice on an HFC diet led to reduced lysosomal cholesterol accumulation and hepatic inflammation.
Conclusions: These data support a causal role for lysosomal cholesterol accumulation in hepatic inflammation and under the potential of 27HC as a treatment for NASH.

Exploring a role for Cyp17a1 in the pathogenesis of cholestasis

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Introduction: Cholesterol serves as a pre-cursor of steroid hormones and bile acids. In the liver, cholesterol escapes the body via bile acid formation and secretion into bile. However, the liver is not considered a steroidogenic tissue, although it expresses several steroidogenic genes under normal conditions. Bile acids (BAs) are intrinsically toxic, therefore their intrahepatic concentrations are tightly controlled. Pregnancy can expose cholestatic disease in genetically predisposed individuals. The nuclear receptor FXR controls BA synthesis by transcriptional activation of SHP, which in turn represses transcription of the rate-limiting enzyme in BA-synthesis (CYP7A1). We previously showed that estrogens interfere with FXR function and may perturb BA homeostasis during pregnancy. Here, we present a novel hepatic target-gene of FXR/SHP that is estrogen-modulated and may contribute to the pathology of intrahepatic cholestasis of pregnancy.Methods: In vivo experiments were conducted on age-matched wild-type and FXR-KO mice. Gene and protein expression was determined by qPCR and western blotting respectively. In vitro experiments including ChIP, EMSA, luciferase assays were conducted according to standard protocols. Results: We find that BAs robustly repress the expression of the steroidogenic enzyme, Cyp17a1, in mouse liver. The effect of BAs on Cyp17a1 are FXR-dependent and liver-specific. Extensive in vitro experiments demonstrate that Cyp17a1 is regulated by a nuclear receptor cascade involving LRH-1, FXR and SHP. As such, the regulation of hepatic Cyp17a1 is strikingly similar to that of the bile acid synthesis enzyme, Cyp7a1. Intriguingly, hepatic Cyp17a1 expression is significantly higher in females than in males, is up-regulated during pregnancy and is induced upon estrogen treatment.
Discussion: 17a-hydroxyprogesterone (a product of Cyp17a1) was recently shown to cause cholestatic liver injury in mice. Our findings raise the possibility that estrogen-mediated dysregulation of FXR during pregnancy may induce hepatic Cyp17a1 and expose cholestatic disease in pre-disposed individuals. The function of Cyp17a1 in liver, and the relevance of its regulation by FXR, is currently under investigation.

Indian Hedgehog is required for intestinal adenoma formation

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Introduction: Activating mutations in the Hedgehog pathway are found in basal cell carcinomas and medulloblastomas. The role of Hedgehog signaling in intestinal tumorigenesis has not yet been clarified. Hedgehog is expressed by differentiated enterocytes and signals in a paracrine manner from the epithelium to the mesenchyme. Hedgehog controls mesenchymal factors such as Bone Morphogenetic Proteins and Activins which negatively regulate the proliferation of precursor cells. Since Indian Hedgehog (Ihh) is the major Hedgehog expressed in the intestinal epithelium we decided to study the potential role of Ihh signaling in intestinal adenoma formation. Methods: In order to study the effect of loss of Ihh signaling in sporadic tumorigenesis we conditionally deleted Ihh in adult mice in the intestinal epithelium using the Cyp1a1Cre promoter. These compound mice were crossed with conditional mutant Apc^{15lox} mice to generate Cyp1a1Cre-$Ihh^{fl/fl}$-$Apc^{fl/+}$ mice. At 4-7 weeks of age mice were intraperitoneally injected with 80 mg/kg b-naphthoflavone for 5 days. Cyp1a1Cre-$Ihh^{+/+}$-$Apc^{fl/+}$ littermates served as controls. Four months after recombination, we sacrificed and analyzed the mice (n=15).Results: Ihh expression was upregulated in polyps of Cyp1a1Cre-$Ihh^{+/+}$-$Apc^{fl/+}$ mice as assessed by in situ hybridization. Deletion of Ihh resulted in a marked reduction of 90.3% in the number of polyps (17.2 ± 13.65 polyps per mouse vs. 1.7 ± 1.5, $P < 0.01$). The average polyp size did not differ between groups. Neither did the number of proliferating or apoptotic cells in the polyps, as assessed by immunostaining for BrdU and cleaved caspase 3. Analysis of Hh responsive cells in the mesenchyme of the polyp showed a decrease of the number of a-sma en desmin double positive cells (smooth muscle cells). COX2 is expressed early in adenoma to carcinoma transition and believed to play an important role in adenoma formation. Stromal cells are known to be a source of COX2. In accordance with this, examination of Cox2 expression by Q-PCR and immunostaining showed up regulation in polyps of Cyp1a1Cre-$Ihh^{+/+}$-$Apc^{fl/+}$ mice in compared to normal intestinal epithelium ($P < 0.01$, resp. $P < 0.05$). In contrast, Cox2 expression in the polyps of Cyp1a1Cre-$Ihh^{fl/fl}$-$Apc^{fl/+}$ mice was not significantly up regulated.
Conclusion: Surprisingly, in contrast to its role as an anti-proliferative signal in the normal epithelium, Ihh acts as a tumor promoter. The expression of Ihh is increased in polyps and mice that lack Ihh develop fewer polyps. This finding is accompanied by loss of smooth muscle cells in the mesenchyme of the polyp and decreased Cox2 expression.

Human liver carcinomas recruit mesenchymal stem/stromal cells that can promote tumor growth via paracrine signaling

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Bone marrow mesenchymal stem/stromal cells (MSCs) can migrate to tumor sites and contribute to the tumor microenvironment. However, it is still hotly debated whether MSCs have a positive or negative effect on tumor growth. This study aims to investigate whether human liver carcinomas contain MSCs and whether MSCs may affect tumor growth. We cultured MSCs from surgical resected hepatocellular carcinoma (HCC) (n=6) and liver metastatic colorectal tumor (LM-CRC) (n=7) (successfully cultured from 11 out of 13 liver tumors). Their MSC properties were characterized by adipocyte and osteocyte differentiation and common mesenchymal markers. Immunohistochemical staining of STRO-1 (the best-known MSCs marker for in vivo detection) was performed in paraffin-embedded patient HCC and LM-CRC tissues (n=24). Notably, in situ staining showed that STRO-1 positive cells are significantly enriched in the tumor, in particular the tumor-stromal region, compared with the adjacent area in HCC and LM-CRC tissues (n=24, $p<0.01$). We also observed that solid tumors formed in mice by subcutaneous engraftment of human hepatoma Huh7 cells were able to recruit MSCs. The effects of MSCs on tumor growth were evaluated in immune-deficient mice. Co-engraftment of Huh7 and MSCs in mice resulted in significant larger tumors than engraftment of Huh7 alone (tumor weight 1.56±0.27 g Vs 0.44±0.19 g, Mean±SEM, n=8, $p<0.01$). Consistently, co-culturing Huh7 with irradiated MSCs significantly increased the number (196±29 Vs 123±36 clonies/5000 Huh7, Mean±SD, n=5, $p<0.01$) and the size (1329±258 Vs 570±155 pixels, n=5, $p<0.01$) of formed colonies. This effect was also observed by treatment of MSCs conditioned medium (MSC-CM), suggesting secreted tropic factors contributing to the tumor promoting effect. Genome-wide gene expression array and pathway analysis confirmed the up-regulation of cell growth and prolife-ration-related processes and down-regulation of cell death-related pathways by treatment of MSC-CM in Huh7 cells. Conclusion: Human liver carcinomas recruit MSCs, which in turn can promote tumor growth. These results shed new light on the crosstalk between MSCs with liver cancer cells but also caution stem cell therapy of using MSCs for liver cancer and other liver diseases with high risk of developing malignancy.

Induction of ER stress identifies potential esophageal stem cell markers

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The esophageal squamous epithelium is a rapidly renewing tissue. It has recently been shown that the esophageal epithelium is hierarchically organized with long lived stem cells and rapidly proliferating cells that maintain cellular renewal, both being localized in the basal layer. To date, no specific markers have been identified that distinguish stem cells from non stem cell proliferating cells. In the intestinal epithelium, long lived stem cells and transcripts that mark stemness are rapidly depleted upon induction of endoplasmic reticulum (ER) stress (unpublished data, Heijmans, Rosekrans, van den Brink). We hypothesize that esophageal stem cell markers exhibit a similar sensitivity to ER stress. We aim to identify stem cell genes that mark a hierarchically distinct population of cells in the basal layer cells by analysis of a gene signature that is lost upon induction of ER stress.Sensitivity of esophageal precursor cells to ER stress was examined in vivo and in vitro. For proof of principle experiments in vivo, we chemically induced ER stress in mice, by injections with thapsigargin. For in vitro experiments, ER stress was induced in vitro in TE7 and OE21 esophageal squamous cell carcinoma (SCC) cell lines using SubAB, a cytotoxin that induces ER stress by depleting the major ER chaperone GRP78. From in vitro experiments, we next performed gene arrays to identify those transcripts that were significantly down regulated in both cell lines upon induction of ER stress. Next, we localized mRNA of all these genes in wild type mouse esophagus by Dig labeled in situ hybridization.Induction of ER stress in mice resulted in rapid depletion of esophageal precursor cells and accelerated differentiation, thus showing that in analogy to the intestine, esophageal stemness is lost. Using RNA micro-arrays, we identified a gene signature of 47 genes that were lost in both individual cell lines upon induction of ER stress. Of these genes, we found 29 genes to be restricted to the basal layer of the mouse esophagus. Out of these 29, nine genes show expression in only a small proportion of the basal cells, potentially marking stem cells.
Conclusion: ER stress depletes esophageal precursor cells. Our in vitro screen combined with in situ hybridization identified nine genes that are specifically expressed in a subset of proliferating genes, thereby potentially marking esophageal stem cells.

The Bone Morphogenetic Protein Pathway either enhances or inhibits the Wnt pathway depending on SMAD4 and p53 status in colorectal cancer

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Background: In intestinal crypt-villus homeostasis, morphogenic signalling pathways such as BMP and Wnt interact to control cell fate. In the normal intestine BMP signalling is responsible for differentiation and apoptosis and inhibits Wnt signalling, which is responsible for proliferation and inducing stemness. In tumourogenesis, cells acquire mutations which result in the disruption of these pathways and changes in pathway-pathway interaction. For example, mutations in SMAD4, a central component of both BMP and TGFβ signalling, reverse the interaction between TGFβ and Wnt signalling and switch TGFβ signalling from being tumour suppressive to promoting invasion and metastasis. We therefore set out to investigate how several of the common mutations found in colorectal cancer might change the interaction between the BMP and Wnt pathways. With cancer therapy increasingly focused on the targeted pharmacological modulation of the specific molecular pathways underlying carcinogenesis, understanding of how the major pathways interact and how mutations influence this is of critical importance.Methods: BMP-Wnt interaction was measured in 8 CRC cell lines. BMPR2 transfection and BMP-2 treatment were used to activate BMP signalling. Noggin and the small molecule LDN-193189 were used to inhibit BMP signalling. Wnt signalling activity was measured using a β-catenin reporter assay. HCT116 SMAD4-/-, HCT116 p53 mutant and shRNA against SMAD4 in LS174T cells were used to investigate BMP-Wnt interaction dependent on SMAD4 and p53 status. Expression of Wnt-target genes was evaluated by q-PCR array and immunoblotting. MTT assays were performed to study cytotoxic effects of 5-FU in CRC cells. Results: Activation of BMP signalling results in downregulation of Wnt signalling only in SMAD4 positive and p53 WT cell lines. qPCR arrays reveal CTNNBIP1 (β-catenin interacting protein) as a possible regulator in this mechanism. Loss of SMAD4 shifts BMP signalling from inhibiting to enhancing Wnt signalling. In p53 mutant cells Wnt signalling inhibition by BMP is abolished. While BMP signalling significantly increases the sensitivity of SMAD4 positive cancer cells to 5-FU, it reduces 5-FU sensitivity in SMAD4 negative cancers. Pre-treatment of SMAD4 negative cancer cells with a BMP inhibitor significantly increases chemo sensitivity.
Conclusions: Our data suggest that BMP signalling either inhibits or enhances the Wnt pathway based on the SMAD4 and p53 status and can therefore be either tumour-suppressive or tumour-promoting. SMAD4 independent BMP signalling is in part responsible for the chemoresistance of SMAD4 negative cancers. Inhibition of BMP signalling increases chemosensitivity in SMAD4 negative colorectal cancer, a chemo-resistant molecular subtype with a poor prognosis.

Preoperative chemoradiotherapy for esophageal or junctional cancer

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The role of neoadjuvant chemoradiotherapy in esophageal cancer remains unclear. The aim of this study was to compare preoperative chemoradiotherapy (CRT) followed by surgery vs. surgery alone in patients with esophageal or esophagogastric junction cancer. Patients with resectable cT1N1M0 or cT2-3N0-1M0 tumors were randomly assigned to preoperative CRT of weekly administrations of carboplatin AUC of 2 and paclitaxel 50 mg·m^{-2} for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week) followed by surgery (CRT+S) or surgery alone (S). From 2004 through 2008, 368 patients were enrolled, of whom 366 could be analyzed: 275/366 (75%) had adenocarcinoma and 84/366 (23%) had squamous cell carcinoma. Some 178 patients were randomized for CRT followed by surgery, 188 patients for surgery alone. The most common major hematologic toxicities in the CRT+S arm were leukopenia (6%) and neutropenia (2%), the most common major non-hematologic toxicities were anorexia (5%) and fatigue (3%). Complete resection with no tumor within 1 mm of the resection margins (R0) was achieved in 92% of patients in the CRT+S arm vs. 69% in the S arm ($p<0.001$). In 47/161 (29%) patients who underwent resection after CRT, a pathologically complete response was achieved. Postoperative complications and in-hospital mortality (4% in both treatment arms) were comparable between treatment arms. Median overall survival was 49.4 months in the CRT+S arm vs. 24.0 months in the S arm. Overall survival was significantly better ($p= 0.003$) in the CRT+S arm (HR 0.657; 95% CI 0.495-0.871).
Conclusion: Preoperative chemoradiotherapy was well tolerated and improved survival in patients with potentially curable esophageal or esophagogastric junction cancer.

Prediction of disease-free survival using relative change in FDG-uptake early during neoadjuvant chemoradiotherapy for potentially curable esophageal cancer

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^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) has been investigated as a tool for monitoring response to neoadjuvant chemoradiotherapy (CRT) and as a predictor for survival in patients with esophageal cancer. It is unknown whether the patients identified as responders show better disease-free survival (DFS) compared to patients identified as non-responders. The aim of the present study was to determine the predictive value of FDG-uptake measured prior to and early during neoadjuvant CRT.Patients treated with neoadjuvant CRT between 2004 and 2009 within a randomized trial were included. FDG-uptake was measured at base and after 14 days of CRT. Patients were followed until recurrence of disease or death. The predictive value of FDG-PET was determined with uni- and multivariable analysis in patients who underwent potentially curative surgery.One-hundred and six patients were included in the analysis. Median follow-up for surviving patients was 44.4 months. FDG uptake at base and relative FDG uptake change after 14 days of CRT were not predictive for DFS (HR 0.99 and 1.00 respectively). No significant differences in 5-year DFS were found between patients with higher or lower uptake than the median uptake at base or between patients with metabolic response, stable disease or progression.
Conclusions: Base FDG uptake and relative change in FDG uptake after 14 days of CRT were not associated with disease-free survival in patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy followed by surgery. These measurements should not be used for prognostication in this specific group of patients.

Timing of surgery and location of residual tumor after neoadjuvant chemo-radiotherapy for esophageal cancer

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Background: Results from the Dutch CROSS trial have shown that in 49% of the squamous cell carcinomas and 23% of the adenocarcinomas no viable tumor cells could be identified in the resection specimen after nCRT. This raises the question, whether this subgroup could reliably be identified after nCRT? First, we analyzed the potential impact of the delay between nCRT and the surgical resection on the grade of pathological tumor response, to possibly gain insight into the optimal timing of clinical restaging. Second, we described the location of residual tumor in the esophagus after nCRT, to potentially better target clinical restaging. Methods: Patients treated with nCRT (5 weekly courses of Carboplatin and Paclitaxel with 41.4 Gy concurrent radiotherapy) for resectable esophageal cancer between 2002 and 2011 were identified. The interval between nCRT and surgery, and the corresponding tumor regression grade (=TRG) in the resection specimen, including adjacent lymph nodes, were determined. For patients from the coordinating center, the TRG was also scored for each individual layer of the esophageal wall and for all resected lymph nodes. Results: Two hundred and forty-seven patients were included in the first part of the study. Median age was 59.8 years and the majority of patients (74.5%) had an adenocarcinoma. A radical resection was performed in 234/247 (95%) patients. The median interval between nCRT and surgery was 47 days [p25-p75: 39-56]. The percentage of pathologically complete responders (TRG1) was higher in patients with an interval of more than 55 days (≥p75) as compared to patients with a shorter interval (<p75) (43% vs. 24%; p= 0.005). However, there was no significant difference in disease-free survival (DFS) between patients with an interval above or below the 75th percentile (HR 1.01 95% CI0.63-1.62). In a subgroup (N=102) from the coordinating center, 71 patients were non-complete responders, of whom 89% (63/71) had residual tumor in the (sub)mucosa. Eight patients had no residual tumor in the (sub)mucosa; five of whom had tumor in the muscle layer and three of whom had tumor in a single lymph node. No patient had tumor in the surrounding stroma (T3) only. Conclusion: In patients with a relatively long interval (>p75) between nCRT and surgery, significantly more pathologically complete responders were observed. These results support a prolongation of the interval between nCRT and subsequent resection in order to facilitate the identification of complete responders. In the great majority of incomplete responders, residual tumor is present in the (sub)mucosa. (Cyto)histological biopsies should therefore be focused on these two layers.

A new fully covered metal stent (HANARO-ECT stent) for the treatment of malignant esophageal strictures: a prospective follow-up study

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Placement of self-expandable metal stents (SEMS) provides effective palliation in patients with malignant dysphagia. Although fully covered SEMS are increasingly used to prevent tissue ingrowth, they are prone to migrate. To reduce migration risk, we developed the HANARO-ECT stent, a fully covered 20-mm SEMS which combines bilateral flared ends and three rows of anchoring flaps on the stent body to prevent migration. We evaluated clinical and technical success and safety of this new stent for the palliation of malignant dysphagia. From June 2011 until October 2012 consecutive patients who underwent HANARO-ECT stent placement in four centers were included. Patients were contacted after 2 weeks and monthly thereafter until death. Forty patients (29 men (72.5%), mean age 68 ± 11 years) were included. Malignant dysphagia was caused by esophageal cancer (n=32), malignant extrinsic compression (n=5), tumor recurrence after esophagectomy (n=2) and gastric cancer (n=1). Four patients (10%) had an esophageal-respiratory fistula and 26 patients (65%) had undergone previous radiation and/or chemotherapy. Stent placement was technically successful in 38 patients (95%), in 1 patient the stent collapsed during repositioning and a second stent was placed through the stent and in 1 patient the stent was placed more distally than intended despite repositioning. Thirty-four patients (85%) remained dysphagia free during follow-up (median 59 days, range 2-397), while 6 patients (15%) had recurrent dysphagia after a median of 39 days (range 9-48), due to stent migration (n=5) and tissue overgrowth (n=1). In 4 of these patients, the stent had partially migrated and could be repositioned endoscopically, while in 2 patients a new stent was placed. One patient presented with recurrent partial migration after 59 days, for which repeat repositioning was performed. Fourteen patients are still alive after a median of 59 days (range 15-397) and 26 patients died after a median of 58 days (range 2-210), due to disease progression (n=20), complicated pneumonia (n=3), cardiac disease (n=1), euthanasia (n=1) and acute hypoxemia due to tumor ingrowth in the trachea (n=1). In total, 24 major complications occurred in 18 patients (47%), including severe pain (n=7), severe nausea and/or vomiting (n=6), bleeding (n=4), aspiration pneumonia (n=4), fistula formation (n=2) and tracheal compression (n=1). Despite the specific anti-migration features of the HANARO-ECT stent, migration was the main cause of recurrent dysphagia. We also observed a relatively high complication rate, especially severe pain, nausea and vomiting. We conclude that further improvements in stent design are needed.

Early pain detection and management after self-expandable esophageal stent placement in incurable cancer patients: a prospective observational cohort study

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Placement of a self-expandable metal stents (SEMS) in the esophagus is an effective palliative treatment for incurable patients with dysphagia due to a malignant esophageal stenosis. This intervention is often complicated by the occurrence of retrosternal pain, but the exact incidence, severity, predictors and optimal management are unknown. In this prospective observational cohort study we included patients with incurable malignant esophageal stenosis, who were eligible for SEMS placement. Patients reported duration and intensity of pain twice a day in a pain diary according to the Numeric Rating Scale (NRS) for 2 weeks (0=no pain, 1-3=mild pain, 4-6=moderate pain, 7-10=severe pain). If pain occurred, acetaminophens were used and in case of ongoing pain an opiate was prescribed. Dose, duration and kind of analgesia were noted.47 patients (75% male; mean age 67 years; range 39-84 years) were included. Twenty-eight patients (60%) reported a pain score of ≥ 4 at day 1, 15 patients (32%) reported a pain score ≥ 4 at day 7 and 11 patients (23%) reported a pain score of ≥ 4 at day 14 after SEMS insertion. The highest pain score was noted at day 1 with a median pain score of 5 (range 0-10). A median pain score of 3 (range 0-7) was noted at day 7 and median pain score of 2 (range 0-8) at day 14. Forty-three patients (91%) needed analgesia in the first week after SEMS insertion. Eighteen patients (42%) used acetaminophen, 5 patients (12%) used an opiate and 18 patients (42%) used a combination of both to obtain a pain score < 4. Acetaminophen with a median dose of 4000 mg (range 0 - 4000 mg) and an opiate with a median dose of 20 mg a day were used for a median of 10 days (range 1-ongoing). No significant correlation between prior chemo- and radiotherapy and the development of a pain score ≥ 4 were found in univariate analysis.Esophageal SEMS insertion for malignant stenosis results in moderate to severe pain in 60% of the patients. Analgesia medication was prescribed in 91% of the cases for an average of 10 days. Patients need to be informed about this very common side effect and preventive prescription of analgesia should be considered to proactively manage post-stent insertion pain in order to improve quality of life of these patients.

Limited diagnostic value of microsatellite instability associated pathology features in colorectal cancer

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Background: The revised Bethesda guidelines for Lynch syndrome recommend molecular testing colorectal cancers (CRC) in patients diagnosed before age 50 years, and in patients between 50 and 59 years with the presence of pathology features associated with microsatellite instability (MSI-H). However, the reproducibility of the histological interpretation of these features is questionable. Aim: To determine the diagnostic test characteristics and the inter-observer variation in the histological diagnosis of MSI-H associated pathology features. Methods: 180 CRC were selected from a prospective study in CRC patients assessed for MSI status (LIMO-study). Cases were blindly evaluated by six pathologists for degree of differentiation, histology subtype, presence of tumor-infiltrating lymphocytes (TIL) and Crohns like infiltrate (CLI). After evaluating a random subset of 90/180, a consensus meeting was organized, after which the remaining 90/180 were evaluated. Diagnostic test characteristics were calculated by using MSI-status as the reference value. Inter-observer agreement was determined by using Kappa statistics. Results: 170/180 CRC (94%) were evaluable for the agreement analysis; 83 in the first and 87 in the second set, of which 39/83(47%) and 33/87(38%) were MSI-H (p=0.23), respectively. In the first set, TIL and CLI were the best discriminators between MSI-H and microsatellite stable (MSS) CRC (OR 5.4(95%CI 1.8-16.8) and 3.5(95% CI 1.1-11.0), with high specificity (89% both). The sensitivities for MSI-H, however, were low (41% and 31%). In addition, inter-observer agreement was moderate (median kappa 0.38 and 0.48). Interpretation of overall histopathology as suggestive for MSI-H performed better than any individual feature; OR 15.0(95%CI 5.2-43.7), sensitivity 77%, specificity 82%, and area under the curve (AUC) 0.79. However, inter-observer agreement was moderate (median kappa 0.53). In the second set, TIL and CLI were scored according to new developed scoring systems. Although both features remained the best individual discriminators (OR 8.3(95%CI 1.6-42.1) and 3.3(95%CI 1.2-9.2), diagnostic test characteristics and inter-observer agreement did not improve. For CLI the AUC remained 0.61, and inter-observer agreement stayed moderate (median kappa 0.53). The AUC of TIL decreased from 0.65 to 0.60, and inter-observer agreement remained moderate (median kappa 0.42). Furthermore, the value of the interpretation of overall histopathology decreased; the AUC decreased from 0.79 to 0.64, sensitivity dropped from 77% to 33% ($p<0.01$), and inter-observer agreement remained moderate (median kappa 0.37).
Conclusion: MSI-H associated pathology features have moderate diagnostic test characteristics in differentiating MSI-H and MSS CRC, and are identified with moderate inter-observer agreement.

The prognostic value of micrometastases and isolated tumour cells in histologically negative lymph nodes of patients with colorectal cancer: a systematic review and meta-analysis

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Background: Detection of occult tumour cells in lymph nodes of stage I and II colorectal cancer patients is associated with decreased survival. However, according to recent guidelines occult tumour cells should be categorized in micrometastases and isolated tumour cells. Current meta-analysis evaluates the prognostic value of immunohistochemically detected occult tumour cells in lymph nodes of patients with stage I and II colorectal cancer, after categorizing these cells as micrometastases or isolated tumour cells. Method: We systematically searched PubMed, Embase, Biosis and the World Health Organization International Trials Registry Platform for papers published until April 2012. Studies on the prognostic value of occult tumour cells in lymph nodes of stage I and II colorectal cancer patients were included if they reported detection with immunohistochemistry. Hazard ratios (HR) for the predictive value of occult tumour cells were extracted or calculated, and odds ratios (OR) for the development of disease recurrence or death in patients with micrometastases and isolated tumour cells were calculated. A random-effects model was performed to pool disease free survival and overall survival. Results: Twenty-seven studies with a cumulative sample size of 3073 patients with stage I and II colorectal cancer were included. The median duration of follow up across all studies was 67 months. The median follow up within the studies ranged from 28 to 128 months. Detection of occult tumour cells in regional lymph nodes was associated with reduced disease free survival (HR 2.41; 95%CI 1.67-3.48) but no significant association could be demonstrated for DSS or OS. Eight studies discriminated micrometastases from isolated tumour cells based on AJCC criteria, and ORs for disease recurrence and death could be extracted from five studies with a total of 841 patients. The OR for disease recurrence and death was significantly higher in the presence of micrometastases compared to isolated tumour cells (OR 1.88; 95%CI 1.29-2.74), but there was no difference in disease recurrence and death between patients with isolated tumour cells and patients without any occult tumour cells (OR 1.22; 95%CI 0.77-1.92). Conclusion: Stage I and II colorectal cancer patients with micrometastases have a worse prognosis than patients with isolated tumour cells. In contrast, the prognosis did not differ between patients with isolated tumour cells and patients without any occult tumour cells. The distinction between isolated tumour cells and micrometastases must be made if the detection of occult tumour cells is incorporated in the clinical decision for adjuvant treatment.

VEGF Expression in lesions of Patients with Colorectal Peritoneal Metastases is Correlated to Survival

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Aim: High levels of Vascular Endothelial Growth Factor (VEGF) are associated with a worse prognosis in colorectal cancer (CRC). Anti-VEGF therapies are known to improve the survival in hematogenously disseminated CRC. CRC patients presenting with peritoneal metastases (PM) can be curatively treated with cytoreductive surgery (CRS) and HIPEC. It is not known whether these patients also benefit from treatment with anti-VEGF treatment. We aim to investigate the levels of expression of VEGF in peritoneal deposits and its prognostic value in HIPEC patients. Materials and Methods: From 2007 to 2010 from the Catherina Hospital Eindhoven all consecutive patients undergoing CRS & HIPEC were investigated for VEGF expression. Patients surviving less than 12 months post-treatment were categorized as short survivors and patients surviving more than 12 months as long survivors. These two groups were compared for VEGF expression using the Chi-square test. VEGF expression was assessed in selected sections of peritoneal metastases by immunohistochemistry on formalin-fixed paraffin embedded tissue. The intensity of the staining was scored as negative, weak, moderate and strong. Results: A total of 49 patients (22 male and 27 female) that underwent CRS&HIPEC for colon carcinoma (n=44) and rectal carcinoma (n=5) were included. The median age was 62 years (range 31-77) and median follow-up was 18 months (range 1-51). Of these patients, 34 survived > 12 months (69%). Moderate to strong VEGF expression was observed in 35 out of 38 successfully analysed cases (92%). Univariate analysis showed that high VEGF correlates with a survival of less than twelve months (p=0,02).
Conclusions: Higher VEGF expression was correlated with a survival of less than twelve months in this group of patients undergoing CRS&HIPEC. The use of anti-VEGF, i.e. Bevacuzimab, in patients undergoing CRS&HIPEC might be of additional clinical value.

Optimal time interval between neo-adjuvant chemo radiotherapy and surgery for rectal cancer

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Background: Neo-adjuvant chemo radiotherapy (CRT) has been proven to increase local control in rectal cancer, but the optimal time interval between CRT and surgery is unclear. We aimed to analyse the influence of variations in clinical practice regarding timing of surgery on pathological response at a population level. Methods: From the DSCA registration, all evaluable patients who underwent preoperative CRT for rectal cancer between 2009 and 2011, were selected. Start date of radiotherapy and date of surgery are available in the DSCA database for the purpose of calculating time intervals. Therefore, the interval between CRT and surgery was calculated from start of radiotherapy. Primary endpoint was complete pathological response (pCR=ypT0N0). Four time interval groups were defined based on the two 2-week periods with the highest pCR rates, and remaining time periods preceding and following these weeks. Secondary endpoints were calculated for the four different time intervals and included (near) pCR (ypT0-1N0), tumour down staging (ypT less than cT) and nodal down staging (ypN less than cN). Multivariable logistic regression analysis was done to identify independent predictors for pCR. Results: A total number of 1593 patients were included, with a median interval of 14 weeks between radiotherapy and surgery (range 6-85 weeks; interquartile range 12-16 weeks). Outcome measures were calculated for intervals up to week 13 (N=312), in week 13/14 (N=511), in week 15/16 (N=406) and after week 16 (N=364). Age, tumour localization and R0 resection rate were equally distributed between the four groups; significant differences were found for cT stage (cT4 17.3%, 18.4%, 24.5%, 26.6% respectively; P=0.010), and cM stage (cM1 4.4%, 4.8%, 8.9%, 14.9% respectively; P=0.000). Resection in week 15/16 resulted in the highest percentage of pCR (18.0%; P=0.013). Results for secondary endpoints in week 15/16 were: T down staging 55.2% (P=0.165), N down staging 58.6% (P=0.036) and (near) complete response 23.2% (P=0.124). Resection in week 15/16 was independently associated with pCR in a multivariable logistic regression analysis (HR 1.6; 95%CI 1.1-2.2).

Conclusion: We conclude that pCR rate after neoadjuvant CRT for rectal cancer is related to the time interval between radiotherapy and surgery. Delaying surgery until the 15th or 16th week after start of CRT seems to result in the highest chance of pCR, both in univariable and multivariable analysis. This corresponds with a time interval of approximately 10 to 11 weeks between end of CRT and surgery, based on a conventional five weeks treatment period.

A history of colorectal neoplasia is associated with an increased risk of ileo-anal pouch neoplasia in a nationwide inflammatory bowel disease cohort

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Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the first choice surgical treatment in ulcerative colitis. Although proctocolectomy substantially reduces colorectal cancer risk in inflammatory bowel disease (IBD) patients, subsequent pouch neoplasia can still develop. Given the scarce data regarding the risk of pouch carcinoma, there is no clear consensus on the need for pouch surveillance in IBD patients. Our aims were to determine the cumulative incidence of pouch neoplasia in patients with IBD and subsequently to identify risk factors for developing pouch neoplasia. A nationwide automated pathology database (PALGA) was searched to identify all IBD patients with IPAA between January 1991 and May 2012 in the Netherlands. Next, we determined the cumulative pouch neoplasia (both dysplasia and carcinoma) incidence. A case control study was performed to identify risk factors for pouch neoplasia. Demographic and clinical data were collected from anonymized patient charts. Subsequently univariable and multivariable Cox regression analyses with backward elimination were used to identify independent risk factors.We identified 1200 IBD patients with IPAA with a total follow-up time of 9465 patient years. Pouch neoplasia developed in 33/1200 patients (2.75%) including 17 low-grade dysplasia and 16 adenocarcinomas. The carcinomas were mainly located at the anal transitional zone (63%). Cumulative incidences at 5, 10, 15 and 20 years were 1.5%, 3.0%, 4.8% and 6.8% for pouch neoplasia and 0.6%, 1.4%, 2.1% and 3.3% for pouch carcinoma, respectively. Patients with prior colorectal dysplasia or carcinoma had statistically significantly higher cumulative pouch neoplasia incidences compared to patients without a history of colorectal neoplasia (log rank $p<0.001$). In the case control study, the Cox model identified previous colorectal neoplasia as the only risk factor associated with pouch neoplasia. Hazard ratios were 3.08 (95% CI 1.31-7.22) for pre- or per operative dysplasia and 13.72 (95% CI 5.97-31.51) for pre- or per operative carcinoma. Duration of IBD, type of IBD, primary sclerosing cholangitis and pouchitis were not associated with the risk of developing pouch neoplasia. Conclusions: The incidence of pouch neoplasia in IBD patients without a history of colorectal carcinoma is relatively low. Prior dysplasia or carcinoma of the colon is associated with an approximately 3 and 14 times increased risk, respectively, for developing pouch neo–plasia. Our data suggest that a targeted surveillance program should be considered in IPAA patients with a history of colorectal neoplasia.

Surveillance for colorectal cancer in colitis patients: effect of the implementation of new British and American guidelines on neoplasia yield

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Patients with longstanding ulcerative colitis and Crohn's colitis are at an increased risk of developing colorectal cancer (CRC). Therefore, colonoscopic surveillance is recommended by the recently updated American Gastroenterological Association (AGA) and British Society of Gastroenterology (BSG) guidelines. As surveillance intervals differ significantly between guidelines, we assessed the difference in neoplasia yield and colonoscopic workload when either the new AGA or BSG guidelines were employed. All IBD patients enrolled in the colonoscopic surveillance program from two general hospitals and three university hospitals were identified using the patients' medical records. Patients were stratified according to the new BSG and AGA guidelines and corresponding surveillance intervals were determined based on risk factors present at the last surveillance colonoscopy and the colonoscopic workload was calculated based on these intervals. The presence of colitis-associated neoplasia (CAN), defined as low-grade dysplasia (LGD) in flat mucosa or a non-adenoma like mass, high-grade dysplasia (HGD) or CRC was documented and the cumulative incidence was compared between risk groups of either guide using Log rank testing.A total of 4514 patients with IBD were identified, of which 1018 patients underwent surveillance (23%). Employing the new BSG surveillance intervals, 204 high risk patients would be assigned to annual surveillance (20%), 393 intermediate risk patients to surveillance every three years (39%) and 421 low risk patients to surveillance every five years (41%), resulting in an average of 420 surveillance colonoscopies/year. When the new AGA surveillance intervals would be applied, 64 patients (6%) would undergo annual and 954 patients (94%) biannual surveillance, resulting in an average of 541 surveillance colonoscopies/year. Thus, implementation of the new BSG guidelines could reduce the colonoscopic workload for surveillance by 22% compared to the new AGA guidelines. The yield of CAN would be 22/204 (11%) in the high risk group (12 LGD, 6 HGD and 4 CRC) and 27/393 (7%) in the intermediate risk group (7%) (21 LGD, 0 HGD and 6 CRC) and 15/421 (4%) in the low risk group (14 LGD, 0 HGD and 1 CRC) if BSG guidelines had been applied (p=0.26). If AGA guidelines had been applied, the yield of CAN would be 13/64 (20%) in high risk group (8 LGD, 4 HGD, 1 CRC) and 51/954 (5%) in the low risk group (39 LGD, 2 HGD, 10 CRC) (p=0.02). Conclusion: Implementation of risk stratification-based intervals as recommended by the new BSG guidelines reduces the colonoscopic workload substantially compared to the AGA guidelines. However, the risk stratification as recommended by the AGA seems to be more effective in discriminating between high and low risk patients than the BSG guidelines.

TPMT genotyping before thiopurine treatment results in lower leucopenia occurrence in a prospective randomized strategy study in 850 patients with inflammatory bowel disease

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Thiopurines play an important role in the treatment of IBD. However, over 20% of the patients discontinue therapy due to adverse drug reactions. Leucopenia is a serious side effect, which is associated with thiopurine S-methyltransferase (TPMT) genotype in retrospective studies. Yet, TPMT pharmacogenetics in order to improve safety and efficacy of thiopurine treatment is only used on a limited scale. Our aim was to investigate the value of pre-treatment TPMT genotyping and thiopurine dose adjustments based on genotype on the occurrence of leucopenia.We performed a prospective randomized trial in thiopurine naïve IBD patients starting thiopurine treatment as part of the Dutch TOPIC study (ClinicalTrials.gov NCT00521950). Patients were randomly assigned to undergo pre-treatment genotyping for three common variants in TPMT (TPMT*2, *3A and *3C) or to undergo standard treatment with azathioprine or 6-mercaptopurine (6-MP). The standard initial dose was 2.0 to 2.5 mg/kg bodyweight for azathioprine and 1.0 to 1.5 mg/kg for 6-MP. In the genotype group, patients that carried one of the TPMT variants were recommended a dose reduction of 50% and for patients with a variant on both alleles a maximum of 10% of the standard dose was recommended. The primary endpoint to assess the effect of pre-treatment genotyping was the rate of leucopenia $<3.0*10^9$ /l in the first 5 months after treatment initiation between both arms.In total 850 patients were randomized (62% with Crohn's disease; 38% with ulcerative colitis) and 64% of these patients were treated with azathioprine and 36% with 6-MP. In both the genotype guided group (n=428) and the standard treatment group (n=422) 42 patients (10%) carried at least one genetic variant in the TPMT gene. Finally 832 patients started with a thiopurine and 65 of these patients (8%) developed leucopenia $<3.0*10^9$ /l. Overall, the rate of leucopenia was not significant different between both groups (7.2% versus 8.1%). However, In the group of intermediate metabolizers, we found a statistically significant reduction of the number of leucopenia cases in the group that underwent pre-treatment genotyping versus standard treatment (2.4% (n=1) versus 21.4% (n=9), p-value 0.003).
Conclusion: In this prospective pharmacogenetic study in thiopurine naïve IBD patients, we demonstrated that pre-treatment TPMT genotyping results in a significant lower occurence of leucopenia in patients with at least one variant in the TPMT gene, which is the case in 10% of the population.

Mercaptopurine therapy in IBD patients modulates GTPase Rac1

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Background and aim GTPase Rac1 is involved in the pathogenesis of IBD, as Rac1 has been identified as a susceptibility gene for IBD. Loss of Rac1 expression protects mice from the development of experimental IBD. The molecular immunosuppressive mechanism of thiopurine therapy is mainly based on inducing T-cell apoptosis by inhibition of Rac1. The aim of this study is to assess the in vivo effect of thiopurine therapy on Rac1 activity and expression in IBD patients. Material and methodsAdult IBD patients with active disease, who initiated thiopurine therapy and healthy control subjects were eligible. Activity of disease was assessed by a combination of clinical (including disease activity scores) and laboratory outcomes. Blood was drawn from all patients prior and after 6 weeks of thiopurine therapy. Erythrocytic thiopurine metabolites were measured after 6 weeks of therapy. Blood from healthy controls was drawn with a time-interval of 6 weeks. Cytosol was isolated from leukocytes. Active Rac1 (Rac1-GTP) levels were determined using a G-LISA Rac activation assay. Levels of Rac1 and ERM were measured by Western blot in the IBD patients. ResultsTen IBD patients (7 Crohn's disease (CD), 3 ulcerative colitis (UC)) and 10 controls were included. All IBD patients were treated with mercaptopurine. No adverse events were observed. The median 6-thioguaninenucleotide levels was 570 (190-960) pmol/8*10^8 RBC. In the majority of patients (6 out of 7) with therapeutic response after initiation of thiopurine therapy, the levels of Rac1-GTP (P=0.028) and Rac1/ERM expression (P=0.028) decreased statistically significant. In those without response (N=3), the levels of Rac1-GTP and Rac1/ERM expression increased. No changes were detected in the healthy controls over time, but levels differed significantly with the IBD patients. No correlations were observed between thiopurine metabolites and Rac1 expression or active Rac1.
Conclusion: Initiation of mercaptopurine therapy in IBD patients modulates the GTPase Rac1 in vivo. In this small scaled study, successful thiopurine therapy led to a decrease in (active) Rac1 expression, while failure led to an increase. These observations implicate that Rac1 may be a (early) pharmacodynamic biomarker of thiopurine efficacy.

Relapse rates during pregnancy in ulcerative colitis are higher than in Crohn's disease

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Background Approximately 25% of inflammatory bowel disease (IBD) females will become pregnant after diagnosis. There is little known about the course of IBD during pregnancy. The purpose of this study was (1) to determine the IBD relapse rate during pregnancy, (2) identify risk factors for relapse during pregnancy and (3) investigate the effect of disease relapse on pregnancy outcomes.MethodsBetween 2008 and 2012, all pregnant IBD pts consulting the IBD pregnancy clinic were prospectively followed. A total of 100 women visited this clinic prior to their pregnancy for counseling on their pregnancy wish in relation to IBD. Another 47 women first visited this clinic in the first trimester of their pregnancy. Medication use, life style, and disease activity were documented. Relapse was defined as disease activity determined by endoscopy, ultrasound or laboratory results.ResultsA total of 141 women were seen at follow-up; 112 pregnancies resulted in 104 live births, 7 miscarriages and 1 stillborn. Of the 112 completed pregnancies, 21 women had a relapse of IBD (18,8%) (median gestational week=24, IQR=19-29,5). Relapse was identified by endoscopy (n=14), by ultrasound (n=2) or by laboratory results (n=5). Pregnant ulcerative colitis (UC) pts showed a significantly higher relapse rate than pregnant Crohn's disease (CD) pts (42,9% versus 10,9%, p=0,001). Periconceptional disease activity also significantly increased the risk of relapse during pregnancy (OR: 6,97 95% CI: 1,08-44,97). Pts who had a relapse vs pts who did not have a relapse were periconceptionally treated with no medication (6/11), steroids (0/3), 5-ASA (3/14), thiopurines (4/15), anti-TNF (3/21), MTX (0/1), anti-TNF and steroids (0/3), steroids and thiopurines (0/2), MTX and anti-TNF (0/1), thiopurines and 5-ASA (4/4), anti-TNF and thiopurines (0/6), anti-TNF, thiopurines and 5-ASA (0/2) and anti-TNF, thiopurines and steroids (1/0). Relapses were treated with steroids (n=15), 5-ASA enema's (n=5), and enteral nutrition (n=1). All relapses were treated successfully.There were no significant differences in gestational age (p=0,11), birth weight (p=0,80) and congenital abnormalities (p=0,49) between pts who had a relapse during pregnancy and pts who did not. ConclusionThis study demonstrates an overall relapse rate during pregnancy of 18,8%. UC pts had a higher relapse rate compared to CD pts. Periconceptional disease activity also increases the risk of relapse during pregnancy. No significant differences were found in pregnancy outcomes for pts who experienced relapse of IBD during pregnancy and pts who did not. This contradicts prior reports, and may be due to the intense follow up.

Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease

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Objectives and Study: Inflammatory bowel disease (IBD) often affects female patients in their reproductive years. Therefore, many physicians face the dilemma whether thiopurines can be taken safely during pregnancy to maintain remission. Data on long-term development outcome of children exposed to maternal thiopurine therapy are very limited. Aim of this study was to assess the long-term effects of intrauterine exposure to thiopurines during pregnancy and lactation on infant health status and psychosomatic development. Methods: A prospective multi-centre follow-up study was performed in children exposed intrauterinely to maternal thiopurine therapy. Physical, cognitive and social aspects of infant health status was assessed with the 43-item TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL). Furthermore, information on visits to general practitioner and medical specialists, and their advice regarding lactation was evaluated. Data was compared with normative data from a large control group consisting of 340 children. Results: Thirty children were included in this study (median 3.8 years (IQR 2.9-4.7). No differences were observed between children exposed to intrauterine thiopurines and the reference group on global medical and psychosocial health status. Intrauterine exposure to maternal thiopurine usage was not associated with increased susceptibility to infection or immunodeficiency in childhood; 21/30 children were exclusively formula-fed following negative advice regarding thiopurine use during lactation by treating physicians.
Conclusion: Thiopurine use during pregnancy and lactation did not affect long-term development or immune function of children up to six years of age. Our results under-score the present notion that mothers using thiopurines should be encouraged to breastfeed their infants.

Magnetic resonance imaging of the hands and knees in patients with inflammatory bowel disease and arthralgia

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Arthralgia (joint pain without clinical synovitis) frequently occurs in inflammatory bowel disease (IBD) patients, resulting in a reduced quality of life compared to those without arthralgia. The underlying cause of arthralgia in IBD is unknown. In this study we assess whether subclinical inflammatory changes can be detected on MRI in patients with IBD and arthralgia.Painful hand (MCP/PIP/DIP) or knee joints for a duration of more than 6 weeks continuously in 15 young (<45years) IBD patients, 12 Crohn's disease and 3 ulcerative colitis, were scanned on a 1.5T extremity MRI. The same joints were scanned in a control group of 15 IBD patients without joint complaints who were matched for type and disease duration of IBD, gender and age. MR imaging was performed according to a standard arthritis protocol. MR images blinded for clinical information were evaluated by two musculoskeletal radiologists in consensus for the presence of inflammatory and structural changes. joint fluid, synovitis, tenosynovitis, enthesitis, erosions, cartilage defects and bone marrow edema.The mean age was 37.7 ± 5.4 years for arthralgia patients and 39.3 ± 5.3 years for the controls. MR imaging of the hand, including either MCP and PIP or PIP and DIP joints, was performed in 11 patients and matched controls, MRI of the knee in 4 patients and matched controls. In total 57 joints, 53 hand joints and 4 knee joints, were evaluated in both groups. Enthesitis was seen in three of the MCP joints of two arthralgia patients (5.3% of all painful joints) and in none of the control group (p=0.24). A small amount of subchondral bone-marrow edema was seen in the metacarpal head of two controls (3.5% of total joints, p=0.50). In one painful knee joint fluid and synovitis was appreciated (1.8%, p=1.00), no abnormalities were observed in the matched controls (p=1.00). This is the first study investigating the presence of anatomical changes on MRI in painful hand or knee joints in IBD patients with arthralgia without clinical arthritis or enthesitis by using MRI. Subclinical inflammation was present in one joint and enthesitis in three joints of arthralgia IBD patients on MRI. However, this was not statistically significant different from non-painful joints of IBD patients without arthralgia.

Adding fuel to the fire – Neutrophils as antigen presenting cells in Crohn's disease

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Introduction: Neutrophils (PMN) are the first of defence against bacterial infection. However, they may also act as antigen-presenting cells (APCs), as is observed in inflammatory diseases like rheumatoid arthritis and bacterial infections. During inflammation, PMN are exposed to proinflammatory cytokines which not only influence PMN survival, but upon prolonged exposure can also lead to their dedifferentiation towards an APC-like phenotype. Neutrophil influx at the site of inflammation in Crohn`s disease (CD) has been described. However, the functional consequences of their presence remain controversial. Here, we show that PMN in mucosa from CD patients acquire APC characteristics. Materials and methods: Freshly isolated peripheral blood PMN from healthy volunteers (HC) and CD patients were cultured for 3 days in the presence of GMCSF 50U/ml, INFγ 100U/ml,IL-4 3ng/ml. Expression of CD80, CD86, MHC II on CD66+ PMN were measured by flowcytometry in peripheral blood and single cell suspensions from biopsies. Neutrophil expression of MHC-II at the site of inflammation was determined by double labelling of biopsies. Results: PMN present in the peripheral blood from CD patients and HCs did not express the co-receptors for antigen presentation. However, mucosal PMN from fresh CD biopsies did express APC co-receptors, both at site of inflammation and in non-inflamed regions (n=5, 13±2 % of PMN vs 15±6%). In contrast, mucosal PMN from healthy control biopsies did not express CD80, CD86 or MHC II. As a confirmation of the flowcytometric data, biopsies from CD patients and HCs were stained for MHC-II in conjunction with the PMN marker CD66b. Double positive cells were found only in active CD colonic and small intestinal biopsies. To investigate whether the propensity to dedifferentiate was intrinsically enhanced in CD PMN, peripheral blood PMN were cultured in the presence of a cytokine cocktail, inducing dedifferentiation and expression of CD80, CD86, MHC II. However, similar percentages of PMN expressed APC markers in CD (9.6±6 %, n= 8) and HC (15±10.6%, n=11) in vitro.
Conclusion: We show for a first time that a subset of neutrophils in active CD patients expresses APC co-receptors. Induction of redifferentiation of PMN from CD and HC in vitro is not different, indicating that in all likelyhood, the local presence of pro-inflammatory cytokines induces this dedifferentiation of mucosal PMN in CD patients. This may serve to enhance presentation of bacterial antigens to T cells, thereby adding fuel to the already over-activated T cell response in CD.

Fecal gas analysis by electronic nose of pediatric IBD patients and healthy controls: a pliot study

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Objectives and Study: The diagnosis of inflammatory bowel disease (IBD) is mainly based on typical macroscopic and histological findings by endoscopy, an invasive procedure with significant burden on patients. Non invasive diagnostic tools therefore are awaited. Patients with IBD often report that the odor of flatus or feces is abnormal during a flare. Analysis of fecal volatile organic compounds (VOCs) with gas chromatography and mass spectroscopy (GC-MS) has shown differences in VOC profiles between adult IBD patients and healthy controls. The aim of this pilot study was to compare fecal VOC profiles of children with ulcerative colitis (UC), Crohn's disease (CD) and of healthy controls (HC), during periods of exacerbation and remission. Methods: From 10 UC children (median 12.6; 8.2-15.8 years of age) and 9 CD children (14.2; 9.8-17.4 years) multiple fecal samples were collected during active disease and during remission. In addition, from 10 HC (6.5; 2.2-9.2 years) fecal samples were collected weekly during 4 weeks. Headspace VOCs of all samples were measured with the Cyranose320® electronic nose (Smiths detection, Pasadena, CA, USA). This portable device for measuring VOC profiles is based on changes in electrical resistance of 32 carbon black polymer sensors. Data were analyzed by principal component reduction and canonical discriminant analysis, which were used to make an internally cross-validated receiver operator characteristic curve (ROC). Results: VOC profiles of HC differed from UC children with active disease ($p=0.011$) (ROC AUC 0.75, sensitivity 75%, specificity 77%) and from CD children with active disease ($p<0.001$) (ROC AUC 0.98, sensitivity 92%, specificity 100%). HC profiles also differed significantly from UC children in remission ($p=0.008$) (ROC AUC 0.80, sensitivity 82%, specificity 77%) and CD children in remission ($p<0.001$) (AUC 1.00, sensitivity 100%, specificity 100%). Headspace prints of the feces of UC children differed also from CD children during active disease and in remission ($p=0.024$) (ROC AUC, 0.71, sensitivity 75%, specificity 58%), and ($p=0.001$) (AUC 0.89, sensitivity 91%, specificity 77%), respectively. Intra-individual variability of VOC profiles from HC subjects in time may reflect daily changes in diet. All HC samples, however, differed statistically significantly from UC and CD, regardless of the week the fecal sample was provided.
Conclusion: Analysis of fecal headspace profiles seems to have potential in the recognition of UC and CD discerning flare and remission. Further research, including external validation and larger sample sizes, is warranted.

A vascular calcification scoring model in the prediction of anastomotic leakage after oesophagectomy for cancer

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This study aimed to analyze the value of a vascular calcification scoring model, as a measure for atherosclerosis, in the risk prediction of anastomotic leakage after oesophagectomy for cancer. All patients that underwent elective oesophagectomy for cancer with gastric tube reconstruction and cervical anastomosis in our tertiary referral center from October 2003 until August 2012 were included. These patients were visually assigned vascular calcification scores on routine pre-operative computed tomographic (CT) images, according to a simple scoring system. The aorta (score 0-3), celiac axis (score 0-3), right post-celiac arteries (common hepatic, gastroduodenal and right gastro-epiploic artery; score 0-2), and the left post-celiac arteries (splenic and left gastro-epiploic artery; score 0-2) were studied for calcifications, as these arteries dominantly supply the gastric tube and cervical anastomosis. Groups with and without anastomotic leakage were then compared in univariate and multiple logistic regression analysis. Weighted-κ (w-κ) statistics were calculated to determine the interobserver and intraobserver agreements in grading the finally chosen scoring model. From 309 patients that underwent oesophagectomy in the studied period, 247 patients were found eligible for inclusion of which 57 patients (23%) experienced anastomotic leakage of the oesophagogastrostomy. The calcification scores in the aorta and right post-celiac arteries were significantly different between patients with and without leakage (mean 1.28 vs. 0.90, p=0.015; and mean 0.09 vs. 0.04, p=0.044; respectively). Also, differences between the two groups for summated calcification scores reached statistical significance for multiple combinations of scores for aorta, celiac axis and right and left post-celiac arteries (p-values ranged from p=0.006 to p=0.046). In multiple regression analysis, the calcification score was an important risk factor for anastomotic leakage. An increase in the scoring model of aorta plus celiac axis and right-post-celiac arteries together (score 0-8), lead to an increased risk for anastomotic leakage of 22% per point (odds ratio 1.22; 95% CI: 1.04-1.43). This model showed excellent interobserver and intraobserver agreement (w-κ 0.87 and 0.91, respectively).
Conclusions. This study demonstrated that atherosclerotic calcifications in the gastric tube supplying arteries form an independent risk factor for anastomotic leakage of the oesophagogastrostomy. Future research should aim to include this new parameter in the development of a risk prediction model for anastomotic leakage after oesophagectomy.

Colonic stenting or emergency surgery for acute malignant colonic obstruction: comparison of long-term outcomes in two general hospitals

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Endoscopic stent placement is widely performed for the management of acute malignant colonic obstruction (AMCO). It can serve both as a 'bridge to elective surgery' (BTS) in a curative setting as well as definitive palliation in incurable or inoperable patients. Recently published randomized studies revealed no superiority of stent placement over acute surgery as well as a relatively high number of stent-related perforations. These perforations raised concerns of potential tumor seeding, which could influence oncologic outcomes. This study aimed to compare long-term outcomes of the different treatment strategies in patients with AMCO. A retrospective comparison of two prospectively collected patient cohorts (2005-2012) from two Dutch general teaching hospitals was performed. In the first hospital, all consecutive patients presenting with AMCO were treated with emergency surgery, while in the other hospital, patients were treated with endoscopic stent placement. The cohorts were sub-divided in 'palliative' (PAL) and 'curative' (CUR) groups. The following outcomes were compared: overall survival (OS), recurrence-free survival (RFS), overall major complication rates (Clavien Dindo grade ≥3) and both initial and long-term stoma-rates (end of follow-up). Besides tumor stage in the CUR-group and tumor location in the PAL-group, patient characteristics (age, gender, chemotherapy administration) did not significantly differ between groups. No significant differences were found in the PAL-group regarding OS (Log-Rank [L-R] 0.178, p=0.183), and the number of overall major complications (p=0.445). In the PAL-group both the initial (12% vs. 48%, relative risk [RR] 1.68 [95% CI: 1.10-2.57]) and long-term stoma-rate (10% vs. 43%, RR 1.58 [95% CI: 1.08-2.32]) were significantly less in stented patients. In the CUR group there were no significant differences when stratified for tumor stage regarding OS (stage I&II L-R 0.046, p=0.831; stage III L-R 0.469, p=0.494; stage IV L-R 0.318, p=0.573) and RFS (stage I&II p=0.84; stage III p=0.18; stage IV p=0.74). In the CUR-group there was no difference in overall major complications (p=0.909). Initial stoma-rate was significantly lower after stent placement (22% vs. 50%, RR 1.56 [95% CI: 1.13-2.15]), while long-term stoma-rates did not differ (20% vs. 22%, RR 1.02 [95% CI: 0.83-1.24]).

Conclusion Despite concerns of potential tumor seeding after stent placement as BTS, oncologic outcomes were not different from acute resection in this non-randomized comparative study. Both treatment strategies are equal with regard to major complications while stent placement does significantly reduce stoma-rates in a palliative setting.

The N0 stage in colon cancer: how many nodes are enough?

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According to the Dutch guidelines for colorectal cancer (2008) as many lymph nodes as possible should be examined to determine the appropriate N-stage, with a minimum number of 10 nodes. In fact, finding less than 10 nodes is being accepted as a means of identifying high-risk patients with stage II tumours, even though evidence is weak at best. We hypothesized that a reliable N0 status can be established by sampling the largest lymph nodes in the specimen. We gathered clinical and pathological data of all patients treated for colorectal cancer in the period 2008-2010. All lymph node specimens were retrieved from our archives and the largest diameter was measured. We analyzed the relationship between lymph node morphology and the presence of metastasis. Furthermore we examined other factors contributing to an N+ status.Our patient group consisted of 156 patients with a median age of 77 years (29-91). A total of 2044 lymph nodes (mean of 13 per patient) were harvested, 1803 (88.2%) without and 241 (11.8%) with lymphatic spread of malignancy. Lymph nodes containing tumour were on average larger than tumour-free nodes (6.0 ± 3.0 versus 4.2 ± 2.3 mm, $P<0.0001$). When all nodes larger than 5 mm were tumour-free in a patient, the chance of finding a metastasis in a lymph node of ≤ 2 mm was only 3.8% (95% CI 1.1 to 9.7%). We gave the positive nodes from our N+ patients a ranking from largest to smallest diameter and found that in 75 out of 76 patients (98.7% (95% CI 92.9 to 99.9%)) at least one positive lymph node ranked in the top 5 largest nodes in that specimen. Other factors associated with positive lymph nodes were differentiation grade, T-stage and presence of distant metastasis. The examination of 10 or more lymph nodes had no effect on finding tumour-positive nodes.
Conclusion: The histological examination of the 5 largest lymph nodes in colorectal specimens can produce a reliable N0 status. If these nodes are tumour negative, the chances of missing a tumour positive node is very small, especially if the remaining nodes are smaller than 2 mm. The meticulous and time-consuming search for more of these small nodes in order to collect the recommended 10 nodes seems to be a waste of the pathologist's time. Selecting patients for adjuvant chemotherapy based on finding less than 10 tumour-negative nodes is questionable in our opinion.

Who determines the N-stage in colon carcinoma: Pathologist or Surgeon?

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There is evidence suggesting that the more lymph nodes are examined in patients treated for colon cancer, the better the disease can be staged and therefore a more accurate prognosis can be given. According to the Dutch guidelines for colorectal cancer, a minimum of 10 nodes should be analyzed in order to produce a reliable N-stage. Dutch qualifications for providing first-rate health care include finding at least 10 lymph nodes in 80% of all patients with colorectal cancer. We analyzed the number of lymph nodes in patients surgically treated in our hospital over a period of three years (2008-2010). Patients who had received neo-adjuvant treatment were excluded. Our patient group consisted of 156 patients with a median age of 77 (range 29-91 years) and mean of 13 nodes per patient. In 106 patients (67.9%) 10 or more nodes were found. In addition to base characteristics and tumour specific data we examined the role of two individual GI-surgeons (A and B), non-GI specialized surgeons (group C) and seven individual pathologists in finding 10 or more lymph nodes.Our univariate model showed that the presence of ≥10 nodes was influenced significantly by tumour size (P=0.050), tumour location (P=0.015) and associated type of resection (P=0.034), individual surgeon (A vs. B; P=0.023) and individual pathologist (A-G; P=0.005). No significant differences were found between GI-surgeons and non-GI specialized surgeons. Individual surgeons (P=0.8) or pathologists (P=0.4) did not influence finding an N+ status.Multivariate factors significantly contributing to finding ≥10 nodes were patient age (P=0.044), type of resection (p=0.007), M-stage (p=0.010) and again individual surgeon (A vs. B; P=0.012) and pathologist (A-G; p=0.004). Odds ratios for finding ≥10 nodes were 4.2 [95% CI: 1.4-12.5] for surgeon B vs. surgeon A and 3.9 [95% CI: 1.1-13.1] for surgeons C vs. surgeon A. Odds ratios between the seven individual pathologists varied from 0,2 [95% CI: 0.03-1.7] to 22,5 [95% CI: 3.8-134.6].
Conclusion: in addition to base characteristics and tumour aspects, individual surgeons and pathologists have influence on finding 10 or more lymph nodes in colorectal cancer patients.

Randomized Controlled Trial of Transoral Incisionless Fundoplication versus Proton Pump Inhibitors for Treatment of GERD: Preliminary data

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Although proton pump inhibitors (PPIs) are effective in controlling GERD, the disease is not cured and patients will often have a lifelong commitment to drug-therapy. In an attempt to create a minimally invasive endoscopic procedure to cure GERD, transoral incisionless fundoplication (TIF) was developed. Aim of this study was to evaluate the effect of TIF on subjective and objective reflux parameters in comparison to PPI-therapy. The study population consisted of patients with chronic GERD, who opted for an intervention over a lifelong drug-dependence. ASA>2, BMI>35, hiatal hernia >2cm and esophageal motility disorders were exclusion criteria. Patients were randomized 2:1 for TIF or continuation of PPI-therapy. Symptoms were evaluated by a disease-specific quality of life questionnaire (GERD-HRQL). 24-h pH-impedance monitoring was performed after cessation of PPIs at base in all patients and evaluated again after 6 months without PPI usage in the TIF-group and with PPI usage in the PPI-group. In 60 randomized patients (TIF n=35, PPI n=19, 6 lost to follow-up, mean BMI=26 and 37 male) GERD-HRQL scores were significantly improved in the TIF group after the procedure (from 25.4±1.4 to 10.2±1.2, p<0.001), but not in the PPI group (from 27.0±2.2 to 24.6±2.3, p=0.41). A significant decrease in esophageal acid exposure was measured in both groups at 6 months follow-up compared to base (TIF from 10.6 ± 1.0% to 6.6 ±1.0%, p<0.01 and PPI from 11.1 ± 1.5% to 5.5 ± 1.5%, p<0.001). The difference in decrease of acid exposure for the PPI-group compared to TIF was not statistically significant (p=0.46). In the TIF group the mean number of liquid and proximal reflux episodes were decreased (resp. from 92.7±6.7 to 70.4±6.1, p<0.01 and from 42.9±4.2 to 27.1±3.6, p<0.01), but no differences were found in the PPI group (resp. 97.1±9.0 to 95.4±9.6, p=0.91 and from 49.3±4.7 to 46.3±7.4, p=0.68).
We conclude that in a selected group of GERD patients endoscopic fundoplication with the TIF-technique resulted in a similar decrease in distal esophageal acid exposure compared to PPI-therapy at 6 months follow-up, but in a higher reduction in the number of liquid and proximal reflux episodes and reflux symptoms.

Genome-wide screening of microRNAs as predictors for response to neoadjuvant chemoradiotherapy in oesophageal adenocarcinoma

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Chemoradiotherapy (CRT) followed by surgery is the treatment of choice for non-metastasized oesophageal cancer. Patients with tumours that respond favourably to neoadjuvant CRT have an improved survival whereas non-responders are exposed to toxicity of CRT and potentially curative surgery is delayed. Therefore, early identification of patients who will benefit from CRT is very relevant. MicroRNAs (miRNAs) are small regulatory RNAs that play a role in cancer initiation and progression as well as modulating response of cancer cells to chemoradiotherapy. Hence, miRNAs could well serve as potential biomarkers for predicting therapeutic responses. The aim of this study is to investigate whether miRNAs expression in oesophageal cancer is associated with response to CRT.25 patients with an adenocarcinoma of the oesophagus or oesophago-gastric junction were selected from a prospective database. Response to CRT was assessed in the resection specimen according to Mandard. From 8 responders and 17 non-responders laser capture microdissection was performed on pre-treatment biopsies in order to obtain tumour specific RNA. MiRNA expression was determined by Affymetrix GeneChip miRNA array, a genome wide identification and quantitative real-time RT-PCR (qPCR). Microarray analysis of tumour RNA of pooled samples of responders and non-responders showed 38 most up and 40 most down regulated miRNAs (fold change > 2.0). Some 17 MiRNAs were selected on the basis of literature and tumour abundance for qPCR analysis. MiR-200c and miR-215 levels were 2.8 and 11-fold higher in non-responders as compared to responders respectively. MiR-134 and miR-708 levels were 4.2 and 3.4 fold higher in responders as compared to non responders respectively. ROC analysis of these four miRNAs revealed an AUC of 0.78, 0.81, 0.95 and 0.77 respectively, indicating good sensitivity and specificity.In conclusion, expression of specific miRNAs in pre-treatment tumour tissue differs between responders and non-responders. MiRNAs represent promising new biomarkers that can potentially be used for predicting response to neoadjuvant chemoradiotherapy. Therefore iteration of analysis is now performed on an independent cohort of patients. Furthermore, the target genes of these miRNAs are being investigated in order to understand their role in chemoradiotherapy sensitivity and resistance.

Epidural analgesia: associated with survival in colon cancer?

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Background: Surgery is still the mainstay of treatment for potentially curable colon cancer. Otherwise, the surgical stress response increases the likelihood of cancer dissemination and metastasis during and after cancer surgery. The possibility that anesthetic drugs can influence cancer recurrence is a subject of more recent debate. Based on animal studies and only a few clinical investigations, epidural analgesia during cancer surgery has been suggested to reduce cancer metastasis.Methods A follow-up study in a historical cohort was performed in 588 patients with colon cancer UICC stage I-IV undergoing surgery at our hospital over the period January 1995 to December 2003. The patients were allocated into two groups; those receiving epidural analgesia peri-operatively and those not receiving epidural analgesia, but patient-controlled analgesia. From all participants additional information was obtained from the Dutch Comprehensive Cancer Centre South. Follow-up measurements and visits were conducted according to the criteria of the Dutch Guidelines and all patients were followed up until January 2011. Mortality risks were estimated with Cox-proportional hazard models. Results Of the 588 primary colon cancer patients, with a mean age of 69 years, 399 (68%) patients underwent colon surgery with epidural anaesthesia and 189 (32%) patients were operated upon without epidural anaesthesia. In patients receiving epidural analgesia a significant better overall survival was found compared to patients who did not receive epidural analgesia (HR 1.30 (95% CI 1,05-1.59), p=0.01). Results were adjusted for age, sex, UICC stage, chemotherapy, emergency surgery status and year of incidence.
Conclusions In our study epidural analgesia during surgery for colon cancer was associated with significant better overall survival even after correcting for many confounding variables. Interestingly, the benefit of epidural analgesia seems to be more than only analgetic. A possible mechanisms is that regional anaesthesia attenuates the immunosuppressive effect of surgery. Also the lower requirements of opioid, which seems to inhibit the immune system, could play a role in the survival benefit. The observed reduction in mortality rate when colon cancer surgery was performed with epidural analgesia suggests that prospective trials evaluating the effects of regional and morphine sparing analgesia on cancer recurrence are warranted.

The role of biological markers of epithelial to mesenchymal transition (EMT) in esophageal adenocarcinoma

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E-cadherin, N-cadherin, Beta-catenin, epidermal growth factor (EGFR) and Cyclin D1 are involved in epithelial to mesenchymal transition (EMT), a biological process which is considered a critical process during metastases and tumor invasion. However, the prognostic significance of, and associations between the different EMT markers is less known in esophageal adenocarcinoma (EAC). Aim of the study was to evaluate the prognostic value of, and the association between different EMT markers in EAC. Tumor cores of 154 esophageal adenocarcinomas were included in a tissue micro array (TMA). Immunohistochemistry (IHC) was used to evaluate the EMT markers and scoring criteria was based on staining intensity. EMT associated markers were expressed in esophageal adenocarcinoma; EGFR over-expression was seen in 56.5%, E-cadherin down-regulation in 11.4%, nuclear Beta-catenin in 12.2% and Cyclin D1 over-expression in 26.0% of tumors. Mesenchymal marker N-cadherin was not expressed in EAC. In univariate analysis, only EGFR over-expression was significantly associated with poor survival (HR 2.213; 95% CI 1.473-3.324, p<.001), However, Cyclin D1 over-expression (HR 1.043; 95% CI 0.675-1.611; p=.850), and E-cadherin down-regulation (HR 0.948; 95% CI 0.519-1.734; p=.864) not. On the contrary, in patients that received palliative therapy, E-cadherin down-regulation and Cyclin D1 over-expression was associated with reduced survival (p=.006 and p=.048, respectively), indicating that both markers modulate the effect of palliative therapy. Furthermore, a positive association was seen between EGFR and Cyclin D1 (R=0.257, p=.002) and between membranous Beta-catenin and E-cadherin (R=0.406, p<.0001), but not between the other EMT markers. In multivariate analysis, EGFR expression was an independent prognostic factor for a poor survival (HR 1.598; 95% CI 1.018-2.509; p=.042) together with T-stage (HR 2.629; 95% CI 1.306-5.295; p=.007) and grade of tumor differentiation (HR 1.853; 95% CI 1.138-3.017; p=.013). It can be concluded that markers associated with EMT were expressed in EAC. Furthermore, EGFR over-expression was independently associated with a poor survival, and with Cyclin D1 over-expression. Moreover, in patients who received palliative therapy E-cadherin down-regulation and Cyclin D1 over-expression were associated with reduced survival. Furture directions might be to add EGFR inhibition therapy and possibly also agents that re-activate E-cadherin expression to the current treatment.

Laparoscopic Total Gastrectomy versus Open Total Gastrectomy for Cancer: A Systematic Review and Meta-Analysis

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The possible advantages of Laparoscopic (Assisted) Total Gastrectomy (LTG) versus Open Total Gastrectomy (OTG) have not been reviewed systematically. The aim of this study was to systematically review the short-term outcomes of LTG versus OTG in the treatment of gastric cancer. A systematic search of Pubmed, Cochrane, CINAHL and Embase was conducted. All original studies comparing LTG with OTG were included for critical appraisal. Data describing short-term outcomes were pooled and analysed. A total of 8 original studies, comparing LTG (n=314) with OTG (n=384) in patients with gastric cancer, fulfilled quality criteria and were selected for review and meta-analysis. LTG compared with OTG was associated with a significant reduction of intra-operative blood loss (weighted mean difference 228 ml; 95% c.i. 311 to 144; p<0.001), a reduced risk of postoperative complications (risk ratio 0.51; 95% c.i. 0.33 to 0.77), and shorter admission time (weighted mean difference 4 days; 95%c.i. 1.3 to 6.5; p<0.001). These benefits were at the cost of a prolonged duration of surgery (weighted mean difference 56 minutes (95% c.i. 25 to 86); p< 0,001). In hospital mortality rates were comparable for LTG (1%) and OTG (2%) (risk ratio 0.68; 95% c.i. 0.20 to 2.36). Conclusion: LTG in eligible patients shows better short term outcomes compared with OTG in patients with gastric cancer. Future studies should evaluate 30-and 60 day mortality, radicality of resection and long-term follow-up in LTG versus OTG, preferably in randomised trials.

MiR-214 is a key-regulator and therapeutic target in colitis-associated colorectal carcinogenesis

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Patients with ulcerative colitis (UC) have an increased risk for developing colorectal cancer (CRC). The pathogenetic mechanisms underlying colitis-associated CRC (CAC) compared to familial or sporadic CRC have many similarities, but substantial differences are currently also being recognized. In CAC, inflammatory transcription factors such as signal transducer and activator of transcription 3 (STAT3) and nuclear factor κB (NF-κB) are constitutively activated but the underlying mechanisms are poorly understood. Thus, it is essential to identify the molecular links between transcription factors involved in chronic inflammation and colon carcinogenesis. We have formulated the hypothesis that microRNAs, small noncoding RNAs that regulate gene expression at the posttranscriptional level, are involved in dynamic networks that connect inflammation to oncogenic transformation and CRC progression. Therefore, we performed a comparative microRNA array analysis on malignant colonic tissue derived from CRC patients with and without a history of UC. In parallel, we performed a microRNA-based genetic screen to identify microRNAs that regulate NF-κB activation in colonic epithelial cells. Integration of the clinical data with the high-throughput analysis revealed that miR-214 is one of the most effective regulators of the NF-κB pathway and is also significantly (almost 14-fold) upregulated in CAC (n=37) compared to sporadic CRC (n=47). MiR-214 upregulation is associated with a 50% to 70% decreased expression of phosphatase and tensin homolog (PTEN) and PDZ-LIM domain protein 2 (PDLIM2) in primary CAC specimens and increased activity of NF-κB in cell lines. Moreover, miR-214 expression is under the control of STAT3 which is activated by the NF-κB/interleukin-6 axis. In agreement with the findings in the CAC tissues, the miR-214/PDLIM2/NF-κB pathway was dysregulated in tumors derived from azoxymethane (AOM)/dextran sulfate sodium (DSS)-treated mice (n=10). Intracolonic administration of a miR-214 inhibitor suppressed tumor growth in AOM/DSS-treated mice by more than 80%. Further analysis of miR-214/PTEN/PDLIM2 expression revealed an intermediate activation of the miR-214 pathway in non-cancerous UC tissue (n=35) compared to control tissue (n=41). Our findings propose a model based on which miR-214 is a member of a reinforced inflammatory circuit that links ulcerative colitis to colorectal cancer. Hyperactivation of this circuit may lead to sustained inflammation and increase the susceptibility of the colonic epithelium to oncogenic transformation. Targeting of miR-214 may be a valuable therapeutic approach for the treatment of colitis-associated colorectal cancer.

MicroRNA-142-5P and mast cell biology in experimental colitis

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Background and aim: The pivotal role of microRNAs in the regulation of gene expression, in particular genes involved in the immune response, indicates that they may play an important role in the pathogenesis of inflammatory bowel disease (IBD) as well. MicroRNAs, by their mechanism of action, are promising new therapeutic agents or targets. Experimental colitis in severe combined immunodeficiency (SCID) mice shares many features of human inflammatory bowel disease (IBD). This model in which transfer of CD4CD45RB^{high} T cells results in colitis in the SCID mice is important for the development of new IBD therapies. MicroRNAs, which are small noncoding sequences, are involved. A number of microRNAs are upregulated during development of experimental colitis in the transfer model among these is microRNA-142-5p (miR-142-5P). The aim of the study is to determine the effect and the target genes of the upregulated microRNA in the development of colitis. Methods: We administered locked-nucleic-acid-modified oligonucleotide (LNA-antimicroRNA) at the moment the mice demonstrated the first signs of disease 3 weeks after the transfer of the CD4CD45RB^{high} T cells. We determined the course of the disease and performed an mRNA analysis (Illumina, Service SX, Leiden) of the spleen of the treated mice to determine the target genes that are expected to be upregulated after blocking this particular microRNA. Results:Blocking experiments with anti-miR-142-5p resulted in a higher survival rate compared to mice treated with anti-scr-microRNA (p=0.0026). The target genes we found for miR-142-5p are related to mucosal mast cells. Four of the top ten targets that show upregulation after blocking miR-142-5p are found in a pathway related to mast cell biology. We checked for the presence of mucosal mast cells in the intestine and found mast cells in the intestine of the mice transferred with CD4CD45RB^{high} T cells. Conclusion:There is a link between the diminution of chronic experimental colitis and mast cell biology.

Stool-based microRNA expression profiling discriminates colorectal cancer patients from healthy individuals

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Secondary prevention is the most realistic approach to reduce colorectal cancer (CRC) death. To this end, CRC population screening will be implemented in the Netherlands in 2013 by using the Fecal Immunochemical Test (FIT). FIT has shown to be easy applicable in CRC screening settings and to reduce CRC death, however it only detects CRC with a sensitivity of 65% and advanced adenomas with 27% sensitivity (specificity 95%). Prospective case-control studies examining the performance of promoter hypermethylation of, for instance GATA4, OSMR and PHACTR3 and mutation analysis of KRAS, TP53 and APC in stool have shown that molecular biomarkers can increase the sensitivity of FIT up to 15%. MicroRNAs (miR) are also interesting molecular biomarkers to improve FIT sensitivity, as they reflect the biology of CRC, are shed directly from the tumor and are stably measurable in stool samples. Our aim is to identify a miR expression signature that improves the current FIT performance. First deep sequencing (SOLiD) was performed on 30 MSS colorectal adenomas and 30 carcinomas. Then the expression of the identified miRs was determined by RT-qPCR in 152 independent colorectal tissues (22 controls, 75 adenomas and 55 CRCs) and 430 stool samples (109 controls, 109 adenomas and 213 CRCs). Mann-Whitney U tests and ROC analyses were applied. Deep sequencing data analyses unraveled 57 differentially expressed miRs between colorectal adenomas and CRCs (FDR<0.2). Follow-up RT-qPCR expression studies including 152 independent colorectal tissue samples showed 17 up- and 5 down-regulated miRs in carcinomas compared to adenomas ($p<0.05$). Expression of 9 of these validated miRs was also detected in stool samples. MiR-A showed 3.6 times higher expression in stool derived from CRC patients than in controls ($p<0.05$) and an AUC of 0.803 (specificity 80%, sensitivity 65%). MiR-B showed a 1.04 higher expression in stool from healthy individuals compared to stool from CRC patients ($p<0.05$) and an AUC of 0.643 (specificity 70%, sensitivity 60%).
In conclusion, based on the expression of 2 miRs in stool samples it is possible to discriminate controls from CRCs with sensitivities between 60 and 65% and specificities between 70 and 80%. The performance of these miRs to detect adenomas is ongoing.

Bi-directional release of microRNAs by hepatocytes to bile and blood: Relation with liver injury and bilirubin secretion

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MicroRNAs (miRNAs) have emerged as important regulators of cellular functions in response to injury. Recent studies have shown that specific miRNAs are released during liver injury into the blood stream and as such can be used as early and sensitive markers of liver injury. The aim of our study was to investigate the release of hepatocyte-derived miRNAs (HDmiRs) into bile and into circulation during normal liver function and at time of injury. Paired bile and serum samples (n=62) from ten liver transplant recipients were collected at different time-points after transplantation trough T-tube drainage. Cell-free solutions were analyzed for HDmiR-122, HDmiR-148a and HDmiR-192, by quantitative RT-PCR. Cholangiocyte-derived miRNAs (CDmiRs) CDmiR-30e, CDmiR-200c, CDmiR-222, and CDmiR-296 served as controls. Fresh cell free bile samples obtained from donor gall bladders during transplantation were used for stability and fractionation experiments (n=8). All HDmiRs and CDmiRs were detectable in serum and bile. The most abundant miRNA in serum and bile was HDmiR-122, whereas all CDmiRs were more abundant in bile. Fractionation of fresh bile showed that HDmiRs are mostly present in non-pelletable molecular complexes. Depending on the miRNA, only 3.8 to 6.3% of the miRNA was found in pelletable cell fragments or microvesicles. Despite the toxic environment of bile, miRNAs were stable and protected from degradation for at least 1 hour at 37°C. Next we investigated HDmiR release in relation to liver injury. Serum levels of all HDmiRs significantly elevated. in patients experiencing liver injury with biopsy-proven acute rejection. In bile, however, only HDmiR-192 was significantly elevated during injury. This suggests that the regulation of HDmiR release into bile and blood compartments differs. To substantiate this, a comparison of liver function based on conjugated bilirubin levels in bile, showed that only levels of HDmiR-122 in bile correlated with good liver function. In contrast, no correlation was found with liver functioning and HDmiRs levels in serum. Levels of most CDmiRs in bile were significantly decreased with high bilirubin secretion.

In conclusion, miRNAs are bidirectionally released into bile and blood by hepatocytes. Release is differentially regulated in functionally healthy or injured livers. Polarized release of HDmiR-122 to the bile significantly correlated with the secretion of bilirubin, whereas HDmiR-192 was elevated in bile during liver injury. Further research currently focuses on the functional role of miRNA in bile as potential epigenetic regulators of enterohepatic recirculation.

IFNα and IFNλ induce distinct response patterns in TLR-activated human macrophages

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Associations between polymorphisms near the gene encoding for interferon lambda (IFNλ) 3 and spontaneous as well as therapy-induced clearance of the hepatitis C virus (HCV) have peaked interest in this particular family of cytokines. Although the IFNλs has been extensively studied for their antiviral activity, little is known about their effect on cells in the leukocyte population. With pegylated-IFNλ3 being introduced as a potential substitute for IFNα in the therapy of chronic HCV infection, much still needs to be learned about the basic biology of the IFNλ family of cytokines, including their cellular targets, function, and the factors that affect these parameters. As a first step to identify cellular targets of IFNλ, we screened various human leukocyte populations for the expression IFNλ receptor 1 (IFNλR1) using flow cytometry and real-time PCR analysis. Further assays were then performed on monocyte-derived and primary macrophages, one of the principal populations found to be positive for IFNλR1. Human monocytes, monocyte-derived macrophages, and Kupffer cells were stimulated with IFNα or IFNλ1 and then further challenged with toll-like receptor (TLR) agonists. Modulation of the phenotype and function of each cell type was then evaluated by flow cytometry, enzyme-linked immunosorbent assay (ELISA), and microarray. In our initial screening, we found that B-cells, T-cells, and monocyte-derived macrophages were all positive for IFNλR1 mRNA expression at varying levels. NK cells, monocytes, and Kupffer cells however, showed limited or no IFNλR1 mRNA expression. Further FACS analysis for protein expression only showed positivity on monocyte-derived macrophages. In functional assays, we observed that IFNα and IFNλ1 differ in their ability to modulate the production of pro-inflamatory cytokines IL-12p40 and TNFα upon TLR-activation by monocytes and monocyte-derived macrophages. Monocytes, which lack the IFNλR1, were unaffected by IFNλ stimulation, whereas macrophage TLR-induced IL-12p40 and TNFα were enhanced in the presence of IFNλ1. Kupffer cells, similar to monocytes, were unaffected by IFNλ1 stimulation alongside TLR challenge in their production of various pro-inflammatory cytokines. To further distinguish the differences of IFNα and IFNλ1 stimulation on macrophages, we performed microarray analysis on resting and TLR-challenged cells, in and without the presence of the respective interferons to identify distinct expression. Further investigation of the basic biology of IFNλ may provide insight on its effects as a therapeutic, and the potential benefits or disadvantages it may have to conventional IFNα based therapy.

Recruited inflammatory monocytes, but not Kupffer cells, play a crucial role in early virus-induced intrahepatic immune responses

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Little is known on the role of Kupffer cells (KC) or inflammatory monocytes (IM) during viral hepatitis infections. Early innate responses to viral pathogens are induced by specific viral molecular patterns that bind to pattern recognition receptors, such as TLR. Previously, we showed that steady state KC phagocytose but only weakly produce cytokines. In the current study we examine the contribution of KC and IM to the immune response during the first 24 hours after Lymphocytic Choriomeningitis Virus (LCMV) infection in C57BL/6 mice, an established mouse model for chronic viral hepatitis. KC and IM were identified as F4/80^{hi}CD11b^{+} and Ly6C^{hi}CD11b^{hi}, respectively. TNFα production by intracellular cytokine staining (ICS) was performed upon ex vivo LPS stimulation. FITC-dextran uptake was used as a measure for endocytic ability. LCMV infection was confirmed by qPCR and plaque assay. LCMV infection induces inflammation and antiviral responses in the liver within 24 hours, based on 4- to 47-fold increased mRNA expression levels of several pro-inflammatory cytokines and chemokines (TNF, IL-6, MCP-1), type I and III interferons (IFNα, IFN β, IL28) and ISGs (OAS-12 and ISG-15). Interestingly, early LCMV infection leads to a progressive loss of intrahepatic KC (upto 40% within 24 hours), while similarly absolute CD45+ cells/gr liver increase. At this timepoint, KC are the predominant LCMV-nucleoprotein positive intrahepatic cells, suggesting that the depletion is directly virus-mediated. In contrast, there is a 5-fold increase in intrahepatic IM, which therefore massively outnumber the remaining KC. Functionally, 39% of KC are dextran FITC+, indicative for a persistent endocytic ability during LCMV infection. In contrast, the number of TNF+ KC is similar to the unstimulated background (around 5%), while 24% of IM are TNF^{+} after ex vivo LPS stimulation.We are currently examining the LCMV-induced apoptosis by TUNEL stainings and gene expression profiles of both KC and IM after cell sorting.
Conclusion: Using the in vivo LCMV infection model, we show that KC isolated from the infected liver are predominant endocytic and possess a weak secretory ability. These features are similar to KC isolated under steady state conditions. Early LCMV infection results in a rapid depletion of these phagocytic cells and induces a massive influx of activated, TNF-producing inflammatory monocytes that outnumber the resident Kupffer cells within 24 hours. These observations suggest a limited role for Kupffer cells during early LCMV infection in the liver, with inflammatory monocytes likely contributing to pathology.

Single centre evaluation of nasojejunal feeding tube placement by nurses using the Cortrak® electromagnetic imaging system

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The Cortrak® electromagnetic imaging system for placement of nasojejunal feeding tubes is minimal invasive and does not need X-ray. Therefore it is a promising alternative for endoscopic or radiologic placement. Furthermore, bedside placement can be performed by nurses, thereby reducing costs and workload for endoscopic teams. First results were promising with a success rate of 78-89%, dependant on the condition of the patient. The purpose of this study is to evaluate the learning curve, results and costs of bedside placement of Cortrak® nasojejunal feeding tubes by nurses in a Dutch university hospital. Three nurses with interest in enteral nutrition were trained in a two day course and had one day instruction in the hospital by an experienced nurse. From March 2011 till December 2012 all patients in which an endoscopic jejunal feeding tube was requested during working hours were screened for Cortrak® placement. Patients with surgically changed anatomy of the upper gastrointestinal tract, signs of stenosis, rupture, varices or Zenker's diverticula of the esophagus or greatly enhanced bleeding risk were excluded. If the reason for placement was gastric paresis, especially on the intensive care units, nurses could request a single dose of erythromycin 250 mg IV before or during placement. Time of procedure, success rate with or without erythromycin, time of procedure and success rate confirmed by X-ray was recorded. Costs were evaluated according to the in-hospital fees. Reduction in costs was calculated by difference in price between endoscopic and Cortrak® placement minus the extra costs of the Cortrak® method if it failed. Cortrak® placement was attempted in 342 cases of which 98 (29%) were on intensive care units. The success rate confirmed by X-ray (discordance in one) was 160 out of 165 (97%), success rate based on electromagnetic imaging alone was 132 out of 177, giving in total a success rate of 85 %. On IC units the success rate was lower (76 vs 90%) and mean duration of procedure was longer (25 vs 18 min). With the use of erythromycin (n=27) success rate on IC-units improved to 89%. Success rates were equal in 2011 and 2012, showing no clear learning curve. Cortrak® feeding tube placement being €210 cheaper than endoscopic placement reduced costs with €51070. In conclusion, placement of the Cortrak® nasojejunal feeding tube by nurses is a safe, minimal invasive, cost effective method with high success rate (90% outside IC-units and in 76% of IC-patients). Erythromycin improves success rates on IC units. We therefore recommend this electromagnetic imaging system for routine nasojejunal tube placement.

Medical doctors underestimate daily calcium intake in patients with osteoporosis

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Calcium supplements are widely used for prevention and treatment of osteoporosis. However, recent literature shows a controversy whether or not excessive calcium supplementation may be associated with increased risk of cardiovascular events. In daily practice, rheumatologists involved in this study use a short calcium list to estimate dietary calcium intake, which is the basis for the prescribed amount of calcium supplementation. An accurate estimation is important to be able to prescribe the adequate amount of calcium supplementation to reach the recommended levels of 1000-1200mg calcium per day, without a possible increase of the risk of cardiovascular events. The aim of this study was to validate a short calcium list with a dietary history (DH), assessed by a dietician, as reference method. This cross-sectional study included patients diagnosed with and treated for primary or secondary osteoporosis, based on a low T-score in hip and/or lumbar spine, with or without vertebral fracture. In addition, subjects with secondary osteoporosis were diagnosed with a rheumatic disorder. The short calcium list calculated calcium intake by portions of milk, yoghurt (multiplied by 180mg calcium per portion), cheese (multiplied by 155mg calcium per portion), and 250mg calcium from other products. The short calcium list was compared with a DH with specific focus on calcium and extra attention for portion sizes. On forehand, a difference of at least 250mg calcium between both methods was formulated as clinically relevant. Sixty-six subjects (31 with primary osteoporosis and 35 with secondary osteoporosis) were included. The mean dietary calcium intake measured via the short calcium list (825±259mg) was lower than via DH (1113±424mg) ($p<0.001$). Furthermore, the mean difference between both methods was 289±346mg calcium: in 37 of the 66 patients (56.1%) the short calcium list scored relevant lower than DH, and in 4 of the 66 patients (6.1%) the short calcium list scored relevant higher than DH. In total, 55 patients (83.3%) reached an overall intake higher than the upper limit of the recommendation of 1200mg calcium per day.
Conclusions: The short calcium list gives a substantial and clinically relevant under-estimation of dietary calcium intake in more than 55% of the patients. Therefore, the list is not an optimal method to measure dietary calcium intake of patients with osteoporosis. This is a clinically relevant finding because of the rumour around an increased risk of cardiovascular events associated with a too high overall calcium intake.

Systematic screening for undernutrition; predictive factors for success

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Background: As of 2007, undernutrition screening has become a Performance Indicator (PI) within the national benchmarks on quality of care by the Dutch Health Care Inspectorate (HCI). The introduction was guided by an implementation project. The aim of this study was to describe the results of the PI undernutrition screening from 2007 to 2010 and to assess predictive factors for high compliance to screening in Dutch hospitals.Methods: The study population consisted of 97 Dutch hospitals. Data on screening results from 2007-2010 were obtained via the Dutch HCI. Specialized hospitals were excluded for further analyses (n=4). A questionnaire was developed to identify additional hospital characteristics. Linear regression analysis was performed to assess predictive factors for the obtained screening results, using the screening percentages of 2010 as dependent variable. Results are presented as B's, which indicate differences in screening percentages between groups (e.g. B=10 indicates a 10% difference in screening percentage). Results: The mean screening percentage increased from 51 ± 28% in 2007 (n=75 hospitals, n=340,000 patients) to 72 ± 17% in 2010 (n=97 hospitals, n=1,050,000 patients). Eighty-one hospitals (87%) returned the questionnaire. Screening results were associated with having a protocol-defined referral (B=10.5, p=0.01), FTE clinical dieticians (middle vs lowest tertile: B=7.9, p=0.04; highest vs lowest tertile: B=3.8, p=0.33), type of hospital (teaching vs general: B=7.8, p=0.03; university vs general: B=-2.2, p=0.69), applied screening tool (SNAQ vs MUST: B=7.0, p=0.08) and participation in the implementation project (B=5.7, p=0.07).
Conclusion: Since the introduction of the performance indicator on undernutrition screening, the screening percentage has increased significantly. High compliance to screening was associated with protocol defined referral, FTE clinical dieticians (middle tertile), teaching hospitals, use of SNAQ, and participation in the implementation project.

Nutritional status in patients with chronic pancreatitis. The value of a nutritional assessment

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Chronic pancreatitis (CP) is a condition that is associated with an increased risk of malnutrition due to exocrine insufficiency and an increased metabolic rate. Early detection of CP patients at risk of malnutrition is essential to prevent clinical deterioration and to maintain good quality of life. Literature about the nutritional status of CP patients is scarce. Simple, sensitive methods to identify those patients at risk are lacking. At most outpatient clinics patients are only screened by monitoring body weight and pancreatic function. According to the recent ASPEN consensus however, malnutrition is also determined by functional decline, changes in body composition and functional impairment. The aim of this study was to explore the nutritional status of CP outpatients and to identify relevant parameters for screening on malnutrition. In this explorative cross sectional study we included 50 patients with chronic or recurrent acute pancreatitis. Nutritional assessment included nutritional screening tools (MUST, MNA), self-reported weight loss and functional impairment, anthropometry, bio-impedance analysis and a quality of life questionnaire. Age and gender specific percentile scores were determined for all anthropometric measures. According to nutritional screening tools 28-50% of the patients had a moderate or high risk of malnutrition. CP patients scored significantly lower on all eight domains of the Short Form Health Survey (SF-36) (all $p \leq 0.001$) compared to Dutch norm values. More than half of the patients scored below the 25th percentile, and 20-35% scored below the 5th percentile on midarm muscle circumference, hand grip strength and fat free mass index. The Mini Nutritional Assessment tool (MNA) identified at most 60-73% of all patients with very low anthropometric scores (<p10). Substantial weight loss (>10%) since diagnosis did not identify all functional comprised patients. Patients who reported evident impairment in muscle strength and physical endurance since diagnosis scored significantly worse on MNA ($p = 0.002$), HGS ($p = 0.03$) and all domains of the SF-36 (all $p<0.01$).
Conclusion: CP outpatients are at risk of malnutrition. Anthropometric parameters regarding muscle mass and function are strongly impaired in a substantial part of these patients, resulting in a significantly worse quality of life. Use of weight loss or nutritional screening tools seems to be insufficient to identify CP patients with impaired body composition and restricted physical functioning. Anthropometry combined with self-reported dec in muscle strength and endurance might be relevant parameters for the assessment of malnutrition in CP outpatients.

Validity of bioelectrical impedance analysis to assess fat-free mass in head and neck cancer patients: an exploratory study

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Assessment and monitoring of fat free-mass (FFM) is of clinical importance, because FFM is reflective of body cell mass, the total mass of protein-rich, metabolically active cells which is affected during malnutrition and therefore related to clinical outcome. In previous research we found that head and neck cancer patients lose about 5% of their pre-treatment FFM (1). Although DXA is a widely accepted method due to its precision and validity to assess FFM in clinical patients, it is relatively expensive and not always available. Bioelectrical impedance analysis (BIA) is a non-invasive, portable, and inexpensive method to assess body composition. However, validity of BIA is population specific, as it is influenced by hydration status, fat fraction, and geometrical body shape. Currently, validity of BIA in head and neck cancer patients is unknown. Therefore, in this exploratory study we tested our hypothesis that BIA, using the Geneva equation, is a valid method to assess FFM in head and neck cancer patients. FFM was assessed in 24 head and neck cancer patients by BIA, using the Geneva equation by Kyle et al. (2), and dual energy x-ray absorptiometry (DXA). Both measurements were performed three times: one week before (T_0), and one month (T_1) and four months (T_2) after cancer treatment. Agreement between FFM by BIA (FFM_{BIA}) and FFM by DXA (FFM_{DXA}) was analyzed by paired t-test, Bland-Altman plots and concordance correlation coefficients (CCC). FFM_{BIA} did not significantly differ from FFM_{DXA} (mean difference ± standard deviation: 0.71±1.9, 0.30±1.9 kg and 0.02±2.1 kg) at T_0, T_1 and T_2 respectively. The correlation between the mean FFM and the difference between FFM_{DXA} and FFM_{BIA} at T_0, T_1, and T_2 were r=0.48 (p=0.017), r=0.29 (p=0.175), and r=0.26 (p=0.228), respectively. Limits of agreement were 3.8, 3.7 and 4.1 kg respectively. CCCs were 0.98 at all time points.

In conclusion, BIA may be used to assess FFM with reasonable validity based on mean-level comparisons, but limits of agreement suggest that differences between BIA and DXA may vary by about 4 kg in an individual patient. The results of this exploratory study need to be confirmed in a larger sample of head and neck cancer patients.

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Leukocyte activation by medium-chain triglycerides is not modulated by fish oil-based lipids

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Medium-chain triglycerides (MCTs) as part of parenteral nutrition formulations activate leucocytes in vitro by mechanisms that remain unclear hitherto. Novel parenteral lipids have been developed containing mixed lipids: MCTs, soybean oil-derived long-chain triglycerides (LCTs), fish oil (FO) and/or olive oil (OO). Aim of this study was to assess whether leukocyte activation by MCTs involves mechanisms that also steer immune modulation by anti-inflammatory lipids (FO and OO). In vitro effects of various lipids, and addition of n-3 fatty acids (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) to LCT/MCT, on expression of surface activation markers and reactive oxygen species (ROS) production of leucocytes was studied. MCT-containing lipids (LCT/MCT, LCT/MCT/FO, LCT/MCT/FO/OO) activated immune cells depending on their MCT content, with decreased L-selectin expression (30, 36, 24%, respectively) and increased degranulation (71, 83, 62%, respectively) and adhesion (46, 48, 37%, respectively) in granulocytes compared to lipid-free medium. Immune cells exposed to MCT-free lipids (LCT, FO, SO/OO) had similar immune status compared to immune cells not exposed to lipids. Stimulus-induced ROS production remained unchanged or decreased in MCT-containing lipids: (LCT/MCT, LCT/MCT/FO, LCT/MCT/FO/OO). Of MCT-free lipid emulsions only incubation with FO resulted in a significant decrease of 13% in ROS production. Incubation with LCT/MCT and micelles of EPA slightly activated granulocytes (8% decrease in expression of L-selectin, 15% increase of degranulation), whereas addition of micelles of DHA did not alter the immune status, compared to LCT/MCT alone. Furthermore, addition of EPA or DHA micelles to LCT/MCT did not alter ROS production. In conclusion, leukocyte activation by MCTs is not modulated by anti-inflammatory lipids, suggesting that MCTs exert their effects via a different pathway.

Features of cachexia in patients with advanced cancer scheduled for treatment with chemotherapy

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Background and aims: The diagnostic framework of cancer cachexia is currently in the center of attention in international cancer literature. Consensus has been reached on the component weight loss in combination with Body Mass Index (BMI) and low muscle mass (Fearon et al, Lancet Oncol. 2011), but not on other potential cachexia features, like inflammation, anorexia and muscle strength. The aim of this study is to assess the prevalence of other potential features of cachexia in patients with advanced cancer scheduled for chemotherapy. Methods: In patients with advanced colon, breast, prostate or lung cancer, we inquired weight loss (WL) history (6 months), measured body composition (BMI, muscle mass: fat-free mass index (FFMI), phase angle, mid-upper arm muscle circumference (MUAMC) and hand grip strength), measured C-Reactive Protein (CRP) in blood and assessed anorexia (VAS, FAACT questionnaire) before start of a new chemotherapy treatment line. Patients were categorized as 'cachectic' (C) if they had experienced >5% WL in 6 months or >2% WL in 6 months in combination with a BMI<20 kg/m^2 or FFMI<5th percentile according to the consensus framework (Fearon et al, Lancet Oncol. 2011)). All other patients were defined as 'non cachectic' (NC). Results: Data were obtained for 122 patients (63.3 ± 10.5 y, 56% male) with cancer: 42% lung, 25% colorectal, 20% prostate and 13% breast. Fourty-one patients (34%) were found to be cachectic. Compared to non-cachectic patients, cachectic patients more often had a low FFMI (C: 51% vs NC: 23%, Chi^2 tests, P<0.01) and more often experienced anorexia (FAACT questionnaire: C: 32%; NC: 15%, Chi^2 tests, P=0.04). The prevalence of other measured variables was not significantly different between the groups, also NC patients showed signs of inflammation, diminished muscle mass and strength: elevated CRP (>8mg/L): C: 71%; NC: 64%, low phase angle: C: 59%; NC: 44%, low MUAMC: C: 36%; NC: 26% and low hand grip strength: C: 71%; NC: 64%.
Conclusions: One-third of patients with advanced cancer were cachectic before start of chemotherapy. Besides FFMI and anorexia according to the FAACT questionnaire, there were no statistically significant differences for features associated with cachexia when using the consensus definition of cachexia. Signs of a poor nutritional status, anorexia and inflammation were also prevalent in patients without cachexia. This substantiates the complexity of the diagnosis of cachexia.

Evaluation of optimal protein and energy nutrition in mechanically ventilated critically ill patients

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Background: Optimal nutrition for ICU patients continues to be debated, the level as well as the kind and timing of feeding. The importance of protein feeding is gaining more attention, but proper and easy ways of evalutation of daily practice in the ICU are not available. Methods: In this retrospective analysis an observational study is revisited, and new data are presented on the daily provision of protein and energy during the early days of admission to a mixed medical-surgical ICU in an academic hospital. In total 871 mechanically ventilated patients were included with measured resting energy expenditure (REE) by indirect calorimetry. Patients with at least 4 days mechanical ventilation were evaluated. Protein and energy provision of day 4 were used as surrogate marker for adequate protein and energy provision. Energy was expressed as percentage of REE measured. Protein was expressed in gram per kg pre-admission body weight, adjusted for BMI below 20 and BMI over 30. Outcome measures were standardised to 28 days, both 28 day mortality and ventilator freed days (VFD). Cox regression was used to analyze the effect of day 4 protein provision and day 4 percentage of REE provided on 28 day mortality, with adjustments for sex, age, BMI, APACHE II, diagnosis, and hyperglycemic index. Linear regression was used for VFD, with same adjustments. Results: Overall 28 day mortality was 18.6% and mean VFD were 6.5 (SD 7.0). Adjusted Hazard ratios for day 4 protein provision indicated significant reduction (HR 0.485; 95%CI 0.262,0.901; p=0.022) and for day 4 energy provision a significant increase (HR 2.998; 95%CI 1.331,6.753; p=0.008) of 28d mortality. Beta for day 4 protein provision was significantly positive (Beta +3.64; 1.59,5.69; p=0.001) and for day 4 energy provision significantly negative (Beta -3.65; -6.35,-0.94; p=0.008).
Conclusions: The current national performance indicator for nutritional treatment is protein intake at day 4 of admission of more than 1.2 g/kg pre-admission weight. This appears to be a relevant instrument to evaluate protein provision to mechanically ventilated critically ill patients. Early overnutrition with energy should be avoided.

The impact of duodenal-jejunal exclusion on satiety hormones

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Bariatric procedures that exclude the proximal small intestine lead to significant weight loss. Hormones that alter appetite such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), ghrelin, cholecystokinin (CCK), and leptin are thought to be involved in this phenomenon by altering gastric emptying and/or food intake. Recently, the endoscopic duodenal-jejunal bypass liner (DJBL) has been shown effective in treating obesity. Here, we investigated the effect of DJBL treatment on hormones that play a role in satiety. Seventeen obese patients (BMI 30-50kg/m^2) with type 2 diabetes received the DJBL for 24 weeks. Plasma levels of GLP-1, PYY, CCK, and ghrelin were analyzed after a standardized meal before, during, and after DJBL treatment. In addition, fasting leptin levels were analyzed. At baseline, patients had an average body weight of 116.0±5.8kg. One week after implantation, subjects had lost 4.3±0.6kg ($p<0.01$). During DJBL treatment, weight loss progressed to 12.7±1.3kg at 24 weeks post-implantation ($p<0.01$). All subjects reported reduced caloric intake following DJBL implantation. In addition, satiety increased in 15/17 patients. As early as one week after implantation, post-prandial GLP-1, PYY, and ghrelin levels were increased (base vs. week 1 vs. week 24 GLP-1: 4,440±249 vs. 6,407±480 vs. 6,008±429pmol/L/min, PYY: 2,584±154 vs. 4,084±418 vs. 4,121±697pmol/L/min, and ghrelin: 7,881±1,783 vs. 11,042±1,807 vs. 10,562±1,783 pg/mL/min, all $p<0.05$). The CCK response to a meal decreased (base vs. week 1 vs. week 24: 434±51 vs. 229±52 vs. 256±51pmol/L/min, $p<0.01$). Fasting leptin levels also decreased, reaching statistical significance at week 24, and positively correlated with BMI (base vs. week 24: 98.4±16.8 vs. 53.1±10.2ng/mL, $p<0.01$ and $rs=0.58$, $p<0.05$ respectively). One week post-explantation, no changes in PYY, ghrelin, or leptin levels were observed. The CCK response was similar to the CCK response observed at baseline.

Conclusions: DJBL treatment appears to cause weight loss by affecting satiety via triggering of the ileal-brake, as indicated by increased PYY and GLP-1 levels. Fasting levels of leptin decreased in parallel with BMI, which may be attributed to decreased adiposity. Interestingly, ghrelin levels increase, likely due to reduced caloric intake. In contrast, CCK levels decreased, possibly due to the absence of chemical triggers related to food in the proximal small intestine.

plattegrond expositie (in kleur)

Alfabetische lijst van standhouders

B = Beneluxhal, D = Doorloop, K = Kempenhal	***Standnummer***
Alvleesklier vereniging	B 9
AstraZeneca BV	K 9
Biolitec Biomedical Technology	B 15
Bristol-Myers Squibb B.V.	D 3
Cablon Medical	K 6
CameraPil BV	K 12
Campro Scientific GMBH	B 21
Cobra Medical BV	K 15
COOK Medical	K 14
Covidien	B 11
Crohn&Colitis Ulcerosa ver. Nederland	B 5
Dr. Falk Pharma Benelux BV	B 4
Endotechniek	B 16
Erbe Nederland BV	D 1
Ferring BV	B 26
FMH Medical BV	K 4
Fresenius Kabi Nederland BV	K 7
Getinge BV	B 14
Gilead Sciences Netherlands BV	B 22
Hitachi Medical Systems	B 7
Janssen-Cilag BV	K 8
Medical Measurements Systems BV	K 3
Medicor	K 17
Mediq Tefa	B 13
Medivators BV	B 19
Merck Sharp&Dohme	K 1
Mermaid Medical	B 23
Mindray Medical Netherlands	B 18
Norgine BV	K 16
Olympus	K 2
Pentax Medical	B 6
Pyramed Nederland	D 2
Roche	K 5
ScoVas Medical BV	B 20
Soluscope SAS	B 17
Surgical Technologies BV	K 11
TIMM Health Care BV	K 10
TRAMEDICO BV	K 13
V&VN MDL	B 10
VCM Medical	B 12
Vereniging Ziekte van Hirschprung	B 8
Vifor Pharma Nederland BV	B 3
Wassenburg Medical Devices BV	B 25
Zambon Nederland BV	B 24

plattegrond koningshof

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