Programma voorjaarsvergadering 20 en 21 maart 2014
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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Ledenvergadering NVMDL i.o.	20 maart, 12.00 uur – zaal 63-64
Nederlandse Vereniging voor Hepatologie	20 maart, 15.00 uur – Baroniezaal

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Tijdstippen diverse ledenvergaderingen tijdens voorjaarsvergadering:

Nederlandse Vereniging van Maag-Darm-Leverartsen	21 maart, 08.00 uur – Zaal 81-82-83
V & VN MDL	21 maart, 11.45 uur – Beneluxhal
Vergadering Sectie Inflammatoire Darmziekten (IBD)	21 maart, 13.00 uur – Parkzaal

Belangrijke mededeling
over de aanwezigheid van farmaceutische industrieën

Aan alle deelnemers aan de voorjaarsvergadering op 20 en 21 maart 2014

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 tijdens het voorjaarscongres worden gekozen voor verschillende kleuren congres-badges.

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 het voorjaarscongres op 20 en 21 maart in NH Conference Center Koningshof te Veldhoven. Zoals gebruikelijk wordt ons congres voorafgegaan door het cursorisch onderwijs op 19 maart, deze keer over oncologie, waarvan u het programma aantreft op bladzijde 6 en 7.

Er is in het voorjaar traditiegetrouw veel ruimte voor voordrachten van wetenschappelijk onderzoek. Dit wordt aangevuld met uiteenlopende symposia, te beginnen met een multidisciplinair symposium over darmfalen op donderdagmorgen.
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. Dit jaar staat dit programma in het teken van *translational medicine.* Onze gastspreker professor E.M. El-Omar – Aberdeen University, UK – zal dit thema ook uiteenzetten in de afsluitende plenaire sessie in de Brabantzaal met een voordracht getiteld *Challenges of Translational GI Research om* 18.00 uur in de Brabantzaal.
Na de lunch is er naast uiteenlopende parallelsessies een symposium van de Nederlandse Vereniging voor Gastrointestinale Chirurgie in het Auditorium en een minisymposium over voeding in de dagelijkse praktijk.
Om 17.00 uur vindt in de Brabantzaal de uitreiking plaats van de Frieda den Hartog Jager Prijs aan professor dr. J.H. Kleibeuker, die aansluitend een ere-voordracht houdt getiteld *Pathogenese en preventie van colorectaal carcinoom: the continuing story*. Om 17.30 uur volgt de President Select, zoals gebruikelijk plenair, met om 18.00 uur de voordracht over translationeel onderzoek van gastspreker professor E.M. El-Omar, editor van GUT.

Op vrijdagochtend is na de ALV van de NVMDL weer veel ruimte voor vrije voordrachten van onder meer de Sectie Gastrointestinale Endoscopie en een klinisch NVH-symposium. Na de koffiepauze wordt in de Brabantzaal gerapporteerd over de resultaten van de PERK-studie met aansluitend aandacht voor de nieuwe richtlijn antistolling. In zaal 80 vindt het NESPEN symposium plaats. Gedurende de gehele vrijdag zijn er genodigde sprekers en vrije voordrachten van de DEGH.
Na de lunch volgt in de Brabantzaal een symposium over poliepen en CRC met het oog op het bevolkingsonderzoek, en wederom abstractsessies van NVGE/NVGIC, NVGE en IBD. In de Beneluxhal wordt door de Verpleegkundigen en Verzorgenden Nederland MDL (V&VN MDL) een eigen programma met lezingen verzorgd, met daarnaast een keuze uit verschillende subsessies.

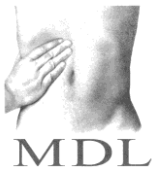
Kortom, een gevarieerd en inspirerend programma.

Dr. J.J. Keller, secretaris
Dr. K. van der Linde, bestuurslid

Woensdag 19 maart 2014

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

Cursuscommissie
Prof. dr. P.D. Siersema (voorzitter), MDL-arts, UMC Utrecht
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. J. Vecht, MDL-arts, Isala Klinieken, Zwolle
Dr. R.A. de Vries, MDL-arts, VUmc, Amsterdam
Dr. P.J. Wahab, MDL-arts, Rijnstate Ziekenhuis, Arnhem



Thema: Oncologie

Poliepen

voorzitters: U.H.W. Beuers en P.D. Siersema

14.15 – 14.30 Opening en kennistoets

14.30 – 14.50 Niet invasieve CRC screeningstesten
Dr. K.H.N. de Boer, MDL-arts, VU medisch centrum, Amsterdam

14.50 – 15.20 Hoe verricht ik een goede coloscopie en hoe kan ik mijn poliepdetectie verhogen?
Prof. dr. E. Dekker, MDL-arts, AMC, Amsterdam

15.20 – 15.40 Een serrated adenoma! Wat betekent dat eigenlijk?
Dr. S. Sanduleanu, MDL-arts, MUMC, Maastricht

15.40 – 16.00 Hoe ga ik om met een “grote” (≥ 2 cm) poliep?
Dr. J. Hardwick, MDL-arts, Leids Universitair Medisch Centrum

Colorectaal carcinoom

16.00 – 16.20 Wanneer moet ik denken aan een erfelijke darmtumor en wat betekent dat voor de patiënt en de familie?
Dr. F.M. Nagengast, MDL-arts, Radboudumc Nijmegen

Woensdag 19 maart 2014

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

16.20 – 16.40	Hoe voorkom ik IBD- en IBD-medicatie gerelateerde carcinomen *Dr. B. Oldenburg, MDL-arts, UMC Utrecht*
16.40 – 17.10	Pauze
17.10 – 17.40	Rol van pathologisch onderzoek bij de keuze van chemo-therapeutische behandeling van CRC *Prof. dr. C.J.A. Punt, medisch oncoloog, AMC, Amsterdam*
17.40 – 18.05	De chirurgische en endoscopische behandeling van CRC en complicaties, en hoe licht ik mijn patiënt voor? *Dr. W.J.H.J. Meijerink, chirurg, VU medisch centrum, Amsterdam*

Potpourri

18.05 – 18.35	Hobbels en bobbels in het maagdarmkanaal: NET en GIST *Dr. H.M. van Dullemen, MDL-arts, UMC Groningen*
18.35 – 18.55	Wat is de rol van de MDL-arts bij lymfomen van het maagdarmkanaal *Dr. H. Boot, MDL-arts, Antoni van Leeuwenhoekhuis, Amsterdam*
18.55 – 19.15	Help, een tumor van het periampullaire gebied: hoe pak ik dat aan als MDL-arts? *Dr. J.W. Poley, MDL-arts, Erasmus MC, Rotterdam*
19.15	Einde programma
19.15 – 20.45	Diner

De cursuscommissie verwacht van de MDL-artsen i.o. dat ze de Cursus Klinische Hepatologie(NVH) tijdens de Dutch Liver Week 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 leverings-voorwaarden van toepassing. Informatie vindt u op de onderwijspagina van www.mdl.nl en www.nvge.nl.

Programma donderdag 20 maart 2014

Donderdag	Brabantzaal	Baroniezaal	Auditorium	Parkzaal
09.00	Ontvangst en koffie	Ontvangst en koffie	Vrije voordrachten Ned. Vereniging voor Gastroinstestinale Chirurgie (aanvang 09.30) pagina 18	Ontvangst en koffie
10.00 - 11.30	Vrije voordrachten Ned. Vereniging voor Gastro-enterologie pagina 10	DEGH-meeting (aanvang 10.30 uur) pagina 22		Multidisciplinair symposium Darmfalen (aanvang 09.30) pagina 26
11.30 - 12.00	Ledenvergadering NVGE		Geen programma i.v.m. Ledenvergadering NVGE	Geen programma i.v.m. Ledenvergadering NVGE
12.00 - 13.00	Lunch in expositiehal	Lunch in expositiehal	Lunch in expositiehal	Lunch in expositiehal
13.00 – 15.00	Vrije voordrachten sectie Gastrointestinale Oncologie pagina 12	DEGH-meeting pagina 23	Symposium NVGIC: 'Van anussparende chirurgie tot rectumsparende endoscopie' pagina 20	Vrije voordrachten sectie Inflammatoire Darmziekten pagina 27
15.00 - 15.30	Theepauze	Theepauze + ALV NVH	Theepauze	Theepauze
15.30 - 17.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie pagina 14	DEGH-meeting pagina 24	Symposium NVGIC: 'Uitkomsten en transparantie van de colorectale diagnostiek en chirurgie' pagina 20	Minisymposium: 'Update Voeding in de dagelijkse praktijk' pagina 30
17.00 - 17.30	Uitreiking Frieda den Hartog-Jager Prijs aan prof. dr. J.H. Kleibeuker pagina 16			
17.30 - 18.00	President Select pagina 16			
18.00 – 18.30	State of the art lecture Professor E.M. El-Omar – Aberdeen University, UK pagina 17			
18.30 - 19.30	Borrel in expositiehal			
19.30 - 22.00	Diner Genderzaal			
22.00 - 01.00	Borrel / Muziek in foyer			

Vrijdag 21 maart 2014

Vrijdag	Brabantzaal	Baroniezaal	Auditorium	Parkzaal
08.30 09.30 – 11.00	Vrije voordrachten sectie Gastrointestinale Endoscopie pagina 31	Posterrondes zaal 19 en 20 (aanvang 09.00) Symposium Ned. Vereniging voor Hepatologie pagina 40	Vrije voordrachten Ned. Vereniging voor Gastroenterologie en Gastrointestinale pagina 35	Vrije voordrachten Ned. Vereniging voor Gastroenterologie en sectie Inflammatoire Darmziekten pagina 48
11.00 - 11.30	Koffiepauze	Koffiepauze	Koffiepauze	Koffiepauze
11.30 - 13.00	Symposium PERK studie en Richtlijn Antistolling pagina 33	DEGH-meeting pagina 45	Vrije voordrachten Ned. Vereniging voor Gastroenterologie pagina 36	Vrije voordrachten Sectie Inflammatoire Darmziekten pagina 49
13.00 – 14.00	Lunch expositiehal	Lunch expositiehal	Lunch expositiehal	Lunch expositiehal
14.00 – 15.30	Symposium: CRC Bevolkingsonderzoek pagina 34	DEGH-meeting pagina 45 Abstract and Poster Prizes and goodbye pagina 47	Vrije voordrachten Ned. Vereniging voor Gastroenterologie en Gastrointestinale Chirurgie -pagina 48	Geen programma in deze zaal in de middag
15.30 – 16.00	Afsluiting in expositiehal		Afsluiting in expositiehal	

Vrijdag 21 maart 2014 - programma V&VN MDL en NESPEN

Vrijdag	Beneluxhal	Zaal 63	Zaal 64	Zaal 80
10.00 – 12.15	Plenair ochtendprogramma V&VN MDL pagina 55			Voordrachten NESPEN, om 10.00. gevolgd door Symposium 'klinisch voedingsonderzoek' pagina 52-53
12.15	Lunch in expo			Lunchbuffet 13.30
13.45 – 15.15	Parallel programma Endoscopie-verpleegkundigen pagina 55	Parallel programma Lever- en IBD-verpleegkundigen pagina 56	Parallel programma Voedingsverpleeg-kundigen en MDL pagina 56	Geen programma in deze zaal in de middag
15.15	Einde programma	Einde programma	Einde programma	

Voordrachten Nederlandse Vereniging voor Gastroenterologie — Brabantzaal

Voorzitters: E.J. Schoon en V.M.C.W. Spaander

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

10.00 Introductie voorzitter(s) op het programma

10.10 Cost effectiveness of Barrett's esophagus surveillance in a prospective followed cohort in the Netherlands (p. 57)

S.H. van Olphen[1], F. Kastelein[1], E.W. Steyerberg[2], C.W.N. Looman[2], M.C.W. Spaander[1], M.J. Bruno[1], E.W. Bekker Grob[2] on behalf of the ProBar study group, [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center Rotterdam, The Netherlands, [2]Dept of Public Health, Erasmus University Medical Center Rotterdam, The Netherlands

10.20 Does use of NSAIDs, statins and proton pump inhibitors prevent development of esophageal adenocarcinoma among patients with Barrett's esophagus? Results from a multinational population based case control study (p. 58)

G.M.C. Masclee[1,2], P.M. Coloma[1], E.J. Kuipers[2], M.C.J.M. Sturkenboom[1,3], [1]Dept of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Dept of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands.

10.30 FISH Biomarkers for the Detection of Dysplasia and Prediction of Malignant Progression in Non dysplastic Barrett's Esophagus (p. 59)

M.R. Timmer[1, 2]; C.T.I. Lau[2]; W. Rosmolen[1]; S.L. Meijer[3]; M.G.W. Dijkgraaf[4]; R.C. Mallant Hent[5]; A.H. Naber[6]; A.H. van Oijen[7]; L.C. Baak[8]; P. Scholten[9]; C. Böhmer[10]; P. Fockens[1]; J.J. Bergman[1]; K.K. Krishnadath[1,2] ,[1.]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam, [3]Dept of Pathology, Academic Medical Center, Amsterdam, Netherlands. [4]Clinical Research Unit, Academic Medical Center, Amsterdam, [5]Dept. of Gastroenterology, Flevoziekenhuis, Almere, Netherlands. [6]Dept. of Gastroenterology, Tergooiziekenhuizen, Hilversum, [7]Dept. of Gastroenterology, Medisch Centrum Alkmaar, Alkmaar, [8]Dept. of Gastroenterology, Onze Lieve Vrouwe Gasthuis, Amsterdam, [9]Dept. of Gastroenterology, Sint Lucas Andreas Ziekenhuis, Amsterdam, Netherlands. [10]Dept. of Gastroenterology, Spaarneziekenhuis, Hoofddorp, Netherlands.

10.40 SOX2 as a novel marker to predict neoplastic progression in Barrett's esophagus (p. 60)

S.H. van Olphen[1, 2], K. Biermann[2], F. Kastelein[1], B.E. Hansen[1], H.A. Stoop[2], M.C.W. Spaander[1], L.H.J. Looijenga[2], M.J. Bruno[1] on behalf of the ProBar study group, [1] Dept of Gastroenterology and Hepatology, Erasmus University Medical Center Rotterdam, The Netherlands, [2]Dept of Pathology, Erasmus University Medical Center Rotterdam, The Netherlands

10.50 The influence of prophylactic proton pump inhibitor treatment on the development of symptomatic marginal ulceration: a historic cohort study (p. 61)

U.K. Coblijn[1], S.M.M. de Castro[1], S.M. Lagarde[2], S.D. Kuiken[3], B.A. van Wagensveld[1], [1]Sint Lucas Andreas Ziekenhuis, Dept of General Surgery, [2]Academic Medical Center Amsterdam, Dept of General Surgery, [3]Sint Lucas Andreas Ziekenhuis, Dept of Gastroenterology

11.00 **MLDS voordracht**

A prospective study on intake of meat and heme iron, nitrite, nitrate and nitrosamines as risk factors for adenocarcinoma of esophagus (EAC) and gastric cardia (GCA), esophageal squamous cell carcinoma (ESCC), and Barrett's esophagus (BE) (p. 62)

P.A. van den Brandt[1], A.P. Keszei1, A.L.C. Driessen[2], C.J.R. Huysentruyt[2], Y.C.A. Keulemans[3], R.A. Goldbohm[4], L.J. Schouten[1], [1]School for Oncology and Developmental Biology (Grow), Dept of Epidemiology, Maastricht University, Maastricht, the Netherlands [2]School for Oncology and Developmental Biology (Grow), Dept of Pathology, Maastricht University, Maastricht, The Netherlands [3]Dept of Gastroenterology, Maastricht University Medical Centre, Maastricht, the Netherlands [4]Dept of Prevention and Health, TNO Quality of Life, Leiden, The Netherlands

11.15 **MLDS voordracht**

Human buccal epithelium acquires microbial hyporesponsiveness at birth, a role for secretory leukocyte protease inhibitor (p. 63)

C.L. Menckeberg[1,8], J. Hol[1,2,3,8], L.F. de Ruiter[1,2], H.C. Raatgeep[1], Y. Simons Oosterhuis[1], D. J. Lindenbergh Kortleve[1], A.M. Korteland van Male[1], S. El Aidy[4], P.P.E. van Lierop[1], M. Kleerebezem[4], M. Groeneweg[5], G. Kraal[6], B.E. Elink Schuurman[2], J.C. de Jongste[2], E.E.S. Nieuwenhuis[1,7,8], J.N. Samsom[1,8] [1]Laboratory of Pediatrics, division of Gastroenterology and Nutrition, Erasmus MC, Rotterdam, The Netherlands [2]Dept of Pulmonary diseases, Sophia Children's Hospital, Rotterdam, The Netherlands [3]Dept of Pediatrics, University Hospital Ghent, Ghent, Belgium [4]Laboratory of Microbiology and Host Microbe Interactomics Group, Wageningen University, Wageningen, The Netherlands [5]Maasstad Hospital, Dept of Pediatrics, Rotterdam, The Netherlands [6]Dept of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands [7]Wilhelmina Children's Hospital, Utrecht, The Netherlands [8]Authors have equally contributed

11.30 Korte ledenvergadering Nederlandse Vereniging voor Gastroenterologie

12.00 Lunch in expositiehal

Donderdag 20 maart 2014

Vrije voordrachten Sectie Gastrointestinale Oncologie — Brabantzaal

Voorzitters: G.H. de Groot en K.M.A.J. Tytgat

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

13.00 Inleiding op de sessie door de voorzitter

13.10 Impact of neoadjuvant chemoradiotherapy on prognostic factors for survival in patients with esophageal or junctional cancer (p. 64)
J. Shapiro[1], H.F. Lingsma[2], P. van Hagen[1], A.K. Talsma[1], B.P.L. Wijnhoven[1], E.W. Steyerberg[2], A. van der Gaast[3], J.J.B. van Lanschot[1], On behalf of the CROSS Study Group, [1]Dept of Surgery, [2]Dept of Public Health, [3]Dept of Med Oncology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

13.20 Palliative care of esophageal cancer in the Netherlands: determinants associated with treatment decisions (p. 65)
J.L. Opstelten[1], L.R. de Wijkerslooth[2], M. Leenders[1], D.J. Bac[3], M.A. Brink[2], B.C.A.J. Loffeld[4], M.J.F. Meijnen-Bult[5], I.M. Minderhoud[6], M.A.M.T. Verhagen[7], M.G.H. van Oijen[1], P.D. Siersema[1], [1]Universit Medical Center Utrecht, Utrecht, [2]Meander Medical Center, Amersfoort, [3]Hospital Gelderse Vallei, Ede, [4]Zuwe Hofpoort Hospital, Woerden, [5]St Jansdal Hospital, Harderwijk, [6]Tergooi Hospitals, Hilversum/ Blaricum, [7]Diakonessenhuis, Utrecht/ Zeist, The Netherlands

13.30 GATA6 expression in Barrett's metaplasia development and progression towards malignancy (p. 66)
K. Pavlov[1], H. Judith[2], C. Meijer[3], W. Boersma[1], F.T. Peters[1], A. van den Berg[4], A. Karrenbeld[4], J.T.M. Plukker[2], F.A.E. Kruyt[3], J.H. Kleibeuker[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Surgical Oncology, [3]Dept of Medical Oncology, [4]Dept of Pathology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

13.40 Clinicopathological characteristics of pancreatic resection specimens of inherited / familial versus sporadic pancreatic ductal adenocarcinoma (p. 67)
F. Harinck[1], F. Boersma[1], I. Konings[1], P. Fockens[2], J.E. van Hooft[2], M. Dijkgraaf[3], W.N. Dinjens[4], K. Biermann[4], M.J. Bruno[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, [2]Dept of Gastroenterology and Hepatology, and [3]Clinical Research Unit, Academic Medical Center, Amsterdam, [4]Dept of Pathology, Erasmus MC, Rotterdam, The Netherlands

13.50 Psychological burden of repeated pancreatic surveillance in high risk individuals for pancreatic cancer (p. 68) *I.C.A.W. Konings[1], G.N. Sidharta[2], F. Harinck[1], C. Aalfs[3], E. Smets[4], J.W. Poley[1], A. Wagner[5], J.E. van Hooft[6], A. van Rens[7], P. Fockens[6], M.J. Bruno[1], E.M.A. Bleiker[2,7], On behalf of the Dutch research group on pancreatic cancer surveillance in high risk individuals, [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, [2]Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, [3]Dept of Clinical Genetics, and [4]Dept of Medical Psychology, Amsterdam Medical Center, University Medical Center, Amsterdam, [5]Dept of Clinical Genetics, Erasmus MC, University Medical Center, Rotterdam, [6]Dept of Gastroenterology and Hepatology, Amsterdam Medical Center, University Medical Center Amsterdam, [7]Family Cancer Clinic, The Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, The Netherlands*

14.00 Structural variant breakpoint detection in advanced colorectal cancer (p. 69)

E. van den Broek[1], O. Krijgsman[1], D. Sie[1], J.C. Haan[1], M. Komor[1], J. Traets[1], D.A.M. Heideman[1], M.A. van de Wiel[2], I.D. Nagtegaal[3], C.J.A. Punt[4], B. Carvalho[1], B. Ylstra[1], G.A. Meijer[1], R.J.A. Fijneman[1], [1]Dept of Pathology, and [2]Dept of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, [3]Dept of Pathology, Radboud University, Nijmegen Medical Center, Nijmegen, [4]Dept of Medical Oncology, Academic Medical Center, Amsterdam, The Netherlands

14.10 Feasibility of adjuvant laparoscopic hyperthermic intraperitoneal chemotherapy in a short stay setting in patients with colorectal cancer at high risk of peritoneal carcinomatosis (p. 70)

D.A.M Sloothaak[1], T.J. Gardenbroek[1], J.Crezee[3], W.A. Bemelman[1], C.J.A Punt[2], C.J. Buskens[1], P.J. Tanis[1], [1]Dept of Surgery, [2]Dept of Medical Oncology, and [3]Dept of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands

14.20 Urological procedures in patients with peritoneal carcinomatosis of colorectal cancer treated with HIPEC: Morbidity and survival analysis (p. 71)

H.J. Braam[1], T.R. van Oudheusden[2], I.H. de Hingh[2], S.W. Nienhuijs[2], D. Boerma[1], M.J. Wiezer[1], B. van Ramshorst[1], [1]Dept of Surgery, St. Antonius Hospital, Nieuwegein, [2]Dept of Surgery, Catharina Hospital, Eindhoven, The Netherlands

14.30 Cytoreduction and hyperthermic intraperitoneal chemotherapy: a feasible and effective option for colorectal cancer patients after emergency surgery in the presence of peritioneal carcinomatosis (p. 72)

T.R. van Oudheusden[1], H.J. Braam[2], S.W. Nienhuijs[1], M.J. Wiezer[2], B. van Ramshorst[2], M.D.P. Luyer[1], I.H.J.T. de Hingh[1], [1]Dept of Oncologic Surgery, Catharina Hospital, Eindhoven, [2]Dept of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

14.40 Oncological follow up of the Stent-In 2 trial: cancer recurrence after curative treatment of malignant colonic obstruction (p. 73)

D.A. Sloothaak[1], M.W. van den Berg[2], M.G. Dijkgraaf[3,4], P. Fockens[2,4], P.J. Tanis[1,4], J.E. van Hooft[2,4], W.A. Bemelman[1,4], [1]Dept of Surgery, [2]Dept of Gastroenterology and Hepatology, and [3]Clinical Research Unit, Academic Medical Center, Amsterdam, [4]Stent-In study group, collaborative Dutch Stent-In study group, Amsterdam, The Netherlands

14.50 Metachronous colorectal cancers: the clinician at fault? (p. 74)

C.M.C. le Clercq[1], C.M. Bakker[2], A. van Nunen[2], E.T.P. Keulen[3], G.L. Beets[4], B. Winkens[5], A.A.M. Masclee[1], S. Sanduleanu[1], [1]Dept of Gastroenterology and Hepatology, Internal Medicine, Maastricht University Medical Center, Maastricht, [2]Dept of Gastroenterology, Atrium Medical Center, Heerlen, [3]Dept of Internal Medicine and Gastroenterology, Orbis Medical Center, Sittard, [4]Dept of Surgery, and [5]Dept of Methodology and Statistics, Maastricht University Medical Center, Maastricht, The Netherlands

15.00 Theepauze in de expositiehal

Voordrachten Nederlandse Vereniging voor Gastroenterologie — Brabantzaal

Voorzitters: M. van Haastert en L.M.G. Moons

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

15.30 Inleiding op het programma door L.M.G. Moons

15.40 Computer assisted instruction before colonoscopy is as effective as nurse counselling, a controlled trial (p. 75)

G. Veldhuijzen[1], M. Klemt-Kropp[1], C.G. Noomen[1], T. van der Ploeg[2], J.P.H. Drenth[3] ,[1]Dept of Gastroenterology and Hepatology, Medical Centre Alkmaar, Alkmaar, The Netherlands, [2]Foreest Medical School, Medical Centre Alkmaar, Alkmaar, The Netherlands, [3]Dept of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, the Netherlands

15.50 Implementing chromoendoscopy for surveillance in inflammatory bowel disease does not increase dysplasia detection compared to conventional colonoscopy with random biopsies: a retrospective study (p. 76)

E. Mooiweer[1] , A.E. van der Meulen-de Jong[2] , E. Dekker[3] , C.Y. Ponsioen[3] H.H. Fidder[1] , P.D. Siersema[1], B. Oldenburg[1] ,[1] University Medical Center Utrecht, Dept of Gastroenterology and Hepatology[2] Leiden University Medical Center, Dept of Gastroenterology and Hepatology[3] Amsterdam Medical Center, Dept of Gastroenterology and Hepatology

16.00 Low inter-observer agreement among endoscopist in differentiating dysplastic from non-dysplastic lesions encountered during colitis surveillance (p. 77)

L.K. Wanders[1] , E. Mooiweer[2] , P.D. Siersema[2] , R. Bisschops[3] , G.R.A.M. d'Haens[1] , B. Oldenburg[2] , E. Dekker[1] ,[1] Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, Netherlands [2]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, Netherlands [3]Dept of Medicine, Division of Gastroenterology, University Hospital Leuven, Leuven, Belgium

16.10 Decreased colorectal cancer risk in Dutch ulcerative colitis patients: results from a population based cohort (p. 78)

T.R.A. van den Heuvel[1,2] , M.H.H. Wassink[1] , S.F.G. Jeuring[1,2] , C.M.D. Glorie[1] , L.E. Oostenbrug[3] , M.J.L. Romberg-Camps[4] , W.H. Hameeteman[1] , A.A.M. Masclee[1,2] , D.M.A.E. Jonkers[1,2] , M.J. Pierik[1,2] ,[1]Maastricht University Medical Center+, Dept of Internal Medicine, Division of Gastroenterology-Hepatology, Maastricht, The Netherlands. [2]Maastricht University Medical Center+, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht, The Netherlands. [3]Atrium Medical Center, Dept of Internal Medicine, Heerlen, The Netherlands. [4]Orbis Medical Center, Dept of Internal Medicine, Sittard-Geleen, The Netherlands.

16.20 Incidence of interval colorectal cancer among inflammatory bowel disease patients enrolled in a colonoscopic surveillance program (p. 79)

W. Kremer[1], E. Mooiweer[1], A.E. van der Meulen – de Jong[2], C.Y. Ponsioen[3], C.J. van der Woude[4], A.A. van Bodegraven[5], J.M. Jansen[6], N. Mahmmod[7], P.D. Siersema[1], B. Oldenburg[1], [1] University Medical Center Utrecht, Dept of Gastroenterology and Hepatology [2]Leiden University Medical Center, Dept of Gastroenterology and Hepatology [3]Amsterdam Medical Center, Dept of Gastroenterology and

Hepatology [4]Erasmus Medical Center Rotterdam, Dept of Gastroenterology and Hepatology [5]VU Medical Center Amsterdam, Dept of Gastroenterology and Hepatology [6]OLVG Amsterdam, Dept of Gastroenterology and Hepatology [7]St Antonius Hospital Nieuwegein, Dept of Gastroenterology and Hepatology

16.30 Faecal calprotectine does not differentiate between IBD and a juvenile polyp (p. 80)

V.G. Pluimakers[1], F.T.M. Kokke[1], P.G.J. Nikkels[2], M.L. Houben[3], R.H.J. Houwen[1], V.M. Wolters[1], [1] WKZ/ UMC Utrecht, Dept of pediatric gastroenterology [2] UMC Utrecht, Dept of Pathology [3]WKZ/ UMC Utrecht, Dept of General Pediatrics

16.40 Fecal immunochemical testing results vary depending on characteristics of colonic lesions (p. 81)

S.C. van Doorn[1]; I. Stegeman[2]; A.K. Stroobants[3], M.W. Mundt[4] , T.R. de Wijkerslooth[1]; P. Fockens[1]; E.J. Kuipers[5], P.M. Bossuyt[2] ; E. Dekker[1] ,[1]Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, Netherlands. [2]Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, Netherlands. [3]Dept of Clinical Chemistry. [4]Dept of Gastroenterology and Hepatology, Flevoziekenhuis Almere. [5]Erasmus Medical Center, Rotterdam, the Netherlands

16.50 Synchronous/metachronous neoplasms predict the presence of lateral spreading tumors (p. 82)

R.M.M. Bogie[1] , C.M.C. le Clercq[1] , M.W.E. Bouwens[1] , B. Winkens[2] , R. de Ridder[1] , T. Kaltenbach[3], R. Soetikno[3] , A.A.M. Masclee[1] , S. Sanduleanu[1] ,[1]Division of Gastroenterology and Hepatology; Maastricht University Medical Center, The Netherlands, [2]Dept of Methodology and Statistics, Maastricht University Medical Center, the Netherlands, [3]VA Healthcare System, Palo Alto, Stanford School of Medicine, USA

Donderdag 20 maart 2014

Prijsuitreiking — Brabantzaal

Voorzitter: P.D. Siersema

17.00 **Uitreiking van de Frieda den Hartog Jager Prijs**
gevolgd door erevoordracht: "Pathogenese en preventie van colorectaal carcinoom: the continuing story"
Prof. dr. J.H. Kleibeuker, MDL-arts, Universitair Medisch Centrum Groningen

Voordrachten President Select — Brabantzaal

Voorzitter: P.D. Siersema

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

17.30 Experience in over 150 patients with the EndoBarrier® / duodenal jejunal bypass liner (p. 83)
B. Betzel[1] , P. Koehestanie[1] , K. Dogan[1] , J. Homan[1] , E.O. Aarts[1] , I.M.C. Janssen[1] , F.J. Berends[1] , P.J. Wahab[2], M.J.M. Groenen[2], Dept of Surgery[1] and Gastroenterology[2], Rijnstate Hospital the Netherlands

17.40 Long-term outcome of low perianal fistulas treated by fistulotomy (p. 84)
P.T.J. Janssen[1], K. Göttgens[1] , J. Heemskerk[2] , F. van Dielen[3] , J. Konsten[4] , T. Lettinga[5] , T.Hoofwijk[6], .L. Beets[1] , L.P.S. Stassen[1] , S.O. Breukink[1], [1]Dept of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Dept of Surgery, Laurentius Hospital, Roermond, The Netherlands, [3]Dept of Surgery, Maxima, Medical Center, Veldhoven, The Netherlands, [4]Dept of Surgery, VieCuri, Medical Center, Venlo, The Netherlands, [5]Dept of Surgery, St. Jans Gasthuis, Weert, The Netherlands, [6]Dept of Surgery, Orbis Medical Center, Sittard, The Netherlands

17.50 Genome-wide association study in autoimmune hepatitis identifies risk variant in the SH2B3 region (p. 85)
Y.S. de Boer[1,#] , N.M.F. van Gerven[1,#] , A. Zwiers[1,2] , B. Verwer[1] , B. van Hoek[3] , K. J. van Erpecum[4], U.H.W. Beuers[5] , H.R. van Buuren[6] , J.P.H. Drenth[7] , J.W. den Ouden[8] , R.C. Verdonk[9,10] , G.H. Koek[11] , J.T. Brouwer[12] , M.M.J. Guichelaar[13] , J.M. Vrolijk[14] , G. Kraal[2] , C. J.J. Mulder[1] , C.M.J. van Nieuwkerk[1] , J. Fischer[15] , T. Berg[15] , F. Stickel[16] , C. Sarrazin[17] , C. Schramm[18] , A.W. Lohse[18] , C. Weiler-Normann[18] , M.M. Lerch[19] , M. Nauck[20] , H. Völzke[21] , G. Homuth[22] , E. Bloemena[23] , V. Kumar[24] , A. Zhernakova[24] , C. Wijmenga[24] , L. Franke[24,$] , G. Bouma[1,2,$] ; The Dutch Autoimmune Hepatitis Study Group, The LifeLines Cohort study, The Study of Health in Pomerania (SHIP) # These authors contributed equally to this manuscript, $ These authors contributed equally to this manuscript , [1]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands [2]Dept of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands [3]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands [4]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands [5]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands [6]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands [7]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands [8]Dept of Gastroenterology and Hepatology, Haga Hospital, The Hague, The Netherlands [9]University of Groningen

University Medical Center Groningen, Dept of Gastroenterology and Hepatology, Groningen, The Netherlands [10]Dept of Gastroenterology and Hepatology, St Antonius Hospital Nieuwegein, Nieuwegein, The Netherlands [11]Dept of Gastroenterology and Hepatology, University Medical Center Maastricht, Maastricht, The Netherlands [12]Dept of Gastroenterology and Hepatology, Reinier de Graaf Hospital, Delft, The Netherlands [13]Dept of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede, The Netherlands [14]Dept of Gastroenterology and Hepatology, Rijnstate Hospital, Arnhem, The Netherlands [15]Dept of Internal Medicine, Neurology and Dermatology, Medical Clinic of Gastroenterology and Rheumatology, Section of Hepatology, University Hospital Leipzig, Leipzig, Germany [16]Dept of Visceral Surgery and Medicine, Inselspital, University of Bern, Bern, Switzerland [17]Dept of Medicine I, University of Frankfurt/M., Frankfurt, Germany [18]Dept of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany [19]Dept of Internal Medicine A, University Medicine Greifswald, Greifswald, Germany [20]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany [21]Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany [22]Interfaculty Institute for Genetics and Functional Genomics, University Medicine and Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany [23]Dept of Pathology, VU University Medical Center, Amsterdam, The Netherlands [24]University of Groningen, University Medical Center Groningen, Dept of Genetics, Groningen, The Netherlands

State of the art lecture — Brabantzaal

Voorzitter: P.D. Siersema

18.00 **Challenges of Translational GI Research**
Prof. dr. E.M. El-Omar, professor of Gastroenterology
Institute of Medical Sciences, Aberdeen University, U.K.

18.30 Einde programma, congresborrel in expositiehal.

Nederlandse Vereniging voor Gastrointestinale Chirurgie — Auditorium

Voorzitter: F. Daams en J. Heisterkamp

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

09.30 In vivo spectroscopy on tissues encountered during colorectal surgery (p. 86)

R.M. Schols[1,2], L. Alic[2], G.L. Beets[1], S.O. Breukink[1], F.P. Wieringa[2], L.P.S. Stassen[1], [1]Dept of Surgery, Maastricht University Medical Center & NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, [2]van 't Hoff Program on Medical Photonics, Netherlands Organization for Applied Scientific Research TNO, Eindhoven, The Netherlands

09.40 The use of endoractor during laparoscopic colorectal surgery; a new solution? pilot study (p. 87)

J.S. Pawiroredjo[1], N. Rijkers[1], A.B. Smits[1] , [1]Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands

09.50 Analysis of open-close HIPEC-procedure patients in peritoneal metstasis of colorectal origin (p. 88)

T.R. van Oudheusden[1], H.J. Braam[2], S.W. Nienhuijs[1], M.J. Wiezer[2], B. van Ramshorst[2], M.D.P Luyer[1], I.H.J.T. de Hingh[1], [1]Dept of Surgery, Catharina Hospital, Eindhoven, [2]Dept of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

10.00 Transanal versus traditional laparoscopic total mesorectal excision for rectal carcinomaA matched case control study (p. 89)

S. Velthuis[1], D.H. Nieuwenhuis[1], T.E.G. Ruijter[2], M.A. Cuesta[1], H.J. Bonjer[1], C. Sietses[1], [1]Dept of Surgery, Gelderse Vallei Hospital, Ede, [2]Dept of Surgery, VU Medical Center, Amsterdam, [3]Dept of Pathology, Rijnstate Hospital, Arnhem, The Netherlands

10.10 Management of major perineal wound complications after abdominoperineal resection for malignant disease. A retrospective cohort study (p. 90)

M.S. Walma[1], J.P.M. Burbach[1], P.M. Verheijen[2], R. van Hillegersberg[1], A. Pronk[3], W.M.U. van Grevenstein[1], [1]Universitary Medical Center Utrecht, Utrecht, [2]Meander Medical Center, Amersfoort, [3]Diakonessenhuis, Utrecht, The Netherlands

10.20 The detrimental effect of diclofenac on intestinal anastomotic healing depends on the location in the gut (p. 91)

S.T.K. Yauw[1], R.M.L.M. Lomme[1], R.J. van der Vijver[1], T. Hendriks[1], H. van Goor[1], [1]Dept of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

10.30 Defunctioning ileostomy does not prevent anastomotic leaks after restorative proctocolectomy; a multicenter evaluation of clinical and surgical risk factors (p. 92)

S. Sahami[1], C.J. Buskens[1], R. Lindeboom[2], T. Young Fadok[3], A. de Buck van Overstraeten[4], A. D'Hoore[4], W.A. Bemelman[1],[1]Dept of Surgery, Academic Medical Center, Amsterdam, [2]Divisions of Clinical Methods and Public Health, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept of Surgery, Mayo Clinic College of Medicine, Arizona, USA, [4]Dept of Surgery, University Hospitals Leuven,

10.40 The course of pulmonary vagus nerve branches (p. 93)
T.J. Weijs[1], J.P. Ruurda[2], M.D.P. Luyer[3], G.A.P. Nieuwenhuijzen[3], R. van Hillegersberg[2], R.L.A.W. Bleys[1], [1]Dept of Anatomy, and [2]Dept of Surgical Oncology, University Medical Center Utrecht, Utrecht, [3]Dept of Surgery, Catharina Hospital Eindhoven, Eindhoven, The Netherlands

10.50 Near-infrared fluorescence sentinel lymph node detection in gastric cancer using indocyanine green coupled to a nanocolloid (p. 94)
Q.R.J.G. Tummers[1], L.S.F. Boogerd[1], F.P.R. Verbeek[1], M.C. Boonstra[1], H.J.M. Handgraaf[1], H.H. Hartgrink[1], W.O. de Steur[1], J.V. Frangioni[2,3], C.J.H. van de Velde[1], A.L. Vahrmeijer[1], [1]Dept of Surgery, Leiden University Medical Center, Leiden, The Netherlands, [2]Dept of Medicine, and [3]Dept of Radiology, Beth Israel Deaconess Medical Center, Boston, USA

11.00 Worldwide trends in surgical techniques in the treatment of esophageal cancer (p. 95)
L. Haverkamp[1], J.P. Ruurda[1], J. Boone[2], R. van Hillegersberg[1], [1]University Medical Center Utrecht, Utrecht, The Netherlands

11.10 Thoracolaparoscopic dissection of lymph nodes involved in the drainage of the esophagus is feasible and safe in human cadavers and swine (p. 96)
H.T. Künzli1[4], M.I. van Berge Henegouwen[5], S.S. Gisbertz[5], M.J. Wiezer[2], C.A. Seldenrijk[3], J.J.G.H.M. Bergman[4], B.L.A.M. Weusten[1,4], [1]Dept of Gastroenterology, [2]Dept of Surgery, and [3]Dept of Pathology, St. Antonius Hospital, Nieuwegein, [4]Dept of Gastroenterology, and [5]Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

11.20 Effect of perioperatively administered glucocorticoids on pulmonary complications after transthoracic oesophagectomy. A meta-analysis (p. 97)
T.J. Weijs[1], J.M. Dieleman[2], J.P. Ruurda[1], A.C. Kroese[2], H.J.T.A. Knape[2], R. van Hillegersberg[1], [1]Dept of Surgical Oncology, Surgery, [2]Dept of Anaesthesiology, Intensive Care and Emergency Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

11.30 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie in de Brabantzaal

12.00 Lunchbuffet in de expositiehal

Donderdag 20 maart 2014

Symposium Ned. Vereniging voor Gastrointestinale Chirurgie **Auditorium**

Voorzitters: E. Dekker en C. Hoff

Van anussparende chirurgie tot rectumsparende endoscopie

In tegenstelling tot de aankondiging in het eerder toegezonden programma zullen de uitkomsten van de TREND studie niet gepresenteerd worden.

13.00 TAMIS
Dr. C. Sietses, chirurg, Ziekenhuis Gelderse Vallei, Ede

13.20 TEM voor en na chemoradiatie
Prof. dr. J.H.W. de Wilt, chirurg, Radboudumc, Nijmegen

13.40 Maatwerk in de preoperatieve radiatie bij het rectumcarcinoom
Radiotherapeut, namens de richtlijnwerkgroep

14.00 TEM vs endoscopische poliepectomie: een literatuur overzicht
J.W.A. Leijtens, chirurg, Laurentius Ziekenhuis, Roermond

14.20 Discussie

14.30 Innovations in colorectal surgery round 1 (room 82 + 83)

15.00 Theepauze expositiehal

Symposium Ned. Vereniging voor Gastrointestinale Chirurgie **Auditorium**

Voorzitters: P.P.L.O. Coene en M. Ledeboer

Uitkomsten en transparantie van de colorectale diagnostiek en chirurgie

15.30 Landelijke registratie endoscopie en complicatieregistratie.
Dr. M. Ledeboer, MDL-arts, Deventer Ziekenhuis

15.50 DSCA: validatie van de data
Dr. M. Wouters, chirurg, Antoni van Leeuwenhoekhuis en secretaris kwaliteit bestuur NVVH

16.10 Is de case mix correctie adequaat voor complexe combinaties van patiënten en procedures?
Dr. P. Tanis, chirurg, Academisch Medisch Centrum, Amsterdam

16.30 Winst van deviatie na rectumchirurgie: winst voor de patiënt of voor de 'score'?
Dr. J.W. Dekker, chirurg, Reinier de Graaf Gasthuis, Delft

16.50 Gebruik bij prothetisch materiaal bij functionele rectumchirurgie: zit ook hier de toekomst in auditing?
Dr. N.A.T. Wijffels, chirurg, Zuwe Hofpoort, Woerden

17.10 Innovations in colorectal surgery round 2 (room 82 + 83)

17.30 Voor de President Select kunt u zich begeven naar de Brabantzaal

18.30 Einde programma, congresborrel in expositiehal.

DEGH-Meeting — Baroniezaal

Voorzitters: J.P.H. Drenth en C.C. Paulusma

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

10.30 Introduction to the abstracts
Prof. dr. J.P.H. Drenth, MDL-arts, Radboudumc Nijmegen

11.00 Fucosyltransferase-2 non-secretor status is associated with non-anastomotic biliary strictures after liver transplantation in recipients with primary sclerosing cholangitis (p. 98)
C.J. Verhoeven[1], L. Maroni[2], P. Gadjradj[1], D. Tolenaars[2], E. de Mare-Bredemeijer[3], S. Mancham[3], S. van de Graaf[2], R. Oude Elferink[2], U. Beuers[2], H.J. Metselaar[3], J. Kwekkeboom[3], L.J.W. van der Laan[1], [1]Dept of Surgery, and [3]Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, [2]Dept of Gastroenterology and Hepatology, Tytgat Institute, Academic Medical Center, Amsterdam, The Netherlands

11.12 Local administration of bone marrow-derived mesenchymal stromal cells after partial hepatectomy ameliorates liver fibrogenesis in a dose dependent manner (p. 99)
D. van der Helm[1], E.S.M. de Jonge-Muller[1], B. van Hoek[1], I. Molendijk[1], A.C. den Dulk[1], J.J. van der Reijden[1], I. Biemond[1], M.J. Coenraad[1], H.W. Verspaget[1], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

11.24 Dopamine protects against cooling and rewarming-induced liver damage in vitro and in vivo (p. 100)
E.M. Verhaag[1,2], H. Room[1], N. Verhoeff[1], G.J. Dugbartey[2], H. Moshage[1], R.H. Henning[2], K.N. Faber[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

11.36 Decellularization of human and porcine livers: Applications for graft engineering (p. 101)
M.M.A. Verstegen[1], S. van den Hoek[1], J. Kwekkeboom[2], H.J. Metselaar[2], J. IJzermans[1], L.J.W. van der Laan[1], J. de Jonge[1], [1]Dept of Surgery, and [2] Dept of Gastroentrology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

11.48 Smad4-dependent regulation of hepatocellular carcinoma growth and progression (p. 102)
P.Y. Hernanda[1], C. Kan[1], A.M. Das[2], K. Sideras[1], S.J.A Bots[1], H.L.A. Janssen[1,3], L.L. Kodach[4], H.J. Metselaar[1], J.Kwekkeboom[1], D. Sprengers[1], M.J. Bruno[1], T.L.M. ten Hagen[2], M.P. Peppelenbosch[1], Q.Pan[1], [1]Dept of Gastroenterology and Hepatology, and [2]Laboratory of Experimental Surgical Oncology, Section Surgical Oncology, Dept of Surgery, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [3]Division of Gastroenterology, University Health Network, Toronto, Canada, [4]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

12.00 Lunchbuffet in de expositiehal

DEGH oral presentations — Baroniezaal

Voorzitters: G.A. Meijer en S.W.C. van Mil

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

13.00 Translational Science Teaching session : Colorectal Carcinoma (CRC)
Prof. dr. G.A. Meijer, VU medisch centrum, Amsterdam

13.30 Sensitization of colon cancer stem cells to chemotherapy by ER stress induced differrentiation (p. 103)
M.C.B. Wielenga[1], S. Colak[2*], J. Heijmans[1], J.F. van Lidth de Jeude[1], S.L. Rosekrans[1], B. Baan[1], J.P. Medema[2], G.R. van den Brink[1], *Both authors contributed equally, [1]Tytgat Institute for Liver and Intestinal Research, and [2]Laboratory of Experimental Oncology and Radiobiology, Academic Medical Center, Amsterdam, The Netherlands*

13.42 Inhibited expression of corticotropin-releasing hormone receptor 2 (CRHR2) correlates with tumor growth, EMT, distant metastasis risk and poor survival in experimental and clinical colorectal cancer (p. 104)
J. Rodriguez[1], H.W. Verspaget[2], D. Iliopoulos[1], S.H. Ypez[3], J.M. Hoffman[1], G.J. Baay-Gusman[3], A.B. Tirado-Rodriguez[3], I.K.M. Law[1], D.W. Hommes[1,2], L. Chang[1], Ch. Pothoulakis[1], S. Baritaki[1], [1]Division of Digestive Diseases and Institute for Molecular Medicine, David Geffen School of Medicine at UCLA, Los Angeles, USA, [2]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands, [3]Unidad de Investigacion en Enfermedades Oncologicas, Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico

13.54 Dual targeting of the VEGF and endoglin/TGF-β pathway in colorectal cancer (p. 105)
M. Paauwe[1], R.C. Heijkants[1], G.W. van Pelt[2], W.E. Mesker[2], C.F.M. Sier[2], C.P. Theuer[3], L.J.A.C. Hawinkels[1], [1]Dept of Molecular Cell Biology, and [2]Dept of Surgery, Leiden University Medical Center, Leiden, The Netherlands, [3]Tracon Pharmaceuticals, San Diego, USA

14.06 Conditional activation of BMP signalling leads to loss of the stem cell compartment (p. 106)
P. Voorneveld[1], L. Kodach[1], R. Jacobs[1], S. Rozekrans[2,3], G. van den Brink[2,3], J. Hardwick[1], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, [2]Dept of Gastroenterology and Hepatology, and [3]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands

14.18 Protein tyrosine phosphatase 1B (PTP1B) expression and phosphatase activity are increased in colorectal cancer which leads to a more invasive phenotype (p. 107)
E. Hoekstra[1], M.J. Bruno[1], M.P. Peppelenbosch[1], G.M. Fuhler[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Donderdag 20 maart 2014

14.30 ER stress depletes Apc mutant intestinal epithelial stem cells downstream of nuclear β-catenin (p. 108)

J.F. van Lidth de Jeude[1], M.C.B. Wielenga[1], S.L. Rosekrans[1], V. Muncan[1], G.R. van den Brink[1], J. Heijmans[1], [1]Tytgat Intstitute for Liver and Intestinal Research, Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

14.42 Fibroblasts promote invasion in SMAD4 negative colorectal cancers by producing BMP-2 (p. 109)

P.W. Voorneveld1, T. de Vos1, S. de Wit1, R.J. Jacobs1, L. Hawinkels2, M. Paauwe2, G. van Pelt3, W. Mesker3, G.R. van den Brink4,5, L. Kodach1, J. Hardwick1, 1Dept of Gastroenterology and Hepatology, 2Dept of Molecular Cell Biology, Cancer Genomics Center Netherlands and Center for Biomedical Genetics, and 3Dept of Surgery, Leiden University Medical Center, Leiden, 4Tytgat Institute for Liver and Intestinal Research, and 5Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

15.00 Ledenvergadering Nederlandse Vereniging voor Hepatologie

Voorzitters: P.A. Boonstra en R.J. de Knegt

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

15.30 Translational science Teaching Session: Viral Hepatitis
Clinical aspects: *Dr. R.J. De Knegt, Erasmus MC, Rotterdam*

15.57 Basic/Translational science aspects: *Dr. P.A. Boonstra, Erasmus MC, Rotterdam*

16.24 Baseline liver gene expression profile associated with combined response in chronic hepatitis B patients treated with peginterferon and adefovir (p. 110)

F. Stelma[1,2], L. Jansen[1,2], A. de Niet[1,2], Z. Makowska[3], M. T. Dill[3], K. A. van Dort[2], R. B. Takkenberg[1], M.H. Heim[3], N. A. Kootstra[2], H.W. Reesink[1], [1]Dept of Gastroenterology and Hepatology, and [2]Dept of Experimental Immunology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [3]Dept of Biomedicine, University of Basel, Basel, Switzerland

16.36 Dichotomal effect of immunosuppressants on hepatitis e virus infection: calcineurin inhibitors stimulate but mycophenolic acid inhibits viral replication (p. 111)

Y. Wang[1], X. Zhou[1], Y. Debing[2], L.J.W. van der Laan[3], J. Neyts[2], H.L.A. Janssen[1,4], H.J. Metselaar[1], M.P. Peppelenbosch[1], Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [2]Rega Institute for Medical Research, Dept of Microbiology and Immunology, KU Leuven, Leuven, Belgium, [3]Dept of Surgery, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [4]Division of Gastroenterology, University Health Network, Toronto, Canada

16.48 Active genuine HBV replication in human liver chimeric uPA$^{+/+}$ NOG mice (p. 112)

M.D.B. van de Garde[1], P. Biesta[1], K. de Groot-Kreefft[1], H.L.A. Janssen[1,2], A. Boonstra[1], T. Vanwolleghem[1], [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Liver Clinic, Toronto Western and General Hospital University Health Network Toronto, Toronto, Canada

17.00 Voor de uitreiking van de Frieda den Hartog Jager prijs met aansluitende lezing door Prof. dr. J.H. Kleibeuker kunt u zich begeven naar de Brabantzaal

Donderdag 20 maart 2014

Multidisciplinair Symposium **Parkzaal**

Voorzitters: J.C. Escher en S.W.M. Olde Damink

Symposium Darmfalen
Van de secties: Kinder-MDL, NESPEN en NVGIC van de NVGE

9.30 Inleiding: Stichting Darmfalen Nederland en DRIFT
Prof. dr. G. Dijkstra, MDL-arts, UMC Groningen

9.35 Eerste resultaten van Dutch Registry for Intestinal Failure
Prof. dr. E.H.H.M. Rings, kinderarts, Erasmus MC Rotterdam & Leids UMC

Behandeling van darmfalen

9.50 Behandeling short bowel syndroom bij volwassenen
Dr. G. Wanten, MDL-arts, Radboudumc, Nijmegen

10.05 Darmrevalidatie bij kinderen
Dr. J.M. Hulst, kinderarts, Erasmus MC, Rotterdam

10.15 Parenterale voeding bij volwassenen
Dr. M.J. Serlie, internist-endocrinoloog, AMC, Amsterdam

Chirurgie bij darmfalen

10.25 Kinderchirurgie bij darmfalen
Prof. dr. R.M.H. Wijnen, kinderchirurg, Erasmus MC, Rotterdam

10.40 Reconstructie chirurgie bij darmfalen van volwassenen
Prof. dr. M.A. Boermeester, chirurg, Academisch Medisch Centrum Amsterdam

10.55 Dunnedarmtransplantatie bij kinderen en volwassenen
Dr. J.W. Haveman, chirurg, UMC Groningen

11.10 Plaatsbepaling en outcome van dunnedarmtransplantatie in Nederland
Prof. dr. G. Dijkstra, MDL-arts, UMC Groningen

11.25 Einde symposium

11.30 Voor de ledenvergadering van de NVGE kunt u zich begeven naar de Brabantzaal

12.00 Lunchbuffet in de expositiehal

Vrije voordrachten Sectie Inflammatoire Darmziekten — Parkzaal

Voorzitters: G.R.A.M. D'Haens en W.R. ten Hove

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

13.00 Gene expression profiles in peripheral blood as early biomarkers for response to induction therapy in Crohn's disease (p. 113)

C.P. Peters[1,2], F.H. van Dooren[1], N.W. Duijvis[1], P.C.F. Stokkers[3], P.D. Moerland[4], C.Y. Ponsioen[2], A.A. te Velde[1], [1]Tytgat Institute for Liver and Intestinal Research, and [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, [3]Dept of Gastroenterology and Hepatology, St Lucas Andreas Hospital, Amsterdam, [4]Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Bioinformatics Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

13.10 NCF4 risk allele affects steroid exposure and dependency in Crohn's disease patients, preliminary results (p. 114)

V.J.A.A. Nuij[1] , R. Somasundaram[1] , K. Diederen[1] , L. Vellekoop[1] , M.P. Peppelenbosch[1] , C. J. van der Woude[1] , G.M. Fuhler[1] ,[1] Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, the Netherlands.

13.20 Fibrosis does not increase with disease duration in ulcerative colitis (p. 115)

J.R. de Bruyn[1,2], S.L. Meijer[3], M.E. Wildenberg[2], G.R. van den Brink[1,2], G.R.A.M. D'Haens[1], [1]Dept of Gastroenterology, [2]Tytgat Institute for Liver and Intestinal Research, and [3]Dept of Pathology, Academic Medical Center, Amsterdam, The Netherlands

13.30 Identification of HLA-A and WWOX as genetic variants associated with recurrent fibrostenotic Crohn's disease (p. 116)

M.C. Visschedijk[1,2], L.M. Spekhorst[1], E.S. van Loo[3], D. de Jong[4], A.E. van der Meulen-de Jong[5], H.W. Verspaget[5], C.Y. Ponsioen[6], V.B. Nieuwenhuijs[7], R. Alberts[2], S. van Sommeren[1,2], G. Dijkstra[1], R.K. Weersma[1], E.A.M. Festen[1,2], On behalf of the Initiative on Crohn and Colitis, [1]Dept of Gastroenterology and Hepatology, [2]Dept of Genetics, and [3]Dept of Surgery, University of Groningen, University Medical Center Groningen, Groningen, [4]Dept of Gastroenterology and Hepatology, Radboud University, Nijmegen Medical Center, Nijmegen, [5]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, [6]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [7]Dept of Surgery, Isala Clinics, Zwolle, The Netherlands

13.40 Leukocyte Scintigraphy as a Tool to Measure Inflammatory Load in Ulcerative Colitis (p. 117)

J.F. Brandse[1], R.J. Bennink[2], S. van Eeden[3], P.A. Baars[4], M. Löwenberg[1], C.Y. Ponsioen[1], G.R. van den Brink[1], G.R. D'Haens[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Nuclear Medicine, [3]Dept of Pathology, and [4]Dept of Experimental Immunology, Academic Medical Center, Amsterdam, The Netherlands

13.50 Comparative efficacies of novel JAK inhibitors to reduce macrophage activation (p. 118)

L.C.S. de Vries1,2, J.M. Duarte1, F.W.M. Hilbers1, V.J. Ludbrook3, M.D. Woodrow3, M.J. Sims3, M. de Winther4, P.D. Moerland5, G.R.A.M. D'Haens2, W.J. de Jonge1,2, 1Tytgat Institute for Liver and Intestinal Research, and 2Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, 3Kinase DPU, GlaxoSmithKline, Stevenage, United Kingdom, 4Dept of Medical Biochemistry, and 5Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands

14.00 Intestinal Epstein- Barr virus is associated with mucosal lymphoproliferation and subsequent intestinal surgery in inflammatory bowel disease patients (p. 119)

L.H.C. Nissen[1], D.J. de Jong[1], I.D. Nagtegaal[2], W. Kievit[1], L.A.A.P. Derikx[1], M.G. Lynch[2], F. Hoentjen[1], J.H.J.M. van Krieken[2], [1]Inflammatory Bowel Disease Center, Dept of Gastroenterology and Hepatology, and [2]Dept of Pathology, Radboud University, Nijmegen Medical Center, Nijmegen, The Netherlands

14.10 Predicting mucosal inflammatory activity in Crohn's disease: a new, validated nonendoscopic disease activity index (p. 120)

I.M. Minderhoud[1], E.W. Steyerberg [2], A.A. van Bodegraven[3], C.J. van der Woude[4], D.W. Hommes[5], G. Dijkstra[6], H.H. Fidder[7], M.P. Schwartz[8] , B.Oldenburg[7], [1]Dept of Internal Medicine and Gastroenterology, Tergooi Hospital, Hilversum, [2]Center for Medical Decision Making, Dept of Public Health, Erasmus MC, Rotterdam, [3]Dept of Gastroenterology, VU Medical Center, Amsterdam, [4]Dept of Gastroenterology, Erasmus MC, Rotterdam, The Netherlands, [5]Center for Inflammatory Bowel Diseases, UCLA Health System, Los Angeles, CA, USA, [6]Dept of Gastroenterology, University Medical Center Groningen, University of Groningen, Groningen, [7]Dept of Gastroenterology, University Medical Center Utrecht, Utrecht, [8]Dept of Gastroenterology, Meander Medical Center, Amersfoort, The Netherlands

14.20 Only one third of Crohn's disease patients have sustained remission of perianal fistulas (p. 121)

I. Molendijk[1], V.J.A.A. Nuij[2], A.E. van der Meulen–de Jong[1], C.J. van der Woude[2], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, [2]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands

14.30 Self-reported disability index in inflammatory bowel disease: results from a large Dutch prospective cohort (p. 122)

M. van der Have[1], H.H. Fidder[1], M. Leenders[1], A.A. Kaptein[2], M.E. van der Valk[1], A.A. van Bodegraven[3,12], G. Dijkstra[4,5], D.J. de Jong[6], M. Pierik[7], C.Y. Ponsioen[8], A.E. van der Meulen-de Jong[9], C.J van der Woude[10], P.C. van de Meeberg[11], M.J.L. Romberg-Camps[12], C.H.M. Clemens[13], J.M. Jansen[14], N. Mahmmod[15], C.J.M. Bolwerk[16], J.R. Vermeijden[17], P.D. Siersema[1], B. Oldenburg[1], On behalf of the COIN study group and the Dutch Initiative on Crohn and Colitis, [1]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, [2]Section Medical Psychology, Leiden, University Medical Center, [3]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [4]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, [5]University of Groningen, Groningen, [6]Dept of Gastroenterology and Hepatology, Radboud

University, Nijmegen Medical Center, Nijmegen, [7]Dept of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, [8]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [9]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, [10]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [11]Dept of Gastroenterology and Hepatology, Slingeland Hospital, Doetinchem, [12]Dept of Gastroenterology and Hepatology, Orbis Medical Center, Sittard, [13]Dept of Gastroenterology and Hepatology, Diaconessenhuis, Leiden, [14]Dept of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, [15]Dept of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, [16]Dept of Gastroenterology and Hepatology, Reinier de Graaf Groep, Delft, [17]Dept of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, The Netherlands

14.40 The relevance of population based IBD biobanks: a meta-analysis and introduction of the IBD-SL biobank cohort (p. 123)

T.R.A. van den Heuvel[1,2], D.M.A.E. Jonkers[1,2], S.F.G. Jeuring[1,2], W.H. Hameeteman[1], L.E. Oostenbrug[3], M.J.L. Romberg-Camps[4], A.A.M. Masclee[1,2], M.P. Zeegers[5,6], M.J. Pierik[1,2], [1]Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, [2]Maastricht University Medical Center, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht, [3]Dept of Internal Medicine, Atrium Medical Center, Heerlen, [4]Dept of Internal Medicine, Orbis Medical Center, Sittard-Geleen, The Netherlands, [5]Dept of Public Health, Epidemiology and Biostatistics, University Hospital Birmingham, Birmingham, United Kingdom, [6]Dept of Complex Genetics, Cluster of Genetics and Cell Biology, Maastricht University Medical Center, Maastricht, The Netherlands

14.50 Is elderly-onset ulcerative colitis a different entity? Natural disease course and treatment response compared to adult-onset disease in a Dutch population-based cohort (p. 124)

S.F.G. Jeuring[1,2], T.R.A. van den Heuvel[1,2], M.P. Zeegers[3,4], W.H. Hameeteman[1], M.J.L. Romberg-Camps[5], L.E. Oostenbrug[6], A.A.M. Masclee[1,2], D.M.A.E. Jonkers[1,2], M.J. Pierik[1,2], [1]Dept of Internal Medicine, Division of Gastroenterology and Hepatology, [2]NUTRIM, School for Nutrition, Toxicology and Metabolism, and [3]Dept of Complex Genetics, Cluster of Genetics and Cell Biology, Maastricht University Medical Center, Maastricht, The Netherlands, [4]Dept of Epidemiology and Public Health, University of Birmingham, Birmingham, United Kingdom, [5]Dept of Internal Medicine and Gastroenterology, Orbis Medical Center, Sittard, [6]Dept of Internal Medicine and Gastroenterology, Atrium Medical Center, Heerlen, The Netherlands

15.00 Theepauze expositiehal

Donderdag 20 maart 2014

Minisymposium: Update Voeding in de dagelijkse praktijk **Parkzaal**

Voorzitters: J.P.H. Drenth en S.W.M. Olde Damink

15.30 Is voeding bij functionele aandoeningen zinvol?
Dr. L.A. van der Waaij, MDL-arts, Martini Ziekenhuis Groningen

15.50 Voeding bij IBD: wat kunnen we van de kinderartsen leren?
Dr. A. Kindermann, kinderarts, Emma Kinderziekenhuis, Amsterdam

16.10 Voedselintoleranties en allergieën: wat is dat eigenlijk?
Dr. T. Rustemeyer, dermatoloog, VU medisch centrum, Amsterdam

16.30 Is er voldoende aandacht voor voeding bij klinische patiënten?
I.A. Meynaar, internist, HagaZiekenhuis, Den Haag

16.50 Einde programma

17.00 Voor de uitreiking van de Frieda den Hartog Jager prijs met aansluitende lezing door
prof. dr. J.H. Kleibeuker kunt u zich begeven naar de Brabantzaal

Vrije voordrachten Sectie Gastrointestinale Endoscopie — Brabantzaal

08.00 Ledenvergadering NVMDL

Voorzitters: M.A.M.J. Jacobs en Y.C.A. Keulemans

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

09.30 Risk of colorectal cancer after endoscopic vs. surgical resection of carcinoma in situ is not different (p. 125)
K. Kessels[1], L.M.G. Moons[1], M.G.H. van Oijen[1], P.D. Siersema[1], M.A.G. Elferink[2], [1]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, [2]Comprehensive Cancer Center the Netherlands (IKNL), Utrecht, The Netherlands

09.40 Endoscopic transpapillary gallbladder drainage in high-risk patients: the use of a double pigtail stent (p. 126)
N. Boogerd[1], L.E. Perk[1], G.J.D. van Acker[1], [1]Medical Center Haaglanden, Den Haag / Leidschendam, The Netherlands

09.50 EUS-guided drainage with a large diameter metal stent is a safe treatment for acute cholecystitis in high risk patients (p. 127)
D. Walter[1], A.Y.B. Teoh[2], T. Itoi[3], M. Pérez-Miranda[4], A. Larghi[5], A. Sanchez-Yague[6], P. Vilmann[7], P.D. Siersema[1], F.P. Vleggaar[1], [1]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands, [2]Dept of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong SAR, China, [3]Dept of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, Japan, [4]Dept of Gastroenterology, Unit of Gastrointestinal Endoscopy, University Hospital Rio Hortega, Valladolid, Spain, [5]Digestive Endoscopy Unit, Catholic University, Rome, Italy, [6]Dept of Digestive Diseases, Endoscopy Unit, Agencia Sanitaria Costa del Sol, Marbella, Spain, [7]Dept of Endoscopy, Gastrointestinal Unit, Copenhagen University Hospital, Herlev, Denmark

10.00 Hydraulic dilation in idiopathic achalasia using the EsoFLIP dilation balloon: a prospective cohort study (p. 128)
W.F.W. Kappelle[1], A. Bogte[1], P.D. Siersema[1], [1]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands

10.10 Predictors for treatment failure after endoluminal fundoplication in GERD (p. 129)
F.G. Smeets[1], N.D. Bouvy[2], A.A.M. Masclee[1], J.M. Conchillo[1], [1]Division of Gastroenterology and Hepatology, and [2]Dept of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

10.20 Are the gastric folds still the optimal landmark for defining the distal border of a Barrett's esophagus in a Western population? (p. 130)
D. Schölvinck[1,2], O. Goto[3], K. Seldenrijk[4], J. Bergman[2], N. Yahagi[3], B. Weusten[1,2], [1]Dept of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [3]Division of research and development for minimally invasive treatment, Cancer Center Keio University, Tokyo, Japan, [4]Dept of Pathology, St. Antonius Hospital, Nieuwegein, The Netherlands

10.30 Cost-effectiveness analysis of radiofrequency ablation for Barrett's esophagus with low-grade dysplasia: results from a randomized controlled trial (SURF) (p. 131)

K.N. Phoa[1], W.D. Rosmolen[1], B.L.A.M. Weusten[1,2], R. Bisschops[3], E.J. Schoon[4], K. Ragunath[5], G. Fullarton[6], M. DiPietro[7], N. Ravi[8], M. Visser[1], G.J. Offerhaus[1], C.A. Seldenrijk[2], S.L. Meijer[1], F.J. ten Kate[1], J.G.P. Tijssen[1], M.G. Dijkgraaf[1], J.J. Bergman[1], [1]Academic Medical Center, University of Amsterdam, Amsterdam, [2]St. Antonius Hospital, Nieuwegein, The Netherlands, [3]UZ Gasthuisberg, Leuven, Belgium, [4]Catharina Hospital, Eindhoven, The Netherlands, [5]Queens Medical Centre, Nottingham, UK, [6]Royal Infirmary, Glasgow, [7]Addenbrookes Hospital, Cambridge, UK, [8]St James Hospital, Dublin, Ireland

10.40 Efficacy and safety of HALO90-RFA-ablation using the simple protocol (3x15J-no cleaning) (p. 132)

H.T. Künzli[1,2] , E.J. Schoon[3], M.H. Houben[4], J.J.G.H.M. Bergman[2], B.L.A.M. Weusten[1,2], [1]Dept of Gastroenterology, St. Antonius Hospital, Nieuwegein, [2]Academic Medical Center, Amsterdam, [3]Catharina Hospital, Eindhoven, [4]HaGa Hospital, The Hague, The Netherlands

10.50 Detection of buried Barrett glands after Radiofrequency Ablation (RFA) with Volumetric Laser Endomicroscopy (VLE) (p. 133)

A. Swager[1], D.F. Boerwinkel[1], D.M. de Bruin[2], D.J. Faber[2], T.G. van Leeuwen[2], B.L. Weusten[1], S.L. Meijer[3], J.J. Bergman[1], W.L. Curvers[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Biomedical Engineering, and [3]Dept of Pathology, Academic Medical Center, Amsterdam, The Netherlands

11.00 Koffiepauze

Sectie Gastrointestinale Endoscopie **Brabantzaal**

Voorzitters: J.W. Poley en B.L.A.M. Weusten

PERK studie

11.30 Kwaliteit van ERCP in Nederland - de PERK studie
V.E. Ekkelenkamp, namens de PERK studiegroep

11.45 Discussie

11.50 "Meten is weten; ERCP kwaliteitsregistratie in Nederland"
Dr. M. Ledeboer, MDL-arts en voorzitter Commissie Kwaliteit NVMDL en A.D. Koch, MDL-arts, Erasmus MC, Rotterdam

12.05 Discussie

12.15 Einde programma Perk studie

Sectie Gastrointestinale Endoscopie **Brabantzaal**

Voorzitters: J.W. Poley en B.L.A.M. Weusten

Richtlijn Antistolling

12.15 Indicaties voor antitrombotische therapie
Dr. M. Brouwer, cardioloog, Radboud universitair medisch centrum, Nijmegen

12.30 Werking en dosering van antitrombotische therapie
A. Prins, apotheker

12.45 Achtergrond en bespreking herziende richtlijn Antitrombotische therapie en endoscopische procedures
Dr. F.T.M. Peters en Dr. M.E. Tushuizen, MDL-artsen

13.00 Lunchbuffet in de expositiehal

Vrijdag 21 maart 2014

Symposium Sectie Gastrointestinale Oncologie **Brabantzaal**

Voorzitters: A. Cats en J.M. van Dieren

CRC bevolkingsonderzoek

14.00 Inleiding
Dr. A. Cats, MDL-arts, Antoni van Leeuwenhoekhuis, Amsterdam

14.10 Serrated polyposis syndroom - is herkenning belangrijk?
Prof. dr. E. Dekker, MDL-arts, Academisch Medisch Centrum, Amsterdam

14.30 CRC - 1 ziekte?
Dr. L. Vermeulen, Center for Experimental Molecular Medicine (CEMM) Academisch Medisch Centrum & Cancer Research UK - Cambridge Institute

14.50 Erfelijke darmkanker - new kids in town
Dr. M. Kets, klinisch geneticus, Radboudumc, Nijmegen

15.10 Poliepectomie: state-of-the-art
Dr. S. Sanduleanu, MDL-arts, Maastricht Universitair Medisch Centrum

15.30 Maligne colorectale poliepen
Dr. M.E. van Leerdam, MDL-arts, Antoni van Leeuwenhoekhuis, Amsterdam

Vrije voordrachten NVGE-NVGIC — Auditorium

Voorzitters: E.J.M. van Geenen en M.I. van Berge Henegouwen

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

09.30 Predictive factors for recurrence of cryptoglandular perianal fistula characterised by pre-operative endoanal ultrasound (EAUS) (p. 134)

Visscher, A.P.[1,] Schuur, D.[1] ,Deen, C.B.H.[3,] Van der Mijnsbrugge, G.J.H.[3,] Meijerink W.J.H.J.[2,] Felt-Bersma R.J.F.[1] ,[1]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, the Netherlands, [2]Dept of Surgery, VU University Medical Center, Amsterdam, the Netherlands, [3]Proctos Kliniek, Bilthoven, the Netherlands

09.40 Long term outcome after surgery for cryptoglandular perianal fistula (p. 135)

Van Nunspeet L.[1]; Sprakel J.[2]; Eddes E.H.[1]; Bosker R.J.I.[1]; de Noo M.E.[1]; [1]Dept of Surgery, Deventer Hospital, Deventer, The Netherlands, [2] Dept of Surgery, Martini Hospital, Groningen, The Netherlands

09.50 Treatment response of EATL patients; a ten year analysis of a national cohort (p. 136)

P. Nijeboer[1] , L. de Baaij[1*] , O. Visser[2] , C.J.J Mulder[1] , S.A.G.M. Cillessen[3,] G.Bouma[1], [1]Dept of Gastroenterology, VU University Medical Center, Amsterdam, the Netherlands, [2]Dept of Haematology, VU University Medical Center, Amsterdam, the Netherlands, [3]Dept of Pathology, VU University Medical Center, Amsterdam, the Netherlands, [*]Both authors contributed equally to this article*

10.00 Surgery for complicated celiac disease (p. 137)

J.M.W. van de Water[a] , P. Nijeboer[a] , J. Zegers[a] , W.J.H.J. Meijerink[b] , C.J.J. Mulder[a] , D.L. van der Peet[b] ,[a] Dept of Gastroenterology and [b] Dept of Surgery, VU University Medical Center, Amsterdam, The Netherlands

10.10 Smooth muscle protein 22 (SM22) in plasma and urine reflects transmural ischemic injury of the intestines (p. 138)

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

10.20 Development of a prediction model to assess the risk of chronic gastrointestinal ischemia in referred patients (p. 139)

J. Harki[1] , Y. Vergouwe[2] , J.A. Spoor[1] , E.J. Kuipers[1,3] , P. B. Mensink[1,4] , M.J. Bruno[1] , D. van Noord[1], E.T.T.L. Tjwa[1,5] ,Depts. of [1]Gastroenterology and Hepatology, [2]Public Health and [3]Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands, [4]Dept of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede, The Netherlands, [5]Dept of Gastroenterology and Hepatology, Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands

10.30 Does inclusion of imaging in the work up of patients with clinically suspected appendicitis reduce the rate of unnecessary surgical procedures? (p. 140)

K.W.A. Gottgens[1] , M.J. Lahaye[2] , D.M.J. Lambregts[2] , E. Mutsaers[2] , B. Essers[3] , N. Bouvy[1] , S.O. Breukink[1] , R.G.H. Beets-Tan[2] ,[1] Dept of surgery, Maastricht University Medical Center, Maastricht, The Netherlands [2] Dept of radiology, Maastricht University Medical Center, Maastricht, The Netherlands [3] Dept of clinical epidemiology and medical technology assessment, Maastricht University Medical Center, Maastricht, The Netherlands

10.40 Prognostication of complications after Roux en Y gastric bypass: evaluation of the OS-MRS and the Clavien-Dindo classification (p. 141)

U.K. Coblijn[1], S.M.M. de Castro[1], S.M. Lagarde[2], W.F. van Tets[1], L.Th. de Wit[1], B.A. van Wagensveld[1], [1]Sint Lucas Andreas Ziekenhuis, Dept of General Surgery[2] Academic Medical Center Amsterdam, Dept of General Surgery

10.50 Peroral endoscopic myotomy for achalasia is safe and effective: a prospective single center study (p. 142)

F.A.M. Ponds[1] , T. Verlaan[1] , A.J.P.M. Smout[1] , A.J. Bredenoord[1] , P. Fockens[1] ,1. Dept of Gastroenterology & Hepatology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands.

11.00 Koffiepauze

Voordrachten Nederlandse Vereniging voor Gastroenterologie Auditorium

Voorzitters: A.J. Bredenoord en J.Ph. Kuijvenhoven

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

11.30 Esophageal epithelial barrier function in GERD patients and healthy controls: an ex-vivo study in the basal state and in response to acid exposure (p. 143)

N.F. Rinsma[1] , M. Elizalde[1] , F.J. Troost[1] , A.A. Masclee[1] , J.M. Conchillo[1] , [1]Dept of Internal Medicine, div. of Gastroenterology-Hepatology, NUTRIM, Maastricht University Medical Center, Maastricht, The Netherlands

11.40 Trends in distribution of diagnostic testing and treatment of hepatocellular carcinoma in the Netherlands between 2003-2011 (p. 144)

S. van Meer[1] , K.J. Erpecum[1] , G.H. Schrier[2] , C. Verhoef[3] , J. Verheij[4] , R.A. de Man[5] , L.G.M. van der Geest[2] ,[1] Dept of Gastroenterology and Hepatology, University Medical Center, Utrecht, The Netherlands. [2] Comprehensive Cancer Center The Netherlands. [3]Dept of Surgical Oncology, Erasmus Medical Center, Rotterdam, The Netherlands. [4]Dept of Pathology, Academic Medical Center, Amsterdam, The Netherlands. [5]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands.

11.50 Gut permeability in IBS is site specific, subtype dependent and affected by confounding factors (p. 145)

Z. Mujagic1, S. Ludidi1*, D. Keszthelyi1, M.A. Hesselink1, J.W. Kruimel1, K. Lenaerts2, N.M. anssen3, J.M. Conchillo1, D.M. Jonkers1, A.A. Masclee1, *Both authors contributed equally, 1Dept of Internal Medicine, Division of Gastroenterology and Hepatology, and 2Dept of Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, Maastricht, [3]Dept of Internal Medicine, CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, The Netherlands*

12.00 Insufficient incorporation of biological meshes after implantation in a clean surgical environment (p. 146)

I.M. Mulder[1] , EB. Deerenberg[1] , W.A. Bemelman[2] , J. Jeekel[3] , J.F. Lange[1] , [1]Dept of Surgery Erasmus MC Rotterdam, [2]Dept of Surgery Amsterdam Medical Centre Amsterdam, [3]Dept of Neuroscience Erasmus MC Rotterdam, The Netherlands

12.10 Distal versus proximal colonic acetate infusions differentially affect human metabolism (p. 147)

C. M. van der Beek[1,2] , E. E. Canfora*[1,3] , K. Lenaerts[1,2] , F. J. Troost[1,4] , A.A.M. Masclee[1,4] , C. H.C. Dejong[1,2] , E.E. Blaak[1,3] ,* Shared first author [1]Top Institute Food and Nutrition, Wageningen, the Netherlands, [2]Dept of Surgery, [3]Dept of Human Biology, and [4]Dept of Internal Medicine, division of Gastroenterology-Hepatology; NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University, the Netherlands*

12.20 Transnasal endoscopic nasoenteral feeding tube placement in routine clinical practice is associated with low success rates (p. 148)

T.K.J. Groenhof[1] , D. Walter[1] , E.M.H. Mathus-Vliegen[2] , P.J. van der Schaar[3] , F.P. Vleggaar[1] , L. Nagtzaam[1] , P.D. Siersema[1] , M.M.C. Hirdes[1] , J.F. Monkelbaan[1] , [1] Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3] Dept of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein

12.30 Excellent long-term survival after autologous stem-cell transplantation for RCDII (p. 149)

P.Nijeboer[1] , R.L.J v Wanrooij[1] , T. v Gils[1] , N.J. Wierdsma[2] , H.J. Bontkes[3] , C.J.J. Mulder[1] , G. Bouma[1], [1]Dept of Gastroenterology, [2]Dept of Nutrition and Dietetics, [3]Dept of PathologyVU University medical centre Amsterdam, The Netherlands

12.40 Clinical impact of liquid-based or cell block preparation of residual material after analysis of cytological smears in endoscopic ultrasound-guided fine-needle aspiration (p. 150)

W.F.W. Kappelle, M.G.H. van Oijen, P.D. Siersema, F.P. Vleggaar, Dept of Gastroenterology and Hepatology, University Medical Center Utrecht

12.50 Lean Six Sigma in health care; Applicability and implementation in a fast track multidisciplinary oncology clinic (p. 151)

Y.L. Basta[1] , K.M.A.J. Tytgat[2] , T. Rohof[3] , M.C. Monster[4] , P. Focken[2] , J.H.G. Klinkenbijl[1] On behalf of the GIOCA group,[1] Chirurgie, AMC [2] MDL, AMC[3] Stafbureau, AMC[4] ING

13.00 Lunchbuffet in de expositiehal

Vrije voordrachten NVGE-NVGIC — Auditorium

Voorzitters: H. Braat en C.H.C. Dejong

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

14.00 Inleiding sessie door de voorzitter

14.10 Quality of life after stent placement for palliation of common bile duct obstruction: a randomized controlled trial comparing plastic and metal stents (p. 152)

D. Walter[1] , P.G.A. van Boeckel[1] , M.J. Groenen[2] , B.L.A.M. Weusten[3] , B.J. Witteman[4] , G. Tan[5] , M. Brink[6], J. Nicolai[7] , A.C. Tan[8] , J. Alderliesten[9] , N.G. Venneman[10] , W. Laleman[11] , J.M. Jansen[12] , A. Bodelier[13], F.L. Wolters[14] , L.A. van der Waaij[15] , R. Breumelhof[16] , F.T.M. Peters[17] , R.C.H. Scheffer[18], M. Leenders[1], M.M.C. Hirdes[1], F.P. Vleggaar[1], P.D. Siersema[1], [1]UMC Utrecht, Utrecht, Netherlands [2]Rijnstate Hospital, Arnhem, Netherlands [3]St. Antonius Hospital , Nieuwegein, Netherlands [4]Gelderse Vallei Hospital, Ede, Netherlands [5]Ziekenhuisgroep Twente Hospital, Hengelo, Netherlands [6] Meander Medical Center, Amersfoort, Netherlands[7] Haga Hospital, Den Haag , Netherlands [8] Canisius Wilhelmina Hospital, Nijmegen, Netherlands [9] Albert Schweitzer Hospital, Dordrecht, Netherlands [10]Medisch Spectrum Twente, Enschede, Netherlands [11] University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium [12]Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands [13] Amphia Hospital, Breda, Netherlands [14]VieCuri Hospital, Venlo, Netherlands, [15]Martini Hospital, Groningen, Netherlands [16]Diakonessen Hospital, Utrecht, Netherlands [17]UMCG, Groningen, Netherlands [18]Jeroen Bosch Hospital, Den Bosch, Netherlands

14.20 Positive predictive value of endoscopic ultrasound (EUS) for the detection of intraluminal filling defects in the common bile duct (CBD) in a large non-academic teaching hospital (p. 153)

L.M.J.W. van Driel[1] , R. Quispel[1] , B. Veldt[1,2] , M. Bruno[2] ,[1]Reinier de Graaf hospital, Delft. [2] Erasmus Medical Center, Rotterdam

14.30 A comparative prospective blinded analysis of the effectiveness of EUS and MRI as screening tools for pancreatic cancer (p. 154)

F. Harinck[1] , I.C.A.W. Konings[1*] , J.W. Poley[1] , N.C. Krak[2] , K. Biermann[3] , J.E. van Hooft[4] , C.Y. Nio[5] C.M. Aalfs[6] , A. van Rens[7] , C. van Eijck[8] , D. Gouma[9] , M.G.W. Dijkgraaf[10] , H. van Dullemen[11] , R. Sijmons[12], P. Fockens[4] , M.J. Bruno[1] , on behalf of the Dutch research group on pancreatic cancer surveillance in high-risk individuals, [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, [2]Dept of Radiology, Erasmus MC, University Medical Center Rotterdam, [3]Dept of Pathology, Erasmus MC, University Medical Center Rotterdam, [4] Dept of Gastroenterology and Hepatology, Amsterdam Medical Center, University Medical Center Amsterdam, [5]Dept of Radiology, Amsterdam Medical Center, University Medical Center Amsterdam, [6]Dept of Clinical Genetics, Amsterdam Medical Center, University Medical Center Amsterdam, [7]Family Cancer Clinic, The Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, [8] Dept of Surgery, Erasmus MC, University Medical Center Rotterdam, [9] Dept of Surgery, Amsterdam Medical Center, University Medical Center Amsterdam, [10] Clinical Research Unit, Amsterdam Medical Center, University Medical Center Amsterdam, [11]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, [12] Dept of Clinical Genetics, University Medical Center Groningen. [*] contributed equally to this work*

14.40 CEA and cytopathological analysis are useful tests to discriminate mucinous from non-mucinous pancreatic cystic lesions (p. 155)

A. van de Vreede[1] , W.K. Utomo[1] , M.J. Bruno[1], B.E. Hansen[1], H. Braat[1], K. Biermann[2] ,[1] Dept of gastroenterology and hepatology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands, [2] Dept of pathology Erasmus MC University Medical Centre, Rotterdam, The Netherlands

14.50 Serous cystadenoma; a single center experience (p. 156)

J. Fest, J. Poley, M. Bruno en H. Braat, Erasmus MC, Rotterdam, The Netherlands

15.00 Diagnostic value of a pancreatic mass on computed tomography in patients undergoing pancreatoduodenectomy for presumed pancreatic cancer (p. 157)

A. Gerritsen[1,2] , T.L. Bollen[3] , C.Y. Nio[4] , I.Q. Molenaar[1], M.G. Dijkgraaf[5] , H.C. van Santvoort[1] , G.J. Offerhaus[6] , E.Sieders[7] , K.P. de Jong[7] , R.M. van Dam[8] , E. van der Harst[9] , H. van Goor[10] , B. van Ramshorst[11] , B.A. Bonsing[12], I.H. de Hingh[13] , M.F. Gerhards[14] , C.H van Eijck[15] , D.J. Gouma[2] , I.H. Borel Rinkes[1] , O.R. Busch[2] , and M.G. Besselink[2] , for the Dutch Pancreatic Cancer Group, [1]Dept of Surgery, University Medical Center Utrecht, [2]Dept of Surgery, Academic Medical Center Amsterdam, [3]Dept of Radiology, St. Antonius hospital Nieuwegein, [4]Dept of Radiology, Academic Medical Center Amsterdam, [5]Clinical Research Unit, Academic Medical Center Amsterdam, [6]Dept of Pathology, University Medical Center Utrecht, [7]Dept of Surgery, University Medical Center Groningen, [8]Dept of Surgery, Maastricht University Medical Center, [9]Dept of Surgery, Maasstad Ziekenhuis Rotterdam, [10]Dept of Surgery, Radboud University Medical Centre Nijmegen, [11]Dept of Surgery, St.Antonius hospital Nieuwegein, [12]Dept of Surgery, Leiden University Medical Center, [13]Dept of Surgery, Catharina hospital Eindhoven, [14]Dept of Surgery, OLVG Amsterdam, [15] Dept of Surgery, Erasmus Medical Center Rotterdam

15.10 Comparison of Incidence Rates of Acute Pancreatitis and Pancreatic Cancer among the general population and type 2 Diabetes Mellitus patients between different Databases in the SAFEGUARD project (p. 158)

G.M.C. Masclee[1] , I.A. Leal[1] , P. Rijnbeek[1] , G. Trifiro[1,10] , G. De Berardis[2] , I. Bezemer[3] , M. Gil[4] , E. Martín[4] , G. Requena[5] , C. Sammon[6] , S. Pecchioli[10] , N. Schmedt[7] , T. Schink[7] , J.D. Seeger[8] , L. Scotti[9], M. Pladevall[1] , M. Smits[12] ,M.C.J.M. Sturkenboom[1] , S. Romio[1,9] ,[1]Dept of Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy, [3] PHARMO Institute, Utrecht, Netherlands, [4]Spanish Agency for Drugs and Medical Devices, Madrid, Spain, [5] Pharmacology Unit, Dept of Biomedical Sciences II, University of Alcalá, Madrid, Spain, [6] University of Bath, Bath, United Kingdom, [7]Leibniz-Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany, [8]The Brigham and Women's Hospital, Harvard Medical School, Boston, United States, [9] University Milano-Bicocca, Milan, Italy, [10] Health Search, Italian College of General Practitioners, Florence, Italy, [11]RTI Health Solutions, Barcelona, Spain, [12]VU University Medical Center, Amsterdam, Netherlands

15.20 Introduction of laparoscopic minor liver surgery in a HPB unit: not necessarily associated with a “learning curve (p. 159)

F. Huisman[1], M. J. Van der Poel[1] , M.G.H. Besselink[1] , P.J. Tanis[1] , T.M. van Gulik[1] , O.R.C. Busch ,[1] Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

15.30 Einde programma

Vrijdag 21 maart 2014

Symposium Nederlandse Vereniging voor Hepatologie **Baroniezaal**

Voorzitters: U.H.W. Beuers en H.R. van Buuren

"Cholestatische en virale leverziekten - een internationaal perspectief"

09.30 PBC: wat hebben onze patiënten en wij geleerd van de 'PBC supergroup'?
Dr. H.R. van Buuren, MDL-arts, Erasmus MC, Rotterdam

09.50 PSC: welke rol hebben genetica voor het ontstaan en de voortgang van PSC?
Prof. dr. R. Weersma, MDL-arts, UMC Groningen

10.10 IAC: is IgG4-gerelateerde ziekte van galwegen en pancreas een beroepsziekte?
Prof. dr. U.H.W. Beuers, MDL-arts, Academisch Medisch Centrum, Amsterdam

10.30 Inleiding hepatologie in Europa
Prof. dr. R.J. Oude Elferink, biochemicus, Tytgat Instituut, AMC, Amsterdam

10.35 De Nederlandse Hepatologie - een Europees perspectief
Prof. dr. P.L.M. Jansen, MDL-arts, AMC Amsterdam, Maastricht UMC

10.45 Inleiding virale hepatitis
Prof. dr. J.P.H. Drenth, MDL-arts, Radboudumc, Nijmegen

10.50 De virale hepatitis zorg in Nederland - gisteren, vandaag, morgen
Prof. dr. S.W. Schalm, MDL-arts, Erasmus MC Rotterdam

11.00 Einde programma

Poster rounds DEGH meeting **Zaal 19**

Theme **Immunology and IBD –** Chairs: G. Bouma and D.M.A.E. Jonkers

09.00 De postersessie van de DEGH vindt plaats tussen 09.00 en 11.00 uur. Vanaf 09.00 uur zullen alle posters worden gepresenteerd in een plenaire sessie met behulp van een powerpoint slide. Na het presenteren van de posters zal er gelegenheid zijn tot het stellen van vragen bij de desbetreffende posters. In de zaal is een ontbijtbuffet aanwezig.

1. Sympathetic rather than vagal activity modulates acute DSS colitis in mice

C. Cailotto[1], B.J. Olivier[1], L. Costes[1], J. van der Vliet[1], F. Hilbers[1], W.J. de Jonge[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands

2. Prediction of response to adalimumab induction therapy in Crohn's disease patients

C.P. Peters[1,2], F.H. van Dooren[1], N.W. Duijvis[1], S.C. Wolfkamp[1], E.W. Vogels[1], C. Verseijden[1], S. Meisner[1], P.C. F. Stokkers[3], P.D. Moerland[4], C.Y. Ponsioen[2], A.A. te Velde[1], [1]Tytgat Institute for Liver and Intestinal Research, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, [3]Dept of Gastroenterology and Hepatology, St Lucas Andreas Hospital, Amsterdam, [4]Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Bioinformatics Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

3. Potential mechanisms of therapeutic cannabis use in chronic pancreatitis

W.K. Utomo[1], K. Parikh[2], M. de Vries[3], H. van Goor[3], M.J. Bruno[1], M.P. Peppelenbosch[1], H. Braat[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, [2]Dept of Cell Biology, University Medical Center Groningen, University of Groningen, Groningen, [3]Dept of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

4. Longitudinal analysis of TRAIL and CD158b expression on peripheral and intrahepatic NK cells in HCV patients during triple therapy

M. Spaan[1], R.A. de Groen[1], G.W. van Oord[1], H.L.A. Janssen[1,2], R.J. de Knegt[1], A. Boonstra[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [2]Liver Clinic University Health Network, Division of Gastroenterology, University of Toronto, Canada

5. Analysis of the transcriptome and immune function of monocytes during IFNα-based therapy in chronic HCV infection revealed induction of TLR7 responsiveness

J. Hou[1], Z.M. Groothuismink[1], L. Koning[1], R. Roomer[1], W. van IJcken[2], K. Kreefft[1], B. Liu[1], H.LA. Janssen[1,3], R.J. de Knegt[1], A. Boonstra[1], [1]Dept of Gastroenterology and Hepatology, and [2]Center for Biomics, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [3]Liver Clinic University Health Network, Division of Gastroenterology, University of Toronto, Canada

6. Rapamycin and everolimus facilitate hepatitis e virus replication: reveal an antiviral function of PI3K-AKT-mTOR pathway

X. Zhou[1], Y. Wang[1], H.L.A. Janssen[1,2], H.J. Metselaar[1], M.P. Peppelenbosch[1], Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [2]Division of Gastroenterology, University Health Network, Toronto, Canada

7. T cell characteristics during acute hepatitis B virus infection

S.B. Willemse[1,2], A. de Niet[1,2], F. Stelma[1,2], M.J. Tempelmans Plat-Sinnige[2], E.B.M. Remmerswaal[2], H.W. Reesink[1], E.M.M. van Leeuwen[2], [1]Dept of Gastroenterology and Hepatology, and [2]Dept of Experimental Immunology, Academic Medical Center, Amsterdam, The Netherlands

8. The number of human commensal bacterium Faecalibacterium prausnitzii is significantly increased in the fecal samples of patients with active Crohn's disease

E. Caljouw[1], M.R.K.L. Lie[1], M. Elizabeth[1], M.P. Peppelenbosch[1], C.J. van der Woude[1], S.R. Konstantinov[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

9. Bacterial translocation to the pancreas revealed after analyses of the pancreatic cyst fluids

V. Narayanan[1], W.K. Utomo[1], M.J. Bruno[1], M.P. Peppelenbosch[1], H. Braat[1], S.R. Konstantinov[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

10. Expression and localization of IL-21 in the gastrointestinal mucosa of pediatric Crohn's Disease patients

L.M.M. Costes[1], D.J. Lindenbergh-Kortleve[1], M.A. van Leeuwen[1], S. Veenbergen[1], C.I. de Bie[1], J.C. Escher[1], L. de Ridder[1], J.N. Samsom[1], [1]Dept of Pediatric Gastroenterology, Erasmus MC, Sophia Children's Hospital, Rotterdam, The Netherlands

11. Overexpression of Cyp27a1 in hematopoietic cells reduces hepatic inflammation independently of 27-hydroxycholesterol levels in plasma and liver

T. Hendrikx, M.L.J. Jeurissen1, V. Bieghs1, S.M.A. Walenbergh1, P.J. van Gorp1, F. Verheyen1, T. Houben1, Y. Dias Guichot1, M.J.J. Gijbels1, G.H. Koek1, E. Leitersdorf2, M.H. Hofker3, D. Lütjohann4, R. Shiri-Sverdlov1, 1Depts of Molecular Genetics, Molecular Cell Biology, Electron Microscopy, Pathology and Internal Medicine; Nutrition and Toxicology Research (NUTRIM) and Cardiovascular Research (CARIM) Institutes of Maastricht, University of Maastricht, Maastricht, The Netherlands, 2Dept of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, 3Dept of Pathology and Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, 4Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Bonn, Germany

12. Characterization and quantification of human dendritic cell subsets in healthy and diseased livers

E. van der Aa[1], P.J. Biesta[1], F. Ayhan[1], H.L.A. Janssen[1], A.M. Woltman[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Poster rounds DEGH meeting — Zaal 20

Theme **Metabolism and therapy –** Chairs: A.A. te Velde and R.K. Weersma

09.00 De postersessie van de DEGH vindt plaats tussen 09.00 en 11.00 uur. Vanaf 09.00 uur zullen alle posters worden gepresenteerd in een plenaire sessie met behulp van een powerpoint slide. Na het presenteren van de posters zal er gelegenheid zijn tot het stellen van vragen bij de desbetreffende posters. In de zaal is een ontbijtbuffet aanwezig.

1. LGR5+ liver organoids as a model to study polycystic liver disease

E.S. Wills[1,2], R. te Morsche[1], R. Roepman[2,3], J.H. de Wilt[4], M. Huch[5], H. Clevers[5], J.P.H. Drenth[1], [1]Dept of Medicine, Division of Gastroenterology and Hepatology, [2]Dept of Human Genetics, [3]Nijmegen Center for Molecular Life Sciences, and [4]Dept of Surgery, Radboud University Medical Center, Nijmegen, [5]Hubrecht Institute for Developmental Biology and Stem Cell Research, University Medical Center Utrecht, Utrecht, The Netherlands

2. MicroRNAs to assess warm ischemic injury during machine perfusion of liver grafts from circulatory death donors

C.J. Verhoeven[1], D. Monbaliu[2], I. Habib[1], J. de Jonge[1], T. Wylin[2], I. Jochmans[2], V. Heedfeld[2], Metselaar[1], J. Kwekkeboom[1], R.W.F. de Bruin[1], G. Kazemier[3], J. IJzermans[1], J. Pirenne[2], L.J.W. van der Laan[1], [1]Dept of Surgery and Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands, [2]Dept of Abdominal Transplant Surgery, University Hospitals/ KU Leuven, Belgium, [3]Dept of Surgery, VU Medical Center, Amsterdam, The Netherlands

3. Increased expression efficiency by codon optimization for viral gene therapy of Crigler-Najjar syndrome

R. van Dijk[1], N. van Til[2], C. Riviere[3], S. Duijst[1], D.R. de Waart[1], U. Beuers[1,4], P.J. Bosma[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, University of Amsterdam, Amsterdam, [2]Dept of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Genethon, Evry, France, [4]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

4. Secretory leukocyte protease inhibitor (SLPI) is a potent regulator of small intestinal myeloid cell driven tolerance

C.L. Menckeberg[1], Y. Simons-Oosterhuis[1], D.J. Lindenbergh-Kortleve[1], L. de Ruiter[1], H.C. Raatgeep[1], L.A. van Berkel[1], P.E. van Lierop[2], E.E.S. Nieuwenhuis[2], L. de Ridder[3], J.C. Escher[3], J.N. Samsom[1], [1]Laboratory of Pediatrics, Division of Gastroenterology and Nutrition, Erasmus MC, Rotterdam, [2]Wilhelmina Children's Hospital, Utrecht, [3]Dept of Pediatric Gastroenterology, Sophia Children's Hospital, Rotterdam, The Netherlands

5. Co-administration of 5-aminosalicylic acid to 6-mercaptopurine reduces in vitro hepatotoxicity in HepaRG cells

M.M.T.J. Broekman[1], H.M.J. Roelofs[1], M. Kerstholt[1], F. Hoentjen[1], W.H.M. Peters[1], G.J.A. Wanten[1], D.J. de Jong[1], [1]Dept of Gastroenterology, Radboud University Medical Center, Nijmegen, The Netherlands

6. High throughput compound library screen to identify selective FXR agonists for inflammatory bowel disease

I.T.G.W. Bijsmans[1], D. Lelieveld[2], D.A. Egan[2], S.W.C. van Mil[1], [1]Molecular Cancer Research, Section Metabolic Diseases, and [2]Cell Screening Center, Dept of Cell Biology, University Medical Center Utrecht, Utrecht, The Netherlands

7. In vitro pancreas toxicity by azathioprine but not 6-mercaptopurine

M.M.T.J. Broekman[1], H.M.J. Roelofs[1], T. Demir[1], F. Hoentjen[1], W.H.M. Peters[1], G.J.A.Wanten[1], D.J. de Jong[1], [1]Dept of Gastroenterology, Radboud University Medical Center, Nijmegen, The Netherlands

8. IMPDH2-targeted constraint of cell growth in hepatocellular carcinoma by mycophenolic acid

K. Chen[1,2], K. Man[3], H.J. Metselaar[1], H.L.A. Janssen[1,4], J. Kwekkeboom[1], D. Sprengers[1], M.J. Bruno[1], M.P. Peppelenbosch[1], Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [2]Xinyuan Institute of Medicine and Biotechnology, College of Life Sciences, Zhejiang Sci-Tech University, Hangzhou, China, [3]Dept of Surgery, the Hong Kong University, Hong Kong, [4]Division of Gastroenterology, University Health Network, Toronto, Canada

9. Ophthalmate levels following paracetamol challenge during hepatectomy: a translational model of liver function

K. van Mierlo[1], S.A.W.G. Dello[1], M.C. de Jong[1], H.M.H. van Eijk[1], T.M. de Kok[3], J.J. Briedé[3], S.W.M. Olde Damink[1,2], C.H.C. Dejong[1], [1]Dept of Surgery, Maastricht University Medical Center and Nutrim School for Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, The Netherlands, [2]Dept of Surgery, University College London Hospitals and University College London, Division of Surgery and Interventional Science, London, United Kingdom, [3]Dept of Health Risk Analysis and Toxicology, Maastricht University Medical Center, Maastricht University, Maastricht, The Netherlands

10. Qualitative comparison between two mouse hepatocyte culture systems for bile salt signalling studies

E.H. Gilglioni[1,2], I.C. Gaemers[1], R.P.J. Oude Elferink[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Physiological Science, State University of Maringá, Brazil

11. Melatonin suppresses the activation of hepatic stellate cells

S. Shajari[1], L. Almudena[1], H. Moshage[1], K.N. Faber[1], [1]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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

F. Huisman[1], K.P. van Lienden[2] J. Verheij[3], T.M. van Gulik[1], [1]Dept of Surgery, [2]Dept of Radiology, and [3]Dept of Pathology, Academic Medical Center, Amsterdam, The Netherlands

13. Intestinal FXR is essential in the hepatic growth response toprolonged cholic acid exposure

M. Doktorova[1], F.A.J.A Bodewes[1], H.J. Verkade[1], J.W. Jonker[1], [1]Center for Liver, Digestive and Metabolic Diseases, Dept of Pediatrics, University Medical Center Groningen, Groningen, The Netherlands

DEGH oral presentations — Baroniezaal

Voorzitters: K.K. Krishnadath en P.D. Siersema

11.30 Translational science teaching Session: Barrett's Esophagus
Clinical aspects: *prof. dr. P.D. Siersema, MDL-arts, UMC Utrecht*

11.55 Translational/basic science aspects: *prof. dr. K.K. Krishnadath, MDL-arts, AMC, Amsterdam*

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

12.20 Overexpression of HOXA13 in Barrett's esophagus is a potential mediator of its posterior phenotype (p. 160)
V.T. Janmaat[1], A.P. Verhaar[1], M.J. Bruno[1], M.P. Peppelenbosch[1], M.C.W. Spaander[1], [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands

12.32 Comprehensive profiling of plasma microRNAs reveals potential biomarkers for Barrett's esophagus and esophageal adenocarcinoma (p. 161)
J.W.P.M. van Baal[1], P. Bus[1], C. Kestens[1], F.J.W. ten Kate[2], W.H.M. Peters[3], J.P.H. Drenth[3], J.M. Roodhart[4], E.E. Voest[4], P.D. Siersema[1], [1]Dept of Gastroenterology and Hepatology, and [2]Dept of Pathology, University Medical Center Utrecht, Utrecht, [3]Dept of Gastroenterology, Radboud University Medical Center, Nijmegen, [4]Dept of Medical Oncology, University Medical Center Utrecht, Utrecht The Netherlands

12.45 Lunchbuffet in de expositiehal

DEGH oral presentations — Baroniezaal

Voorzitters: G. Dijkstra en P.C.F. Stokkers

14.00 Translational Science Teaching Session: Inflammatory Bowel Disease
Clinical aspects: *Dr. P.C.F. Stokkers, MDL-arts, St. Lucas Andreas Ziekenhuis*

14.24 Translational/Basic science aspects: *Prof. dr. G. Dijkstra, MDL-arts, UMC Groningen*

Vrijdag 21 maart 2014

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

14.48 Trans-ethnic association study of IBD identifies 14 new disease loci and demonstrates pervasive sharing of genetic risk factors and phenotypic features between Europeans and Non-Europeans (p. 162)

S. van Sommeren[1,2], J.Z. Liu[3]*, A. Takahashi[4], J.C. Lee[5], B.K. Thelma[6], R. Malekzadeh[7], J.C. Barrett[3], J.H. Cheon[8], H. Huang[9], A. Franke[10], International IBD Genetics Consortium, M. Parkes[5], A.P. Morris[11], B.Z. Alizadeh[12], S.C. Ng[13], C.A. Anderson[3], M. Kubo[14], R.K. Weersma[1], [1]Dept of Gastroenterology and Hepatology, and [2]Dept of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, [3.] Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK, [4]Laboratory for Statistical Analysis, Center for Genomic Medicine, RIKEN, Yokohama, Japan, [5]Inflammatory Bowel Disease Research Group, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK, [6]Dept of Genetics, University of Delhi South Campus, New Delhi, India, [7]Digestive Diseases Research Institute, Shariati Hospital, Tehran, Iran, [8]Dept of Internal Medicine and Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea, [9]Analytic and Translational Genetics Unit, Dept of Medicine, Massachusetts General Hospital, Boston, Massachusetss, USA, [10]Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel, Kiel, Germany, [11]Welcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK, [12]Dept of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, [13]Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong, [14]Laboratory for Genotyping Development, Center for Genomic Medicine, RIKEN, Yokohama, Japan*

15.00 Interleukin-10 inhibits human IFNγ-secreting effector T cells indirectly by controlling antigen-presenting cell function (p. 163)

S. Veenbergen[1], M.A. van Leeuwen[1], G.J. Driessen[2], L.F. de Ruiter[1], H.C. Raatgeep[1], D.J. Lindenbergh-Kortleve[1], Y. Simons-Oosterhuis[1], L. de Ridder[1], J.C. Escher[1], J.N. Samsom[1], [1]Dept of Pediatric Gastroenterology, Erasmus MC, Sophia Children's Hospital, Rotterdam, [2]Dept of Pediatric Infectious Disease and Immunology, Erasmus MC, Rotterdam, The Netherlands

15.12 The role of microRNA-142-5P in experimental colitis (p. 164)

C. Kunne[1], 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, [2]Dept of Pathology, [3]Dept of Neuro-genetics, and [4]Dept of Cinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands

15.24 Identification of novel non-transcriptionally acting glucocorticoid receptor ligands that suppress T cell activation but lack adipogenic activity (p. 165)

A.P. Verhaar[1,2], R. Dvorsky[3], M.E. Wildenberg[2], M. Löwenberg[2], M.P. Peppelenbosch[4], D.W. Hommes[1,5], G.R. van den Brink[2]*, *Both authors contributed equally, [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, [2]Tytgat Institute for Liver and Intestinal Research and Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [3]Max Planck Institute of Molecular Physiology, Dortmund, Germany, [4]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [5]Center for Inflammatory Bowel Diseases, University of California Los Angeles, Los Angeles, USA*

15.36 Differential induction of dendritic cell-mediated T cell tolerance in the small and large intestine (p. 166)

S. Veenbergen[1], M.F. du Pré[1], L.A. van Berkel[1], F. Luk[1], Y. Simons-Oosterhuis[1], J.N. Samsom[1], [1]Dept of Pediatric Gastroenterology, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands

15.48 Efficacy of a novel JAK1-specific inhibitor in a mouse model of acute and chronic colitis (p. 167)

J. Duarte[1], L. de Vries[1,4], F. Hilbers[1], M. de Winther[2], M. Sims[3], V. Ludbrook[3], M. Woodrow[3], J. Witherington[3], G. D'Haens[4], W.J. de Jonge[1,4], [1]Tytgat Institute for Liver and Intestinal Research, and [2]Dept of Medical Biochemistry, Academic Medical Center, Amsterdam, The Netherlands, [3]Kinase DPU, GlaxoSmithKline, Stevenage, UK, [4]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

16.00 **Abstract and Poster prizes**

16.10 Einde programma

Voordrachten Ned. Vereniging voor Gastroenterologie en Sectie IBD — Parkzaal

Voorzitters: J.J. Keller en J.J. Kolkman

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

09.30 Gluten degrading enzyme effectively digests gluten in the stomach and small intestine of healthy volunteers (p. 168)

B. Salden[1] , V. Monserrat[3*], F.J. Troost[1], M.J. Bruins[2] , L. Edens[2] , R. Bartholomé[4] , B. Winkens[5] , F. Koning[3], A. Masclee[1],[1]Dept of Internal Medicine, division of Gastroenterology-Hepatology, NUTRIM, Maastricht University Medical Center, Maastricht, The Netherlands; [2] DSM Biotechnology Centre, Delft, The Netherlands; [3] Dept of Immunohematology and Blood Transfusion, Leiden University Medical Centre, Leiden, The Netherlands; [4]Dept of Pharmacology and Toxicology, NUTRIM, University Maastricht, The Netherlands; [5]Dept of Methodology and Statistics, Maastricht University Medical Center, Maastricht, The Netherlands; [*] these authors contributed equally to this work.*

09.40 High frequency of concomitant immune-mediated diseases in celiac disease in a large Dutch cohort (p. 169)

Spijkerman M[1] , Visschedijk MC[1,2] , Withoff S[2] , Wijmenga C[2] , Kolkman JJ[1,3] , Weersma RK[1] ,[1] University Medical Centre Groningen, Dept. of Gastroenterology and Hepatology, The Netherlands, [2]University Medical Centre Groningen, Dept. of Genetics, The Netherlands,[3] Medical Spectrum Twente, Dept. of Gastroenterology and Hepatology, The Netherlands.

09.50 Relapse rates of type 1 and 2 autoimmune pancreatitis: long-term outcome (p. 170)

J. Buijs[1], D.L. Cahen[1], M.J. van Heerde[1], E.A. Rauws[2], L.J. Maillette de Buij Wenniger[2], B.E. Hansen[1], K. Biermann[1], J. Verheij[2], F.P. Vleggaar[3] , M.A. Brink[4] , U.H.W. Beuers[2], H.R. van Buuren[1], M.J. Bruno[1],[1] Erasmus University Medical Center, Rotterdam, The Netherlands[2] Academic Medical Center, Amsterdam, The Netherlands[3] University Medical Center Utrecht, The Netherlands[4] Meander Medical Center, Amersfoort, The Netherlands

10.00 Incidence of Microscopic Colitis in the Netherlands. A Nationwide Population-Based Study from 2000-2012 (p. 171)

B.P.M. Verhaegh[1,2] ; D.M.A.E. Jonkers[1,2] ; A.Driessen[3] ; M.P. Zeegers[2,4,5] ; A.A.M. Masclee[1,2] ; M.J. Pierik[1,1] Division Gastroenterology-Hepatology, Dept of Internal Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands[2] NUTRIM, School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center+, Maastricht, the Netherlands[3] Dept of Pathology; Maastricht University Medical Center+, Maastricht, the Netherlands[4] Dept of Complex Genetics, Cluster of Genetics and Cell Biology, Maastricht University Medical Center+, Maastricht, the Netherlands[5] Dept of Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, United Kingdom

10.10 Immunoglobulin-bound bacteria in pediatric IBD patients (p. 172)

R.A.A.M. Govaarts[1,2] , D. Zaidi[1,2] , R. Valcheva[2] , Y. Lou[1,2] , C.J.J. Mulder[4] , L.A. Dieleman[2,3] , E. Wine[1,2,] [1]Division of Pediatric Gastroenterology, Dept of Pediatrics, University of Alberta, Edmonton, Alberta, Canada [2] Centre of Excellence for Gastrointestinal Inflammation and Immunity Research, University of Alberta, Edmonton, Alberta, Canada [3] Division of Gastroenterology, Dept of Medicine, University of Alberta, Edmonton, Canada, [4]Department of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, the Netherlands

10.20 Lower abundance of Uncultured Clostridiales in PSC patients (p. 173)
N.G.M. Rossen[1] , S. Fuentes[2] , K. Boonstra[1] , G. D'Haens[1] , H.G.H.J. Heilig[2] , E.G. Zoetendal[2] , W. M. de Vos[2], C.Y. Ponsioen[1].,[1] Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands. [2]Laboratory of Microbiology, Wageningen University, Wageningen, the Netherlands.

10.30 High Infliximab trough levels are associated with impaired quality of life in IBD patients in clinical and biochemical remission on maintenance IFX therapy (p. 174)
L.M.C. Vos, J.F. Brandse, C. Ponsioen, G. van den Brink, G.R.A.M. D'Haens, M. Löwenberg, Academisch Medisch Centrum, Amsterdam, The Netherlands

10.40 Low dose naltrexone in therapy resistant IBD, a case series (p. 175)
M.R.K.L. Lie , G.M. Fuhler, A. de Lima, C. van der Ent , C.J. van der Woude , Dept of Gastroenterology, Erasmus University Hospital, Rotterdam, The Netherlands

10.50 Interspace microbiome profiling (IS-pro) enables to differentiate IBD subclasses and disease activity by specific loss of bacterial diversity (p. 176)
M.E. Grasman[1] , R. van der Borden[1, 2] , A.E. Budding[2] , A. Eck Hauer[2] , P.H.M. Savelkoul[2] , A.A. van Bodegraven[3] ,[1]VU Medisch Centrum, afdeling Gastroenterologie en Hepatologie, [2]VU Medisch Centrum, afdeling Medische Microbiologie en Infectiepreventie, [3]ORBIS Medisch Centrum, afdeling Gastroenterologie en Hepatologie

11.00 Koffiepauze

Vrije voordrachten Sectie Inflammatoire Darmziekten — Parkzaal

Voorzitters: G. Dijkstra en R. West

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

11.30 Preconception care in IBD women leads to less disease relapses during pregnancy (p. 177)
A. de Lima[1] , Z. Zelinkova,[1,2] , C. van der Ent[1] , C.J. van der Woude[1] ,[1] Erasmus Medical Center, Rotterdam, The Netherlands[2] University Hospital, Bratislava, Slovakia

11.40 Anti-TNF is safe to stop in the second trimester of pregnancy in IBD women in remission (p. 178)
A. de Lima[1], Z. Zelinkova[1,2] , C. Van der Ent[1], C.J. van der Woude[1] ,[1]Erasmus Medical Center, Rotterdam, Tthe Netherlands[2] University Hospital, Bratislava, Slovakia

11.50 Decision-making, counselling and course of pregnancy in female inflammatory bowel disease patients (p. 179)

J. Hoekstra[1], J.E. Baars[1], A.H.C. van Roon[1], M. Kimmel[1], M. Zwijnenburg[2], F.C. Bekkering[2], A.J.P. van Tilburg[1], R.L. West[1], [1]Dept of Gastroenterology and Hepatology, Sint Franciscus Gasthuis, Rotterdam, [2]Dept of Gastroenterology and Hepatology, IJsselland Hospital, Capelle aan de IJssel, The Netherlands

12.00 The Pharmacokinetics of Infliximab and Markers for Response to Induction Therapy in Patients with moderate to severe Ulcerative Colitis (p. 180)

J.F. Brandse[1], J.M. Jansen[2] , D. van der Kleij[3] , G.J. Wolbink[3,4] , I.M. Rigter[5] , P.A. Baars[6] , M. Löwenberg[1], C.Y. Ponsioen[1], G.R. van den Brink[1] , R.A. Mathôt[5] , G.R. D'Haens[1], [1] Dept of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands [2] Dept of Gastroenterology, Onze Lieve Vrouwe Gasthuis, Amsterdam [3] Biologicals Laboratory, Sanquin Diagnostic Services, Amsterdam [4] Dept of Rheumatology, Jan van Bremen Research Institute, Reade, Amsterdam [5] Dept of Hospital Pharmacy, Academic Medical Center, Amsterdam [6] Dept of Experimental Immunology, Academic Medical Center, Amsterdam

12.10 Large variation in infliximab trough levels is associated with disease activity in pediatric Inflammatory Bowel Disease (p. 181)

D.R. Hoekman[1] ; J.F. Brandse[2] ; T.G. de Meij[3] ; T.Z. Hummel[1] ; M. Lowenberg[2] ; M.A. Benninga[1] ; G.R.A.M. D'Haens[2] ; A. Kindermann[1], [1]Pediatric Gastroenterology and Nutrition, Academic Medical Center/Emma Children, Amsterdam, Netherlands. [2]Gastroenterology, Academic Medical Center, Amsterdam, Netherlands. [3]Pediatric Gastroenterology, VU University Medical Center, Amsterdam, Netherlands.

12.20 Top-down versus step-up treatment in newly diagnosed Crohn: no difference in long-term outcome (p. 182)

J.A. Stibbe[1] ; D.R. Hoekman[1] ; F.J. Baert[2] ; P. Caenepeel[3] ; P. Vergauwe[4] ; M. De Vos[5] ; S.A. Vermeire[3] G.R.A.M.S. D'Haens[1] ,[1]Dept of Gastroenterology, Academic Medical Center, Amsterdam, the Netherlands [2]Dept of Gastroenterology, AZ Delta, Roeselare, Belgium [3]Dept of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium [4]Dept of Gastroenterology, AZ Groeninge Hospital, Kortrijk, Belgium [5]Dept of Gastroenterology, Ghent University Hospital, Ghent, Belgium

12.30 Skewed thiopurine metabolism leads to early therapeutic failure in the majority of patients with inflammatory bowel disease (p. 183)

Kreijne, J.E.[1] , M.L. Seinen, M.L[1] , Sinjewel, A.[2] , Bouma, G[1] , Mulder, C.J.[1] , van Bodegraven, A.A.[1] and de Boer, N.K.H[1], [1]VU University Medical Center, Gastroenterology and Hepatology, Amsterdam, Netherlands [2]VU University Medical Center, Pharmacy Dept, Amsterdam, Netherlands

12.40 Early assessment of thiopurine metabolites predicts thiopurine-induced leukopenia in inflammatory bowel disease patients (p. 184)

D.R. Wong[1] , M.J.H. Coenen[2] , L.J.J. Derijks[3] , C.J. van Marrewijk[2] , S.H. Vermeulen[2,4] , A.L.M. Verbeek[4] , B. Franke[2,6] , H-J. Guchelaar[7] , D.J. de Jong[8] , L.G.J.B. Engels[9] , P.M. Hooymans[1] ; on behalf of the TOPIC study group.,[1] Dept of Clinical Pharmacy and Toxicology, Orbis Medical Centre, Sittard-Geleen, The Netherlands; [2] Dept of Human Genetics, Radboud University Medical Centre, Nijmegen, The Netherlands; [3] Dept of Clinical Pharmacy, Máxima Medical Centre, Veldhoven, The Netherlands; [4] Dept for Health Evidence, Radboud University Medical Centre, Nijmegen, The Netherlands; [5] Dept of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, The Netherlands; [6]Dept of Psychiatry, Radboud University Medical Centre, Nijmegen, The Netherlands; [7] Dept of Clinical Pharmacy and Toxicology, Leiden University Medical Centre, Leiden, The Netherlands; [8]Dept of Gastroenterology, Radboud University Medical Centre, Nijmegen, The Netherlands; [9] Dept of Gastroenterology, Orbis Medical Centre, Sittard-Geleen; The Netherlands

12.50 FcR-mediated effector function contributes to the therapeutic response of anti-TNF monoclonal antibodies in a mouse model of IBD (p. 185)

A.D. Levin,[1] M.E. Wildenberg,[1] G.R.A.M. D'Haens,[2] and 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

13.00 Korte ledenvergadering Sectie Inflammatoire Darmziekten

13.15 Lunchbuffet in de expositiehal.

Abstract meeting NESPEN — Zaal 80

Voorzitters: C.F. Jonkers en G.J.A. Wanten

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

10.00 Interrater reliability of the Chicago Classification in pediatric high-resolution esophageal manometry recordings (p. 186)

M.J. Smits[1], M.M.J. Singendonk[1,2], I.E. Heijting[a] , M.P. van Wijk[1], S. Nurko[3], R. Rosen[3], P.W. Wijenborg[6], R. Abu-Assi[2] , D.R. Hoekman[1] , G. Seiboth[2] , M.A. Benninga[1] , T.I. Omari[2,4,5] S. Kritas[2], [1]Dept of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital AMC, Amsterdam, The Netherlands; [2] Gastroenterology Unit, Women's and Children's Health Network, North Adelaide, Australia; [3]Center for Motility and Functional Gastrointestinal Disorders, Division of Gastroenterology, Children's Hospital Boston, Boston, USA; [4] School of Medicine, Flinders University, Bedford Park, South Australia; [5]Translational Research Center for Gastrointestinal Diseases, University of Leuven, Belgium; [6] Dept of Gastroenterology and Hepatology AMC, Amsterdam, The Netherlands

10.10 The effect of oral vitamin B_{12} supplementation on fatigue in patients with irritable bowel syndrome or inflammatory bowel disease (p. 187)

A.M. Scholten[1], E. Vermeulen[2], M. Koopmann[3], T. Verhagen[4], R.A. Dhonukshe-Rutten[5], B.J.M. Witteman[6], [1]Dept of Nutrition and Dietetics, Haagse Hogeschool, The Hague, [2]Dept of European Law, University of Groningen, [3] Dept of Clinical Pharmacy, Gelderse Vallei Hospital, Ede, [4]Dept of Nutrition, NCOI, Eindhoven, [5]Dept of Human Nutrition, Wageningen University, [6]Dept of Gastroenterology, Gelderse Vallei Hospital, Ede, The Netherlands

10.20 Comprehensive nutritional status of patients with (refractory) coeliac disease and EATL at diagnosis (p. 188)

N.J. Wierdsma[1], P. Nijeboer[2], M.A.E. de van der Schueren[1], G. Bouma[2], A.A. van Bodegraven[2], C.J.J. Mulder[2], [1]Dept of Nutrition and Dietetics, and [2]Dept of Gastroenterology, VU University Medical Center, Amsterdam, The Netherlands

10.30 Taurine and major surgical trauma, role of the route of nutrition (p. 189)

F.F.B.M. Heesakkers[1], P.G. Boelens[3], M.D.P. Luyer[1], K.W.Y. van Barneveld[4], A.N. Roos[2], J. Bakker, N.D. Bouvy[4], H.J.T. Rutten[1,5], [1]Dept of Surgery, and [2]Dept of Intensive Care Medicine, Catharina Hospital, Eindhoven, [3]Dept of Surgery, Leiden University Medical Center, Leiden, [4]Dept of Surgery, and [5]Research Institute Growth and Development, Maastricht University Medical Center, Maastricht, The Netherlands

10.40 Unimpaired anabolic response to oral meal feeding in patients with pancreatic cancer cachexia (p. 190)

D.P.J. van Dijk[1], M.C.G. van de Poll[1,2], A.G.W. Moses[3], T. Preston[4], S.W.M. Olde Damink[1], S.S. Rensen[1], N.E.P. Deutz[1], P.B. Soeters[1], J.A. Ross[3], K.C.H. Fearon[3], C.H.C. Dejong[1,3], [1]Dept of Surgery, Maastricht University Medical Center and NUTRIM School of Nutrition, Toxicology and Metabolism, Maastricht University, [2]Dept of Intensive Care Medicine, Maastricht University Medical Center, The Netherlands, [3]Dept of Surgery, Royal Infirmary of Edinburgh, Scotland, [4]Stable Isotope Biochemistry Laboratory, Scottish Universities Environmental Research Centre, East Kilbride, Glasgow, Scotland

10.50 Enteral glutamine administration increases urea production (p. 191)
M.C.G. van de Poll[1,2], S.W.M. Olde Damink[1], C.H.C. Dejong[1], [1]Dept of Intensive Care Medicine, and [2]Dept of General Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

11.00 Koffiepauze

Symposium NESPEN — Zaal 80

Symposium 'klinisch voedingsonderzoek'

Voorzitters: Dr. M. de van der Schueren, Lector HAN, research diëtist VUmc
Dr. G. Wanten, gastroenterologist Radboudumc

11.15 Introductie en doelstellingen symposium
(Platform research dietitians and nurse practioners)
Dr. M.A.E. de van der Schueren

11.30 Sarcopenie, do's and don'ts met voeding bij ouderen
Prof. dr. ir. Marjolein Visser, hoogleraar 'Gezond ouder worden' aan het VUmc

12.10 Discussie

Presentaties onderzoek: 7 minuten presenteren / 3 minuten discussie

12.20 Rustmetabolisme van patiënten die in aanmerking komen voor een levertransplantatie in het LUMC
A. Donker en A. Droop, diëtisten LUMC

12.30 Cross-culturele adaptatie van de Scored Patiënt-Generated Subjective Global Assessment (PG-SGA) naar de Nederlandse setting
M.J. Sealy, RD, BSc, Hanze Hogeschool Groningen

12.40 Onderzoek naar de fysiologische bijwerkingen op de korte- en lange termijn bij kinderen met refractaire epilepsie behandeld met het ketogeen dieet
E.J.T.M van der Louw, RD, EMC/ Sophia Kinderziekenhuis

12.50 Protein-enriched 'regular products' and their effect on protein intake in hospitalized older adults; a randomized controlled trial
S. Stelten, diëtist VUmc

13.00 Validity of the "rate a plate" method to estimate energy and protein intake in hospitalized patients
I.M. Dekker diëtist, VUmc

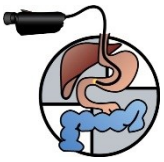
13.10 Proefschriftprijs presentatie

13.25 Uitreiking proefschriftprijs door voorzitter NESPEN

13.30 Wat hebben we vandaag geleerd … waar willen we naartoe
C.F. Jonkers, RD, secretaris NESPEN

13.30 Lunchbuffet in de expositiehal

Programma V&VN MDL — Beneluxzaal



10.10 Opening door de voorzitter

10.15 Barrett slokdarm, endoscopische detectie en behandeling vroegcarcinomen
Mw. W. Rosmolen, MDL-arts i.o., AMC, Amsterdam

10.40 Maagcarcinoom
Mw. J. van Dieren, MDL-arts, Antoni van Leeuwenhoek Zks, Amsterdam

11.05 Behandeling van levermetastasen bij colorectaal carcinoom
Mw. H. Kleijwegt, verpleegkundig specialist, Zks Gelderse Vallei, Ede

11.25 Behandeling van darmkanker met chemotherapie
Mw. S. de Bie, verpleegkundig specialist, Medisch Centrum Alkmaar

11.45 Algemene ledenvergadering
Mw. T. Korpershoek, voorzitter V&VN Maag Darm Lever

12.15 Lunchbuffet in de expositiehal

Middagprogramma Endoscopieverpleegkundigen — Beneluxzaal

Voorzitter: W. Kok

13.45 Endo-echo en MDL oncologie
Mw. A. Vehmeijer, MDL-arts, Kennemer Gasthuis, Haarlem

14.15 Hoe gaat het verder na de scopie; operaties bij colorectaal carcinoom
Dhr. R. Smeenk, chirurg, Atrium MC, Heerlen

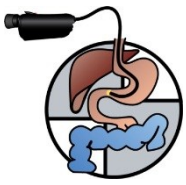
14.45 ERCP bij maligniteit
Dhr. M. Tushuizen, MDL-arts, Amstelland Ziekenhuis, Amstelveen

15.15 Einde programma

Vrijdag 21 maart 2014

Middagprogramma Lever-/IBD verpleegkundigen — Zaal 63

Beroepsvereniging van zorgprofessionals
Maag Darm Lever



Voorzitter: N. Ipenburg

13.45 Hepatocellulair carcinoom
Dhr. K.J. van Erpecum, MDL-arts, UMC Utrecht

14.15 IBD en extra-intestinale maligniteiten
Mw. L. Nissen, AIOS MDL, UMC St Radboud, Nijmegen

14.45 Screening colorectaal carcinoom bij IBD
Dhr. B. Oldenburg, MDL-arts, UMC Utrecht

15.15 Einde programma

Programma Voedingsverpleegkundigen / MDL kliniek verpleegkundigen — Zaal 64

Voorzitter: A. Pouwelsen

13.45 Parenterale voeding bij de oncologische patiënt
Mw. W. van Amsterdam, diëtist, Antoni van Leeuwenhoek Ziekenhuis, Amsterdam

14.15 Stomazorg na operatie voor colorectaal carcinoom
Mw. J. Boots, stomaverpleegkundige, Gelre Ziekenhuis, Apeldoorn

14.45 Screening hereditair colorectaal carcinoom
Mw. M. van Vugt, IBD verpleegkundige, UMC St Radboud, Nijmegen

15.15 Einde programma

Cost-effectiveness of Barrett's esophagus surveillance in a prospective followed cohort in the Netherlands

S.H. van Olphen[1], F. Kastelein[1], E.W. Steyerberg[2], C.W.N. Looman[2], M.C.W. Spaander[1], M.J. Bruno[1], E.W. Bekker Grob[2] on behalf of the ProBar study group, [1]Dept of Gastro-enterology and Hepatology, Erasmus University Medical Center Rotterdam, The Netherlands, [2]Dept of Public Health, Erasmus University Medical Center Rotterdam, The Netherlands

Surveillance is recommended for patients with Barrett's esophagus (BE) to detect esophageal adenocarcinoma (EAC) at an early stage. However, the value of surveillance is under discussion given the overall low risk of neoplastic progression, large screening base and lack of discriminative tests for risk stratification. The aim of this study was to evaluate the cost-effectiveness of different surveillance strategies in a large prospective cohort of BE patients. 720 BE patients were included in a multicenter prospective cohort study and followed during surveillance for a median of 7 years, according to the ACG guidelines. We used a Multi-State-Markov model to calculate misclassification and true progression rates from BE without dysplasia (ND) to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and eventually EAC. These progression rates were incur-porated in a decision-analytic model, which included estimates of costs and quality of life data associated with different surveillance strategies. We evaluated strategies with different surveillance intervals for patients with ND or LGD, endomucosal resection (EMR) and/or radiofrequency ablation (RFA) for patients with HGD or mucosal EAC and esophagectomy with or without neoadjuvant chemoradiotherapy for patients with invasive EAC. The incremental cost-effectiveness ratio (ICER) was calculated for each strategy in terms of costs per quality-adjusted life year (QALY) gained. The willingness-to-pay threshold was set at € 20.000 per QALY gained. The estimated true annual progression rate for ND to LGD was 0.020, for LGD to HGD or early EAC 0.032 and for HGD or early EAC to invasive EAC 0.355. Surveillance every four or five years with RFA for HGD or early EAC and esophagectomy for invasive EAC had ICERs of € 61.800 and € 4.800 per QALY gained, respectively. Strategies using EMR for visible abnormalities before RFA had similar effects (QALYs) compared to strategies using RFA alone, but costs for these strategies were slightly higher. Strategies with shorter surveillance intervals than four years provided substantial higher costs with similar or even less QALYs.
Conclusion: Based on a willingness-to-pay threshold of € 20.000 per QALY, endoscopic surveillance with an interval of 5 years combined with RFA for HGD or early EAC and esophagectomy for invasive EAC is a cost-effective strategy for the management of patients with BE without dysplasia at baseline.

Does use of NSAIDs, statins and proton pump inhibitors prevent development of esophageal adenocarcinoma among patients with Barrett's esophagus? Results from a multinational population based case control study

G.M.C. Masclee[1,2], P.M. Coloma[1], E.J. Kuipers[2], M.C.J.M. Sturkenboom[1,3], [1]Dept of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Dept of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands.

Background: Barrett's esophagus (BE) is an established risk factor for esophageal adenocarcinoma (EAC). Several studies reported that use of non steroidal anti- inflamematory drugs (NSAIDs), proton pump inhibitors (PPIs) and statins may inhibit the progression from BE to EAC. However, these studies did not adjust for important confounders, nor addressed dose- and duration-relationships. Aim: To evaluate the risk of EAC among BE patients in relation to use of NSAIDs, statins and PPIs. Design: Case-control study nested within a BE cohort using two European primary care databases (DB) (United Kingdom (UK); the Netherlands (NL) (1996- 2013). BE and EAC cases were identified using disease-specific READ codes (UK) and free text search with manual validation (NL). Cases were adult persons (≥18 years (yrs)) with EAC diagnosis ≥1 yr after BE diagnosis. Controls, being EAC-free, were matched to cases on age (± 5 yrs), sex, year of BE diagnosis (± 1 yr) and DB. Drug use was determined from BE diagnosis until matching date. Odds ratios (OR) with 95% CI were calculated by conditional logistic regression on patient-level pooled data, while adjusting for confounders (ORa), including BMI, smoking and alcohol use. Results: Within the BE cohort (n=15,134), 45 EAC (UK: 40, NL: 5) and 12 HGD cases (UK: not applicable, NL: 12) were identified. The risk for EAC was equal for BE subjects with or without hiatal hernia; presence of esophagitis or gastritis at BE diagnosis. Current smoking increased the risk of EAC (OR: 2.6; 95%CI:1.1-6.1) as current excessive alcohol use (OR:1.9 ; 1.0-3.7). NSAIDs were used by 29% of cases and 23% of controls. When adjusting for confounders, OR for NSAID use >1 yr was 1.2 (0.3-5.6). OR for statin use (27% use by cases;35% by controls) 2-3 yrs was 0.6 (0.1-4.9) and ORa 0.6 (0.1-4.8); for > 3yrs). OR for statin use > 3 years was 0.5 (0.1-1.7) and ORa 0.4 (0.1-1.6). In the matched and adjusted analyses receiving more doses of NSAIDs showed lower OR compared to no use; and statins (>730 defined daily doses) showed an OR of 0.6 (0.2-1.7) and ORa 0.5 (0.2-1.6). When including HGD as outcome as well (n=57), ORa for NSAID use was 0.97 (0.5-1.9). Statin use for 2-3 yrs showed an OR of 1.2 (0.3-5.3) and >3 yrs 0.5 (0.1-1.8),while ORa were 1.1 (0.3-5.0) and 0.5 (0.1-1.7) respectively. The risk of EAC and EAC-HGD was equal users and non-users of PPIs; no duration- or dose response was seen. Conclusion: Among BE patients the risk of EAC was not decreased by use of PPIs. Longer duration of statins provided a non-significant decrease in risk of EAC and of EAC-HGD up to 52%. NSAID use was associated with a non-significant 3% decrease in risk of HGD, but was not associated with EAC.

FISH Biomarkers for the Detection of Dysplasia and Prediction of Malignant Progression in Non-dysplastic Barrett's Esophagus

M.R. Timmer[1, 2]; C.T.I. Lau[2]; W. Rosmolen[1]; S.L. Meijer[3]; M.G.W. Dijkgraaf[4]; R.C. Mallant Hent[5]; A.H. Naber[6]; A.H. van Oijen[7]; L.C. Baak[8]; P. Scholten[9]; C. Böhmer[10]; P. Fockens[1]; J.J. Bergman[1]; K.K. Krishnadath[1,2] ,[1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam, [3]Dept of Pathology, Academic Medical Center, Amsterdam, Netherlands. [4]Clinical Research Unit, Academic Medical Center, Amsterdam, [5]Dept. of Gastroenterology, Flevoziekenhuis, Almere, Netherlands. [6]Dept. of Gastroenterology, Tergooiziekenhuizen, Hilversum, [7]Dept. of Gastroenterology, Medisch Centrum Alkmaar, Alkmaar, [8]Dept. of Gastroenterology, Onze Lieve Vrouwe Gasthuis, Amsterdam, [9]Dept. of Gastroenterology, Sint Lucas Andreas Ziekenhuis, Amsterdam, Netherlands. [10]Dept. of Gastroenterology, Spaarneziekenhuis, Hoofddorp, Netherlands.

Barrett's esophagus (BE) is associated with an increased risk of esophageal adenocarcinoma (EAC). The use of biomarkers may improve accurate detection and grading of dysplasia and prediction of malignant progression. In a community-based cohort of BE patients from 6 general hospitals and one academic center in the Netherlands, we evaluated 7 genetic biomarkers for their ability to accurately distinguish different stages of dysplasia and EAC. Subsequently, we conducted a long-term prospective follow-up study of non-dysplastic BE patients to determine which genetic markers were predictors of progression to high-grade dysplasia (HGD) or EAC. Genetic analysis was performed by fluorescence in situ hybridization (FISH) on brush cytology specimens using a set of fluorescently labelled DNA probes for P53, P16, Her-2/neu, 20q, and MYC, and for the centromeric regions of chromosome 7 and 17 to detect aneuploidy. Univariable and multivariable logistic regression analyses were performed to create a marker-model with the best classification performance for each stage of dysplasia. The predictive value of the markers was evaluated using univariable and multivariable survival analysis. In total, 601 patients were enrolled between 2002 and 2010. Histology showed IM in 486 patients, low-grade dysplasia (LGD) in 34 patients, HGD/EAC in 29 patients and gastric metaplasia in 52 patients. A panel combining P53, Her-2/neu and aneuploidy most accurately identified prevalent dysplasia/EAC in patients undergoing surveillance (c statistic 0.79). The markers P16, Her-2/neu, aneuploidy and MYC could be used to distinguish HGD/EAC from non-dysplastic BE (c statistic 0.91). Moreover, P53, MYC, and aneuploidy distinguished LGD from non-dysplastic BE (c statistic 0.66), while the combination of Her-2/neu, MYC, and 20Q distinguished HGD from LGD (c statistic 0.87). During prospective follow-up (median 45 months), 22 of the 428 patients progressed from no-dysplasia to HGD (n=13) or EAC (n=9). The overall rate of progression to HGD/EAC was 1.09% per patient-year. Univariable analysis revealed that P16 and aneuploidy were significantly associated with progression as well as the clinical variables age and maximum Barrett segment length. The remaining markers showed a non-significant tendency towards increased odds of progression. In a Cox proportional-hazards model, adjusted for clinical risk factors, the markers P16 and aneuploidy significantly predicted the risk of progression (HR 3.23; 95% CI 1.32-7.95). Patients positive for these markers had an annual progression risk of 1.85% versus 0.58% for the marker negative group (P=0.015).
Conclusion: Our data suggest that the 7-gene biomarker panel described here can aid in distinguishing dysplasia stages in patients with BE while the markers P16 and aneuploidy identified non-dysplastic BE patients at risk for the development of HGD/EAC.

SOX2 as a novel marker to predict neoplastic progression in Barrett's esophagus

S.H. van Olphen[1, 2], K. Biermann[2], F. Kastelein[1], B.E. Hansen[1], H.A. Stoop[2], M.C.W. Spaander[1], L.H.J. Looijenga[2], M.J. Bruno[1] on behalf of the ProBar study group, [1] Dept of Gastroenterology and Hepatology, Erasmus University Medical Center Rotterdam, The Netherlands, [2]Dept of Pathology, Erasmus University Medical Center Rotterdam, The Netherlands

The value of surveillance for patients with Barrett's esophagus (BE) based on histological diagnosis of low grade dysplasia (LGD) remains debated given the lack of discriminative power to stratify BE patients at high risk for neoplastic progression of those at low risk. The use of biomarkers in addition to histological assessment improves risk stratification and has the potential to improve cost-effectiveness of BE surveillance. SOX2 plays a pivotal role in the development of esophageal and gastric epithelium and is down regulated in intestinal metaplasia and gastric cancer. The aim of this study was to investigate the value of SOX2 in BE patients to predict neoplastic progression and to combine the results with our previously reported p53 immunohistochemical data within the same cohort. We conducted a case-control study within a large prospective cohort of 720 BE patients, with a total follow-up time of more than 5600 years. In total 44 BE patients with neoplastic progression defined as development of high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC)(cases) and 44 BE patients without neoplastic progression (controls) were selected and matched for age and gender. SOX2 protein was detected by immunohistochemistry in more than 3000 biopsies and was scored independently by two investigators blinded for long-term outcome. The results were combined with p53 immunohistochemical data. Hazard ratios (HRs) were calculated by Cox-regression models adjusted for age, gender, BE length and esophagitis. Normal BE epithelium showed homogeneous strong nuclear expression of SOX2, while expression of SOX2 was progressively lost in dysplastic epithelial cells. Loss of SOX2 expression was seen in 9.5% of biopsy series without dysplasia, in contrast to 37% of biopsy series with LGD and 70% of biopsy series with HGD or EAC. Multivariate analysis showed that loss of SOX2 expression (HR 3.3; 95% CI:1.6-6.6) and aberrant p53 expression (HR 4.5; 95% CI:2.8-8.9) were independent predictors for neoplastic progression, whereas presence of LGD was no longer predictive. The positive predictive value for neoplastic progression increased from 47% with histological diagnosis of LGD, to 83% with LGD and concurrent aberrant SOX2 expression, to 87% with LGD and concurrent aberrant p53 expression and to 91% with aberrant SOX2 and p53 expression.
Conclusion: Loss of SOX2 and aberrant p53 expression are independent predictors for neoplastic progression in patients with BE and more powerful than the histological diagnosis of LGD. SOX2 and p53 immunohistochemistry may be useful as a discriminative test to improve risk stratification of Barrett surveillance.

The influence of prophylactic proton pump inhibitor treatment on the development of symptomatic marginal ulceration: a historic cohort study

U.K. Coblijn[1], S.M.M. de Castro[1], S.M. Lagarde[2], S.D. Kuiken[3], B.A. van Wagensveld[1], [1]Sint Lucas Andreas Ziekenhuis, Dept of General Surgery, [2]Academic Medical Center Amsterdam, Dept of General Surgery, [3]Sint Lucas Andreas Ziekenhuis, Dept of Gastroenterology

Background and study aim: Marginal ulceration (MU) at the gastrojejunostomy (GJS) is a complication of laparoscopic Roux-en- Y gastric bypass surgery (LRYGB) for morbid obesity occurring in 1 to 16 % of the patients. In an attempt to minimize the incidence of this complication, some institutions prescribe prophylactic proton pump inhibitors (PPI). Aim of this study was to inventory the effectiveness of PPI prophylaxis in preventing MU. Methods: A prospective consecutive database of patients who underwent LRYGB from November 2007 till September 2012 in a single institution was retrospectively reviewed. Minimal follow up was 15 months. In August 2011 the postoperative protocol was altered and the prescription of Pantozol 40 mg® one dose daily was added from immediately postoperative till 6 months after surgery.Results: A total of 685 patients underwent LRYGB, of those patients 137 (20.0%) underwent revisional surgery. 341 (49.8) patients received PPI's according to protocol compared to 344 patients (50.2%) who were operated prior to August 2011 and did not. The groups were not comparable. In the group receiving PPI's there were less patients with diabetes, NSAID's and corticosteroids preoperatively were less used and also fewer patients suffered from esophagitis. Six (1.8%) versus 23 (6.7%) patients developed MU (p = 0.001). This remained statistical significant in multivariate analysis (p = 0.02). Of the six patients developing MU under PPI prophylaxis, two patients appeared not to use the PPI's, one patient used Diclofenac 50 mg® 1 - 3 times daily and one patient developed an ulcer next to the nasogastric feeding tube for prolonged enteral feeding after pouch perforation. In patients using PPI's the symptoms were less severe, no perforation due to MU occurred compared to five patients who presented with perforated MU in the non-PPI group. Conclusion: The standard prescription of PPI's after LRYGB decreases the incidence of marginal ulceration. Attention should be paid to patient compliance.

MLDS voordracht - A prospective study on intake of meat and heme-iron, nitrite, nitrate and nitrosamines as risk factors for adenocarcinoma of esophagus (EAC) and gastric cardia (GCA), esophageal squamous cell carcinoma (ESCC), and Barrett's esophagus (BE)

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Prospective data on red and processed meat, and associated constituents, in relation to risk of esophageal and gastric cancer subtypes are scarce. We aimed to investigate the influence of (red) meat intake (especially heme-iron) on the risk of EAC, BE and GCA, and of processed meat intake (esp.nitrite/nitrosamine) on ESCC. In the Netherlands Cohort Study, 120,852 individuals aged 55-69 years were recruited in 1986, and dietary intake was assessed using a 150-item food frequency questionnaire. After 16.3 years of follow-up, 107 ESCC, 145 EAC, 163 GCA, 489 gastric non-cardia adenocarcinomas (GNCA), and 3,923 subcohort members were included in a case-cohort analysis. Follow-up for BE occurrence consisted of record linkage to PALGA. Pathology reports were evaluated for more specific Barrett's histology with a pathologist. Out of 868 available incident BE cases after 16.3 years of follow-up, 646 met the strict definition of BE including intestinal metaplasia. Processed and red meat intake were positively associated with ESCC in men. Hazard ratios for highest vs. lowest quintile of processed and red meat were 3.47 (95% CI: 1.21-9.94; p for trend: 0.04) and 2.66 (95% CI: 0.94-7.48; p for trend: 0.06), respectively. No association was seen for EAC or gastric cancer subtypes, or for any of the 4 subtypes among women. Nitrite, N-nitrosodimethylamine (NDMA), and heme iron intake, as well as the index of endogenous NOC formation (ENOC) were positively associated with ESCC in men, while there was no association with EAC and GCA risk. There was a suggestive association between NDMA intake and GNCA risk, but intake of nitrate, nitrite, and heme iron and ENOC was not associated with GNCA risk. Interaction analyses for ESCC showed antagonism between red or processed meat intake and vegetable and fruit intake. There was also suggestive interaction between heme iron/ nitrite intake and vitamin C, but not chlorophyll intake. Among women, a positive association was found only between NDMA and ESCC. Taken together, the results suggest that both red meat and processed meat intake may increase the risk of ESCC but not EAC or gastric cancer subtypes. No association was found between red and processed meat, NDMA, nitrite and heme iron intake and the risk of BE. These results are consistent with the results obtained for EAC risk. We found an inverse association between nitrate intake and BE risk in men and a positive association in women. Similar associations were not seen for EAC. Although the number of women with EAC was very low, these results suggest that mechanisms underlying the association between nitrate intake and BE risk may be distinct from N-nitrosation.

MLDS voordracht - Human buccal epithelium acquires microbial hypo-responsiveness at birth, a role for secretory leukocyte protease inhibitor

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Repetitive interaction with microbial stimuli renders epithelial cells (EC) hyporesponsive to microbial stimulation. Previously, we have reported that buccal EC from a subset of pediatric Crohn's disease patients are not hyporesponsive and spontaneously released chemokines. We now aimed to identify kinetics and mechanisms of acquisition of hyporesponsiveness to microbial stimulation using primary human buccal epithelium. To this end buccal EC collected directly after birth and in later stages of life were investigated. Chemokine release and regulatory signaling pathways were studied using primary buccal EC and the buccal EC TR146. Findings were extended to the intestinal mucosa using murine model systems. Directly after birth primary human buccal EC spontaneously produced the chemokine CXCL-8 and were responsive to microbial stimuli. Within the first weeks of life these EC attained hyporesponsiveness, associated with inactivation of the NF-Ä¸B pathway and upregulation of the novel NF-Ä¸B inhibitor SLPI but no other known NF-Ä¸B inhibitors. SLPI protein was abundant in the nucleus of hyporesponsive buccal EC where it can directly bind to an NF-κB p65 consensus sequence in the promoter region of the CXCL-8 gene to block transcription. Knock-down of SLPI in buccal EC induced loss of hyporesponsiveness with increased NF-Ä¸B activation and subsequent chemokine release. This regulatory mechanism extended to the intestine, in particular the colon, as colonization of germfree mice elicited SLPI expression which was associated with reduced EC chemokine expression. We identify SLPI as a new player in acquisition of microbial hyporesponsiveness by buccal- and intestinal- epithelium in the first weeks after microbial colonization.

Impact of neoadjuvant chemoradiotherapy on prognostic factors for survival in patients with esophageal or junctional cancer

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Objective To compare prognostic factors for survival in patients with potentially curable esophageal or junctional cancer treated by primary surgery (S) or neoadjuvant chemoradiotherapy plus surgery (nCRT+S). Background data Prognostic factors for survival have mainly been identified in the era of primary esophagectomy, while nCRT+S is the current standard for potentially curable esophageal or junctional cancer. Methods We included patients with esophageal or junctional cancer, treated by S or nCRT+S (according to CROSS) between 1991 and 2011. Patients who did not undergo esophagectomy were excluded. We used univariable- and multivariable Cox regression to relate pretreatment and posttreatment clinicopathological predictors to overall survival. Interaction between predictors and treatment was tested. Results We included 698 patients in the S group and 329 in the nCRT+S group. The pretreatment characteristics age (HR per 10 years= 1.3[1.2-1.4]) and cT-stage (HR cT1-cT2 vs. cT3-cT4= 0.6[0.4-0.7]) were statistically significant predictors in the S group, while cN-stage (HR cN0 vs. cN1= 0.6[0.4–0.8]) was the only significant predictor in the nCRT+S group. Of the posttreatment characteristics transhiatal resection (HR= 1.5[1.1–2.0]), radicality (HR R1-R2 vs. R0= 1.8[1.5–2.2]), pT-stage (HR pT1 vs. pT3-pT4= 0.5[0.3–0.7]; HR pT2 vs. pT3-pT4= 0.6[0.5–0.8] and pN-stage (HR pN0 vs. pN1= 0.6[0.4–0.7]; HR pN2-pN3 vs. pN1= 1.5[1.1–1.8]) were significant predictors for survival in the S group. In the nCRT+S group only pN-stage (HR pN0 vs. pN1= 0.6[0.4–0.9]; HR pN2-3 vs. pN1= 2.2(1.3–3.8)) was a significant predictor. The prognostic effect of cN-stage (p-interaction=0.02) and radicality (p-interaction=0.04) differed significantly between treatment groups. Conclusions The addition of nCRT to surgery significantly increases the prognostic value of clinical N-stage and significantly reduces the value of radicality. Clinical- and pathological N-stage are the most important predictors for survival in patients with potentially curable esophageal or junctional cancer treated by neoadjuvant chemoradio-therapy plus surgery.

Palliative care of esophageal cancer in the Netherlands: determinants associated with treatment decisions

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BackgroundOver 50% of patients with esophageal cancer present with incurable disease. Although various palliative treatment modalities are currently available, the optimal therapeutic approach is not well defined. The aim of this study was to assess the types of initial treatment in patients with esophageal cancer, who were not eligible to undergo a surgical resection, and to identify factors associated with treatment decisions. Methods. We performed a retrospective cohort study of all patients diagnosed with stage III or IV carcinoma of the esophagus or esophagogastric junction as registered by the Netherlands Cancer Registry (NCR) in the region of Utrecht (2001-2010). Patients who underwent esophagectomy were excluded. Data were obtained from the NCR and medical records of 7 participating hospitals. Initial treatment options were compared for disease stages and hospitals. Multivariable logistic regression analysis was performed to identify independent determinants of treatment decisions. ResultsA total of 736 patients were included and underwent the following treatments: best supportive care (21%), stent placement (19%), chemotherapy (18%), external beam radiotherapy (EBRT) (16%), a combination of brachytherapy with EBRT (6%), brachytherapy (6%), a combination of chemotherapy with EBRT (5%), or other therapies (9%). Initial treatment varied significantly between disease stage ($p<0.01$) and hospital of diagnosis ($p<0.01$). Several independent determinants for initial treatment decisions were identified. Hospital of diagnosis was associated with stent placement, with odds being different between hospitals (odds ratio [OR] 0.18, 95% confidence interval [CI] 0.06-0.54). Tumor histology was associated with chemotherapy, with patients with squamous cell carcinoma being less likely treated with chemotherapy compared to adenocarcinoma (OR 0.27, 95%-CI 0.09-0.79). Tumor localization was associated with EBRT, with odds being higher in patients with a tumor localized in the middle third compared to the lower third of the esophagus (OR 4.17, 95% CI 1.60-10.89).
Conclusion. Initial palliative treatment of esophageal carcinoma varies considerably between disease stages, tumor histology and localization, and hospitals. In order to overcome this variation, a web-based decision tool is currently being developed to assist physicians in making standardized palliative treatment decisions, based on available clinical evidence supplemented by expert opinion.

GATA6 expression in Barrett's metaplasia development and progression towards malignancy

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Barrett's metaplasia is a premalignant condition characterized by the presence of columnar metaplastic epithelium in the esophagus. Barrett's metaplasia can progress towards esophageal adenocarcinoma (EAC) through a metaplasia-dysplasia-carcinoma sequence, but the underlying mechanisms are poorly understood. The transcription factor GATA6 is known to be involved in columnar differentiation and proliferation. GATA6 gene amplification was recently linked with poor survival in EAC. Our aim was to investigate the expression pattern of GATA6 in Barrett's metaplasia development and progression towards EAC and to correlate GATA6 expression to survival outcome in EAC. We studied GATA6 expression in a total of 136 patient tissue samples containing normal squamous esophageal epithelium, metaplasia, dysplasia and EAC and a tissue microarray containing tumor samples from 92 EAC patients. All samples were stained with a polyclonal antibody against GATA6 and a subset of samples was also stained with a monoclonal antibody against KI-67. GATA6 expression in EAC patients was related to clinicopathological variables, Overall Survival (OS) and Disease Free Survival (DFS). The percentage of GATA6-positive cells was low in squamous epithelium but increased progressively during BE development and progression towards malignancy. GATA6 expression partially overlapped with KI-67, suggesting a role for GATA6 in proliferation. However, in our cohort GATA6 expression was not associated with OS or DFS in EAC patients ($p=0.599$ and $p=0.700$ respectively)

Clinicopathological characteristics of pancreatic resection specimens of inherited/ familial versus sporadic pancreatic ductal adenocarcinoma

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There is a growing interest towards pancreatic cancer screening in individuals with an increased inherited or familial risk for this disease. When designing screening programs aiming to identify high-risk lesions for early resection, knowledge of the pathology of the disease is essential. In this current study we focus on the clinicopathological characteristics of pancreatic resection specimens of patients with inherited or familial pancreatic cancer in comparison to sporadic cases.Pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) were quantified in surgical resection specimens of patients with inherited/familial pancreatic cancer and patients with sporadic pancreatic cancer. Inherited/familial pancreatic cancer was defined as patients with at least one first degree relative with pancreatic cancer and/or carriers of a pancreatic cancer prone gene mutation. Pancreatectomy specimens were evaluated from 16 patients with inherited/familial PDAC (mean age 63, SD 8.9) and 19 patients with sporadic PDAC (mean age 69, SD 8.9). The overall density of all precursor lesions was 0.48 for the inherited/familial group and 0.33 for the sporadic group (p=0.32). PanIN lesions were the most common precursor lesions for both groups, IPMNs were seldom detected. A significant difference was observed between the mean number of precursor lesions (9.3 vs. 2.7, p=0.04) and the density of high-grade precursor lesions (0.05 vs 0.01, p=0.05). The number of patients in whom at least two high-grade precursors were detected was significantly higher in the inherited/familial group. More patients within the inherited/familial group had PanIN-3 lesions and the number of PanIN-3 lesions found in these patients was significantly higher compared to the sporadic group. Furthermore, in significantly more patients within this group multiple PanIN lesions were detected.
Conclusion This study shows that the number and density of high-grade precursor lesions are significantly higher in patients with inherited or familial PDAC. Since these high-grade precursor lesions are key targets for early detection, our findings have important implications within the context of screening/surveillance of individuals at high risk for developing PDAC.

Psychological burden of repeated pancreatic surveillance in high risk individuals for pancreatic cancer

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Pancreatic cancer (PC) is one of the most fatal malignancies with a median survival of <6 months. There is great interest in PC surveillance for high risk individuals to detect PC or precursor lesions in an earlier, potentially curable stage. Studies assessing the feasibility of such PC surveillance programs have not addressed the psychological burden for participants. The aim of this ongoing, prospective study is therefore to evaluate the psychological burden of repeated pancreatic surveillance of individuals at genetically high risk to develop PC. Individuals with a lifetime risk of developing PC>10%, who are offered yearly pancreatic surveillance with MRI and endoscopic ultrasound (EUS) in a Dutch ongoing prospective multicenter cohort study (FPC-study), were invited to complete a questionnaire each year to assess their experience with MRI/EUS, and their psychological distress (assessed with the Cancer Worry Scale (CWS) and the Hospital Anxiety and Depression Scale (HADS)). The questionnaires were sent after intake for participation but before the first MRI and EUS (T1), after the first MRI and EUS (T2), and after the MRI and EUS one (T3), two (T4) and three years (T5) after intake. A total of 134 out of 152 individuals (88%) returned one or more completed questionnaires (n= 69, 66, 108, 85 and 51 at T1,T2,T3,T4 and T5 respectively; response-rate varying between 79-94% per assessment). An average of 90% experienced the MRI as 'not' or 'a little' burdensome (88%, 91%, 90% and 92% at T2,T3,T4 and T5 respectively) vs. an average of 91% in case of an EUS (89%, 92%, 94% and 86% at T2,T3,T4 and T5 respectively). The percentage of individuals who dreaded a next MRI was low (5%, 5%, 2% and 0% at T2,T3,T4 and T5 respectively), as well as the percentage of individuals who dreaded a next EUS (3%, 7%, 4% and 6%). The mean CWS-score (12.8) remained stable and low as surveillance progressed. An average of 7% showed clinical relevant anxiety levels (HADS-A-score ≥11; 3%, 8%, 6%, 6% and 10% at T1,T2,T3,T4 and T5 respectively) and an average of 5% showed clinical relevant depression levels (HADS-D-score ≥11; 4%, 2%, 5%, 7% and 4% at T1,T2,T3,T4 and T5 respectively).

Conclusion: The psychological burden of repeated pancreatic surveillance seems tolerable with an average of >90% of high risk individuals experiencing no or little burden of the yearly MRI and EUS. Participants also have limited worries about cancer and the percentage of individuals with clinical relevant levels of anxiety and depression is comparable to that of the general population. Therefore, from a psychological point of view, yearly pancreatic surveillance of high risk individuals seems feasible.

Structural variant breakpoint detection in advanced colorectal cancer

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Development of colorectal cancer (CRC) is accompanied by genomic alterations that drive tumor initiation and progression. Gains and losses of large chromosome segments result in DNA copy number alterations and subsequently quantitative changes in mRNA and protein expression levels. Interestingly, the accompanying chromosome breakpoints represent structural variants (SV) that may affect gene architecture and thereby normal gene function. The aim of this study was to identify recurrent SV breakpoints in advanced CRC. Previously a series of 352 advanced CRC samples from CAIRO and CAIRO2 clinical studies [Koopman et al. Lancet 2007; Tol et al. N Engl J Med 2009] was characterized for genome-wide DNA copy number alterations. DNA from formalin-fixed paraffin-embedded (FFPE) tumor and patient-matched normal tissue was subjected to high-resolution array-Comparative Genomic Hybridization (Agilent 180K arrays). Using these data, we now determined the prevalence of recurrent breakpoints in genes in CRC by computational analysis. In addition, multiplexed amplicon analysis involving 48 cancer-related genes (Illumina TruSeq Amplicon Cancer Panel) was applied to determine mutation frequencies. Multi-Dendrix was used to identify modules of (mutually exclusively mutated) cancer driver genes. We identified 748 recurrent SV breakpoints in genes (FDR<0.1). The highest frequency of recurrent breakpoints was detected in MACROD2, in up to ~40% of CRC samples. Patients with a breakpoint in MACROD2 tend to have a better median overall survival of 20.4 months versus 15.6 months (p=0.08). Most recurrent breakpoints occurred in less than 5% of all tumors, and have not been reported before in CRC. Mutation frequencies in APC, TP53 and KRAS were conform expectations (60%, 58%, and 48%, respectively). Multi-Dendrix analysis revealed modules of cancer driver genes that included both the commonly mutated CRC cancer genes as well as genes with recurrent breakpoints, suggesting that several of the SV breakpoint genes are candidate drivers of the carcinogenic process. Conclusions: We were able to pinpoint the prevalence of 748 recurrent SV breakpoint regions in genes using array-CGH data from 352 CRC samples. Moreover, our studies revealed several breakpoints in genes that are mutually exclusive with the commonly mutated APC, KRAS, and TP53 genes, and therefore represent novel candidate cancer driver genes. Further studies are required to investigate their functional and clinical significance.

Feasibility of adjuvant laparoscopic hyperthermic intraperitoneal chemotherapy in a short stay setting in patients with colorectal cancer at high risk of peritoneal carcinomatosis

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Background: Treatment of clinically manifest peritoneal carcinomatosis (PC) of colorectal cancer (CRC) origin is relatively ineffective and often associated with significant morbidity. This raises the question whether we should focus on prevention of the development of PC. We determined the feasibility of adjuvant laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) in a short stay setting.Methods: A prospective single centre pilot study was conducted between January 2011 and July 2012. Ten patients at risk of developing PC of CRC origin were included. Risk factors were defined as pT4 tumours, (resected) local peritoneal nodules in the close proximity of the primary tumour, primary tumour presenting with obstruction and/or perforation, positive cytology in peritoneal lavage, ovarian metastasis or omental metastasis. A laparoscopic HIPEC procedure with Mitomycin-C of 90 minutes was intentionally performed at a maximum of 8 weeks after resection of the primary tumour, followed by routine systemic chemo-therapy as soon as possible. Laparoscopic HIPEC was considered feasible if postoperative hospital stay was three days or shorter in six patients, and if a maximum of one conversion and one re-admission occurred within 30 days. Intervals are presented as medians with interquartile range (IQR).Results: HIPEC was performed after 6 weeks (IQR 3-9 weeks). Postoperatively, one patient was admitted for three days, four patients for two days and five patients were discharged at day one. Laparoscopic adhesiolysis resulted in small bowel injury in one patient, but no conversion to open surgery and no postoperative complications were observed. One patient was readmitted within 30 days due to a clostridium infection. No port-site infection, intra-abdominal abscess, pulmonary complications, thrombo-embolic events, delayed gastric emptying or hematologic toxicity occurred. Follow up of patients was 13 months (IQR 10-26). Patients started with systemic treatment 9 weeks (IQR 7-10) after initial surgery which corresponds to 3 weeks (IQR 2-6) after HIPEC. One patient refused adjuvant systemic chemotherapy and was lost to follow up. None of the other patients had peritoneal or distant metastasis at the last date of follow-up.
Conclusion: The necessity of adhesiolysis determines the complexity of the laparoscopic HIPEC procedure and requires an operating team with experience in minimally invasive abdominal surgery. However, adjuvant laparoscopic HIPEC appeared to be feasible in a short stay setting based on this small pilot study. The next step is to determine which patients to select as candidates and to determine the oncological effectiveness of adjuvant HIPEC.

Urological procedures in patients with peritoneal carcinomatosis of colorectal cancer treated with HIPEC: Morbidity and survival analysis

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The goal of this study was to investigate whether cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a feasible and effective option in patients with urological involvement of peritoneal carcinomatosis of colorectal cancer. The characteristics of patients with peritoneal disseminated colorectal cancer treated with CRS+HIPEC between April 2005 and June 2013 in two tertiary referral centres were analyzed. Postoperative complications were graded according to Clavien-Dindo. Odds ratios were formed using logistic regression for the development of postoperative complications. For survival a Kaplan-Meier survival analysis was performed. In total 267 patients were treated for histological proven peritoneal carcinomatosis of colorectal cancer with CRS+HIPEC. Forty-one patients (15%) had an associated urological procedure during cytoreduction. In 14 patients the resection involved the ureter and in 27 patients the resection involved the bladder. The ureteral procedures consisted of partial ureteral resection in 13 patients and nephrectomy in one patient. Partial cystectomy was performed in 22 patients, and complete cystectomy with urinary diversion according to Bricker in 5 patients. At a median follow-up of 26.7 months, 160 patients (60%) were alive. The overall median survival was 31.9 months. There was no significant difference between the overall survival following CRS+HIPEC in these groups (median survival: 32.0 versus 26.9 months, P=0.48). In patients with an associated urological procedure during CRS+HIPEC, severe complications (grade≥3) occurred in 18 patients (44%), compared to 20% in patients without an associated urological resection (OR 3.06, 95%-CI: 1.53 - 6.15, P=0.002). In patients with an associated urological procedure, the most frequent complications were gastrointestinal leakage (n=9) or intra-abdominal abscess formation (n=5). In univariate analysis, in addition to an urological procedure, the following variables were significantly correlated to severe postoperative complications, regional PC score (OR 1.22, 95%-CI: 1.00 - 1.48, P=0.05), intraoperative blood loss (OR 1.36, 95%-CI: 1.05 - 1.78, P=0.02), operation duration in hours (OR 1.45, 95%-CI: 1.20 - 1.76, P<0.001). In multivariate analysis, only operation duration was significantly correlated to severe postoperative complications (OR 1.39, 95%-CI: 1.08 - 1.78, P=0.01)

Conclusions: CRS+HIPEC in patients requiring an urological resection during cytoreduction is a feasible and effective treatment option. However, severe complications are prevalent, which are mostly correlated to the extent of the peritoneal spread.

Cytoreduction and hyperthermic intraperitoneal chemotherapy: a feasible and effective option for colorectal cancer patients after emergency surgery in the presence of peritoneal carcinomatosis

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Background: Patients presenting with acute symptoms (e.g. obstruction or perforation) of colorectal cancer requiring emergency surgery are known to have an unfavourable long-term oncological outcome. At least 5% of CRC patients will also be diagnosed with peritoneal carcinomatosis (PC). When both of these factors are present, further treatment with curative intent may seem futile. Therefore, the aim of the current study was to investigate the feasibility and effectiveness of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal cancer patients who previously had emergency surgery in the presence of peritoneal carcinomatosis (PC). Methods: All patients with synchronous peritoneal metastasis of colorectal origin referred to two tertiary referal centers between April 2005 and June 2013 were included in this study. Operative, post-operative and survival details were compared between patients presenting with acute symptoms and those presenting in an elective setting.Results: In total, 178 patients with synchronous PC were referred to evaluate the possibility of CRS+HIPEC of which 127 underwent cytoreductive surgery and HIPEC. Among those, 32 (25.2%) initially presented with acute symptoms requiring emergency surgery. Acute presentation did not result in a longer interval between the initial operation and HIPEC (2.3 vs. 2.1 months, P=0.41). When comparing operative outcomes, no significant differences were found in blood loss (P=0.37), operation time (P=0.25) or completeness of cytoreduction. Also, complication rates, degree and types of complication did not differ between the groups. Five-year survival rate was 48% for emergency presentation compared to 47% in the elective group for patients treated with CRS+HIPEC (P=0.79).
Conclusion: This study shows that CRS and HIPEC may be performed safely in PC-patients of colorectal origin presenting with acute symptoms requiring emergency surgery. More importantly, the five-year survival rate in these patients is equal to elective cases and should be regarded as promising. Therefore, treatment with curative intent should also be considered in these patients.

Oncological follow up of the Stent-In 2 trial: cancer recurrence after curative treatment of malignant colonic obstruction

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Background: The Stent-in-2 trial randomized patients with acute malignant colonic obstructions between treatment with endoscopic stent as a bridge to elective surgery and emergency surgery. The rate of clinical and subclinical stent related tumour perforations was unexpectedly high. Potential oncological consequences of such (sub)clinical perforations are not clear. Aims & Methods: We analysed the risk of cancer recurrence after endoscopic stenting compared to emergency surgery for acute malignant colonic obstructions. Medical charts from eligible patients of the Stent-in-2 trial (n=97), with proven malignancy of the obstructing tumour and potential curable disease (n=58), were reviewed. Data was collected about adjuvant treatment, cancer recurrence and survival. We calculated the 5 year overall and locoregional recurrence rate and used a competing risk analysis to analyze differences in the cumulative incidence of recurrence. Patients in the stent group with a (sub)clinical perforation (n=6) were identified for a subgroup analysis. Results: Emergency surgery was performed in 32 (55%) patients and endoscopic stenting as a bridge to surgery in 26 (45%) patients. Patient and tumour characteristics and the use of adjuvant chemotherapy were comparable between the two groups. The median follow up was 38 months (IQR 18-44) for the emergency surgery group and 36 months (IQR 34- 49) for the stent group. The 5 year overall recurrence rate was 25% (n=8) and 42% (n=11), respectively (p=0.027). The locoregional recurrence rate was 9% (n=3) and 19% (n=5), respectively (p=0.052). The cumulative incidence of overall recurrences in patients with a (sub)clinical stent related perforation was 83% [CI95% 58-100] which was significantly increased compared to emergency surgery and non perforated patients from the stent group (26% [CI95% 14-47], 34% [CI95% 18-65], respectively, p = 0.0072) (figure 1). The cumulative incidence of locoregional recurrences within 5 years was increased as well (50% [CI95% 22-100], 11% [CI95% 3-41], 10 [CI95% 3-28], respectively, p = 0.053).
Conclusion: Although the small number of patients in our study can be considered as a limitation, our results concern a prospective cohort with a low risk of allocation bias. Clinical and subclinical perforations after endoscopic stenting for malignant colonic obstructions seem to be associated with an increased risk of recurrent disease.

Metachronous colorectal cancers: the clinician at fault?

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Although a number of studies estimated the incidence rates of colorectal cancer (CRC) during post-CRC surveillance (i.e. metachronous CRC, mCRC), the precise etiologic factors are unknown. We therefore explored the rates and potential etiology of mCRCs in a population-based study. We reviewed clinical and histopathology records from all patients diagnosed with CRC at three large-volume (one university and two non-university) hospitals in South-Limburg, from 2001 through 2010. We employed clinical charts, the national pathology database (PALGA) and the Netherlands Cancer Registry. Patients with hereditary forms of CRC or inflammatory bowel disease were excluded. We defined mCRCs as second primary colorectal adenocarcinomas, diagnosed at least 6 months after the primary CRC. We characterized the CRCs according to location, size, shape and clinical stage. Using a modified algorithm for ascribing the potential etiology, we classified the mCRCs into cancers due to non-compliance with surveillance recommendations, inadequate examination (incomeplete or suboptimal bowel prep), incomplete resection (CRC in same segment as previous advanced adenoma), missed lesions (CRCs found <36 months after a colonoscopy; or large/advanced stage CRCs found after >36 months), and newly developed cancers (small/early stage CRCs found >36 months after a colonoscopy) [Pabby et al, Gastrointest Endosc, 2005].We included a total of 5,157 CRC patients with 5,357 CRCs (mean age 70.0 yrs; 53.7% males). Of these, 93 (1.8%) patients with 98 mCRCs were examined (mean age at index CRC diagnosis: 67.3 yrs, range 36-88). Metachronous CRCs were diagnosed on average (range) 81 (7-356) months after the initial CRC diagnosis, of which 40.8% were diagnosed within 3 years. Of the mCRCs, 43.0% were attributable to non-compliance with surveillance guidelines, 3.2% to inadequate examination, 5.4% to incompletely resected advanced lesions, 43.0% to missed lesions, and 5.4% to newly developed cancers. Logistic regression analyses, adjusting for age and gender showed that mCRCs were significantly smaller in size (OR 0.8, 95%CI 0.7-0.9) and had more often a flat macroscopic appearance (OR 1.8, 95%CI 1.2-2.7) than sporadic CRCs. No significant differences were found between mCRCs and sporadic CRCs with regard to location and stage of tumor at the time of diagnosis. Similar rates of mCRCs were found across hospitals.
Conclusions: In our experience, mCRCs accounted for 1.8% of all CRCs and the vast majority could be explained by missed lesions or non-compliance with surveillance recommendations. Our findings highlight potential targets for quality improvements in post-CRC surveillance by colonoscopy.

Computer assisted instruction before colonoscopy is as effective as nurse counselling, a controlled trial

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Background. Better patient education prior to colonoscopy improves adherence to instructions for bowel preparation and probably leads to cleaner colons. We hypothesized that computer assisted instruction (CAI) supported by video and 3D animations improves the effectiveness of nurse counselling, with potential operational advantages. Aim. To assess the effectiveness of CAI for patient education prior to colonoscopy regarding bowel cleanliness and patient knowledge, comfort and anxiety. Methods. We included patients >18 years referred for colonoscopy in a general teaching hospital in the Netherlands. Exclusion criteria were illiteracy in Dutch and audiovisual handicaps. Patients were divided into two consecutive groups, one receiving nurse counselling and one receiving CAI followed by a brief nurse contact shortly before colonoscopy. The CAI was reviewed by expert endoscopists. For the main outcome measure, cleanliness of the colon during examination, endoscopists measured the Ottawa Bowel Preparation Scale (OBPS) and the Boston Bowel Preparation Scale (BBPS). We assessed patient anxiety, patient comfort and general information using three questionnaires validated by expert consensus, which were issued after counselling or CAI and shortly before and after colonoscopy. We assessed knowledge of information provided earlier through a pre-colonoscopy test. Statistical analyses included Mann-Whitney. Results. We included 385 patients, 197 receiving nurse counselling and 188 receiving CAI. Overall response rates for the three patient questionnaires were 99%, 76.4% and 69.9% respectively. Of the endoscopists, 60.8% returned a questionnaire. Base characteristics were similarly distributed among groups. Bowel cleanliness did not differ significantly: on the OBPS, the counselling group scored 6.07 (SD 2.53) and the CAI group 5.80 (SD 2.90), and on the BBPS the scores were 6.54 (SD 1.69) and 6.42 (SD 1.62) respectively. Anxiety scores did not differ significantly. Patient comfort scores were significantly lower after CAI only, but became significantly higher after a brief nurse contact shortly before colonoscopy. Knowledge scores were similar in both groups, with 7.08 (SD 1.17) and 7.31 (SD 1.11).
Conclusion. CAI is a safe and practical modality for instructing patients before colonoscopy. This study found no difference in bowel cleanliness and patient knowledge after nurse counselling or CAI. Since brief personal contact yielded significantly better patient comfort scores, we recommend the combination of CAI with a brief nurse contact for daily practice.

Implementing chromoendoscopy for surveillance in inflammatory bowel disease does not increase dysplasia detection compared to conventional colonoscopy with random biopsies: a retrospective study

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Randomized trials showed that chromoendoscopy is superior to white light endoscopy (WLE) with random biopsy sampling for dysplasia detection in patients with inflammatory bowel disease (IBD). Whether implementing chromoendoscopy can indeed increase dysplasia detection in clinical practice is currently unknown. Patients with ulcerative colitis (UC) or Crohn's disease (CD) undergoing regular surveillance between January 2000 and November 2013 in three referral centers were identified using the patients' medical records. In the past, surveillance was performed with WLE and random biopsies every 10 cm. In recent years, high-definition chromoendoscopy was implemented in all three centers using segmental pancolonic spraying of methylene blue 0.1% or indigo carmine 0.3% with targeted biopsies of suspicious lesions only. All surveillance procedures during the study period were performed by or under close supervision of experienced gastroenterologists in all three centers.The endoscopy and pathology reports were reviewed to identify which surveillance method was used and the number of lesions with dysplasia was compared between the chromoendoscopy and WLE + random biopsy procedures. Procedures in which bowel preparation was deemed inadequate or in which the cecum was not reached were excluded in both groups. In all, 443 colonoscopies in 403 patients (64% UC) were performed using chromoendoscopy and 1950 colonoscopies (67% UC) in 870 patients using WLE with random biopsies. There were no significant differences for the known risk factors for IBD-associated CRC including gender, age, type and duration of IBD, disease extent, concomitant primary sclerosing cholangitis and presence of post-inflammatory polyps between the chromoendoscopy and WLE + random biopsy group (all p>0.05). In the chromo-endoscopy group, dysplasia was detected during 48 surveillance procedures (11%), compared to 216 procedures (11%) in the WLE + random biopsy group (p=0.90). Between the three centers, dysplasia detection rate was comparable (11% vs 10% vs 12% respectively, p=0.31). Targeted biopsies yielded 62 dysplastic lesions in 48 colonoscopies (11%) in the chromoendoscopy group, which was comparable to the 249 dysplastic lesions in 184 colonoscopies (9%) using targeted biopsies in the WLE + random biopsy group (p=0.30). Random biopsies yielded an additional 32 colonoscopies (2%) with dysplasia in the WLE + random biopsy group.
Conclusion: Despite compelling evidence from randomized trials, implementation of chromoendoscopy for IBD surveillance did not increase dysplasia detection compared to the conventional random biopsy protocol in clinical practice.

Low inter-observer agreement among endoscopist in differentiating dysplastic from non-dysplastic lesions encountered during colitis surveillance

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Introduction: During endoscopic surveillance in patients with longstanding colitis a variety of lesions can be encountered. Differentiation between dysplastic, especially low grade dysplasia, and non-dysplastic lesions can be challenging, but the accuracy of endoscopic differentiation has never been objectified. Methods: We assessed the inter-observer agreement among gastroenterologists in differentiating low grade dysplastic from non-dysplastic lesions. An on questionnaire was constructed containing 30 cases. For each case, a short medical history was given and an endoscopic image of a lesion found during surveillance employing chromoendoscopy was shown. Ten cases contained low-grade dysplasia and 20 cases contained non-dysplastic lesions. The participants were asked to classify each lesion as dysplastic, with the subcategories sporadic adenoma, adenoma-like DALM or non-adenoma-like DALM, or as non-dysplastic with the subcategories normal mucosa, inflammation, post-inflammatory polyp or hyperplastic polyp. Referral center gastroenterologists who performed at least 100 surveillance colonoscopies were classified as experts, the remaining endoscopists were classified as non-experts, including non-academic gastroenterologists and fellows in training.The inter-observer agreement for the differentiation between dysplastic lesions from non-dysplastic lesions and the subtypes was calculated using Fleis Kappa. The sensitivity and specificity was assessed, using histopathology as reference standard. Results: In total, 17 endoscopists, 8 experts and 9 non-experts, assessed all 30 cases. The overall inter-observer agreement in differentiating between dysplastic and non-dysplastic lesions was fair 0.24 (95% CI 0.21-0.27); for experts 0.28 (95% CI 0.21-0.35) and for non-experts 0.22 (95% CI 0.17-0.28). The overall inter-observer agreement for differentiating between subtypes was fair 0.21 (95% CI 0.20 - 0.22); for experts poor 0.19 (95% CI 0.17 - 0.22) and non-expert fair 0.23 (95% CI 0.21 - 0.25). The overall sensitivity and specificity for identifying neoplasia were 76% (95% CI 70-82) and 51% (95% CI 46-56), respectively. Experts showed a sensitivity of 79% (95% CI 69-86) versus 74% (95% CI 65-82, p=0.44) for non-experts whereas the specificity was 57% (95% CI 49-64) for experts versus 46% (95% CI 38-53, p=0.04) for non-experts. Conclusion: Endoscopists, both experts and non-experts, cannot reliably differentiate between neoplastic and non-neoplastic lesions. This emphasizes the value of pathological assessment of all lesions encountered during chromoendoscopic colitis surveillance.

Decreased colorectal cancer risk in Dutch ulcerative colitis patients: results from a population based cohort

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Although many studies found an increased colorectal cancer (CRC) risk in ulcerative colitis (UC), this increase is less pronounced or absent in recent literature. A nationwide Danish study even demonstrates a protective effect in the last decade, possibly due to changes in IBD management. It is unclear whether risk estimates of extra-intestinal cancers (EIC) have also changed in the last decade. Here, we aim to confirm the protective effect in CRC, and to assess the risk of EICs in a Dutch population based cohort. As use of immunomodulators and anti-TNF rises, we also assess the risk of immunosuppression-related cancers (IRC). All IBD-SL patients diagnosed with UC between 1991 and 2011 were followed until 2012. Observed primary cancers were determined by scrutinizing all hospital records and the Dutch Pathology Database. Local incidence rates of cancers were derived from the Dutch Cancer Registry. Age- and sex-adjusted Standardized Cancer Incidence Ratio (SIR) were calculated for overall cancer, CRC, common EICs (i.e. breast, prostate and overall skin cancer) and IRCs (i.e. basal-cell carcinoma, melanoma and lymphoma). Confidence intervals were determined by Byar's approximation. In total, 1595 UC patients (54% male) were diagnosed between 1991 and 2011. Mean age at diagnosis and mean disease duration were 46.5 (SD 16.3) and 9.4 years (SD 5.9), respectively. The overall cancer risk in UC patients was similar to the normal population (SIR 0.89, 0.95%CI 0.75-1.04), but the risk was decreased for CRC (SIR 0.45, 0.95% 0.19-0.88). Furthermore, the risk for prostate cancer and overall skin cancer did not differ (SIR 1.22, 0.95%CI 0.75-1.89, and SIR 1.14, 0.87-1.47, respectively), whereas the risk for breast cancer was decreased (SIR 0.28, 0.95%CI 0.14-0.51). The risk for IRCs (basal-cell carcinoma, melanoma and lymphoma) did not differ from the normal population.
Conclusion: We confirmed a decreased CRC risk in the UC patients of our population based cohort. We could not find an increased risk of IRC, despite frequent use of immunosuppressants (33%) in our cohort. Furthermore, no differences were found for overall cancer, prostate cancer and skin cancer risk, as compared to the normal population, whereas risk for breast cancer was clearly decreased. This may in part be explained by a decreased prevalence of lifestyle risk factors.

Incidence of interval colorectal cancer among inflammatory bowel disease patients enrolled in a colonoscopic surveillance program

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Patients with inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer (CRC) and are therefore advised to undergo colonoscopic surveillance. To study the effectiveness of this strategy, we determined the incidence of CRC after a negative surveillance colonoscopy (interval cancer). Patients with ulcerative colitis (UC) or Crohn's disease (CD) enrolled in a surveillance program were identified in seven centers using the patients' medical records. A colonoscopy was classified as surveillance when either random biopsies were sampled or chromoendoscopy with targeted biopsies was performed as stated in the colonoscopy report. Patients were followed from the date of first surveillance colonoscopy until the last surveillance colonoscopy, colectomy or diagnosis of CRC. Two definitions of interval cancer were used: a strict definition including advanced stage CRC (Dukes stage C or D) diagnosed within one year in patients with PSC or low-grade dysplasia, or two years in the remaining patients after a normal surveillance colonoscopy. For the second definition, early stage CRC diagnosed within the appropriate surveillance interval was also counted as interval cancer. A total of 1275 IBD patients (34% CD and 66% UC) were enrolled in a surveillance program and underwent 4319 surveillance colonoscopies during 6823 years of follow-up. CRC was diagnosed in 17 patients (1.3%), with an incidence of 2.5 per 1000 follow-up years. The median interval between the last surveillance colonoscopy and CRC diagnosis was 21 months (range 5 – 42 months). Advanced stage CRC was diagnosed within the appropriate surveillance interval in six patients (35%) and these were therefore classified as interval cancer. when including early stage CRC as well, three more cases of interval cancer were identified (nine in total, 53%). The remaining eight CRC cases were diagnosed after the appropriate surveillance interval, although all CRC's developed within five years after the last surveillance colonoscopy (range 21 – 42 months). Total number of biopsies, cecal intubation rate and prevalence of inadequate bowel preparation were similar when surveillance colonoscopies directly preceding the CRC diagnosis were compared with the surveillance colonoscopies of patients without CRC (all $p>0.05$).

Conclusion: The finding that the overall incidence of CRC among IBD patients enrolled in a surveillance program was low is reassuring. However, as one third of all CRC cases were interval cancers, further studies are needed to identify the group of IBD patients at high risk of developing CRC.

Faecal calprotectine does not differentiate between IBD and a juvenile polyp

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Objectives and study: Faecal calprotectin is commonly used as an initial screening test in patients with suspected IBD. Generally a cut off value above 50 µg/gr faeces is used, resulting in a 98% sensitivity for detecting IBD and a 44% specificity. Using a higher cut of value increases specificity, but reduces sensitivity, with a suggested optimal cut-of value of 300 µg/gr faeces. Only a small proportion of non-IBD patients are reported to have a faecal calprotectin above this value (Henderson et al, Am J Gastroenterol 2012). Our clinical impression was that patients with a juvenile polyp (JP) also frequently present with levels exceeding 300 µg/gr faeces. Therefore our aim was to investigate faecal calprotectin levels in patients with JP and compare these levels with patients with newly diagnosed IBD. Methods: Files of all patients who had a diagnostic endoscopy between January 2009 and August 2013 were studied. A diagnosis of JP or IBD was made based on histology. Faecal calprotectin for all patients with either JP or IBD was retrieved, if available. Results: Amongst the 2169 diagnostic endoscopies done in the study period a total of 37 patients with a juvenile polyp ((histological proven) were identified, and 77 patients with newly diagnosed IBD. Faecal calprotectin was determined in 19 of the patients with JP (mean level 1329 µg/gr, range <30-5250) and in 76 patients with IBD (mean level 3105 µg/gr; range <30-24013, P<0.001). All patients with IBD had a faecal calprotectin above 50 µg/gr faeces, and 18/19 patients with JP. A calprotectin above 300 µg/gr was found in 13/20 patients with JP and in 74/76 patients with IBD. Conclusions: Elevated faecal calprotectin levels are frequently found in patients with a juvenile polyp as well as in pediatric IBD. Levels of calprotectine do not help in differentiating these conditions. Henderson P, Casey A, Lawrence SJ, Kennedy NA, Kingstone K, Rogers P, Gillett PM, Wilson DC. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease. Am J Gastroenterol. 2012 Jun;107(6):941-9.

Fecal immunochemical testing results vary depending on characteristics of colonic lesions

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Most European colorectal cancer (CRC) screening programs are based on biennial fecal occult blood testing (FOBT). The fecal immunochemical test (FIT) is a quantitative test for haemoglobin. We hypothesized that the FIT result varies depending on the characteristics of the colonic lesions. 10.050 average risk persons aged between 50 and 75 years were invited to participate in three consecutive rounds of a biennial FIT based screening pilot in the Netherlands. Consenting participants performed a FIT (OC-Sensor, Eiken, Tokyo, Japan); those with a test result above 10 µg Hb/g feces (corresponding to 50 ngHb/ml buffer OC-Sensor) were considered positive and recommended to undergo colonoscopy. During colonoscopy all detected lesions were removed and sent for histopathology. We evaluated the mean FIT result and the association with characteristics of the most advanced lesion detected: histopathology, size, colorectal location and polyp morphology. In three rounds of FIT based screening, 877 participants had a positive test with a mean FIT-result of 74 µg Hb/g and underwent subsequent colonoscopy. In 226 participants (26%) no lesions were detected. Serrated lesions were found in 85 participants (10%) and non-advanced adenomas in 195 participants (22%). In 331 participants (38%) advanced adenomas were detected and 39 colorectal carcinomas (4%). FIT results differed significantly between subgroups of participants with different histopathology; higher values were observed in participants with advanced adenomas or carcinomas than in participants with no colonic lesions, non-advanced adenomas or serrated lesions ($p<0.001$). Also between polyp morphology subgroups the FIT results differed significantly, with higher values in pedunculated polyps than in flat and sessile lesions ($p<0.001$). FIT results also differed for size and location: participants with a polyp sized 10 mm or larger had a significantly higher FIT result than those with smaller polyps, and lesions located in the distal colon had a higher FIT value than those proximally located (both with a p- value <0.001). In a FIT based screening program, FIT results vary depending on the characteristics of the most advanced colonic lesion per participant. Participants with advanced lesions and carcinomas have a significantly higher mean FIT result than participants without any colorectal lesions; however participants with non-advanced lesions do not have higher FIT results than participants without lesions. This suggests that non-advanced lesions are coincidental findings which are not detected by FIT.

Synchronous/metachronous neoplasms predict the presence of lateral spreading tumors

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Lateral spreading tumors (LST) are challenging to recognize and resect endoscopically and a subset may progress more rapidly to cancer, indicating such lesions contribute to the occurrence of postcolonoscopy colorectal cancers. A comprehensive characterization of the clinical phenotype associated with presence of LSTs is presently lacking. In this large population-based study, we explored the incidence, clinical features and risk profile of patients with LSTs. We reviewed prospectively collected clinical, endoscopic and histopathology data from all patients who underwent an elective colonoscopy at our hospital from Feb 2008 to Feb 2012. We asked all participants to fill in a questionnaire regarding risk profiles (i.e. smoking, alcohol intake, BMI and aspirin use). Endoscopists (faculty and trainees) were previously trained in the recognition and detection of flat, depressed neoplasms, and serrated polyps. We defined a LST as a flat appearing neoplasm >10 mm in size. We excluded patients with hereditary CRC syndromes, inflammatory bowel disease or a history of colon resection. In total, 8039 patients undergoing colonoscopy for symptoms (84.6%), screening (6.7%) or surveillance (8.7%) were included. Of them 61.8% filled in the questionnaire. Overall, 224 LSTs in 180 patients were identified of which 78.1% were proximally located. Patients with LSTs were significantly older than those with any lesion (n=2746) (66.5 vs 63.9 yrs), and were more likely under surveillance at time of inclusion (21.1 vs 14.4%, age and gender adjusted OR: 1.6, 95% CI 1.1-2.3). Logistic regression analysis, adjusted for age and gender, showed that patients with LSTs had significantly more often adenomas (OR 1.5), advanced adenomas (OR 2.6) and sessile serrated adenomas/polyps (SSA/Ps) (OR 4.9), and also greater numbers of synchronous neoplasms (OR 1.1). Gender, smoking, alcohol intake, BMI and aspirin use did not differ significantly between groups. Of the 224 LSTs, 160 were of nongranular, 54 granular and 10 of unknown subtype. Histopathologic examination showed 34 hyperplastic polyps, 32 SSA/Ps, 140 adenomas, and 18 CRCs (8 TNM-stage I, 10 stage II-IV). Compared with polypoid neoplasms larger than 10 mm (n=964), LSTs contained significantly less often villous histology (28.6 vs 41.8%) and more often serrated histology (14.2 vs 4.0%).
Conclusion: In our experience, patients with LSTs accounted for 2.2% of this population, were older and had more often synchronous advanced adenomas and SSA/Ps. A pancolonic chromoendoscopy within 3-6 months after the initial examination may improve identification of LSTs and thereby augment the effectiveness of colonoscopy in cancer prevention.

Experience in over 150 patients with the EndoBarrier®/ duodenal jejunal bypass liner

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The EndoBarrier®/ duodenal-jejunal bypass liner is a novel endoscopic, non invasive, bariatric technique. The EndoBarrier® consists of a metal frame which is placed in the duodenal bulb with a 60cm impermeable fluoropolymer liner attached. This prevents contact between food in the proximal intestine, which supposedly induces weight loss and improves glucose control in type 2 diabetes. The aim of our study is to evaluate feasibility, safety and effects on overweight and diabetes of the EndoBarrier®. Inclusion criteria for EndoBarrier® placement were: age 18–65 years, BMI 28–45 kg/m^2, fasting plasma C-peptide >0.27 nmol/L, negative serum H. pylori test, and use of at least two different types of oral anti-diabetics or insulin. Patients using non-steroidal anti-inflammatory drugs or anticoagulant medication were excluded. The EndoBarrier® was explanted after three and six months in the first series and twelve months at present. Between October 2007 and December 2013, 165 patients underwent the EndoBarrier® implantation procedure of which 152 (92.1%) implantations were successful. In thirteen patients the device could not be placed because of anatomical difficulties or bulbar ulcerations. Up till now, forty patients with an intended implantation duration of one year, completed their follow-up. Body weight decreased from 106.1 ± 15.6kg to 95.7 ± 14.7kg (p= 0.000), BMI dropped from 34.4 ± 3.7kg/m^2 to 30.9 ± 3.8kg/m^2 (p= 0.000) and HbA1c decreased from 66 ± 15mmol/mmol to 62 ± 16mmol/mmol (p= 0.128). Nine of nineteen patients on insulin therapy were stopped with insulin (mean 64 IU; range 24 – 116) at time of explantation. Seven patients still received oral medication and two were converted to a GLP-1 analog. The additional ten patients decreased their insulin dosage (mean 56 IU; range 2 – 108). Fifteen (9.9%) complications were reported in the total group of 152 patients, including bleeding (n=7), mild pancreatitis (n=2), liver abscesses (n=1), perforation of the anchor (n=1), endoluminal obstruction (n=1), mucosal damage of esophagus during implantation (n=1) and esophageal rupture during explantation (n=2). In 16 (10.5%) patients the EndoBarrier® was removed early because of pain or discomfort.

Conclusions In our first experience, the EndoBarrier® is feasible and effective in the treatment of obesitas and diabetes. Serious complications may occur. Therefore we recommend dedicated teams to perform the procedures.

Long-term outcome of low perianal fistulas treated by fistulotomy

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Perianal fistulas still pose a challenge to surgical treatment. The majority of literature addresses the treatment of high perianal fistulas which are known for considerable recurrence rates and potential postoperative incontinence. Less is known regarding low perianal fistulas involving the lower one-third of the anal sphincter complex. Best treatment is considered to be a fistulotomy. The goal of this study was to evaluate the results of fistulotomy for low perianal fistulas in a multicentre setting retrospectively. All patients treated with a fistulotomy for a low perianal fistula in seven surgical centres between 2008 and September 2013 were evaluated. Data regarding closure of the fistula, incontinence, quality of life and sexual functioning was collected. All patients were contacted by telephone to evaluate closure of the fistula and were asked to fill in questionnaires regarding incontinence, quality of life and sexual functioning. Closure of the fistula was defined as a visibly closed wound without fistula openings and without discharge. In total 237 patients were included. Median age was 45 years (range 10 – 81). 166 patients were male (70.0%). 156 (65.8%) patients had a primary fistula, 76 (32.1%) had a recurrent fistula and in 5 patients (2.1%) the origin could not be identified. Median duration of follow-up was 33 months (ranging from 2 to 74). Data showed that the aetiology of the fistula was mostly cryptoglandular with 154 patients (65.0%). Median time until healing was 38 days (ranging from 6 to 380). A recurrence was seen in 40 (16.9%) cases. Median time until recurrence was 93 days (ranging from 7 – 666). The recurrence were treated with a seton in 4 (10%) patients, a seton + fistulotomy in 1 (2.5%) patient, a fistulotomy in 28 (70%) patients. Four (10%) patients were not treated and in 3 (2.5%) patients secondary treatment was unclear. Eighteen (45%) of these patients' with recurrent fistulas healed, 15 (37.5%) remained with a recurrent fistula, and in the remainder the result was unclear. Outcome regarding incontinence, quality of life and sexual functioning are still under determination.
Conclusions: Treatment of low perianal fistulas by fistulotomy shows a high primary closure rate of 83.1% and an even higher secondary closure rate of 90.7%. Treatment with a fistulotomy seems to be a good surgical intervention for low perianal fistulas, although the results of incontinence levels, quality of life and sexual functioning will have to be awaited.

Genome-wide association study in autoimmune hepatitis identifies risk variant in the SH2B3 region

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Background & Aims: Autoimmune hepatitis (AIH) is a rare autoimmune liver disease of unknown aetiology. In this study we sought to identify genetic variants that predispose to AIH using a genome wide association and replication study approach. Methods: We performed a genome-wide association study in 668 Dutch adult AIH type-1 patients and included 13,436 previously genotyped Dutch control subjects using the CytoSNP 12.0 platform. To confirm initial associations, we performed a replication analysis in an independent set of 466 German AIH cases and German 4,103 controls. Discovery and replication results were used in combined meta-analysis. We subsequently performed impution and association analysis of classical HLA genotypes in the discovery set. RESULTS: We identified a strong association in the MHC region at rs2187668 ($P = 1.7 \times 10^{-78}$). Imputation of the MHC region in the discovery cohort revealed HLA-DRB1*0301 ($P = 1.2 \times 10^{-48}$) as primary and HLA-DRB1*0401 (OR 2.3, $P = 6.2 \times 10^{-19}$) as secondary AIH susceptibility genes. In addition, we identified an association to SH2B3 (rs3184504, 12q24, $P = 9.8 \times 10^{-8}$) and a suggestive association to CARD10 (rs6000782, 22q13.1, $P = 4.2 \times 10^{-6}$). Strong inflation was found for SNPs associated with other immune mediated diseases ($\lambda_{AI} = 1.61$) but not for randomly selected SNPs ($\lambda_{MB} = 1.01$). Conclusions: We unequivocally established AIH as a complex genetic disorder with strong involvement of the MHC region and identified SH2B3 as a novel genetic risk locus for AIH. Our findings support a complex genetic basis for AIH pathogenesis and indicate that part of the genetic susceptibility overlaps with other immune-mediated diseases.

In vivo spectroscopy on tissues encountered during colorectal surgery

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The ability to visually distinguish vital anatomy is of great importance during colorectal surgery to prevent iatrogenic vascular or ureter injury. In particular during laparoscopy, when spatial perception from direct sight and haptic feedback from direct touch are absent, a reliable tool to enhance the visual contrast of these vital structures is desirable for more accurate intraoperative detection and preservation. Exploring the optical spectral range beyond the abilities of the naked human eye might offer a roadmap towards such a tool. Aerospace science already combines "in-flight" hyperspectral camera technology with "ground-truth" spectra recorded on the earth surface to create satellite images for e.g. agricultural purposes and military and homeland security applications. The present translational study is a first step in applying a similar approach in surgical procedures with the ultimate goal of obtaining tissue-specific contrast enhancement. Goal is to assess optical spectroscopic signatures for automatic enhancement of vital anatomy (mesenteric arteries and ureters) during colorectal surgery. We collected 263 in vivo spectra from 6 different tissue types (i.e. colon, mesenteric adipose tissue, muscle, mesenteric artery, mesenteric vein, and ureter) during open colorectal cancer resections. All data was acquired as a single point diffuse reflectance spectrum (350-1830 nm range, 1 nm resolution).Statistical analysis of all separate tissue spectra was applied to estimate distinctive features in these spectra enabling tissue-specific recognition. Distinctive spectral features (partly within wavelengths invisible to the naked human eye) were identified for artery- and ureter-specific contrast enhancement.
Conclusion: a first step towards using hyperspectral camera technology for intraoperative tissue-specific contrast enhancement was set.

The use of endoractor during laparoscopic colorectal surgery; a new solution? Pilot study

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Aim of the study Performing laparoscopic colorectal surgery of the distal colon and rectum, requires maintaining an adequate surgical field. Steep Trendelenburg position is a common used technique, but is associated with cardiac and pulmonary complications due to higher intra-thoracic pressure. Postoperative measures to prevent these complications are already implemented, however peri-operative measures can still be improved. A prospective pilot study is conducted in which the Endoractor®, a cellulose compressed sponge, is used. This device provides the possibility to keep the small intestines aside and reposition the patient in (nearly) horizontal position. This study focuses on the cardiac and pulmonary complications to support the hypothesis that there are less cardiac and pulmonary complications due to a less steep Trendelenburg position. Methods In the period from October 2012 until October 2013 in total 45 patients were prospectively included, who underwent a laparoscopic (low) anterior resection or rectum amputation treated peroperatively with the Endosponge®. Patients were historically matched to 45 patients who were treated according to the conventional method, in Trendelenburg position without the Endosponge®. During surgery a 100% cellulose compres–sed sponge (Endoractor®, Kawamoto Corps, Osaka, Japan) was inserted. The group treated with the sponge was compared to the conventionally treated group. Length of postoperative hospital admission, mortality rate and postoperative complications, notable decompensatio cordis and pneumonia, were registrated in both groups. ResultsThe sponge group developed less cardiac complications (1 decompensatio cordis) in contrast to the conventional group (3 decompensatio cordis, 1 myocardial infarction). Both groups showed no pulmonary compli–cations. The mean BMI in the sponge group was 24.6 kg/m^2, while the BMI in the conventional group was 21.3 kg/m^2. In the sponge group the mean age was 65,4 years (range 29-93 years), whereas the mean in the conventional group was 63,1 years (range 40-83 years). Patients who were treated with the sponge left the hospital earlier (5.4 days), compared to the conventional group (7 days). No patients died as a postoperative complication within 30 days or showed signs of anastomotic leakage.
Conclusion Introduction of this innovative device during laparoscopic colorectal surgery has shown fewer cardiac complications and a decrease of length of hospital admission. Regarding the results, the use of the Endoractor® has been a positive experience, though further research is necessary to validate these results.

Analysis of open-close HIPEC-procedure patients in peritoneal metastasis of colorectal origin

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Background: Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is currently the only curative intervention for peritoneal carcinomatosis of colorectal origin. It has been established that when disease presentation is to severe, performing this extensive operation will not result in survival gain and a palliative treatment is favorable. This study aimed to investigate which factors lead to poor presentation resulting in cancellation of the HIPEC-procedure. and to report on factors influencing survival. Methods: All consecutive patients with peritoneal carcinomatosis of colorectal origin who underwent exploratory surgery to determine whether cytoreduction and HIPEC was feasible were included in this study. All interventions took place in two tertiary referral centres between April 2005 and August 2013. Data was extracted from a prospective database, focussing on pre-operative patient characteristics, perioperative outcomes, palliative treatment and survival. Results: In total, 178 patients with synchronous PC were referred to evaluate the possibility of CRS+HIPEC of which 124 (69.7%) underwent CRS and HIPEC and 54 (30.3%) were labelled as open-close. The reason for discontinuing surgery was disease spread in 51.9%, irresectability of the primary tumor in 27.8% and extensive small bowel involvement in 11.1%. In a significant proportion of open-closed patients, T and N stage could not be determined prior to exploratory laparotomy. Also, more open-close patients had a primary tumor localized in the right colon (49.1.% vs 34.0 P=0.05). 5-year survival rate was 0% compared to 36% in those treated with CRS and HIPEC (P=0.00). Primary tumor resection had no effect on survival (p=0.380). Palliative adjuvant chemotherapy increased overall survival (p=0.026)
Conclusion: This study shows that the main reason for not being able to perform CRS + HIPEC is the extensiveness of the intraperitoneal spread, followed by an irresectable presentation of the primary tumor. Right colon and indeterminable T and N stage more often resulted in open-close procedures. More importantly, no strong predictors were found, marking the relevance of referral to a dedicated HIPEC centre to evaluate potential treatment options.

Transanal versus traditional laparoscopic total mesorectal excision for rectal carcinoma. A matched case control study

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Objective: To investigate the pathological quality of specimens after transanal total mesorectal excision (TME) and to compare these with specimens after traditional laparoscopic TME.Summary Background Data: After TME surgery, patients with an incomplete mesorectumhave an increased risk of local and overall recurrence. With the introduction of the laparoscopic TME, an improved quality of the specimen was expected. However, the quality-related results were comparable to the results after traditional open surgery. The transanal TME is a new technique in which the rectum is mobilised by using a single port and endoscopic instruments through the so called 'down to up' procedure. This new technique potentially leads to an improved specimen quality. Methods: This matched case control study compared the specimens of a cohort of consecutive patients who underwent a transanal TME with the specimens after traditional laparoscopic TME. The pathological quality of the mesorectum was determined by the definitions of Quirke as 'complete', 'nearly complete', or 'incomplete'. Results: From June 2012 until July 2013, 25 consecutive patients underwent a transanal TME because of a rectum carcinoma. Within the transanal TME group, 96% of the specimens had a complete mesorectum, while in the traditional laparoscopic group 72% was deemed complete ($p<0.05$). Other pathological characteristics, such as the circumferential resection margin, were comparable between the two groups.
Conclusions: Transanal TME appears associated with a significant higher rate of completeness of the mesorectum. Further studies are necessary to evaluate this novel technique.

Management of major perineal wound complications after abdominoperineal resection for malignant disease. A retrospective cohort study

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Abdominoperineal resection (APR) is one of the treatment modalities for distal rectal cancer. Perineal wound complications are a main problem after this type of surgery. Because the low amount of evidence on how to treat a complex infected perineal wound, decision-making on which therapy to start is still based on clinical perception. This study aimed to describe and compare the different kinds of management of the complex infected perineal wound after APR for malignant disease. Patients undergoing APR for malignant disease between 1st January 2007 and 31st December 2012 were identified. Patients' charts were studied retrospectively for perineal wound complications and its management. When treatment with wound dressings and irrigation was sufficient, wound infections were considered as minor. When more invasive therapy was necessary, wound infections were considered as a major complication. Duration of healing of the perineal wound was measured. Within the major perineal infected wounds, different kinds of management were described. In total 186 patients were identified. Minor and major perineal wound infections occurred in 84 (45.2%) and 37 (19.9%) patients respectively. Wound healing within 3 months occurred in 64.3% of patients with a minor perineal wound infection and in 35.1% of patients with a major infection. Specific management for major infected perineal wounds consisted of flap reconstruction (n = 2) or vacuum-assisted closure (VAC) therapy (n = 13). One of the patients treated with flap reconstruction developed a wound infection afterwards and needed reoperation. Time to wound healing did not differ between patients treated with or without VAC therapy. In conclusion a perineal wound infection is a major problem after APR for malignant disease and its treatment depends on surgeon's preferences. Prospective studies are warranted to investigate the effectiveness of VAC therapy and myocutaneous flap reconstructions compared to conservative treatment for the complex perineal infected wound. Furthermore the use of preventive methods, for example meshes, needs further investigation and might become more important in future surgery.

The detrimental effect of diclofenac on intestinal anastomotic healing depends on the location in the gut

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NSAIDs have been associated with intestinal anastomotic leakage in two retrospective studies and a review of randomized trials, but debate concerning this association remains. In animal experiments diclofenac causes leakage of anastomoses in the ileum, but not in the distal colon. The exact pathophysiological mechanism is still unknown. Apart from COX1 and COX2 inhibition, diclofenac alters intraluminal factors like bile and microflora, which might also affect anastomoses. In this experiment we studied the effects of diclofenac on anastomoses of the proximal colon, where morphology resembles the distal colon, but intraluminal content corresponds more to that of distal ileum.Ninety-five male Wistar rats were randomly allocated to 6 groups with an anastomosis (day 0) of either the ileum (IL), proximal colon (PC) or distal colon (DC). Group PC- (n=15) did not receive diclofenac. Groups IL+ (n=10), DC+ (n=10) and PC+ (n=30) all received diclofenac from day 0 until sacrifice on day 3. Groups PC1+ (n=15) and PC2+ (n=15) were given diclofenac from day 1-4 and from day 2-5 respectively. The primary outcome was anastomotic leakage. Secondary outcome was mechanical strength.In group PC+ 22 out of 30 anastomoses leaked. This was significantly more than in group DC+ (1/10; p=0.001) and group PC- (1/15; p<0.001)). All of the 10 anastomoses in group IL+ leaked. Delayed administration of diclofenac with one or two days resulted in a drop of leakage rates (10/15; p<0.743 and 6/15; p=0.050 respectively). Mean bursting pressures were correspondingly low in groups with higher leakage rates, with significant difference between group PC+ (68±9SEM mmHg) and PC2+ (206±11SEM mmHg; p<0.001). Breaking strength in group PC+ (0.50±0.06N) was higher than in group IL+ (0.10±0.05 N; p=0.004), but lower than group DC+ (1.16±0.11 N; p<0.001). It was the highest in group PC2+ (1.47±0.14N; p<0.001).
Conclusion. Diclofenac causes leakage of anastomoses in the rat ileum and proximal colon, but not in the distal colon. This suggests a role for the ileal and proximal colonic content in the pathophysiology of anastomotic leakage caused by diclofenac. The results add to the increasing evidence that caution should be taken using NSAIDs as perioperative analgesic in intestinal surgery. Future experiments should aim at delineating the role of the biliary metabolites of diclofenac and the influence of the gut microflora on anastomotic leakage.

Defunctioning ileostomy does not prevent anastomotic leaks after restorative proctocolectomy; a multicenter evaluation of clinical and surgical risk factors

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Anastomotic leakage (AL) is a serious complication after restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) that could lead to pelvic sepsis and ultimately to pouch failure. Previous studies have shown significantly decreased leak rates in diverted patients with less severe clinical consequences. The last decade, a trend has been seen towards more extensive medical treatment in IBD patients, leaving refractory patients in a worse condition when it comes to surgery. Since timely identification of high-risk patients could influence surgical decision-making and diminish the risk for complications, the aim of our study is to identify clinical and surgical parameters associated with AL and to analyse whether a defunctioning ileostomy should be considered as standard care in patients undergoing IPAA. In a retrospective study, 691 patients undergoing IPAA for IBD, dysplasia, or FAP were identified from prospectively maintained databases of three large IBD centres. The creation of an ileostomy was left at the discretion of the surgeon. AL was defined as any leak confirmed by either contrast extravasation on imaging or by re-laparotomy. Multivariable regression models were developed to identify risk factors for AL. In 305 IBD patients (49.1%), an ileostomy was created during IPAA. A comparable overall leak rate was found in the stoma group when compared to non-diverted patients (16.7% vs 17.1%, p=0.92). This unexpected finding of high leak rates despite stoma formation could probably be explained by the increased use of anti-TNF (12.6% versus 4.6%, p<0.001), steroids (33.0% vs 12.1%, p<0.001), and weightloss (>5% of body-weight) (14.6% vs 8.5%, p=0.02) when compared to non-diverted patients. Despite having a stoma, a high leak rate (40.0% vs 15.1%, p=0.02) was found in patients treated with a combination of anti-TNF and steroids. This was also emphasized by the fact that patients undergoing subtotal colectomy with IPAA at a later stage (weaned of medication) had a significantly decreased leak rate when compared to patients undergoing primary IPAA (11.6% vs 20.7%, p=0.003). Multivariable regression models demonstrated, long-term disease course (OR 2.01, 95%CI 1.27-3.19), high ASA score (OR 1.94, 95%CI 1.09-3.47) and a combination of anti-TNF and steroid treatment (OR 5.61, 95%CI 1.71-18.48) as independent risk factors for AL. These results imply that in daily practice surgeons perform ileostomy in more fragile and disease affected patients. This strategy seems ineffective in the prevention of AL in these series implicating that a staged procedure, that is subtotal colectomy followed by completion proctectomy and IPAA after weaning of the medication, is more appropriate when preoperative risk factors are identified. Long-term disease course, high ASA score, and a combination of anti-TNF and steroid treatment within 3 months before IPAA were all independent risk factors for AL.

The course of pulmonary vagus nerve branches

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Pulmonary complications are frequently observed after transthoracic oesophagectomy. It has been hypothesized that these could be reduced by sparing pulmonary vagus nerve braches to the lung; especially since recently the important regulatory role of the vagus nerve in inflammation has been described. However, current descriptions of the regional anatomy are insufficient. Therefore we aimed at providing a detailed description of the pulmonary vagus nerve branches. In 6 fixed adult human cadavers without signs of thoracic surgery or disease bilateral microscopic dissection of vagus nerve branches to the lungs was performed. The level of branching, number and calibre of nerve branches, and their distribution inside the lung were described. Nerve fibres were additionally identified by neurofilament staining, and nerve calibre was measured by computerized image analysis. Vagus nerve branches reached the lung through pulmonary nerve plexuses anterior and posterior to the main bronchus. The right lung was supplied by 3-5 small to medium sized branches from the anterior pulmonary plexus, and 17-22 small to large sized branches from the posterior pulmonary plexus. The left lung was supplied by 2-6 small to large sized branches from the anterior pulmonary plexus, and 8-16 small to large sized branches from the posterior pulmonary plexus. Lung innervation from the large posterior pulmonary plexus was segmentally organised: superior branches supplied superior lung lobes, inferior branches supplied the medial and inferior lung lobes.
Conclusion: This study provides a detailed description of the extensive pulmonary innervation by the vagus nerves. Extensive mediastinal lymphadenectomy during oesophagectomy denervates the lung. Further research has to determine the feasibility of sparing pulmonary vagus nerve branches without compromising lymphadenectomy.

Near-infrared fluorescence sentinel lymph node detection in gastric cancer using indocyanine green coupled to a nanocolloid

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Fluorescent imaging using near-infrared probes is an innovative technique to intra-operatively visualize lymphatic pathways and lymph nodes. Previous studies already demonstrated that sentinel lymph nodes (SLNs) in gastric cancer can be successfully detected with the use of indocyanine green (ICG) either preoperatively (1-3 days before surgery) or intraoperatively injected around the tumor. Preoperative injection resulted in a higher accuracy rate and less false negative SLNs. However, the mean number of SLNs detected in the preoperatively injected group was significantly higher due to prolonged time of ICG availability in lymphatic vessels and staining of non-specific LNs. The use of ICG coupled to a nanocolloid appears to have a better retention in SLNs in breast cancer patients. The aim of this study was to examine the feasibility of intra-operative sentinel lymph node mapping in gastric cancer patients using near-infrared fluorescence imaging and indocyanine green coupled to nanocolloid (ICG:Nanocoll). Patients with cT1-T4 N0-N1 M0 gastric cancer, planned for (partial) gastric resection, were included in this study. During surgery, ICG:Nanocoll was injected subserosally in four quadrants around the tumor. Intraoperative lymph node mapping was performed using the Mini-Flare imaging system. Patients underwent standard of care (partial) gastric resection with lymphadenectomy. All detected SLNs were tagged during surgery and assessed on tumor-involvement after surgery. Eight consecutive patients were included. Two patients were excluded during surgery due to irresectability and technical failure of the injection. In all six remaining patients SLNs were detected with an accuracy rate of 83.3%. The false negative rate was 16.7%: one patient with a T4 tumor had LN metastasis in non-SLNs. In this patient, metastases were demonstrated in the second echelon. These preliminary results show that ICG:Nanocoll fluorescence imaging allows favourable detection of SLNs in gastric cancer patients. More extensive results have to be awaited to draw solid conclusions about the false negative rate of the procedure and the accuracy of the use of ICG:Nanocoll in detection of SLNs.

Worldwide trends in surgical techniques in the treatment of esophageal cancer

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Background Surgical resection is the cornerstone in the treatment of esophageal cancer. Worldwide surgical strategies vary between countries and surgeons. The aim of this study was to evaluate the trends in surgical techniques over the past 6 years. Materials & Methods. An international survey was performed amongst surgical members of the International Society for Diseases of the Esophagus (ISDE) and the World Organization for Specialized Studies on Disease of the Esophagus (OESO). The participants filled in a web based questionnaire about surgical strategies for esophageal resection. The findings of this survey were compared to a similar survey that was conducted in 2007.
Results. In total 230 surgeons filled in the survey in 2013, of which 72 (31%) were OESO members and 158 (69%) ISDE members. In 2007 a total of 269 surgeons responded, who functioned as a reference group. The responders from 2013 represented 40 countries from 6 different continents. In 2013 the preferred approach to esophagectomy was minimally invasive transthoracic in 42%, compared to 14% who preferred minimally invasive esophagectomy in 2007. A right sided incision for throracomtomy was preferred in 94% in 2013, which is comparable to 91% in 2007. The preferred lymph node dissection was 2-field in 86% in 2013, which was favored by 73% of surgeon in 2007.A gastric conduit was the preferred method of reconstruction in 96% in 2013, compared to 85% in 2007. The preferred location of the anastomosis was cervical in 52% in 2013, which is comparable to 56% in 2007. The preferred technique of construction of the cervical anastomosis was hand-sewn in 64% and stapled in 36%, whereas the intrathoracic anastomosis was stapled in 77% and hand-sewn in 23% in 2013. These last figures were comparable to those found in 2007.
Conlcusion. This international survey shows a preference for transthoracic esophagectomy with 2-field lymph node dissection and gastric conduit reconstruction. A strong worldwide trend towards minimally invasive surgery was observed with a 3 fold increase. The preferred location of the anastomosis remained cervical.

Thoracolaparoscopic dissection of lymph nodes involved in the drainage of the esophagus is feasible and safe in human cadavers and swine

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Low-risk early esophageal cancer can safely be managed endoscopically. In case of high-risk cancer (i.e. submucosal invasion, poor tumor differentiation, or lymphovascular invasion), esophagectomy with lymph node (LN) dissection is advocated given the relatively high rates of LN metastasis in these patients. However, this procedure is associated with substantial morbidity and mortality and a reduced quality of life. Endoscopic radical local resection (by means of ESD or EMR) followed by thoraco-laparoscopic LN dissection without concomitant esophagectomy could be an attractive alternative. Our aim was to evaluate the feasibility and safety of thoracolaparoscopic dissection of LN involved in the drainage of the esophagus in human cadavers(1) and swine(2).(1)In fresh human cadavers, thoracolaparoscopic dissection of LN involved in drainage of the esophagus was performed. Following LN dissection, esophagectomy was performed and the resection specimen was analysed for any retained LN. (2)In the animal survival study, thoracolaparoscopic dissection of LN was performed in swine. 28 days after the procedure, the swine were sacrificed and esophagectomy was performed. Outcome parameters included the number of dissected LN during lymphadenectomy, and the number of retained LN in the esophagectomy specimens. In the animal survival study, outcome parameters also included the presence of ischemia and/or stenosis in the esophagectomy specimens. Technical success was defined as a ratio ≥ 0.9 between the number of dissected LN during lymphadenectomy and the total (resected plus retained) number of LN.(1)In 5 fresh human cadavers, a median of 26 LN (IQR 22-46) was dissected. In 2 esophagectomy specimen, 1 retained LN was found (1 high para-esophageal, 1 low paraesophageal). All procedures were considered technically successful. (2)In 8 female swine, a median of 11 LN (IQR 6-16) was dissected. In 4/8 esophagectomy specimens, a median of 4 retained LN (IQR 3-6) were found (para-esophageal and around the lesser curvature). One pig died because of ventricular fibrillation during the procedure, all others survived uneventfully. The esophagectomy specimens showed no signs of ischemia or stenosis. In conclusion, thoracolaparoscopic dissection of lymph nodes involved in the drainage of the esophagus appears to be feasible in human cadavers and swine. The animal survival study suggests that the esophageal vascularity is not severely compromised by this procedure. Further human studies on this new algorithm of radical endoscopic resection followed by thoracolaparoscopic lymph node dissection in patients with high-risk early esophageal cancer however, are warranted.

Effect of perioperatively administered glucocorticoids on pulmonary complications after transthoracic oesophagectomy. A meta-analysis

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Severe pulmonary complications occur frequently following transthoracic esophagectomy. Most likely an exaggerated immunological response is a main driving factor, which could be prevented by perioperative glucocorticoid administration. The objectives of this study were to determine the clinical benefits and harms of perioperative glucocorticoids for transthoracic esophagectomy, using pulmonary complications as primary outcome. Mortality, anastomotic leakage and infections were secondary outcomes. A systematic review of literature and meta-analysis of randomized controlled trials (RCTs) was conducted conform the PRISMA statement. The search retrieved 7 RCTs and 4 non-randomized studies. In total 367 patients received perioperative glucocorticoid versus 415 patients who did not. Meta-analysis of the RCTs showed no significant effect of glucocorticoid. For pulmonary complications the pooled risk ratio was 0.69 (95% confidence interval [CI], 0.26 to 1.79); for anastomotic leakage 0.61 (95% CI, 0.23 to 1.61) and for infections 1.09 (95% CI, 0.41 to 2.93). A subgroup analysis of RCTs that used weight dependant dosing within 30 minutes preoperatively showed a pooled risk ratio of 0.28 (95% CI, 0.10 to 0.77) for pulmonary complications compared to placebo. In this meta-analysis perioperative glucocorticoid administration did not affect the risk of pulmonary complications after transthoracic esophagectomy, nor did it cause adverse effects. Subgroup analysis showed that a weight dependant dose of 10-30 mg/kg methylprednisolone within 30 minutes preoperatively, might be the most promising dosing regimen for further research.

Fucosyltransferase-2 non-secretor status is associated with non-anastomotic biliary strictures after liver transplantation in recipients with primary sclerosing cholangitis

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Non-anastomotic biliary strictures (NAS) are the second cause for graft loss after liver transplantation. Because of the clinical similarities that are seen between transplant recipients with NAS and patients suffering from Primary Sclerosing Cholangitis (PSC), it is thought that both conditions share a similar pathophysiology. Recently, GWAS analyses identified the polymorphism rs601338 (G>A) in the Fucosyltransferase-2 (FUT2) gene as a risk factor for PSC. Homozygosity for rs601338 (AA) leads to a truncated, dysfunctional FUT2 enzyme, affecting epithelial glycocalyx integrity and leading to absence of ABH antigens (FUT2 non-secretor status) in body fluids. The aim of this study was to investigate whether FUT2 rs601338 genotype is a risk factor for NAS after liver transplantation. Genotyping was performed in n=258 donors and n=343 recipients, by qPCR on DNA isolated from blood or spleen cells that were collected from consecutive transplantations. Secretor (GA or GG) and non-secretor (AA) status of donors, recipients or paired donors and recipients were compared between recipients who developed NAS and recipients who did not. A sub-analysis on a cohort of transplanted PSC patients (n=67) was performed. In the entire study cohort, 21,5% of the donors and recipients were non-secretor (AA) for FUT2. Cox-regression analyses showed no association between NAS and FUT2 genotype in donors. FUT2 AA-genotype in PSC recipients, however, showed an increased incidence of NAS after LT in patients compared to PSC patients with either GA or GG genotype (P=0.006, HR:5.1), while this association with FUT2 genotype was not shown in non-PSC recipients. Analysis of paired donors and recipients disclosed that a FUT2 mismatch, namely the combination of GG-donors and AA-recipients, provided the highest risk for development of NAS (P=0.038). This suggests that, in PSC patients undergoing liver transplantation, an aggravated immune response could be triggered by implanting a liver graft with functional FUT2 proteins into a recipient with dysfunctional FUT2. Further studies are needed to confirm our findings.
Conclusion. FUT2 genotype in PSC patients strongly influences the risk to develop NAS after liver transplantation. This is potentially related to an aggravated immune response induced by FUT2 mismatching between donors and recipients.

Local administration of bone marrow-derived mesenchymal stromal cells after partial hepatectomy ameliorates liver fibrogenesis in a dose dependent manner.

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Background and aims: Chronic liver injury results in the secretion of multiple mediators that activate diverse cell types, resulting in hepatic fibrogenesis. Key features are accumulation of fibroblasts and myofibroblasts, accompanied by a progressive deposition of extracellular matrix. We assessed whether fibrosis and cirrhosis can be reversed by induction of liver regeneration through partial hepatectomy and concomitant treatment with increasing doses of bone marrow-derived mesenchymal stromal cells (MSCs). In addition, homing of MSCs was assessed in regenerating livers. Methods: Liver fibrosis and cirrhosis were established in mice by chronic administration of CCL4 for 6 and 12 weeks respectively. Partial hepatectomy followed by a local injection of NaCl, $1x10^6$ or $2x10^6$ MSCs in one of the two remaining fibrotic/cirrhotic liver lobes was performed. Homing was studied using MSCs derived from bone marrow of transgenic GFP mice. Eight days after treatment mice were sacrificed and livers removed. Liver damage was determined by ALT and AST serum levels. Results: Histochemical analyses, by routine histology and Sirius red staining, revealed that in the liver lobes of healthy animals no fibrotic septa or lobuli closure were present. Cirrhotic livers showed more liver damage compared to fibrotic livers vs control animals according to increased septa formation/lobule closure (81% resp 65% vs 0%) and higher ALT (164 resp 127 vs 23 U/L) and AST levels (105 resp 90 vs 41 U/L). In the regenerated cirrhotic livers a significant reduction of collagen content in the locally injected lobes was observed in mice that received $2x10^6$ MSCs compared to mice that received NaCl (80% vs 67% reduction $p<0.05$). Mice treated with $1x10^6$ MSCs showed an intermediate reduction of 76%. In the non-MSC-treated liver lobe counterpart no significant differences in collagen deposition reduction were observed between all treatment groups (range 68%-73%). In mice with fibrotic livers similar, but not significant, effects of NaCl, $1x10^6$ and $2x10^6$ MSCs treatments were observed (71%, 75%, 80% collagen deposition reduction). After regeneration GFP positive cells were detected throughout the liver parenchym, without obvious differentiation or preferential localization. Co-staining for macrophages showed no co-localization or phagocytosed MSCs.
Conclusions: Local administration of MSCs in cirrhotic liver lobes after partial hepatectomy results in a significant and dose-dependent local reduction of collagen deposition in the regenerated livers. Comparison between fibrotic vs cirrhotic livers lead to the hypothesis that the effect of MSC treatment is probably related to the severity of the disease.

Dopamine protects against cooling and rewarming-induced liver damage in vitro and in vivo

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Introduction: Cooling and rewarming causes organ damage, which is in part the result of oxidative stress during the rewarming phase. Hibernating mammals have a natural resistance towards organ damage as they undergo repetitive cycles of hypothermia and rewarming without apparent organ damage. One of the protective mechanisms in hibernators consists of the endogenous production of hydrogen sulfide (H2S) by enzymes like cystathionine-β-synthase (CBS). Dopamine can activate CBS and boost endogenous H2S production in (non-hibernator) rat smooth muscle aortic cells. In this study, we investigated whether dopamine protects against cooling and rewarming-induced damage in the HepaRG cell in vitro and rat liver in vivo. Methods: Wistar rats (n= 6 per group) were anesthetized with ketamine with or without dopamine (125 µg/kg/min) in combination with the CBS inhibitor aminooxyacetic acid (AOAA) and cooled to 15°C core-temperature for 3 hours, followed by rewarming to 37°C for 1 hour. Serum transaminases were analyzed to determine liver damage. The HepaRG cell was exposed to hypothermia (7 °C) for 24 hours and rewarmed (37°C) for 4 hours and apoptosis (caspase-3 activity) and necrosis (LDH leakage) were analyzed. Results: Cooling and rewarming of HepaRG cells induced caspase-3 activity 9-fold and LDH leakage 3.3-fold above control levels. Dopamine treatment limited the increase in capase-3 activity to a 2-fold induction and normalized LDH leakage to control levels. Cooling and rewarming increased serum AST and ALT levels (204 ± 37 U/L and 160 ± 74 U/L, respectively) in rats anesthetized with ketamine compared to sham operated rats (AST 89 ± 2 U/L and ALT 53 ± 1 U/L). Dopamine infusion completely prevented the increase in AST and ALT levels (22 ± 7 U/L and 15 ± 7 U/L, respectively) in these rats, which was partly reversed by co-administration of AOAA (AST 98 ± 3 U/L and ALT 58 ± 2 U/L). Treatment with AOAA alone (in ketamine anaesthetized rat) resulted in AST levels of 169 ± 25 U/L and ALT levels of 86 ± 6 U/L.
Conclusion: Dopamine prevents cooling and rewarming-induced liver damage, in part through activation of CBS. Dissecting the molecular mechanisms that prevent organ damage in hibernating animals hold great promise to improve results of liver transplantation and possibly treatment of acute liver failure.

Decellularization of human and porcine livers: Applications for graft engineering

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Liver transplantation is the only effective treatment for end stage liver disease, however, the number of good quality liver grafts is not sufficient to meet the need. Alternative approaches need to be explored to overcome this shortage, including the use of bioengineered hepatic tissue as transplantable grafts. Recent evidence from rodent models, suggests that decellularization of whole liver organs is feasible and provide an excellent scaffold for reseeding liver cells and stem cells for graft engineering. However, currently there is limited experience with decellularization of larger liver sizes from pigs or humans. The aim of this study is to develop an effective method for decellularization of porcine and human livers.Whole or partial porcine (n=3) and human livers that are rejected for transplantation(n=4) were cannulated via the portal vein and the hepatic artery and perfused (60 ml/min) with heparinized 0.9% NaCL to remove blood, followed by 4% Triton X-100 + 1% NH_4OH to remove all cells present in the liver. This process takes 8 hours in which 4L detergent is recircutated and refreshed every 4 hours. In between recirculation rounds, 2L Triton-solution is perfused through the liver. After the decellularization procedure, the extracellular matrix (ECM) is rinsed with 0.9% NaCL and DNase to remove all remnants of cells and nucleases. The decelled matrix was analyzed for the absence of cells, RNA and DNA content and for the presence of matrix proteins. Histological analysis (H&E staining) showed that with the current method, virtually all nuclei were removed and that the elastin and collagen fibers (Weigert's Resorcin-Fuchsin staining) was not affected by the decellularization process. We found a 93% ± 3% (average ± SD) reduction of RNA and a 47% ± 22% (average ± SD) reduction of DNA content. Preliminary results of re-seeding the ECM with green-fluorescent labeled mesenchymal stem cells (MSC) indicate that the matrix is not toxic for stem cells. MSC adhere to the matrix and spread.In conclusion, we established a method to make acellular ECM from porcine and human livers. These decellularized matrices provide an excellent scaffold for reseeding liver cells, liver organoids and/or stem cells for graft engineering.

Smad4-dependent regulation of hepatocellular carcinoma growth and progression

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SMAD4 is recognized as a central mediator of Transforming Growth Factor Beta (TGF-b) and Bone Morphogenetic Protein (BMP) signaling pathways which are involved in regulating tumor progression. In general, SMAD4 is considered a tumor suppressor. Here we investigated the role of SMAD4 in hepatocellular carcinoma (HCC). We performed immunohistochemical stainings in paraffin embedded-tissue microarray patient HCC (n=42). Three HCC cell lines were used for functional assay in vitro and in immune-deficient mice. The results were SMAD4 protein level was significantly higher in human HCC tissue compared with adjacent liver tissue (n=42, $P<0.05$). High SMAD4 levels were significantly associated with higher recurrence rate ($p=0.05$), shorter time to recurrence ($p<0.05$) and more tumor lesion ($p<0.01$). Interestingly, high SMAD4 levels were associated with low p-SMAD 1/5/8 (a downstream target of BMP signaling) expression, both in patients and HCC cell lines. Knockdown of SMAD4 in HCC cell lines showed a significant decrease of migratory and colony formation capacity, whereas ectopic overexpression of SMAD4 resulted in increased migration activity demonstrated by the ring-barrier migration assay. However, knockdown of SMAD4 conferred resistance to the anti-growth effects of BMP4, TGF-b and Activin in HCC cell lines. Interim analysis (at day 12) of xenograft experiment showed that Smad4 knockdown appears to delay tumor initiation of HCC cells in nude mice.
Conclusion: Basal SMAD4 expression is required for the anti-tumor function of BMP signaling in HCC. Elevated Smad4 expression correlates with poor outcome in HCC patients and more aggressive phenotype and function of HCC cells.

Sensitization of colon cancer stem cells to chemotherapy by ER stress induced differentiation

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Introduction: In cancer, a small subpopulation of cells is responsible for tumor-initiation and -growth. These so called cancer stem cells (CSCs) are more resistant to chemotherapy than differentiated tumor cells that represent the bulk of the tumor. We recently showed that an ER stress induced unfolded protein response (UPR) forces differentiation of normal intestinal stem cells in a PERK-eIF2α dependent manner (Heijmans, Cell Reports, 2013). Here we investigated whether the UPR forces CSCs into a more differentiated state, which could sensitize them to the effects of chemotherapy. Methods: We used a previously described colon cancer stem cell culture (Vermeulen, Nat Cell Biol 2010) with a TCF/LEF driven GFP reporter for Wnt signaling activity. This allowed us to compare cancer stem cells (Wnt-high) with more differentiated cancer cells (Wnt-low) within the same experiment. The UPR was activated with SubAB, a toxin that depletes ER chaperone GRP78, or with salubrinal which specifically prevents dephosphorylation of eIF2α. For in vivo experiments, we treated xenotransplanted mice with salubrinal, oxaliplation or combination therapy once a week for four weeks. Results: Activation of the UPR resulted in loss of stem cell markers OLFM4 and LGR5 and gene array analysis revealed down regulation of a previously described colon cancer stem cell gene set (De Souza, Cell Stem Cell 2011), NES -1.54, $P<0.001$. SubAB treatment reduced clonogenic capacity of Wnt-high cells (1.3% vs 20.8% sphere initiating cells) and increased the percentage of differentiated spheres in matrigel 3D culture (90% vs 11%). Wnt-high cells where more resistant to oxaliplatin induced apoptosis that Wnt-low cells (23% vs 47%). SubAB treatment alone did not induce apoptosis in Wnt-high cells but increased their sensitivity to oxaliplatin induced apoptosis to that observed in Wnt-low cells (42% vs 51%). In vivo treatment with Salubrinal alone did not decrease tumor growth but when combined with Oxaliplatin, xenografts grew markedly slower and survival was increased (54 vs 27 days after last treatment).
Conclusion: ER-stress forces colon cancer stem cells into differentiation and sensitizes CSC's to oxaliplatin induced apoptosis. ER stress inducing agents may be developed as adjuvants in chemotherapy of colorectal cancer.

Inhibited expression of corticotropin-releasing hormone receptor 2 (CRHR2) correlates with tumor growth, EMT, distant metastasis risk and poor survival in experimental and clinical colorectal cancer

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Background & Aims: Chronic inflammation is a driving force for development and progression of colorectal carcinoma (CRC). We explored the contribution of the corticotropin-releasing-hormone (CRH) family of peptides and receptors in CRC growth and metastatic potential through regulation of inflammatory responses. Methods: We analyzed the expression of all CRH family members in human CRC (N=56) and control tissues (N=46) as well as in 7 CRC cell lines by qRT-PCR. Expression of pro-inflammatory cytokines, cell proliferation, migration, invasion and colony formation were compared between parental and CRHR2-overexpressing (CRHR2high) CRC cell lines. Targets of CRHR2/Ucn2 signaling were identified by gene superarray and immune-blot analyses. CRHR2/Ucn2-targeted effects on tumor proliferation and epithelial -to-mesenchymal transition (EMT) were validated in nude mice (n=6/group) carrying parental- or CRHR2high-SW620 xenografts and treated with Ucn2. Results: CRC tissues and cells had diminished CRHR2 (>4-fold) and elevated Ucn2 (>5-fold) mRNA expression compared to control specimens and the immortalized epithelial colonic NCM460 cells, respectively. Ucn2 stimulation of CRHR2high cells reduced IL1b ($p<0.03$), IL6 ($p<0.001$) and IL6R ($p<0.03$) mRNAs, IL6-mediated cell proliferation ($p<0.03$), migration ($p<0.01$), invasion ($p<0.03$) and colony formation ($p<0.02$). At the molecular level, CRHR2/Ucn2 signaling in CRHR2high cells inhibited (>2 fold) the expression of cell cycle and EMT inducing genes in the presence of IL6 stimulation, while it augmented (>2 fold) the expression of cell cycle- and EMT-suppressors under the same conditions. In the SW620 xenograft model, CRHR2high tumors had significantly decreased growth and proliferation rates, increased apoptosis and necrosis, as well as reduced expression of EMT-inducers and elevated levels of EMT-suppressors (>2 fold). All the above changes were further augmented following the same trend under Ucn2 treatment conditions (all p values<0.02). In CRC clinical samples, CRHR2 mRNA expression was inversely correlated with IL6R and vimentin levels, as well as metastasis occurrence, while positively correlated with E-cadherin expression and 5-year survival post surgery (all p values<0.03). Conclusions: CRHR2 reduction in CRC has a protective role in tumor progression, expansion and metastatic potential through maintenance or promotion of the existing colonic inflammation. In addition, CRHR2low CRC phenotypes are linked with distant metastases and poor clinical outcomes.

Dual targeting of the VEGF and endoglin/TGF-β pathway in colorectal cancer

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Angiogenesis plays a key role in tumor progression and metastasis and has therefore been intensely studied for therapeutic purposes. Both the vascular endothelial growth factor (VEGF) and the endoglin/transforming growth factor-β (TGF-β) pathway play a crucial role in (tumor)-angiogenesis and are therefore explored in the clinic. However, clinically, anti-angiogenic therapies did not meet the high potential that was expected based on preclinical models, mainly due to therapy resistance. One way tumors are able to escape anti-angiogenic treatment is by upregulating alternative pro-angiogenic pathways. Therefore, in this project, we aimed to study the potential of combined targeting of the VEGF and endoglin/TGF-β pathway.In a group of rectal cancer patients, we assessed pre-surgical biopsies and surgical resection specimens from patients either treated with chemoradiation therapy or chemoradiation therapy combined with the anti-VEGF antibody Bevacizumab. Adjuvant treatment with Bevacizumab led to a marked increase in endoglin/TGF-β signaling in angiogenic endothelial cells (ECs) compared to pre-treatment biopsies or tumors from patients which only received chemoradiation therapy. Based on these observations we explored the potential redundancy between the VEGF and endoglin/TGF-β pathway in ECs in vitro. We showed that treatment with the endoglin neutralizing antibody TRC105 led to an increase in phosphorylated-ERK1/2, which is downstream in the VEGF signaling. This suggests redundancy between the two pro-angiogenic pathways. Next, when combining the VEGF-Receptor kinase inhibitor SU5416 with TRC105, we could show synergistic inhibition of angiogenesis in 2- and 3-dimensional in vitro angiogenesis assays. These results imply that the targeting of both pro-angiogenic pathways simultaneously more efficiently inhibits angiogenesis, than targeting each pathway separately. Preliminary data from ongoing experiments in an orthotopic mouse model for colorectal cancer suggest that TRC105 and especially TRC105/SU5416 combined anti-angiogenic therapies affect tumor progression in this model.In conclusion, we show that redundancy exists between pro-angiogenic pathways, which may underlie the therapy resistance that is observed in the clinic. The therapy resistance upon sole VEGF targeting that is observed in the clinic may be caused by overactivation of endoglin/TGF-b signaling. Combined targeting of these pathways in patients may result in enhanced tumor responses and thereby increased survival. Currently phase-2 clinical trials evaluating this approach this are ongoing.

Conditional activation of BMP signalling leads to loss of the stem cell compartment

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Introduction In the normal intestinal epithelium Bone Morphogenetic Protein (BMP) signalling is active in a decreasing gradient from top to bottom along the vertical crypt-villus axis. BMP signalling is essential for normal intestinal epithelial homeostasis with Juvenile Polyposis and Hereditary Mixed Polyposis both resulting from germ mutations in BMP signaling components. In transgenic mice inactivation of BMP signalling, results in the development of polyps in both BMPR1A floxed mice and mice with overexpression of the BMP sequestering inhibitor Noggin. This approach only alters the existing BMP activity at the top of the villi and does not affect BMP levels in the stem cell compartment, where BMP signalling is virtually non-existent. To study the importance of the BMP axial gradient we used an inducible mouse model in which BMP signalling can be constitutively activated in both the crypt and villi. Methods We used mice containing an inducible constitutively active human BMPR1A sequence and crossed these with CypCre$^{+/-}$ mice. Cypcre leads to recombination in both villus and crypt (except for paneth cells) and mostly in the proximal part of the small bowel. Eight-week-old mice were injected intraperitoneally with β-naftoflavone for 5 consecutive days. Cre-negative caBMPR1A mice injected with β-naftoflavone were used as controls. The mice were sacrificed 1 day, 3 days, 5 days, 1 month, 3 months and 6 months after induction. Immunohistochemistry was performed to investigate recombination (GFP), proliferation (BrdU & Ki-67), apoptosis (Caspase3), differentiation (CAII, Villin & Alcain Blue), BMP signalling activity (pSMAD1,5,8) and Wnt signalling (β-catenin). In situ hybridization was performed to investigate intestinal stem cell marker OLFM4. Results Conditional induction of BMP activity results in a major disruption of the small intestinal crypt-villus architecture at days 3 and 5 and a 5% loss of body weight. Morphological changes include crypt fission, crypt enlargement, loss of villi and the appearance of cystic like structures. Paneth cells are mispositioned and shifted upwards, nuclear β-catenin is lost at the base of the crypt and expression OLFM4 is completely absent. Subsequently the mice recover to regain a normal small intestinal phenotype. Recovery is preceded by the re-expression of OLFM4 day 5 after induction.
Conclusion We conclude that the axial gradient of BMP activity in the crypt-villi is important for maintaining intestinal epithelial homeostasis. Low BMP activity at the bottom of the crypt is imperative for the preservation of the stem cell compartment.

Protein tyrosine phosphatase 1B (PTP1B) expression and phosphatase activity are increased in colorectal cancer which leads to a more invasive phenotype

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Background: Cell signaling is dependent on the balance between phosphorylation of proteins by kinases and dephosphorylation by phosphatases. This balance if often disturbed in colorectal cancer (CRC), leading to increased cell proliferation and invasion. For many years research has focused on the role of kinases as potential oncogenes in cancer, while phosphatases were commonly assumed to be tumor suppressive. However, this dogma is currently changing as phosphatases have also been shown to stimulate cancer growth. One of these phosphatases is protein tyrosine phosphatase 1B (PTP1B). The aim of this study was to investigate the expression and phosphatase activity of PTP1B in CRC, and elucidate its effects on cellular functions and signaling. Methods: PTP1B expression was analysed by immunohistochemistry on sections from biopsies of dysplasia (n=6), carcinoma (n=9) and control (n=5), as well as by western blotting of paired freshly frozen CRC and normal adjacent tissue (n=11). Phosphatase activity was also assessed in these latter samples by immunoprecipitating PTP1B under saturating conditions, followed by a phosphatase activity assay using PNPP as substrate. To investigate the effects of PTP1B on signaling and cell function, we manipulated the PTP1B expression in vitro by lentiviral transduction of HCT116 and Caco-2 cells with 2 shRNAs against PTP1B. Results: PTP1B expression in intestinal epithelial cells (IECs) is low in normal colon (14% positive; mean intensity 0.2±0.1) and increases from dysplasia to carcinoma (100% positive IECs; with mean intensity rising from 1.4±0.3 to 1.8±0.3 respectively). These results were confirmed by western blot analysis. The intrinsic enzymatic activity of PTP1B is significantly increased in cancer compared to adjacent normal tissue (mean OD 1.0 in CRC compared to 0.2 in normal tissue) (p=0.001). Knocking down PTP1B in CRC cells reduced the phosphorylation of the mitogenic kinase ERK by approximately 50%, and decreased mRNA levels of target genes involved in proliferation (e.g. c-Myc). Furthermore, adhesion, migration, and proliferation were significantly reduced in shPTP1B cells.
Conclusion: Not only is the expression of PTP1B increased in colorectal cancer as compared to normal tissue, but strikingly, the intrinsic enzymatic activity of this phosphatase is also enhanced, suggesting a role for PTP1B activity in CRC progression. Knocking down PTP1B in CRC cells results in a less invasive phenotype with lower adhesion, migration and proliferation capabilities, by interfering in the RAS- ERK pathway. These results suggest that inhibition of PTP1B activity is a promising new target in the treatment of colorectal cancer.

ER stress depletes Apc mutant intestinal epithelial stem cells downstream of nuclear β-catenin

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Wnt signaling drives self-renewal of intestinal epithelial stem cells (ISCs) through activation of β-catenin. Hyperactivation of Wnt signaling causes stem cell expansion and constitutes a first step in development of colorectal cancer. We have previously shown that endoplasmic reticulum (ER) stress signaling causes loss of self-renewal capacity in ISCs, but how these two functionally opposite pathways interact remains elusive. By deletion of ER stress repressor Grp78 we investigate effects of ER stress on ISCs that lack the Wnt gatekeeper gene Apc and thus exhibit hyperactive Wnt signaling. To validate knockout of Grp78 as a model of ER stress we generated organoids of intestinal epithelium from Grp78fl/fl mice and analysed gene expression using illumina mRNA beadarrays. For in vivo studies we used inducible VillinCreERT2-Apcfl/fl-Grp78fl/fl mice in which simultaneous deletion of Apc and Grp78 results in hyperactivation of Wnt signaling and concomitant ER stress. Analysis of Grp78fl/fl organoids showed robust upregulation of a panel of ER stress markers, conforming Grp78 deletion as a bona fide model for the study on ER stress. Deletion of Apc from mouse intestinal epithelium resulted in accumulation of nuclear β-catenin, hyperproliferation, crypt enlargement and crypt fissioning 3 days post induction (p.i.). Induction of ER stress in Apc mutant epithelium by combined deletion of Apc and Grp78 resulted in a marked 39% reduction of BrdU+ cells as well as 32% reduction of crypt length at day 3 p.i. (both $P < 0.001$). These reductions occurred in Grp78 deficient crypts indicating a short term rescue of the Apc mutant phenotype. Assessment of consecutive time points showed that Grp78 deficient crypts were eventually repopulated by Grp78 proficient, wild type cells, indicating loss of self-renewal capacity. While loss of the Apc mutant phenotype and self-renewal capacity occurred, cells in Apc-Grp78 double mutant crypts maintained nuclear localization of β-catenin indicating constitutive activation of the Wnt signaling pathway. Conclusion: Homozygous deletion of Apc results in a known hyperproliferative phenotype ultimately causing tumor formation. We show that concomitant depletion of Apc and Grp78 results in short term rescue of the Apc mutant phenotype while maintaining nuclear localization of β-catenin, the hallmark of activated Wnt signaling. Thus ER stress mediated stem cell loss is dominant over hyperactivation of the Wnt signaling pathway and may interfere with stemness downstream of β-catenin. These results highlight a role for ER stress as a potential target in development of novel cancer therapy.

Fibroblasts promote invasion in SMAD4 negative colorectal cancers by producing BMP-2

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Introduction For decades the focus of cancer research has been on tumour cells, but recently the influence of the tumour stroma has been acknowledged as a major factor in tumour development. It has been shown that SMAD4 negative colorectal cancers (CRC) surrounded by large quantities of tumour stroma have a worse prognosis compared to stroma low cancers. This suggests that the tumor-stroma interaction is particularly important in SMAD4 negative cancers , but the exact mechanism remains to be elucidated. SMAD4 is the central critical component of the BMP signalling pathway, which plays an important role in CRC as we and others have shown. We set out to investigate the role of the BMP pathway in the tumour-stroma interaction, especially in SMAD4 negative cancers. Methods We manipulated SMAD4 expression in CRC cell lines using either SMAD4 knockdown by lentiviral shRNA transduction or stable re-expression of SMAD4. We treated the SMAD4 positive and negative clones with fibroblast conditioned medium (CM) or BMP ligands and performed transwell invasion assays and qPCR for Epithelial-to-Mesenchymal Transition (EMT) markers. In reverse experiments we treated fibroblasts with SMAD4 positive and SMAD4 negative CRC CM and performed a BMP/TGFβ specific PCR array. Finally we stained and scored the invasive front of 88 stage III CRCs for SMAD4 and BMP ligand expression and correlated this with patient survival. Results Treatment with fibroblast CM results in an increase in invasion and EMT markers in SMAD4 negative CRC cells, but not SMAD4 positive cells. A qPCR screen including all BMP/TGFβ ligands and several BMP/TGFβ downstream targets revealed that BMP2 expression is upregulated in fibroblasts when treated with CM from SMAD4 negative CRC cells, but not with CM from SMAD4 positive cells. SMAD4 negative CRC cells treated with BMP2 showed an increase in. We observed high stromal BMP2 expression in 34,1% of the CRC tissue. High stromal BMP2 expression is associated with a poor patient survival only when the cancer is SMAD4 negative (p=0.007). In SMAD4 positive cancers stromal BMP2 expression is not associated with a poor prognosis (p=0.95).
Conclusion We show that fibroblasts produce soluble factors that are prometastatic for SMAD4 negative CRC cells. SMAD4 negative CRC cells in turn produce soluble factors that stimulate BMP2 expression in fibroblasts. BMP2 has prometastastic effects specifically in SMAD4 negative CRC cells. This is supported by the fact that stromal BMP2 expression at the invasive front of CRC tissue is associated with a poorer patient survival only in SMAD4 negative cancers. This would suggest that patients with SMAD4 negative CRC might benefit from inhibition of BMP signalling.

Baseline liver gene expression profile associated with combined response in chronic hepatitis B patients treated with peginterferon and adefovir

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Despite the chance of a sustained off-treatment response in chronic hepatitis B (CHB) patients treated with peginterferon (peg-IFN) based therapy, the majority of patients do not achieve a satisfactory outcome. In addition, peg-IFN treatment can provoke significant side-effects. Selection of patients with a higher chance of response may optimize treatment and avoid unnecessary side-effects and costs. Here, we analyzed gene expression patterns in liver biopsies obtained before treatment aiming to identify genes associated with response to IFN-based therapy.In total, 40 CHB patients (19 HBeAg-positive; 21 HBeAg-negative) were treated with peg-IFN alfa-2a and adefovir for 48 weeks and had pre-treatment frozen liver biopsies available for gene expression analysis. Response was defined as a combined response (HBeAg negativity, HBV DNA ≤ 2.000 IU/ml and ALT normalization) after 48 weeks of treatment-free follow-up. Rates of combined response were 33% (13/40). Gene expression profiling of 21,462 annotated genes was performed in 15 biopsies using Affymetrix Human Gene 1.0 ST microarrays (identification set). An additional 25 biopsies were used for confirmation by qPCR (validation set).In total, 41 genes were differentially expressed between responders and non-responders in the validation set (>1.5 fold change, $p < 0.05$). Gene ontology term analysis on the most significant genes specifically showed enrichment of biological processes related to the immune response, including antigen processing and presentation. Of the 41 significant genes in the identification set, 17 genes were selected for confirmation by qPCR in the validation set based on p-values and/or proven immunological function. In this validation set, gene expression values of 6 genes were significantly up-regulated in responders (CXCL11, HCP5, HLA-DPB1, HLA-DMA, IL17RB, and CPVL) and 1 gene in non-responders (SERPIN-E1). KappaNearest-Neighbor (KNN) analysis identified a 3-gene set (HLA-DPB1, CXCL11, and SERPIN-E1) to be most accurate in predicting response in the identification set (86% accuracy). In addition, using this gene set 15/25 (60%) patients in the validation set could be correctly classified. This included all 4 patients with a combined response, resulting in an optimal negative predictive value (11/11).
Conclusions: In this study we identified genes whose expression patterns in pre-treatment liver biopsies correlated with response to treatment with Peg-IFN and adefovir. These novel associations could lead to better understanding of IFN responsiveness in CHB patients, and possible selection of those patients who are most likely to benefit from peg-IFN combination treatment.

Dichotomal effect of immunosuppressants on hepatitis e virus infection: calcineurin inhibitors stimulate but mycophenolic acid inhibits viral replication

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Chronic hepatitis following hepatitis E virus (HEV) infection in orthotopic organ transplantation patients is becoming an urgent health issue. Although chronic HEV infection is generally linked to immunosuppressive medication, there is little insight how different immunosuppressants affect HEV infection, prompting research in this area. A subgenomic HEV replication model expressing luciferase reporter gene and a full-length infectious model were used to compare the effects of different forms of immunesuppressive medicine on HEV replication. As a result, steroids have no significant effects on HEV replication. Cyclosporine A (CsA) promoted HEV replication in both subgenomic and infectious models. RNA interference mediated gene silencing of Cyclophilin A and B, the cellular targets of CsA, resulted in dramatic increase of HEV genomic RNA levels by 4.0±0.6-fold and 7.2±1.9-fold (Mean±SEM, n=6, $P<0.05$), respectively. These results demonstrated that both Cyclophilin A and B have antiviral effects against HEV, which explains the proviral effects of CsA by inhibition of these two targets. In addition, high dose of another calcineurin inhibitor, FK506, also showed promotion of viral infection. In contrast, mycophenolic acid (MPA), an inhibitor of inosine monophosphate dehydrogenase (IMPDH), potently inhibited HEV replication. But supplementation with exogenous guanosine completely abrogated its antiviral activity, suggesting that depletion of cellular nucleotides is the main mechanism. Combination of MPA with ribavirin demonstrated additional antiviral potency.
Our results show that different immunosuppressants have specific effects on HEV replication and strongly argue against the use of calcineurin inhibitors whereas favor the use of IMPDH inhibitors in HEV-infected organ recipients.

Active genuine HBV replication in human liver chimeric uPA$^{+/+}$NOG mice

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Although new therapeutic compounds for viral hepatitis advance rapidly to the clinic, animal models remain essential for pathogenesis studies. We have previously shown that both the hepatitis B and C virus can replicate in chimeric uPA-SCID mice after transplantation with human hepatocytes. These experiments are however hampered by high colony maintenance costs, as only uPA+/- animals are fertile, while transplantation is exclusively successful in uPA+/+ mice. In addition, half of these fragile animals die during the 1st 6 weeks after transplantation, leading to low overall transplantation and infection efficacies. To reduce costs associated with this valuable animal model, we aimed to increase output set up a new mouse colony with lower liver-specific uPA-transgene levels on a profound immune deficient Nod-SCID-IL2Rγ$^{-/-}$ (NOG) background. Six to 9 week old uPA$^{+/+}$NOG mice were transplanted with upto 1 million cryopreserved human hepatocytes via intra-splenic injections. Human Albumin (hAlb) levels in serum were measured 5 to 8 weeks post transplantation (pTx) via ELISA. Well repopulated chimeric mice were infected intraperitoneally with 7 log IU HBV genotype A, 8 weeks pTx . HBV DNA levels were measured in mouse serum using the COBAS TaqMan HBV Test. HBV-specfic immunohistochemistry (IHC) for both the HBcAg and HBsAg was performed on formalin fixed livers 12 weeks after inoculation. Mixed uPA$^{+/+}$ male and uPA$^{+/-}$ female matings yielded a mean of 6 to 7 pups per nest. Transplantation of human hepatocytes resulted in excellent survival rates of 97,9% of acceptor mice within 6 weeks pTx and no spontaneous deaths thereafter. The fraction of mouse liver occupied by human hepatocytes as shown with HE staining, correlated with hAlb levels in mouse plasma. HBV was inoculated in 4 mice with hAlb levels ranging from 580-1120 µg/ml. HBV DNA levels increased in mouse serum from 4 weeks post infection to a maximum of 7 log IU at 12 weeks post infection, indicating active viral replication. HBV viremia at sacrifice correlated with HBsAg and HBcAg detection by IHC in human clusters . No changes were observed in hAlb levels during active HBV replication. Conclusions: Based upon a higher breeding efficacy, higher survival rate after hepatocyte transplantation and subsequent susceptibility to HBV, uPA-NOG mice are a more cost-efficient model to perform translational in vivo studies for viral hepatitis.

Gene expression profiles in peripheral blood as early biomarkers for response to induction therapy in Crohn's disease

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Background. Monitoring of remission induction therapy for active Crohn's disease (CD) is hampered by the lack of objective markers for therapy response. This also impedes development of new drugs since only subjective markers for therapeutic response can be used in clinical trials. Therefore, measurements of objective biomarkers are best applicable in peripheral blood. Biomarkers should differentiate therapy response from non-response, preferably early during therapy. This study aimed to identify biomarkers in peripheral blood distinguishing responders from non-responders at an early stage of remission induction therapy. MethodsWhole blood RNA was obtained before therapy and after 3, 7, 14 and 56 days of remission induction from 10 responders and 10 non-responders. To identify a biomarker for therapy response in general and not for a specific treatment, both anti-TNF-ï¡ and prednisone remission induction strategies were included. Response was defined by ≥20% improvement in CDEIS at colonoscopy after 8 weeks of therapy. Differential gene expression profiles between responders and non-responders during induction therapy were determined using a linear model and a moderated F-test to compare base with all other time points ($P < 0.05$). Paired comparisons between base and any of the other time points were assessed using a moderated t test ($P < 0.01$). Results. Before the start of therapy, 133 probesets were differentially expressed ($P < 0.001$) between responders and non-responders, including ATG16L2. Furthermore, after one week of induction therapy, 62 gene expression profiles could differentiate non-responders from responders ($P<0.01$). The most differentially expressed genes comprise FLG2, CNOT4, ANK1, MICAL2, FHL2, IGF2BP2, S100A6 and MAPK8IP3. When taking the diagnostic accuracy into account, MICAL2, FLG2, IGF2BP2 and FHL2 remain interesting candidate biomarkers to predict response after one week of therapy.
Conclusions. Here we describe the first study on gene expression profiles from peripheral blood distinguishing non-responders from responders to CD remission induction therapy. These early gene expression profiles are candidates to be prospectively validated in an independent cohort as biomarkers for non-response to remission induction.

NCF4 risk allele affects steroid exposure and dependency in Crohn's disease patients, preliminary results

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Background: NCF4 plays a role in the production of reactive oxygen species (ROS) by granulocytes. A single nucleotide polymorphism (SNP) in NCF4, rs4821544, is associated with ileal Crohn's disease (CD). We recently showed that ROS production in cells primed with granulocyte-macrophage colony-stimulating factor (GM-CSF) is reduced in patients (pts) carrying the NCF4 risk allele (C), which could hamper bacterial clearance, and thereby contribute to ongoing inflammation in risk allele carrying pts. Steroids affect not only T-cells and B-cells, but also phagocytes. Aside from reducing granulocyte migration, much like GM-CSF, glucocorticosteroids enhance granulocyte survival and ROS production. Thus, steroids may compensate impaired phagocyte function in pts carrying the NCF4 risk allele and it is conceivable that genetic NCF4 status may affect response to treatment in CD. The aim of this study was to assess the requirement, effects and side-effect of steroids in CD pts carrying the NCF4 risk allele. Methods: CD patients in whom DNA was available, were included in a database. rs4821544 SNP status was determined by KBiosciences. This study was approved by the medical ethical board. Results: In this pilot study, 87 CD pts were included, of whom 63.2% (55 pts) were female. Median age at diagnosis was 24.5 (range 6-50) and the median duration of the disease was 16.5 years (range 2.8-49.1). The NCF4 risk allele was present in 44.8% (39 pts) of the patients of which 18.2% (6 pts) were homozygous. The risk allele and non-risk allele carrying patients did not differ regarding disease location and disease behavior. Significantly more risk allele patients were prescribed prednisone, compared to non-risk allele patients (p=0.019). Furthermore, there was a trend towards a higher prednisone dependency in patients carrying the NCF4 risk allele (p=0.096). In a logistic regression analysis the correlation between the NCF4 risk allele and prednisone dependency (OR 2.6, CI 1.06-6.23) was confirmed.
Conclusion: Patients carrying the NCF4 risk allele were more exposed to prednisone and were highly steroid dependent. This could indicate that steroids work exceedingly well in these patients, while other treatments might be less effective. These results could be confounded by disease severity, however, preliminary analysis does not show differences in disease characteristics thus far. We will further investigate this in a larger population, with a special interest in the effects of other drugs.

Fibrosis does not increase with disease duration in ulcerative colitis

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Intestinal fibrosis in Crohn's disease is a process stimulated by chronic inflammation leading to an increased presence of myofibroblasts in all layers of the intestinal wall. Ulcerative colitis (UC) is classically considered to be a purely mucosal disease although rarely transmural complications such as strictures and stenosis develop. Fibrogenesis in UC has not been studied systematically yet and may be a neglected phenomenon. We therefore investigated whether there is a different fibrotic load in acute vs longstanding UC and whether the degree of fibrosis in UC correlates with the severity of inflammation.We therefore reviewed colectomy specimens from all UC patients operated between 2007-2012. Specimens from patients with recent onset refractory therapy UC (diagnosis < 2 years) and longstanding UC with dysplasia (> 10 years) were selected. Patients operated for colon cancer without UC served as controls. On H&E stainings the Geboes histological inflammatory activity score (0-22 points) was determined. Sirius Red stainings and collagen I and III immunohistochemistry stainings were performed for collagen, and α-smooth muscle (αSMA) for detection of myofibroblasts and smooth muscle cells. Staining intensity signals were investigated by image analysis software (Image J, NIH).We examined 13 colectomy specimens from patients with acute UC, 16 from patients with longstanding UC, and 7 colorectal cancer controls. Patients with short disease duration had a higher Geboes score of 19 (13-20) points, versus 8.5 (2-16) points in specimens with longer disease duration (p=0.001). Acute and longstanding UC had a thicker muscularis mucosa (MM) than controls (0.10 vs 0.10 vs 0.05 mm, p=0.019). Both UC groups had less submucosal αSMA expression (number of αSMA positive vs total number of cells; 29% vs 33% vs 54%, p=0.009). Between acute and late UC there was no difference in collagen deposition, however between UC together and controls there was more collagen I expression in the mucosa, MM and muscularis externa (50% vs 10%, p=0.02; 28% vs 10%, p=0.048; 71% vs 20%, p=0.003).In both early and long UC duration, we did not find a correlation between inflammation or collagen deposition or MM thickness. There was a negative correlation between inflammation and αSMA positivity in the submucosa (R=-0.51, p=0.003) and MM (R=-0.37, p=0.04).
Conclusion: In our series of colectomy specimens, there is more collagen deposition in UC than in controls. No association between disease duration and increased collagen deposition could be found. Expression of αSMA however is lower in UC and correlates with inflammation. Fibrosis in UC does not appear to increase significantly over time.

Identification of HLA-A and WWOX as genetic variants associated with recurrent fibrostenotic Crohn's disease

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Crohn's Disease (CD) is a chronic inflammatory disease with unpredictable disease behaviour. Insights obtained from genetic studies, have advanced our understanding of the complex disease biology identifying 163 genetic risk loci involved in disease development. However, from the clinical point of view it is equally important to identify genetic risk factors associated with disease behaviour or prognosis. In the current study we aim to identify genetic risk factors that are associated with fibrostenotic disease behaviour in CD with ileal localization. To increase power to identify these disease modifying genetic variants we compared so called "extreme phenotypes". Severe CD (n=242) was defined as patients who underwent a small bowel resection at least two times due to confirmed stenosis. The control group consisted of 279 patients with mild inflammatory disease behaviour CD (Montreal classification B1), defined as CD for more than 5 years without any progression to stenosis, fistulae, or resection. All patients were of European descent and were genotyped with the Immunochip genotyping array. After stringent quality control in total 166251 SNPs were tested. Allelic association analysis (χ^2 test) was performed with PLINKv1.07 software. SNPs showing an association of <1E-05 were selected for replication (ongoing). In the initial analysis SNPs in the WWOX gene showed a genome-wide-significant association (p-value 1E-08), whereas SNPs in the HLA-A gene showed a robust band of association (p-values 6E-05).
Conclusions: WWOX is an essential mediator of tumor necrosis factor-alpha-induced apoptosis; a key factor in the treatment of CD patients through anti-TNF therapy. The HLA-A gene has been reported to be associated to M. Graves and HIV control, and can play a major role in CD as an antigen presenting modifier. Both are functional interesting, potential, disease modifying genes for fibrostenotic disease behaviour in CD. A replication cohort will shortly be selected from the biobank of the Parelsnoer Instituut, a unique biobank that will contain phenotype data and DNA of IBD patients of all eight university medical centres in the Netherlands. According to our schedule, we will complete the replication before March 2014.

Leukocyte Scintigraphy as a Tool to Measure Inflammatory Load in Ulcerative Colitis

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Assessing inflammatory activity is essential in therapeutic decision making in Ulcerative Colitis (UC). Although leukocyte scintigraphy has been suggested as a potential method to image inflammatory activity, novel state-of-the-art scintigraphy including SPECT-CT has not been validated for the measurement of inflammatory load in UC in comparison with other inflammatory markers. We aimed to prospectively validate leukocyte SPECT-CT as a tool to measure and quantify inflammatory load in patients with different extent and severity of UC.UC patients with an indication for colonoscopy were included. Within 1 week and without any changes in therapy both colonoscopy (Mayo score, UCEIS) with biopsies (Geboes score) and leukocyte scintigraphy were performed. In addition, serum CRP and fecal calprotectin (Bühlmann ELISA) were measured and clinical questionnaires (CCAI, Mayo) were collected. Patients' peripheral blood leukocytes were isolated and labelled with 200 MBq technetium-99m HMPAO. SPECT combined with a low-dose CT was performed 60 min after reinjection of labelled cells. To quantify inflammation in each colon segment the maximum uptake of leukocytes was calculated as a ratio to the mean uptake in bone marrow of 4 lumbar vertrebrae and expressed as SPECT inflammation classification of each colon segment and a Summed Activity Score (SAS) for the inflammatory activity in all 5 colonic segments.Twenty-six UC patients were studied. 3/26 were using anti-TNF, 4/26 thiopurines, 3/26 prednisone and 20/26 5-ASA at inclusion. At endoscopy 6/26 (23%) of patients had proctitis, 8/26 (31%) left-sided and 12/26 (46%) pancolitis. According to endoscopic Mayo score, 1/26 (4%) of patients had inactive, 5/26 (19%) mild, 8/26 (31%) moderate or 12/26 (46%) severe disease. The median (IQR) full Mayo score was 7 (5-10), CCAI: 6 (2-9), serum CRP 4.1 mg/L (1.7-12.5) and fecal calprotectin 449 ug/g (245-1142). According to SPECT-CT patients were classified as having 9/26 Mild, 12/26 Moderate, 5/26 Severe disease for their most affected colon segment. Significant correlations (Spearman) were observed between this SPECT inflammation classification and endoscopic Mayo: r 0.54 ($P<0.01$), UCEIS r 0.56 ($P<0.01$) and histologic Geboes score r 0.59 ($P<0.01$). The Summed Activity Score correlated better with fecal calprotectin r 0.55 ($P<0.01$) than with CRP: r 0.24 ($P=0.24$), CCAI: r 0.43 ($P<0.05$) or clinical Mayo: r 0.54 ($P<0.01$).
Conclusions SPECT-CT classification of disease severity of the most inflamed colon segment is correlated with both endoscopic and histologic scores for UC. The total inflammatory load in UC at SPECT-CT is better reflected by fecal calprotectin compared to serum CRP.

Comparative efficacies of novel JAK inhibitors to reduce macrophage activation

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A non-selective inhibitor of Janus Kinase 1, 2 and 3 (pan-JAKi) has demonstrated clinical efficacy ulcerative colitis (UC). However, side effects such as neutropenia, can be explained by activity towards JAK2. JAK-inhibitors interfere with the innate immune response by inhibiting JAK1 dependant interferon (IFN) type 2 signalling. This prevents IFNγ driven monocyte differentiation of inflammatory macrophages in UC. To specify further the mechanism of JAK-inhibitors, we aimed to determine whether a selective JAK1-inhibitor (JAK1i, formerly known as GLPG0555 and in-licensed by GSK from Galapagos), was equally potent to interfere with pro- and anti-inflammatory cytokine secretion seen in inflammatory macrophages when compared to a pan-JAKi. Bone marrow-derived macrophages (BMDM) were cultured from C57BL/6 mice by exposure to M-CSF(L929) for 8 days. BMDM were stimulated with LPS (100 ng/ml) and IFNγ (20 ng/ml) for up to 360 min. in the presence of a pan-JAKi or a selective JAK1i in concentrations varying from 10 to 1000 nM. A microarray was performed to assess genes affected by the JAK1i on LPS/IFNγ transcriptional responses after six hours of stimulation. We then compared the potential of JAK inhibitors to inhibit IFNγ/LPS-induced STAT1 phosphorylation by Western blotting. Cytokine secretion by BMDM of TNFα, CXCL2, CXCL10, IL-10 and IL-6 was analyzed by ELISA. The potential of the pan-JAKi and the JAK1i to reduce phosphorylation of STAT1 was seen at 100 nM and above. This was observed after 20 and for up to 180 min. for both compounds. At protein level, the pan-JAKi, but not the Jak1i, enhanced IL-10 and TNFα secretion by BMDM at concentrations of 100nM up to 6 hours of stimulation ($p<0.05$). Both compounds caused a significant ($p<0.05$) decrease of CXCL10, and IL-6 secretion by BMDM after three hours of stimulation (IC50 app. 150nM for all measured). CXCL2 was unaffected by both compounds. The microarray showed that the JAK1i selectively inhibited transcription of IFNγ inducible genes such as, SOCS1, MHCII, IL12R1, IL12R2, CCR5 and CXCL9, while IL10 and CXCL1 transcripts were up regulated, as compared to LPS/IFNγ vehicle. Further, transcription of STAT1 and JAK1 genes were not affected. CONCLUSION: A selective JAK1i was equally potent at interfering with pro-inflammatory cytokine secretion seen in inflammatory macrophages in comparison to a pan-JAKi. At the transcriptional level, a JAK1i selectively down regulates a fraction of IFNγ induced genes. These data under the benefit of a more selective JAK1-inhibitor to intervene in inflammatory monocyte differentiation and activation and suggests the potential of this selective JAK1i in the treatment of UC.

Intestinal Epstein- Barr virus is associated with mucosal lymphoproliferation and subsequent intestinal surgery in inflammatory bowel disease patients

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Background and aims:Thiopurine therapy increases the risk of (Epstein- Barr virus (EBV) associated) lymphomas for Inflammatory Bowel Disease (IBD) patients up to four times. EBV can cause a wide spectrum of lymphoproliferative reactions, ranging from morphologically benign with normal B lymphocytes (BL) and lymphoplasmacytic infiltrate in the lamina propria (LI) to aggressive lymphomas with atypical BL and LI.EBV can be detected in colonic mucosa in up to 60 % of the IBD patients, but there is no consensus on when to perform EBV testing on intestinal mucosa. We hypothesized that EBV testing can be guided by histological features including morphology of BL and LI.The aim of this study was to determine the value of the histology of the inflammation in predicting EBV presence in intestinal mucosa and to correlate EBV positivity with clinical endpoints such as intestinal surgery and development of lymphoma.Methods:All IBD patients who underwent EBV testing by EBV-encoded RNA – in situ hybridization (EBER) in intestinal biopsies between January 2005 and October 2013 in our centre were identified. All biopsies were revised by a blinded, expert gastro-intestinal pathologist and scored on three histological features: number of EBV positive cells per high power field (HPF); normal or atypical LI and normal or atypical BL. Demographic and clinical data were collected from patient charts. Adverse events that were registered included intestinal surgery and lymphoma. We used the Chi square test or Fisher's exact test to identify an association with EBV positivity. Results: 58 IBD patients were included, 28 were EBV positive and 30 were EBV negative. Ulcerative colitis was more frequent in the EBV positive group (82,1 % versus 56,7 %; p=0.052)EBV positive patients had significantly more frequent atypical LI (57,1 % versus 3,3 %; p =<0,001). The specificity for predicting EBV presence of the atypical LI is high (96,7 %), just as its positive predictive value (94,1 %). The sensitivity and specificity of atypical BL for predicting EBV are 42,9 % and 83,3 %. At time of biopsy, EBV positive patients used more often combinations of two or more anti-inflammatory drugs (5-aminosalicytes excluded; 50 % versus 16,7 %; p=0,007)Eighteen EBV positive patients (64,29 %) had 20 pre-defined complications (18 colectomies, 2 lymphoma's). Within the group of EBV positive patients, those who developed complications had a significantly higher EBV load (50 % versus 10 %; p=0,048), expressed as the frequency of ≥ 10 EBV positive cells per HPF.
Conclusion:In the present study, atypical LI was associated with mucosal EBV in IBD patients. A high EBV load correlated with adverse events.

Predicting mucosal inflammatory activity in Crohn's disease: a new, validated non-endoscopic disease activity index

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Mucosal healing is presently considered one of the primary goals in treatment of Crohn's disease, but this can only be confirmed by endoscopy. We aimed to design and validate a Crohn's disease activity index based on a combination of clinical characteristics and readily available laboratory parameters, that reliably predicts the severity of mucosal inflammation. Thirteen clinical characteristics and laboratory variables were selected for analysis. Mucosal inflammation was assessed by the Crohn's disease Endoscopic Index of Severity. A linear regression model was based on 93 ileocolonoscopies performed in 82 Crohn's disease patients, and internally validated by bootstrap resampling. Subsequently, the newly developed model was validated in a cohort of 99 ileocolonoscopies. The number of liquid stools during one day*0.25 + C-reactive protein (mg/L) *0.1 + platelet count (10^9/L) *0.01 + fecal calprotectin (mg/L) *0.001 - mean platelet volume (fL) *0.2 optimally predicted the severity of mucosal inflammation (bootstrap adjusted R^2=0.50). The model demonstrated good agreement in the external validation (r =0.7), especially for (ileo)colonic Crohn's disease (r = 0.8). The negative predictive value of the model was 0.87.
Conclusions: This newly developed non-endoscopic, disease activity index was found to reliably predict mucosal inflammation in Crohn's disease patients. It can be expected to facilitate clinical decision making and might prove valuable in clinical trials.

Only one third of Crohn's disease patients have sustained remission of perianal fistulas

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Background: Despite more potent drugs and advanced surgical techniques the treatment of perianal fistulizing Crohn's disease (CD) remains challenging. With this study we aimed to assess the different treatment strategies used in perianal CD and their effect on remission (no discharge on history and physical examination), response (decrease of discharge, pain and bleeding from the fistula tract) and relapse. Methods: Patients (pts) with perianal fistulizing CD visiting our hospital between the 1-1-1980 and the 1-1-2000 were identified through hospital system search. Exclusion criteria were: diagnosis CD after fistula diagnosis, perianal fistulas that commenced <0.5 yrs after surgery or delivery, follow-up <0.5 yrs, no data on fistula complexity. Demographics, fistula characteristics and all received medical and surgical treatments aimed and the outcome of these strategies were noted. The Mann-Whitney U-test and the Fisher's exact test were used to determine association between variables. Results: In total 232 pts were identified (98 men; 42.2%). Median age at CD diagnosis was 22.8 yrs (4.0-68.7) and the median duration of CD was 16.9 yrs (0.6-46.5). CD localization was: upper GI tract (4.7%), small bowel (6.9%), ileocecal (15.1%), large bowel (37.9%), small and large bowel (28.9%), whole GI (0.9%) and isolated perianal disease (5.6%). In 41.1% there was rectal involvement. Follow-up was median 10.0 yrs (0.5-37.5). Fistula diagnosis was at a median age of 29.4 yrs (9.1-77.3), time to fistula was <10 yrs of CD diagnosis in 78.9%. Median duration to fistula formation was 7.0 yrs (0.7-38.0). Complex fistula (according to Sandborn criteria) were present in 78.0%. Medical treatment (antibiotics, steroids, immunosuppressants, anti-TNF) commenced in 79.7% of the pts and in 53.2% surgery (colectomy, fistulectomy, stoma, rectum amputation) was performed. Remission rate was 69.8% after a median duration of 2.3 yrs (0-25.3). Pts with simple fistulas had a higher remission rate (88.2% vs. 64.6%; p<0.001). Involvement of the rectum was not associated with a lower remission rate in both simple and complex fistulas (p=0.321 vs. p=0.255). Anti-TNF therapy did not alter remission rate in simple fistulas, however complex fistulas healed significantly less often after anti-TNF treatment (p=0.012). Initially healed fistulas recurred in 26.7% in case of simple fistulas and in 41.9% in case of complex fistulas (p=0.051) with an overall rate of 37.7%.
Conclusion: Only one third of perianal fistulizing CD pts had a sustained remission after conventional treatment strategies. Simple fistulas were more likely to heal than complex fistulas and less of these healed fistulas relapsed. Rectum involvement was not associated with lower remission rates.

Self-reported disability index in inflammatory bowel disease: results from a large Dutch prospective cohort

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The natural history of inflammatory bowel disease (IBD) is marked by periods of relapse and remission, over time leading to intestinal dysfunction and surgery. This may induce a wide spectrum of physical, psychological, familial, and social problems, collectively coined as disability, with potential impact on direct healthcare costs (DHC), productivity losses and quality of life (QOL).Therefore, factors associated with self-reported disability, and associations between self-reported disability and three-monthly DHC, productivity losses, and QOL were determined.IBD patients from seven peripheral and seven academic hospitals were prospectively followed for two years. Three-monthly questionnaires were filled-out, assessing demographics, clinical characteristics, illness perceptions, DHC, and productivity losses. At two years, patients completed the self- reported version of the IBD disability index. Linear regression analysis was used to determine the impact of demographics, clinical characteristics, and illness perceptions on disability. Associations between disability, three-monthly DHC and productivity losses, and QOL were assessed. A total of 978 IBD patients (57% CD, mean age 56 years, 48% male, median disease duration 20 years) completed the IBD disability index. In CD, clinical characteristics and illness perceptions contributed towards, respectively, 50% and 12% of the variance of disability. Greater disability was associated with increased disease activity (p=0.000), depression (p=0.000), stronger illness identity (higher number of symptoms attributed to IBD) (p=0.000), and stronger emotional response (negative beliefs about how IBD affects one's emotional well-being) (p=0.017). In UC, clinical characteristics and illness perceptions contributed towards, respectively, 47% (p=0.000) and 8% (p=0.000) of the variance of disability. Greater disability was associated with increased disease activity (p=0.000), stronger illness identity (p=0.029), and stronger emotional response (p=0.010). IBD patients with self-reported disability scored higher three-monthly DHC (€1,247 vs. €830, p=0.004) and productivity losses (€1,051 vs. €466, p=0.008), and a lower QOL (160 vs. 199, p=0.000) than IBD patients without self-reported disability.
Conclusions: Disability in IBD is mainly determined by clinical disease activity and illness perceptions, but not by disease duration or disease phenotype. Self-reported IBD disability is associated with higher costs and lower QOL. As potentially modifiable factors, illness perceptions may provide an additional target for biopsychosocial interventions, aimed at improving disability and reducing costs.

The relevance of population based IBD biobanks: a meta-analysis and introduction of the IBD-SL biobank cohort

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To investigate IBD pathophysiology and markers for predicting disease course, biobanks with extensively phenotyped data of unselected IBD populations are warranted. Since no such biobanks are available, we started a prospective population based (PB) biobank cohort (IBD-SL). Here we report the design of the IBD-SL biobank cohort, and the characteristics of included ulcerative colitis (UC) patients. Additionally, we aimed to test the widely used assumption that hospital based (HB) settings comprise a different subset of IBD phenotypes than PB settings, by using the UC characteristics of IBD-SL in a meta-analysis. Since 1991, adult incident IBD patients attending one of 3 regional hospitals were enrolled in IBD-SL. Missed patients were captured by scrutinizing the National Pathology Database and cross-checks with GPs, resulting in a completeness of 93%. Data on IBD phenotype, medication, surgery, extra intestinal manifestations, and demographics are collected at time of diagnosis and during follow-up. Since 2009, plasma, serum, faeces, and biopsies are being biobanked. Additionally, we performed a meta-analysis, including IBD-SL data, to calculate the pooled proportion of proctitis (E1), left-sided colitis (E2) and extensive colitis (E3) in PB settings (N=10) versus HB settings (N=13; DL random effect, Ln-transformation). In total, 1748 UC patients (53% male) patients were included in IBD-SL. Mean age at diagnosis and mean disease duration were 44.2 (SD 16.8) and 9.6 years (SD 6.0), respectively. Proportions of E1, E2 and E3 at diagnosis were 35%, 47%, and 18%, respectively. Ninety-eight percent ever used mesalamine, 32% immunomodulators and 10% anti-TNF agents. Eight percent had undergone (partial) colectomy. Ten percent ever had an extra intestinal manifestation (skin, eyes, joints and/or liver) during disease course, of which artropathy (3%) was most frequent. Additionally, pooled E1 proportion was higher for PB (39%, 95%CI 33-45) than for HB (21%, 95%CI 17-27, $p<0.001$). Pooled E3 proportion was lower for PB (24%, 95%CI 21-28) than for HB (35%, 95%CI 30-42, $p<0.001$).

Conclusion: Biobanks should be representative for the entire IBD population when studying pathophysiology and markers for predicting disease course. Observed phenotypic differences between population based and hospital based settings support the relevance of population based biobanks, such as IBD-SL.

Is elderly-onset ulcerative colitis a different entity? - Natural disease course and treatment response compared to adult-onset disease in a Dutch population-based cohort

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Population ageing is a worldwide demographic phenomenon. Since the incidence of ulcerative colitis (UC) is increasing, elderly-onset UC will become more prevalent in the near future. It is unclear whether elderly-onset UC is a different phenotypic subgroup, requiring alternative treatment strategies. Information on disease course and treatment response of elderly-onset UC patients is scarce and conflicting, and mostly derived from small, selected UC populations. Therefore, we aimed to compare disease course and treatment response between adult- and elderly-onset UC in our population-based cohort. Since 1991, incident IBD cases in our area in The Netherlands are included in our population-based cohort. The natural disease course was compared between adult-onset UC (i.e. <60 years of age at diagnosis) and elderly-onset UC (i.e. ≥60 years of age at diagnosis) in terms of progression of disease extent, use of immunosuppressive or anti-TNFα agents, hospitalisation and colectomy. Also long-term response to immune-suppressive and anti-TNFα treatment was assessed. Data were analysed with a Kaplan-Meier survival curve, and hazard ratios (HR) of age at diagnosis were calculated using a Cox regression model, while correcting for confounders. In total, 373 UC patients with elderly-onset (EO) and 1288 with adult-onset (AO) were included. Median follow-up was 7.1 years (IQR 3.7-13.5) and 9.0 years (IQR 4.6-15.2), respectively. The proportion of elderly in newly-diagnosed UC patients gradually increased over time (9.2% to 17.4%, r2=0.51, p<0.01). In elderly, more left-sided disease (56.7% vs. 45.3%, p<0.01) and less rectal disease (26.3% vs. 36.4%, p<0.01) were observed at diagnosis. The risk of hospitalisation was higher in EO patients (35.9% vs. 29.3%, HR 1.38 (95%CI 1.10-1.73)), while the risk of more hospitalisations (14.6% vs. 14.9%, HR 1.10 (95%CI 0.75-1.60)), the risk of colectomy (8.0% vs. 10.9%, HR 0.96 (95%CI 0.61-1.51)), and the risk of progression of disease extent (23.7% vs. 27.9%, HR 1.00 (95%CI 0.74-1.35)) did not differ between groups. EO patients were less likely to receive immunosuppressive (22.8% vs. 35.4%, HR 0.66 (95%CI 0.50-0.87)) or anti-TNFα treatment (7.8% vs. 18.0%, HR 0.42 (95%CI 0.25-0.72)). Risk of treatment failure was comparable between groups for both thiopurine (40.9% vs. 32.9%, HR 1.26 (95%CI 0.79-2.01) and anti-TNF treatment (34.0% vs. 36.6%, HR 1.14 (95%CI 0.45-2.88). Conclusion In this population-based UC cohort, elderly-onset UC behaved differently compared to adult-onset UC, reflected by a reduced use of immunosuppressive and anti-TNFα treatment, without subsequent increased need for multiple hospitalisations or colectomy.

Risk of colorectal cancer after endoscopic vs. surgical resection of carcinoma in situ is not different

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Background: Although endoscopic resection (ER) is considered to be the first- treatment for colorectal carcinoma (CRC) in situ (CIS), it is unknown whether the risk of CRC during follow-up is similar to that of surgical resection (SR). AIM: To evaluate whether ER and SR of CIS are equally effective in prevention of CRC at 5- and 10-year follow-up; and to identify risk factors for detection of CRC during follow-up. Methods: Patients diagnosed with a CIS in the period 1995 to 2005 were selected from the Netherlands Cancer Registry, which contains data on patient-, tumor- and treatment characteristics of all newly diagnosed malignancies in the Netherlands. Patients with no resection or with an event (i.e. diagnosis of CIS, CRC, death or loss to follow-up) within 6 months after primary diagnosis of CIS were excluded. Patients with a new CRC during follow-up were compared with patients without an event using standard descriptive statistics, and CRC incidence and mortality were evaluated over time between ER vs. SR. Results: A total of 3,069 patients with a CIS were included. ER was performed in 1,884 (61%) and SR in 1,185 (39%) patients. From 1995 to 2005, the proportion of ER as treatment modality ranged from 54% to 67% per year, but no trend was observed. Younger age (OR 1.01, 95%CI 1.00-1.01) and proximal location of the CIS (OR 7.09, 95%CI 5.52-9.09) were associated with SR. The number of newly detected CRCs at 5-year follow-up (47/1,884 (2.5%) in the ER group vs. 30/1,185 (2.5%) in the SR group, p=0.95) and 10-year follow-up (75/1,884 (4.0%) in the ER group vs. 43/1,185 (3.6%) in the SR group, p=0.62) was not different between both groups. Patients with a newly detected CRC were older compared to patients without an event at 5-year follow-up (68.2 ± 9.9 years vs. 65.8 ± 11.6 years; p=0.04) as well as 10-year follow-up (67.2 ± 10.8 years vs. 63.6 ± 11.1 years; p<0.01) but no differences were found for primary resection type, gender and primary CIS location at 5- and 10-year follow-up. Kaplan Meier analysis of time to CRC was not different between ER and SR at 5-year follow-up (log rank p=0.99) as well as 10-year follow-up (log rank p=0.54). Overall survival at 5-year follow-up was higher in the SR group compared to the ER group (log rank p=0.01); however, at 10-year follow-up this difference was no longer found (log rank p=0.93).
Conclusions: In this large case cohort study, ER of CRC in situ was equally effective in the prevention of CRC as SR at 5- and 10-year follow-up. Overall survival benefit in only the first years after surgical resection was probably due to selection of relatively younger and therefore healthier patients for surgery.

Endoscopic transpapillary gallbladder drainage in high-risk patients: the use of a double pigtail stent

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Percutaneous gallbladder drainage (either transperitoneal or transhepatic) is still treatment of choice for patients with acute cholecystitis and a high surgery risk. Recent studies –mainly from Asian countries- have demonstrated that endoscopic transpapillary gallbladder drainage using a double pigtail stent can be an effective treatment for high risk patients with acute cholecystitis and/or recurrent symptomatic gallbladder disease. In this prospective feasibility study we describe 12 patients treated by endoscopic transpapillary gallbladder drainage from sept 2012-nov 2013. All included patients had persistent symptomatic gallbladder disease after failure of primary treatment and a (temporary or prolonged) high surgery risk. An endoscopic retrograde cholangiography (ERC) was performed and a double pigtail stent was left to guarantee drainage from the gallbladder to the duodenum. The technical success, clinical success (defined as resolution of symptoms) and direct and late complications related to the pigtail stent placement were analysed. The pigtail stent was removed when related symptoms occurred and replaced after one year. Pigtail stent placement was technically succesfull in 11 patients (92%); one patient developed symptoms of recurrent cholecystitis 7 months after stent placement (clinical success: 91%). Postprocedural complications occurred in one patient with mild post-ERCP pancreatitis (early complications: 9%); cholangitis, bleeding or perforation were not seen. In four patients a cholecystectomy was performed after the temporary contra-indication for surgery was cleared. Late complications did not occur.
Conclusion: Endoscopic transpapillary gallbladder drainage is technically possible and can be an effective and safe procedure for patients with persistent symptomatic gallbladder disease who are at high risk for surgery. This procedure can either serve as a 'bridge to surgery' or as a permanent treatment for gallbladder drainage in patients with a prolonged increased surgery risk.

EUS-guided drainage with a large diameter metal stent is a safe treatment for acute cholecystitis in high risk patients

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Percutaneous gallbladder drainage is the treatment of choice in high-risk surgical patients with acute cholecystitis. However, continuous drainage is associated with patient discomfort and risk of inadvertent drain removal. Recently, EUS-guided transmural drainage has been reported as alternative treatment. Our aim was to determine the safety and feasibility of EUS-guided gallbladder drainage with a large diameter metal stent (AXIOS) in patients with acute cholecystitis at high risk for surgery. We performed a prospective, international, multicenter study aiming to include 30 patients. Patients were daily followed until resolution of cholecystitis and stent removal was performed after 3 months. To date, 26 patients (9 men, median age 84±8) were included. An ASA score >2 was the most common cause why patients were at high risk for surgery (n=11, 43%). Median time between onset of symptoms and stent placement was 2 days (IQR 1-6 days). In 11 patients (42%) a transgastric approach and in 15 patients (58%) a transduodenal approach was performed. Stent placement was technically successful in 24 patients (92%). In two patients an additional stent was placed due to problems with stent deployment. Clinical success was achieved in all patients after a median of 3 days (IQR 3-5 days). Stent removal was successfully performed in 8 patients (31%) after a median of 100 days (range 68-120), 5 patients (19%) died before stent removal due to an unrelated disorder (median 10 days, range 5-25), in 2 patients (7%) the stent was left in place because of tissue overgrowth (after 105 and 150 days) and in 11 patients (42%) the stent was still in place because of follow-up <3 months. Stent removal was rated as easy in 7 patients, while removal was difficult in one patient due to severe tissue overgrowth (after 125 days). Causes of death included urosepsis (n=1), pneumonia (n=1), myocardial infarct (n=1) and progression of pancreatic carcinoma (n=2). In the latter, infection parameters increased in one patient but no infectious cause could be found. Major complications were reported in two patients (7%). One patient presented with melena due to mucosal gangrene of the gallbladder for which irrigation of the gallbladder was performed. One patient developed fever due to food contents in the gallbladder for which stent removal was performed. This same patient developed acute biliary pancreatitis 21 days later. Conclusion: EUS-guided gallbladder drainage with a large diameter metal stent is feasible in high-risk surgical patients, with high technical and clinical success rates. Although the number of major complications was low, tissue overgrowth may preclude safe stent removal.

Hydraulic dilation in idiopathic achalasia using the EsoFLIP dilation balloon: a prospective cohort study

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Pneumatic dilation is often used in achalasia patients. Fluoroscopy can be of help during dilation to position the balloon at the esophagogastric junction (EGJ) but has the disadvantage of radiation exposure. An important element of dilation is esophageal distensibility, defined as compliance of the wall at a certain point, which can be used to assess the effect of dilation and possibly the risk of perforation. Distensibility cannot be measured during pneumatic dilation. A new hydraulic dilation balloon, the EsoFLIP, is able to visualize the shape of the balloon in vivo and measures distensibility during dilation. The aim of this study was to evaluate technical feasibility and safety of the 30mm EsoFLIP hydraulic dilation balloon in patients with a new diagnosis of achalasia. Consecutive patients with newly diagnosed achalasia were dilated on two separate days using the EsoFLIP balloon under endoscopic visualization. Patients were contacted 1 week, 1 month and 3 months after dilation. Technical success (placement at the EGJ and successful dilation while measuring diameter, pressure and distensibility), clinical success and major complications were evaluated. Nine patients (4 male [44%], median age 40 years, range 28-62) were included between August and December 2013. Patients were symptomatic for a median of 9 months (range 3-23). Technical success was achieved in all cases. Gradual inflation showed that the balloon had a strong tendency to move proximally/distally but in vivo imaging enabled precise placement. On day 1, the median minimal diameters (mm) of the GEJ before and after dilation were 9.5 (range 7.2-12.9) and 16.3 (range 13.4-21.4), respectively. On day 2, these were 13.1 (range 8-15.2) and 16.7 (range 14.5-18.6), respectively. Median difference in diameter before the first and after the second dilation was 7.3 (range 3.2-9.2). Median pressures (mmHg) used during the first and second dilation were 551 (range 310-1130) and 603 (range 390-815), respectively. Median esophageal distensibilities (mm^2/mmHg) on day 1 before and after dilation were 1.2 (range 0.2-2.2) and 10.4 (range 0.8-20.1), while on day 2 these were 1.7 (range 1-4.3) and 7.3 (range 3.3-29.3), respectively. Median difference in distensibility was 6 (range 2-28). No major complications were seen. Two patients (22%) reported recurrent dysphagia for which Heller myotomy was performed.
Conclusion: Dilation with the EsoFLIP balloon in achalasia is feasible and safe. In vivo imaging of the balloon shape facilitates placement of the balloon while esophageal distensibility measurements allow for a personalized dilation regimen, which may improve effectiveness and safety of the procedure.

Predictors for treatment failure after endoluminal fundoplication in GERD

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Transoral Incisionless Fundoplication (TIF) is an endoluminal fundoplication developed for treatment of patients with gastroesophageal reflux disease (GERD). Studies evaluating predicting factors for treatment outcome of the TIF procedure have reported inconsistent results. Therefore, the aim of the present study was to assess which predicting factors affect treatment outcome of the TIF procedure. Fifty-four consecutive GERD patients (37 males; mean age 45) underwent the TIF procedure. Endoscopy, 24 hr pH-impedance monitoring and manometry were performed preoperative and at 6 months follow-up. Pathological bipositional reflux was defined as abnormal acid exposure time (AET) in both upright (>4.4%) and supine (>1.2%) position; pathological upright reflux as acid exposure >4.4% in upright position and normal exposure in supine position (<1.2%); pathological supine reflux as normal acid exposure in upright position (<4.4%) and >1.2% in supine position. Patients with normalization of AET (pH<4 for ≤4% of time) at 6 months follow-up were considered as responders. Multivariate logistic regression analysis, adjusting for gender and age, was performed to evaluate preoperative AET, BMI and LES resting pressure as possible predicting factors. Patients with bipositional reflux (n=31) tended to have more severe GERD according to AET than patients with pathological upright reflux (n=21) (total: 10.2 (6.4-16.2) vs. 8.0 (5.7-11.2) (median (IQR), p=0.08). No differences were found in number of reflux episodes or symptom scores between patients with and without bipositional reflux. Six months after TIF, 26 (48%) patients were considered as responders and 28 (52%) patients as non-responders. Presence of preoperative esophagitis was associated with treatment failure (X^2 = 4.9, p=0.03) and preoperative esophagitis was present in 43% of non-responders and in 15% of responders. However, there was no association between preoperative reflux pattern and treatment failure (X^2 = 1.16, p=0.28). At six months follow-up, no difference was found in total AET (6.7 (3.3-13.0) vs. 3.8 (2.5-8.8), p=0.29) and presence of esophagitis (X^2 = 0.90, p=0.34) between patients with and without bipositional reflux. Multivariate logistic regression analysis showed that patients with a high BMI have an increased risk of treatment failure (OR 1.23, 95% CI 1.01-1.51, p=0.04) and there was a tendency for an association between preoperative AET and treatment failure (OR 1.16, 95% CI 0.99-1.36, p=0.06).

Conclusions: Preoperative esophagitis and high BMI are predictors for treatment failure after TIF in GERD patients, whereas preoperative reflux pattern is not associated with treatment outcome.

Are the gastric folds still the optimal landmark for defining the distal border of a Barrett's esophagus in a Western population?

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The definition of the esophagogastric junction (EGJ) for a diagnosis of Barrett's esophagus (BE) is not uniform: in Western guidelines the EGJ is located at the top of the gastric folds (GF) in expiration. In contrast, in Japan the EGJ is defined by the distal end of the palisade vessels (PV). Yet, PV are faint and often poorly visible in Western patients. Narrow Band Imaging (NBI) enhances contrast in mucosal structures and vessels. The new Olympus EXERA III endoscopy system combines bright NBI with dual focal high-resolution endoscopy, and may more easily visualize PV, even in Western BE patients. The aim was to evaluate the detection rate of PV using the EXERA III system, to quantify the discordance between the Western and Japanese criteria for the distal border of BE, and to evaluate the presence of intestinal metaplasia (IM) in this "zone of discordance" (ZoD), in Western BE patients. Consecutive Dutch patients with BE segment of ≥ 2 cm (no or low-grade dysplasia) on previous endoscopy were enrolled. Endoscopies were performed by a Western expert endoscopist, assisted by a Japanese endoscopist. The distance of the GF and distal ends of PV (when visible) to the incisors were determined in in- and desufflated conditions. Any difference in distance between the top of the GF (in expiration) and the distal end of the PV was considered a ZoD. Two biopsies were taken from the cardia (either 1 cm below the distal end of the PV, or 1 cm below the GF in case of absence of PV), 2 biopsies from the ZoD when present, and 4-quadrant biopsies 1 cm proximal of the GF to determine the presence of IM. Twenty-five patients (19 males, median 66 yrs, median BE C5M7) were included. PV were seen in 96%, and more often in inspiration (96%) than in expiration (76%; p=0.06). PV were located in a constant position during in- and expiration. In patients with visible PV, in 63% (n=15) a ZoD was present in expiration with the GF median 1 cm (range 1-2) proximal to the PV. In patients with a ZoD, IM was present in 6/30 (20%) of the ZoD biopsies. This was less in the cardia biopsies (0/30; 0%; p=0.01) and more in the biopsies obtained proximal of the GF (35/60; 58%; p<0.001). In 10 patients without ZoD biopsies of the cardia and proximal of the GF contained IM in 0% and 63% respectively. In Western patients PV are frequently seen with the newest NBI-system. PV are best observed under optimal insufflation. In a substantial subset of patients the GF and PV differ in location and IM can be detected in biopsies from this "zone of discordance" whereas no IM is detected in biopsies distal to the PV. These results question the value of the GF as the distal margin of the Barrett's segment.

Cost-Effectiveness Analysis of Radiofrequency Ablation for Barrett's Esophagus with Low-Grade Dysplasia: Results from a Randomized Controlled Trial (SURF)

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Background: Recent data from a European randomized trial (SURF) showed that radiofrequency ablation (RFA) for Barrett's esophagus (BE) with confirmed low-grade dysplasia (LGD) significantly reduced the risk of progression to high-grade dysplasia and esophageal adenocarcinoma with 25%. Ablation for BE-LGD may therefore be of clinical utility if the risk of neoplastic progression is reduced at an acceptable cost profile. Modeling studies have suggested that RFA might be a cost-effective management strategy for confirmed and stable BE-LGD, but these studies were limited by the available data on the natural history of BE-LGD. This is the first trial-based cost-effectiveness analysis of RFA vs endoscopic surveillance in the management of BE patients with confirmed LGD. Methods: This cost-effectiveness analysis was built from the trial data from randomization to end of follow-up (median 36 months,IQR 30-36), and was developed from a Netherlands hospital perspective. RFA and endoscopic surveillance were performed according to international guidelines for the management of BE patients. Direct medical costs generated during treatment (including complications) and follow-up period of the trial, and direct medical costs of endoscopic/surgical management of neoplastic progression, were estimated using hospital unit costs or Dutch reference costs. 95% confidence intervals of costs in each group were constructed using 1000 times bootstrap resampling. Incremental cost-effectiveness ratios were defined as the cost of ablation to prevent one case of neoplastic progression. Results: Neoplastic progression occurred in 1/68 ablation patients vs 18/68 surveillance patients ($p<0.001$). Mean total costs per patient during the trial (until the primary endpoint of progression was reached) were €10464 (95%CI:9469-11399) for ablation and €1902 (95%CI:1722-2068) for surveillance. For subsequent treatment of progression mean total costs per patient were €16 (95%CI:0-33) for ablation and € 2208 (95%CI:1399-3163) for surveillance. To prevent one case of progression the amount to pay for ablation is €504 based on trial costs. When taking into account the additional costs for treatment of progression, the amount to pay to prevent one case of progression is reduced to €375 for ablation. The main cost drivers were therapeutic endoscopies and esophagectomy.
Conclusions: Based on data from a randomized trial, the costs of ablation were only marginally higher than for endoscopic surveillance in preventing one case of neoplastic progression among BE patients with confirmed LGD. Implementation of ablation as the first management strategy for confirmed BE-LGD may be acceptable from a provider perspective.

Efficacy and safety of HALO90-RFA-ablation using the simple protocol (3x15J-no cleaning)

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Radiofrequency ablation (RFA) is a safe and effective treatment modality for Barrett's esophagus (BE). RFA-treatment generally starts with circumferential balloon-based ablation followed by multiple focal RFA sessions using a cap-based device. In Europe, the standard protocol for focal RFA consists of double 15 J/cm2 ablation, cleaning of the ablated areas and catheter, followed by a second double 15J/cm2 ablation (2x15J-clean-2x15J). A randomized trial has shown that a simple protocol (3x15J-no cleaning) obtains comparable results for treatment of individual Barrett's islands. However, no data are available on the efficacy and safety of this simple protocol for treating the whole BE, including circumferential ablation of the esophagogastric junction (EGJ), nor about the effect of subsequent focal RFA sessions using this regimen. The more aggressive triple application might be associated with complications such as stenosis. Our aim was to evaluate the efficacy and safety of HALO90-ablation of BE including the EGJ, using the simple (3x15J-no cleaning) protocol. From Jan'11-Nov'13 all BE patients scheduled for focal RFA in 4 tertiary referral centers were treated with the simple protocol. The EGJ was ablated circumferentially in addition to any BE islands or tongues. Patients were excluded if they underwent RFA with focal devices other than the HALO90-device, or when treated with a protocol other than the simple protocol. Primary outcome parameters were complete remission of dysplasia (CR-DYS), intestinal metaplasia (CR-IM) and stenosis requiring dilatation. Secondary outcome was complications leading to hospital admission. Eighty-two patients with dysplastic BE (60 males, mean age 68 yrs, median BE C1M3) were enrolled. 65/82 (79%) of these patients underwent an endoscopic resection (ER) of a visible lesion before RFA treatment. In an intention-to-treat analysis (counting drop-outs as failures), after a median number of 2 RFA treatments (range 1-5), 77/82 (94%) patients achieved CR-DYS, while 72/82 (88%) achieved CR-IM. In a per-protocol analysis (censoring for drop-outs), all 77 patients (100%) achieved CR-DYS, while 72/77 patients (94%) achieved CR-IM. Stenosis, requiring a median of 2 (IQR 1-2) dilatation sessions, developed in 7/82 (9%) patients. Three patients (4%) were admitted following RFA: two patients because of severe pain, one patient because of food impaction 7 days after RFA-treatment.
In conclusion, a treatment algorithm incorporating the simple protocol for all HALO90 treatments including circumferential treatment of the EGJ, appears to be effective and safe with results comparable to those reported on the standard protocol.

Detection of buried Barrett glands after Radiofrequency Ablation (RFA) with Volumetric Laser Endomicroscopy (VLE)

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Background: The prevalence and clinical relevance of Buried Barrett's (BB) epithelium after radiofrequency ablation (RFA) in Barrett's esophagus (BE) is questioned. Recent studies using small optical coherence tomography (OCT) catheters for scanning underneath the neosquamous epithelium demonstrated a high prevalence of tissue structures that might correspond to BB. Histological correlation, however, is lacking. Volumetric Laser Endomicroscopy (VLE) is a novel balloon-based OCT imaging technique that provides a 6-cm long circumferential volumetric scan of the esophageal wall layers to a depth of 3 mm with a resolution comparable to low-power microscopy. Aim: To evaluate if post-RFA subsquamous structures, detected with VLE, actually correspond to BB and to pursue direct histological correlation of VLE images. Methods: In-vivo VLE was performed to detect subsquamous structures suspicious for BB in patients with 100% endoscopic regression of dysplastic Barrett's epithelium after RFA. Areas with suspicious subsquamous VLE structures were marked with electrocoagulation after which in-vivo VLE was repeated to confirm that the correct area was demarcated. These areas were subsequently resected endoscopically, followed by immediate ex-vivo VLE scanning to reconfirm the presence of the subsquamous VLE structures. Extensive histological sectioning was then performed and all histopathology slides were evaluated by an expert BE pathologist (blinded for VLE images). Results: In 9 patients, 6 areas with suspicious subsquamous structures were seen on in-vivo VLE and resected. Ex-vivo VLE of these 6 ER specimens reconfirmed the presence of these subsquamous structures in 5 ER specimens. Extensive histological sectioning of these areas showed BB in one area. The other subsquamous VLE structures corresponded to dilated (ducts of) (sub)mucosal glands or blood vessels.
Conclusion: VLE may potentially detect BB under endoscopically normal appearing neosquamous epithelium. However, most post-RFA subsquamous structures identified by in-vivo VLE did not correspond to BB. Further studies are required to identify VLE features that allow for differentiation of BB from normal subsquamous structures.

Predictive factors for recurrence of cryptoglandular perianal fistula characterised by pre-operative endoanal ultrasound (EAUS)

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Introduction: To adopt the best surgical strategy for fistula-in-ano and avoid recurrences, it is necessary to gather precise information regarding fistula location and anorectal structures affected. Aim: The main aim of this study was to determine predictive factors for fistula recurrence during pre-operative EAUS. Methods: A review of all patients who underwent pre-operative evaluation for anal fistula using endoanal ultrasound (EAUS) between 2002 and 2012 was performed in a tertiary centre and in a clinic specialized in proctologic surgery. Cox proportional hazards models were constructed after performing univariate and multivariate analysis for gender, academic centre and private clinic, previous incision and drainage of a perianal abscess (I&D), previous fistula operation, internal fistula opening (IO) identified in EAUS, fistula complexity, age at surgery (<45 or >45), I&D during surgery and type of surgical treatment. Univariate variables with a p-value lower than 0.05 were included. Backward selection was performed to select the strongest predictors. Kaplan Meier survival curves were calculated for surgical treatment and fistula complexity. Results: 146 patients were included. Complex fistulas were present in 40%. Mean follow up time was 36 months (SD 27). Low fistulas were surgically treated by fistulotomy (FT, n = 96), high fistulas by fistulectomy (FC, n=30) or mucosal advancement flap (MF, n = 20). The recurrence rate for fistulas treated by FT was 11% (CI 7 – 15%) after 1 yr and 15% (CI 9-21%) after 3 yrs. In the FC group the recurrence rate was 42% (CI 28 – 56%) after 1 yr and 58 % (CI 44 – 72%) after 3 yrs. In the MF group the recurrence rate was 27% (CI 17 – 37%) after 1 yr and 36% (CI 26 – 46%) after 3 yrs. The risk of recurrence was higher for patients with previous I&D (HR 1.9 (C.I. 0.96 – 3.50), P = 0.043), for patients with an unidentifiable IO during EAUS (HR 2.0 [1.10 – 3.87]; P = 0.032) and for patients with a complex fistula (HR 4.8 [2.21 – 10.58]; P< 0.001). When adjusting for type of surgery the association between recurrence and complexity grew stronger (HR 8.3 (C.I. 2.90 – 25.77), P = <0.001) whilst the other risk factors remained stable.
Conclusion: Pre-operative EAUS is a useful pre-operative adjunct with excellent accuracy in relation to evaluation under anaesthesia. The strongest predictor for fistula recurrence was fistula complexity which increased the chance for recurrence with 38%. An unidentifiable opening during pre-operative EAUS increased recurrence with 10% and previous I&D with 9%. Pre-operative EAUS is mandatory in patients with previous perianal fistula or abscess related surgery as complexity can be expected.

Long term outcome after surgery for cryptoglandular perianal fistula

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There is still a lot of debate about the best treatment for cryptoglandular anal fistula. We have analysed the results and outcome of patients treated in our centre and identify risk factors for recurrence and incontinence. Three hundred and eleven patients who had surgery for cryptoglandular anal fistula in the period 1995-2010 were analysed. Exclusion criteria were fistulas of secondary origin, prior surgery, younger than 18 years and no operation report. After exclusion, demographics, fistula type, treatment modality and recurrence data were collected. Primary outcome was the recurrence rate within 2 years after surgery. Univariate and multivariate analysis were used to assess various risk factors. During exam under anaesthesia fistulas were classified in submucosal (12.5%), intersphincteric (33.1%), low transsphincteric (10.0%), high transsphincteric (9.6%), suprasphincteric (1.6%), extrasphincteric (0.6%), Parks-unclassifiable low fistula (20.3%) and unclassifiable fistulas (12.3%). A multivariate Cox regression analysis was performed showing that non-identification of the internal opening (p=0.035. aHR 3.9 [95%CI 1.1-14.2]) and secondary extensions (p=0.017. aHR 3.3 [95%CI 1.2-8.9]) were independent factors for recurrence. Multivariate logistic binominal regression analysis showed that the number of fistula tracks (p=0.015. aRR 3.8 [95%CI 1.3-11.0]) and the number of fistula operations (p=0.012. aRR [95%CI 2.2-455.5]) were independent factors for the development of faecal incontinence.
Conclusion The overall 2-year recurrence rate of 15.4% is acceptable, but the absence of common definitions and variation in classification makes it difficult to compare this in current literature. Total eradication of the fistula track during the first surgery is essential to achieve low recurrence rates, especially the identification of the internal opening and secondary extensions are important. The lay open technique (fistulotomy) is excellent for fistulas after a well-advised choice of the surgeon and patient.

Treatment response of EATL patients; a ten year analysis of a national cohort

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Enteropathy-associated T-cell lymphoma (EATL) is a rare T-cell Non-Hodgkin Lymphoma. Based on clinical presentation EATL can be divided into two subgroups; EATL can arise in celiac disease (CD) patients without a known history of celiac disease (EATL de novo) or EATL manifests in adult patients with previously diagnosed (refractory) celiac disease who clinically deteriorate (secondary EATL). Currently, there are no standardized treatment protocols and prognosis of EATL remains poor. We evaluate extended follow-up of EATL patients referred to our tertiary celiac disease center (1999-2013). A total of 61 patients with EATL were included. The diagnosis of EATL was established according to the WHO. We evaluated treatment stategies and overall survival (OS). Treatment response was assessed as complete remission (CR), stable disease (SD) or progressive disease (PD). In 31/61 patients (51%) EATL was diagnosed in patients without previous history of (refractory) celiac disease (EATL de novo). The remaining 30/61 (49%) patients suffered from secondary EATL (RCDII n=19. CD n=11). Nineteen patients (31%) were treated with chemotherapy combined with surgery. Treatment consisted of systemic chemotherapy in 12 (20%), surgery in 12 (20%), chemotherapy and resection with autologous stem-cell transplantation (auSCT) in 5 (8%) and chemotherapy and resection with allogenic stem-cell transplantation (alloSCT) in 2 (3%). CR was achieved in 23 patients (38%), SD in 5 patients (8%), and PD in 33 patients (54%). CR was mainly achieved after SCT therapy. Overall the relapse rate in CR patients was 52% with a median follow-up of 13 months after therapy (range 1-54 months). Patients treated with chemotherapy and resection with auSCT showed a relapse rate of 40%. With a median survival of 6 months (range 0 – 142 months), 50/61 patients died (82%). One, three- and five-years OS was 37 %, 16 % and 10 % respectively. Patients who were treated with chemotherapy and resection with auSCT showed a median survival of 15 months. Patients with EATL de novo showed better survival compared to patients with secondary EATL (P = 0.006).
Conclusion: best treatment response and the lowest relapse rate is achieved after intensive therapy (auSCT). Overall survival remains poor, although intensive chemo-therapy and resection with auSCT improve survival. International cooperation is warranted to evaluate new treatment options.

Surgery for complicated celiac disease

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The prevalence of celiac disease (CD) is 0.5-1% in the Western population. A small percentage (2-5%) of adult-onset CD patients develops refractoriness or (pre)malignant complications, like ulcerative jejunitis (UJ) and Enteropathy Associated T-cell Lymphoma (EATL). Especially in stenotic UJ and EATL surgery is indicated. Most of the EATL patients present with ulcerative lesions, stenotic lesions and perforation. Surgery serves as pre-therapy treatment in order to treat or prevent perforation of the small bowel during (chemo)therapy. After surgery patients receive immuno-, chemotherapy and/or stem cell transplantation. Our aim is to report our experience in surgery on patients with complicated celiac disease. Over the past 10 years 37 CD patients were treated with above mentioned approach. Twenty-one of them were male. In 41% urgent surgery was needed, mainly because of small bowel perforation (n=10). Perforation and stenosis were the main indications for surgery in these patients. Thirty-six patients had a partial small bowel resection. In twelve patients the the tumor was only partially resectable. Surgery was complicated in half of the patients leading to reoperation in 41%. In one patient reoperation was needed because of mechanical ileus two years after small bowel resection. In a second patient recurrent EATL perforations occurred. Final diagnosis was UJ in 3 patients and EATL in 34 patients. The patients with UJ were adjuvant treated with cladribine. To date, 23 patients with EATL received chemotherapy, followed by stem cell transplantation in 7 patients. During postoperative treatment no complications were observed. Twenty-five of the EATL-patients died during follow-up. The median survival after surgery was 14 months (range 0-121 months). Although survival remains poor and complications after surgery do occur surgery aids as a definitive diagnostic modality in UJ and EATL. Furthermore surgery can be used as pre-treatment option to prevent the potentially lethal perforations following chemotherapy for EATL.

Smooth muscle protein 22 (SM22) in plasma and urine reflects transmural ischemic injury of the intestines

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Acute mesenteric ischemia is an abdominal emergency requiring rapid diagnosis and treatment since the duration of ischemia is the most important determinant of outcome. Current biomarkers only detect ischemic mucosal injury, whereas differentiation between mucosal and transmural ischemic intestinal damage is imperative because only the later needs emergency surgery. A previous study showed that SM22 (22-kDa protein exclusively expressed in visceral smooth muscle tissue) is a potential biomarker for intestinal muscularis externa injury. Our aim is to study SM22 release test characteristics and its usefulness in differentiation between mucosal and transmural damage in patients.
SM22 release was investigated in rats subjected to mesenteric ischemia by 0, 2, 4, 6, 8, 12, 24 hours jejunal blood supply ligation. One day after laparotomy blood, urine and tissue was sampled and SM22 concentrations were measured using a newly build ELISA. Organ-specific SM22 release and clearance was studied in blood drawn from portal, hepatic, renal vein and a (radial) artery in rats and in 10 patients undergoing major upper abdominal surgery. SM22 and I-FABP (a sensitive marker to study enterocyte damage) were quantified in plasma of 12 patients with proven intestinal ischemia and 50 healthy volunteers. Tissue sections were stained with haematoxylin/eosin (HE) and SM22. In rats, histological assessment revealed degeneration of the mucosa and necrosis of the muscular layers of the intestinal wall in jejunum exposed to 24h ischemia as compared to control. Staining for SM22 revealed a decrease in staining intensity or even a total absence of SM22 protein in the muscular layers after 24h ischemia. Base plasma SM22 levels were ≤0.1 ng/ml in all animals. After ischemia, SM22 plasma levels continued to rise significantly for the 24h period compared to control ($p < 0.05$). Urinary SM22 concentrations were significantly higher in rats with intestinal ischemia compared to control ($p < 0.05$). Transorgan measurements showed that SM22 was specifically released from the intestines and removed from circulation by the kidneys, resulting in a plasma half-life of about 16 minutes in rats and 22 minutes in man. SM22 levels were significantly higher in patients with histopathological proven transmural infarction compared to patients with only ischemic mucosal injury and healthy controls (5.9 ng/ml vs 0.6 ng/ml and 0.4 ng/ml ($p < 0.001$), respectively).
In conclusion, SM22 is released into the circulation after severe intestinal ischemic injury and is potentially useful as a marker for the detection of transmural injury during intestinal ischemia.

Development of a prediction model to assess the risk of chronic gastrointestinal ischemia in referred patients

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Background and aim: Chronic gastrointestinal ischemia (CGI) is a challenging disease entity. Clinical symptoms may differ amongst patients. The aim of this study was to establish predictors for the diagnosis of CGI based on self-reported variables and to combine these in a prediction model. Patients and Methods: We analyzed data of a prospective cohort study. Between November 2006 and March 2013 self-reported symptoms were collected by a structured questionnaire of 431 consecutive patients referred to an academic hospital for evaluation of possible CGI. All patients received the standard work-up of CGI, consisting of radiological imaging of the gastrointestinal arteries, and functional testing for detection of mucosal ischemia by means of visible light spectroscopy (VLS) or tonometry. The results were discussed in a multidisciplinary expert panel leading to a consensus diagnosis, which was monitored during follow-up. Predictors for the diagnosis of CGI were obtained by comparing the self-reported symptoms in the questionnaire to the diagnosis of CGI. Multivariable logistic regression analysis was used to combine the strongest predictors in a prediction model. A simple score was developed based on the prediction model to distinguish low, intermediate and high risk patients for CGI. Results: Postprandial pain, exercise-induced pain or weight loss was present in 93% of patients. The majority of patients (n=288, 67%) was diagnosed with CGI and had persistent clinical response after treatment. Self-reported risk profiles showing strong association with CGI were female gender (OR 2.5, 95% CI 1.6-3.9), age > 60 years (OR 1.4 for 10 year increase, 95% CI 1.0-2.0), concomitant diabetes mellitus (OR 2.0, 95% CI 0.99-4.0), smoking (OR 1.5, 95% CI 0.98-2.3), and use of alcohol (OR1.3, 95% CI (0.96-1.7). Consequently, a c-statistic of 0.68 for the combination of predictors was obtained. Based on these predictors, a 6-point scoring system was developed categorizing patients in low (predictive risk <51%), intermediate (>51 - <66%) or at high risk (>79%) for CGI, indicating whether further diagnostic work-up is required.

Conclusions: We present a scoring system for the presence of CGI on clinical features and risk profiles alone for patients suspected of CGI. This tool may be useful for clinicians to assess the risk of CGI and to decide whether further diagnostic work-up by means of radiological imaging of the gastrointestinal arteries and functional testing is indicated and worthwhile.

Does inclusion of imaging in the work up of patients with clinically suspected appendicitis reduce the rate of unnecessary surgical procedures?

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Since February 2010 new Dutch guidelines have been implemented recommending the use of ultrasound (US) or computed tomography (CT) to confirm or refute clinically suspected appendicitis before (laparoscopic) surgery. For equivocal cases with US additional imaging (CT/magnetic resonance imaging (MRI)) is recommended. This study aimed to see whether these new guidelines lowered the percentage appendix sana. This retrospective study included all consecutive patients operated for clinically suspected appendicitis at our hospital from 2008-2009 (before guidelines) and 2011-2012 (after guidelines). The use of imaging (none versus US, CT and/or MRI) and its findings were recorded. Surgical and histopathological findings -when available- were identified. The primary study endpoint was the number of appendix sana before and after the guide implementation. 1556 patients were included, of which 756 were collected before the implementation of the guidelines and 800 after. During the pre-implementation period, 36,3% of the patients received imaging focussed on the appendix. Post-implementation, 97,4% of the patients received imaging before surgery. The average percentage of an appendix sana before the guidelines was 23,2%. After implementation, this average percentage dropped significantly to 6,2% ($p<0.001$).
Conclusion: Use of preoperative imaging in all patients with suspected clinically appendicitis result in a significant reduction in the percentage of appendix sana. This suggests that the implementation of imaging in the work up of these patients could be an effective strategy to reduce the number of unnecessary surgeries.

Prognostication of complications after Roux en Y gastric bypass: evaluation of the OS-MRS and the Clavien-Dindo classification

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Background: The performance of bariatric surgery is increasing world wide. The Obesity Surgery Mortality Risk Score (OS-MRS) is a validated instrument for the assessment and risk stratification regarding mortality of patients undergoing Roux-en-Y gastric bypass (RYGB). The incidence of peri-and postoperative mortality due to the procedure is low. Post-bariatric (severe) complications are more common. Some centers also use the OS-MRS in an attempt to predict postoperative complications. Aim: The aim of this study was to assess the OS-MRS as an instrument to predict post-operative complications in addition to mortality.Methods: The OS-MRS was applied to a single center prospective, consecutive database with patients undergoing laparoscopic RYGB or laparoscopic sleeve gastrectomy (LSG) between November 2007 till October 2013 with a minimal follow up of 30 days. The endpoint was classified according to the Dindo classification ranging from no intervention till death. Results: A total of 1159 patients underwent LRYGB or LSG either as primary or revisional (20.1 %) procedure. 945 (81.5%) of the patients was female, mean age was 44.2 years (range 18-66) and mean BMI 45.0 (range 30.0-77.6). 650 (56.1%) of the patients belonged to class A, 470 (40.6%) to class B and 39 (3.4%) to class C. Mortality due to bariatric surgery occurred in 3 of the 1159 patients (0.3 %), all three had revisional surgery and belonged to class B. A total of 125 (10.8 %) patients experienced adverse events within 30 days, distributed as 64 (9.5%) in class A, 57 (12.1%) in class B and 4 (11.4%) in class C. These differences are not statistical significant. Also the distribution of complications with serious consequences (Dindo >2) was not significant. The only, multivariate significant predictor for all and for severe complications was revisional surgery ($p = 0.007$; CI -0.1 till -0.02 and $p = 0.009$; CI-0.07 till 0.01).
Conclusion: The OS-MRS is validated for the prediction of mortality after bariatric surgery. However, it is not reliable to predict morbidity. No difference was found between LRYGB or LSG. The only, independently predictive for the risk of postoperative morbidity is revisional surgery.

Peroral endoscopic myotomy for achalasia is safe and effective: a prospective single center study

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The treatment of achalasia is complicated by a considerable recurrence rate and risk for treatment-related complications. Peroral endoscopic myotomy (POEM) was developed to provide an alternative treatment for achalasia that is equally or more effective but less invasive. The aim of this study was to evaluate the feasibility, safety and clinical efficacy of POEM. All POEM procedures were performed under general anesthesia. The procedure was carried out with subsequent mucosal incision in the mid-esophagus, creation of a submucosal tunnel using spray coagulation on the lesser curvature side, myotomy of circular muscle fibers starting 2 cm distal from the mucosal incision up to 2 cm in the cardia and finally the mucosal entry was closed with hemoclips. Procedure duration was measured and for the assessment of safety, adverse events and complications were assessed. Efficacy was measured using symptom questionnaires, high-resolution manometry (HRM) and timed barium esophagogram at base and three months after treatment. Since August 2011 POEM was performed in 46 achalasia patients (25 males; mean age 44.8 ± 2). Previous treatment was performed in 19 patients (16 pneumodilation, 1 pneumodilation + Heller myotomy, 1 botox, 1 esophageal stent). POEM was technically successful in all but one patient. In this patient the procedure could not be performed due to extensive fibrosis of the submucosa and mucosa. Only minor complications (21.7% pneumoperitoneum, 8.7% minor bleeding, 2.2% mucosal laceration) were observed. The median procedure time was 100 (85-120) minutes (median (IQR)). The length of the submucosal tunnel and myotomy were 14 (13-15) cm and 10 (9-11.5) cm respectively. After three months all patients were in symptom remission and the Eckardt score had improved significantly from 7 (5-8.3) to 1 (0.8-1), p <.01. Lower esophageal sphincter relaxation pressure was significantly reduced after treatment (pre 20 (14.8-27.1) mmHg versus post 8.1 (4.9-12.1) mmHg, p <.01). Stasis during the timed barium esophagogram was also significantly reduced, from 6.8 (4-9) cm to 0 (0-3) cm, p <.01. 17 (37%) patients reported reflux symptoms post-treatment which were effectively treated by PPI in all. At 6, 12 and 24 months the percentages of patients with symptom remission were 100%, 93% and 77.8% respectively.
Conclusions: POEM is a feasible and safe procedure for the treatment of achalasia with high short- and long-term symptom improvement. Randomized controlled trials with a long-term follow-up comparing POEM to the current standard treatments will determine its place in achalasia treatment in the future.

Esophageal epithelial barrier function in GERD patients and healthy controls: an ex-vivo study in the basal state and in response to acid exposure

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Background: Esophageal epithelial integrity is considered an important factor in the prevention of tissue damage by gastric refluxate. We hypothesized that in patients with gastroesophageal reflux disease (GERD) the esophageal epithelial barrier function is impaired and less resistant in response to acid exposure. We therefore investigated esophageal epithelial integrity in GERD patients and in healthy controls both in the basal state and in response to acid exposure Methods: 14 patients with chronic GERD (8 with erosive esophagitis, 6 with non-erosive reflux disease) and 10 healthy controls (HC) were enrolled. Before endoscopy, GERD patients discontinued PPI therapy for 7 days. Six esophageal biopsies from macroscopically normal mucosa were obtained approximately 5 cm above the gastroesophageal junction and directly transferred to a mini-Ussing chamber system. After an equilibration period, base TEER was assessed. Half of the biopsies were then exposed at their luminal side to an acidic solution (pH1) for 30 minutes. During exposure and after removal of the acidic solution, changes in TEER were analyzed relative to base TEER. Permeation to the paracellular permeation marker fluorescein (375 DA - 1 mg/ml) was assessed in all biopsies (previous acid-exposed and non-exposed) for 120 minutes. Only subjects with at least two adequate biopsies (one for acid exposure, one as a control) were included. Results: Esophageal epithelium of GERD patients showed lower base TEER (127.7±13.3 â„¦ vs. 174.3±17.6 â„¦, p=0.04) and a trend toward higher transmucosal permeation of fluorescein in the non-exposed biopsies when compared to healthy controls (serosal concentration (pmol/ml) after 120 min: 48.2 (7.6-66.7) vs. 6.8 (3.6-20.2), p=0.09 and AUC: 79.8 (12.9-135.6) vs. 9.0 (5.5-31.3), p=0.07). Acid exposure provoked a fall in TEER that was equal for the biopsies of GERD patients and healthy controls (-52.1±2.5% vs. -50.0±4.4% of base TEER). After removal of the acidic solution, TEER recovered also to a similar extent in GERD patients and healthy controls (89.6±3.8% vs. 93.8±3.0% of base TEER). However, maximum TEER was reached earlier in biopsies of GERD patients (54±9 min vs. 83±6 min (HC), p=0.02) and at the end of the experiment, TEER relative to base was lower in biopsies of GERD patients (73.7±5.8% vs. 89.7±3.3% (HC) of base TEER, p<0.05).
Conclusion: The esophageal epithelial barrier function of GERD patients is impaired, reflected by lower base transepithelial electrical resistance and a trend toward higher fluorescein permeation, and seems to be less resistant in response to acid exposure ex-vivo.

Trends in distribution of diagnostic testing and treatment of hepatocellular carcinoma in the Netherlands between 2003-2011

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The incidence of hepatocellular carcinoma (HCC) in the Netherlands has increased. However, despite new treatment options, the prognosis remains poor. In this retrospective study (n= 2915 patients) trends in diagnostic testing and initial treatment (i.e. within 9 months after diagnosis) of patients with HCC in the period 2003-2011 are described, based on data of the Dutch Cancer Registration. Influence of hospital type (academic versus non-academic) and volume (<5 versus ≥5 resections respectively sorafenib treatments anually) on postoperative and long term mortality after resection or sorafenib treatment were evaluated with uni- and multivariate logistic regression analysis and Cox proportional hazard analysis. The proportion of patients with palliative treatment increased significantly, whereas the proportion of patients treated by resection remained stable (approximately 10%). Tumour biopsies were performed in virtually all hospitals and in 50% of all cases, despite a significant 10% decrease with time. The number of hospitals where active treatment was performed increased significantly (from 33% to 62% of all hospitals) and the contribution of academic hospitals decreased significantly (from 83% to 75% of all treatments). Transarterial chemoembolization, radiofrequency ablation and resection were mainly performed in academic centers (respectively 99%, 95% and 79%), whereas half of sorafenib treatments were given in non-academic centers. Liver resection was performed in 272 patients and initial sorafenib was started in 227 patients. Only in a few academic hospitals, at least five resections were annually performed and/or (only during the last three years) at least five patients annually started on sorafenib. In multivariate analysis, resection in non-academic centers was associated with higher postoperative mortality (odds ratio 3.38, 95% confidence interval (95%CI) 1.37-10.68) and higher long-term mortality (hazard ratio 1.12, 95%CI 1.04-1.40). Sorafenib treatment in non-academic centers was also associated with higher long-term mortality (hazard ratio 1.38, 95%CI 1.06-1.81). Hospital volumes were no independent factor for mortality after resection or sorafenib.
Conclusion: There was no trend towards centralization of diagnostic testing and treatments for HCC in the past decade. In low incidence countries like the Netherlands, hospital type could affect outcome after resection and sorafenib treatment for HCC.

Gut permeability in IBS is site specific, subtype dependent and affected by confounding factors

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Altered intestinal barrier function is one of the assumed pathophysiological mechanisms of irritable bowel syndrome (IBS). Intestinal permeability has previously been studied in small IBS populations, but findings were contrasting. Objectives of the present study were 1) to assess intestinal permeability at different sites of the GI tract, in a large group well characterised IBS patients and healthy controls (HC) and investigate differences between subtypes, and 2) to assess potential confounding effects of multiple patient-related factors.IBS patients and HC of a large IBS cohort underwent a validated multi-sugar test to assess intestinal permeability on four sites of the GI tract. Sucrose excretion and the lactulose/rhamnose (L/R) ratio in 0-5 h urine indicated gastroduodenal and small intestinal permeability, respectively. Sucralose/erythritol (S/E) ratio in 0-24 and 5-24 h urine was used as indicators of whole gut and colonic permeability, respectively. Linear regression analysis was used to assess the association between IBS and IBS subtypes and intestinal permeability and to adjust for possible confounding factors, i.e. demographics (age, sex, BMI), psychological symptoms (anxiety or depression), lifestyle factors (smoking history, (defined as current or previous smoker) and alcohol intake >15 units/week), and use of medication in the 2 weeks prior to inclusion (NSAID, PPI, SSRI and medication that affects motility).91 IBS patients, i.e. 37% diarrhoea predominant (IBS-D), 23% constipation predominant (IBS-C), 33% with mixed (IBS-M) and 7% with unspecified stool pattern (IBS-U), and 94 HC were enrolled. Sucrose excretion was significantly increased in the total IBS group versus HC (median [Q1 ; Q3] in µmol: 5.26 [1.82 ; 11.03] vs. 2.44 [0.91 ; 5.85], $p<0.05$), as well as in IBS-C (7.40 [2.37 ; 18.29], $p<0.01$) and IBS-D (4.22 [2.12 ; 8.03], $p<0.05$) versus HC. However, the differences attenuated when adjusting for confounders. Factors with significant confounding effects were higher BMI, smoking history and use of drugs that positively affect motility.Furthermore, the L/R ratio was increased in IBS-D patients compared to HC (0.023 [0.013 ; 0.038] vs. 0.014 [0.008 ; 0.025], $p<0.05$), which remained significant after adjustment for confounders. There was no significant difference between groups in 0-24 and 5-24 hour S/E ratio.
Conclusion: Small intestinal, but not gastroduodenal, colonic and whole gut permeability is increased in patients with IBS-D when compared to HC, irrespective of possible confounding factors. Adjustment for possible confounders is necessary when studying intestinal permeability, especially in a heterogeneous disorder as IBS.

Insufficient incorporation of biological meshes after implantation in a clean surgical environment

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Biological meshes have been developed for implantation in a contaminated environment to prevent the formation of incisional hernia. In addition these meshes have been massively implanted in clean contaminated surgery for example after gastro-intestinal surgery. However, little is known with regard to the characteristics of mesh in a clean environment, as it differs from that in a contaminated one. This experiment investigates the incorporation and complications after biological meshimplantation in a clean environment. Intraperitoneal meshimplantation was performed in 64 rats with 4 different meshes: Strattice® (non-crosslinked porcine dermis), Surgisis® (non-crosslinked porcine submucosa), Permacol® (crosslinked porcine dermis) and CollamendFM® (crosslinked porcine dermis). Incorporation, adhesion formation, mesh infection and shrinkage were evaluated on postoperative day (POD) 90 and 180. During the experiment 7 animals from CollamendFM and 1 from Surgisis were euthanized prior to the intended endpoint because of transcutaneous prosthesis migration. In total 15 rats had macroscopic meshinfection at sacrifice (Collamend 11/16, Surgisis 2/16, Permacol 2/16). Incorporation of non-infected meshes did not differ between groups on POD 90 (median 13.2%, IQR 0-24%). On POD 180, all Surgisis meshes were degraded, which was scored as 0% in incorporation. The most incorporation was found in Permacol (20.7%, 5.7-24.5), although this was not significantly different from Strattice (13.7%, 10.3-22.4). Surgisis had the highest adhesion score on POD 90 (90%, 32.5-100%), which was higher than the other meshes ($p>0.023$). Strattice had less adhesions covering the mesh (5%, 5-5%) than the other groups ($p<0.029$). On POD 180, CollamendFM had the highest rate of adhesion coverage (100%, 100-100%) due to the amount of infected meshes. Strattice had the least adhesions (5%, 5-5), which was less than Surgisis and Permacol ($p<0.001$ respectively). On POD 90, mesh shrinkage was highest in Surgisis (57%, 37-69.5%), which was higher than the other meshes ($p<0.01$ respectively). On POD 180, shrinkage was lowest for Permacol (7%, 4-14%) and highest for Strattice (29%, 0-64.2%), although again not significantly different between groups. Implantation of biological meshes in a clean environment is not without risks. Substantial transcutaneous migration and macroscopic infection was seen after implantation of CollamendFM, Permacol and Surgisis, none of which were completely incorporated after 180 days. Therefore we conclude that implantation of biological meshes is accompanied by various infectious complications and will most likely not prevent the formation of incisional hernia.

Distal versus proximal colonic acetate infusions differentially affect human metabolism

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Gut-derived short chain fatty acids (SCFAs), formed by microbial fermentation of dietary fiber, are believed to be involved in the etiology of obesity and type 2 diabetes. The aim of this study was to investigate the effects of proximal versus distal colonic infusions with the SCFA sodium acetate on human fat oxidation and energy metabolism. In this randomized, double-blind, placebo-controlled, cross-over study, six healthy male subjects with BMI ≥ 25 kg/m^2 ≤ 34.9 kg/m^2 were included. Subjects were studied during two experimental periods of 3 days each with at least a 7 day wash-out in between. During one period a feeding catheter was endoscopically placed in the proximal colon, and during the other period in the distal colon, the order of placement being randomized. Each period, the catheter remained in the colon for 3 consecutive days during which sodium acetate (180mM or 100mM) or placebo was instilled in random order on separate days via the catheter. During each test day, the subjects received colonic infusions during fasted conditions and after an oral glucose load resembling a postprandial state. The primary outcome, fat oxidation, was measured via an open-circuit ventilated hood system. Blood samples were collected during fasted and postprandial conditions before, and 10, 15, 20, 30, 60, 90 and 120 minutes after colonic infusion. Overall, distal colonic infusions with 180mM sodium acetate increased fat oxidation in the fasted state by 23% ($p<0.05$). Next to this, distal colonic infusion with 180mM sodium acetate decreased fasted carbohydrate oxidation ($p<0.01$), increased fasted PYY ($p<0.05$), and increased postprandial plasma glucose and insulin (both $p<0.05$). Interestingly, fasted TNF-α concentrations significantly decreased after 100mM distally administered sodium acetate. Proximal administration of 180mM sodium acetate significantly decreased postprandial plasma glucose and insulin after 60 minutes, but had no effect on fat or carbohydrate oxidation. There was no effect on energy expenditure or on plasma GLP-1, free fatty acids, triglycerides, free glycerol, IL-1β and IL-6.
In conclusion, this study showed that sodium acetate infusions in different parts of the colon modulate whole body substrate metabolism, with a pronounced increase in fat oxidation after distal acetate infusion. Modulating colonic acetate may yield new mechanisms for treating or preventing metabolic diseases.

Transnasal endoscopic nasoenteral feeding tube placement in routine clinical practice is associated with low success rates

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In case of short term intolerance to gastric feeding, nasoenteral feeding tubes are commonly used for nutritional support. Tube placement using transnasal endoscopy is a minimally invasive technique for post-pyloric feeding tube placement at the bedside. Although success rates of transnasal endoscopic placement in trials usually are 90% or higher, it is unkown whether these high success rates are also achieved in clinical practice in teaching hospitals. The aim of this study was to determine the success rate of endoscopic transnasal feeding tube placement in routine clinical practice and to identify independent predictors for incorrect tube placement. We performed a retrospective, multicenter study in three Dutch teaching hospitals. Consecutive adult patients undergoing endoscopic nasoenteral feeding tube placement followed by abdominal X-ray were included. Successful tube placement was defined as post-pyloric tube tip placement as confirmed by abdominal X-ray. Altered duodenal anatomy was an exclusion criterion. Analysis was performed as per-placement analysis. Multivariable logistic regression analysis was performed to identify independent predictors for incorrect tube placement.Data of 690 feeding tube placements in 495 adult patients were included. Common indications for nasoenteral feeding tube placement included delayed gastric emptying (37%), low dietary intake (19%) and obstruction proximal to the stomach (19%). Most feeding tube placements were performed by trainee endoscopists (67%) and under conscious sedation (66%). A single lumen tube was used in 79% of patients and a triple lumen tube in 21% of patients. Abdominal X-ray showed that in 28% the tip of the tube was located in the stomach, in 11% in the proximal duodenum, in 13% in the distal duodenum and in 48% in the jejunum, resulting in a success rate of 72%. Multivariable analysis showed that the use of triple lumen tubes was the only independent predictor for incorrect tube placement (OR 2.3, 95% CI 1.51-3.41). Tube placement by a trainee instead of staff endoscopist, ICU admission or presence of a large residual content in the stomach (>300 cc) were not associated with an increased risk of incorrect tube placement.
Conclusion: In daily practice, the success rate of endoscopic nasoenteral feeding tube placement is lower (72%) than those reported in trial settings. Furthermore, the only risk factor for incorrect placement was found to be the use of triple lumen tubes. Our results suggest that an abdominal X-ray to confirm correct placement after transnasal endoscopic tube placement should be considered, especially when triple lumen tubes are placed.

Excellent long-term survival after autologous stem-cell transplantation for RCDII

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RCDII can be defined as a low-grade intraepithelial lymphoma. This entity frequently transforms into an aggressive enteropathy-type-associated T cell lymphoma (EATL) with dismal prognosis. Current treatment strategies include cladribine (2-CDA) and autologous stem cell transplantation (AST) but their effectiveness in prevention of EATL is not well documented. Here we evaluated long-term follow-up and survival of 2-CdA monotherapy and 2-CdA-AST combination therapy. Diagnosis of RCDII was based on persisting or recurring clinical symptoms and small intestinal villous atrophy, in patients with celiac disease, despite a strict GFD for over 12 months and a clinically validated cut-off value of more than 20% aberrant intraepithelial lymphocytes (IELs) detected by flow cytometric analysis. Patients received either 2-CDA monotherapy (n=25) or combination therapy (n=11) 2-CDA followed by AST. AST was performed in patients <70 years. Overall survival, EATL development and change in clinical, histological and immunological parameters were monitored. Median age of the diagnosis RCD II was 63 years (range 42-78). Overall, 16 out of 36 patients (44%) died during a median follow-up of 59 months. In the monotherapy group, 14 out of 25 patients died (56%). Eigth out of 14 (57%) died due to an EATL and 2 due to progressive refractory state. Progression into EATL developed after a median follow-up of 22 months after RCDII diagnosis (range 4-72 months). In the 2-CdA-AST combination therapy group, only 2 out of 11 patients died (18%), one as the consequence of an EATL. Overall survival in the monotherapy group was 47 months (range 3-106 months) compared to 87 months (range 18-190 months) in the combination-therapy group ($P < 0,05$). One, three- and five-years OS in the combination therapy group was 100%, 91% and 81% respectively, compared to 81%, 66% and 56% in the monotherapy group. No significant differences could be identified in clinical characteristics, histological or immunological response in those who developed EATL and those who did not.

Conclusion: both monotherapy and combination therapy induce improvement in the majority of patients, however progression to EATL was found and dismal outcome was found more often in the monotherapy group. These observations argue for an aggressive therapeutic approach for those RCDII patients eligible for AST.

Clinical impact of liquid-based or cell block preparation of residual material after analysis of cytological smears in endoscopic ultrasound-guided fine-needle aspiration

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Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is an accurate technique to biopsy lymph nodes and masses for cytological analysis. Residual tissue or lymph node contents can be used for liquid-based or cell block preparation, which may be useful when smears are inadequate and/or immunohistochemistry is required. For liquid-based preparation, residual material is placed in hemolytic solution and then placed on a slide, resulting in a thin layer of cells. For cell block preparation, residual material is clustered, embedded in a fixative and then cut, enabling analysis of tissue particles that are too thick to be analyzed with cytological smears. The diagnostic value of these additional tests is unclear. The aim of this study was to evaluate the additional diagnostic yield of liquid-based or cell block prepared residual material after routine cytological smear analysis in EUS-FNA procedures. All EUS-FNA procedures between September 2002 and September 2011 were identified. Diagnostic yield and accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of cytological smears and smears combined with residual material were calculated. Diagnostic yield was defined as the proportion in which the pathologist could make a diagnosis. Diagnostic accuracy was defined as the proportion in which the diagnosis of the pathologist was in with the histology, surgical resection or clinical follow-up result. In total, 421 cases were identified. EUS-FNA was successful in 395 (93.8%) cases, direct evaluation was performed in 361 (85.7%). A lymph node was targeted in 311 (78.7%) and a mass in 84 (21.3%) cases. The subcarina (n=195, 49%), pancreas (n=55, 14%) and aortopulmonary window (n=28, 7.1%) were targeted most frequently. Residual material was analyzed in 135 cases (34.3%) and benefited the diagnosis directly in 11 cases (8.1%). In 5 (1.3%) cases this resulted in a diagnosis and in 6 (1.5%) cases immunohistochemistry enabled differentiation with regard to tumor origin. When only analyzing cytological smears, the diagnostic yield was 89% and accuracy 90% (sensitivity 90%, specificity 79%, PPV 94% and NPV 79%). If analysis of cytological smears was combined with residual material analysis, the yield increased to 91% and accuracy to 91% (sensitivity 94%, specificity 79%, PPV 94% and NPV 79%). Number needed to test residual material with regard to a diagnosis was 12. Conclusion: Additional analysis of liquid-based or cell block prepared residual material increased diagnostic yield, accuracy and sensitivity of EUS-FNA. Future studies are warranted to establish whether adding these tests is indeed cost-effective.

Lean Six Sigma in health care; Applicability and implementation in a fast track multidisciplinary oncology clinic

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Long waiting times, both during the diagnostic path and for the initiation of treatment, in cancer care can cause patients considerable psychosocial stress. To reduce waiting times, a one-stop fast track multidisciplinary outpatient clinic for gastrointestinal cancer has been initiated. Since initiation there has been a 3-fold increase in patients. To cope with increasing numbers, without compromising on waiting times, the logistic processes needed to be improved. The manufacturing industry has substantial experience with the improvement of logistic processes. Lean Six Sigma (LSS) is a proven strategy in this industry to systematically identify and address the suboptimal performance of a (logistic) process. Similarly to the safety concepts adapted from aviation, it is possible that LSS can be a valuable addition to ameliorate the medical logistics system.Our aim was to test the applicability of Lean Six Sigma in a complex medical system. Subsequently LSS was implemented to decrease the percentage of patients with an admission time (AT) longer than five administrative days. In a prospective intervention study, the tools offered by LSS were used to identify key bottlenecks in the logistics of the AT for the clinic. The AT was defined as the time from first referral until the appointment to the outpatient clinic. To compare differences in admission time, two groups were identified. The AT of group I was measured and analyses using the tools offered by LSS. Subsequently, root causes were identified and addressed. Group II was used to observe whether our interventions had led to any improvements. The data was non-parametrically distributed; Mann-Whitney-U test was used to compare data. In both groups the admission time for 197 patients was observed. Group I was observed for 75 days and group II for 66 days. In group I, 47% (n=94) patients had an AT longer than five administrative days, the mean AT was 6 days (min 1; max 20). In group II, 32% (n=64) had an AT longer than five administrative days, the mean AT was 5 days (min 1; max 22). The percentage of patient with an AT longer than 5 days has been decreased with 32%. This is a significant improvement (p=0,019). The reduction in AT coincided with an increase in production capacity without any extra increase in personnel.
Conclusions Lean Six Sigma is applicable in a multidisciplinary high care facility. Root causes in the logistics of a complex medical facility can be identified and improved. The viability of all tools offered by Lean Six Sigma should be further explored in different aspects of logistics in a high care medical facility.

Quality of life after stent placement for palliation of common bile duct obstruction: a randomized controlled trial comparing plastic and metal stents

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Endoscopic stent placement is the procedure of choice for palliation of common bile duct (CBD) obstruction. It is known that self-expandable metals stents (SEMS) are superior to plastic stents in terms of stent patency and rate of stent dysfunction requiring reintervention. However, it is unknown whether this also results in improved quality of life (QoL). Our aim was to compare QoL between patients treated with a plastic stent or SEMS for the palliation of CBD obstruction. We performed a randomized multicenter trial in 18 hospitals with 219 patients randomized to plastic stent (n=73) or SEMS (n=146) placement. QoL was assessed with two general questionnaires (EQ-5D and QLQ-C30) and one disease specific questionnaire (PAN-26). Questionnaires were filled out before treatment and after 14 days, 1-6, 8, 10 and 12 months. QoL scores for were compared with repeated measurement analysis. Quality-adjusted life months (QALMs) were calculated using EQ-5D utilities. A total of 150 (68%) patients were willing to fill out the QoL questionnaires. In 50% of patients one or more questionnaires were missing due to a deteriorating patient condition. The number of missing questionnaires (p=0.12) and mean survival (165 vs 140 days, p=0.13) were not different between the two groups. Stent dysfunction occurred in 31 patients (43%) in the plastic stent group and in 22 patients (15%) in the SEMS group (p<0.05). On the QLQ-C30, global health status was significantly different between the two stent types in favor of SEMS (p=0.02). In the SEMS group, the health status significantly improved during follow-up (p=0.005), while this slightly decreased in the plastic stent group (p=0.35). Physical functioning also slightly improved in the SEMS group (p=0.70) but significantly deteriorated in the plastic stent group (p=0.01), resulting in a significant difference between both stents (p=0.02). On the PAN-26 a reduction of hepatic symptoms was seen for both SEMS (p<0.005) and plastic stents (p<0.005), with no difference between both stents (p=0.43). Digestive symptoms significantly increased in the plastic stent group (p=0.01), while this remained stable in the SEMS group (p=0.97). All other items on the PAN-26 and QLQ-C30 remained stable during follow up with no differences between both stents. Mean QALMs were 1.9 in patients with a plastic stent and 2.2 in patients with SEMS (p=0.28). Patients with CBD obstruction treated with a SEMS reported a significant improved QoL regarding global health status, digestive symptoms and physical functioning compared to patients with a plastic stent. In addition, the number of QALMs was higher in the SEMS group, although this was not significant.

Positive predictive value of endoscopic ultrasound (EUS) for the detection of intraluminal filling defects in the common bile duct (CBD) in a large non-academic teaching hospital

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Introduction: In small academic studies, endoscopic ultrasound has been shown a reliable and safe method to assess the presence of common bile duct stones. Aims & Methods: The aim of this study was to calculate the positive predictive value (PPV) for the presence of CBD stones with EUS. For this we retrospectively included all patients in whom CBD stones were detected with EUS and who subsequently underwent endoscopic retrograde cholangiography (ERC). This study was performed in a large non-academic teaching hospital in The Netherlands between November 2006 and January 2011. PPV was calculated by dividing the number of true positives by the total number. Results: EUS detected CBD stones in 99 patients who subsequently underwent ERC. The median time-interval between EUS and ERC was 5 days (interquartile range 1-15 days). The PPV for the total group was only 56% (57/99). However, the PPV depended on the time-interval between EUS and ERC, being: 80% (8/10) within 24 hours, 63% (32/51) within 1-6 days, and 47% (18/38) after one week. Moreover, the PPV differed substantially depending on the type and number of intraluminal filling defects in the CBD, namely sludge (10/21, PPV 48%), or one stone (29/51, PPV 58%), or more than one stone (18/24, PPV 75%), or more than one stone with acoustic shadow (8/10, PPV 80%).
Conclusion: EUS performed in a large non-academic teaching hospital has a lower PPV for detection of CBD stones than overall reported in literature. This seems to be explained at least in part by the large variation in time-intervals between EUS and ERC indicating that ERCP should promptly follow a positive EUS and may be delayed a few days after the onset of symptoms to allow for spontaneous stone passage. Sludge in the CBD as finding on EUS has the lowest PPV when compared with stones with or without an acoustic shadow.

A comparative prospective blinded analysis of the effectiveness of EUS and MRI as screening tools for pancreatic cancer

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Previous studies suggest that endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) are promising tests to detect asymptomatic, non-invasive precursor lesions and early stage pancreatic cancer (PC) in high-risk individuals (HRI). However, most studies were not performed in a blinded fashion. Therefore, it is still unclear which screening technique is to be preferred. We aimed to compare the effectiveness of EUS and MRI in their ability to detect pancreatic lesions in HRI in a prospective blinded fashion. In the interim-analysis of this ongoing Dutch multicenter prospective study, results of 140 asymptomatic HRI undergoing first time screening by EUS and MRI are described. HRI (>10% lifetime risk of PC) were defined as (1) mutation carriers of PC prone gene mutations and (2) first-degree relatives of patients with familial PC. Results were compared in a blinded, independent fashion. A total of 101 focal lesions were detected by any of the two tests in 46 out of 140 HRI (32.9%). Twenty-five HRI (54.3%) had ≥2 lesions and the mean number of lesions per patient was 2.2 (SD 1.3). The majority of lesions (n=75, 74.3%) were small cystic lesions with a mean size of 6 mm (range 2-36, SD 5.0). Three solid lesions (3.0%) were detected in 3 HRI with a mean size of 7 mm (range 2-11, SD 4.5). The remaining lesions were either hypo-echoic lesions of unknown clinical relevance on EUS (n=7) or ductectasias (n=16). Twenty-five lesions (24.8%) were detected by both tests, 21 (20.8%) by EUS only and 55 (54.5%) by MRI only. EUS predominantly missed small cystic lesions (mean size 5 mm, SD 3.7). Lesions missed by MRI included 2 solid lesions of 11 and 7 mm, which after resection proved to be a stage I adenocarcinoma and multifocal PanIN-2 lesions. Disease recurrence was seen within 2 years in the carcinoma-case. The overall agreement between EUS and MRI was poor, even when analyzing only lesions >10 mm. In 11 HRI (7.9%), abnormalities were detected that prompted for a change in clinical management (2 resections and 9 shortened surveillance interval). In 8 of these cases (72.7%) the decision to change clinical management was based on abnormalities detected by EUS; in the remaining cases it was based on the results of both tests. Conclusion: EUS and/or MRI showed any type of pancreatic lesions in about one third of HRI. The overall agreement between EUS and MRI was poor. In this series, changes in clinical management were predominantly based on EUS results. Before it can be definitely decided which technique is superior, more cases need to be included and, importantly, results of follow-up investigations must be taken into consideration.

CEA and cytopathological analysis are useful tests to discriminate mucinous from non-mucinous pancreatic cystic lesions

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Introduction: Pancreatic carcinoma is a highly aggressive disease with dismal prognosis and a mortality rate equalling the incidence rate. Pancreatic cystic neoplasms, such as Mucinous Cystic Neoplasm (MCN) and Intraductal Papillary Mucinous Neoplasm (IPMN), are known precursor lesions of invasive pancreatic adenocarcinomas, the latter being the most common form of pancreatic cancer. Hence, it is important to discriminate these potentially malignant mucinous neoplasms from mostly benign serous pancreatic cystic neoplasms and reactive lesions such as pseudocysts. The objective of this single center study was to assess the value of the biochemically detected CEA as well as pathological analysis of the cyst fluid to discriminate between mucinous and non-mucinous neoplasms/lesions. Methods: All patients with pancreatic cysts that underwent initial EUS-FNA in 2009-2013 with known carcinoembryonic antigen (CEA) levels were retrospectively analysed. During endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), pancreatic cyst fluid was obtained for cytological and biochemical analysis. Next to the CEA levels, pathology and histology data were collected. All fluid pathology samples were revised by one expert-pathologist on presence or absence of mucinous-background. Cases with unknown CEA level and non-diagnostic cytology material were excluded. The main outcome measure was the diagnosis, based on histological results of the resection specimens or imaging combined with clinical follow-up. Results: Cystic lesions of 64 patients were analysed, including 25 patients with resection specimens and subsequent histological diagnosis. Mean CEA level was higher in mucinous cysts (3292.86 ng/ml; n=37) than in non-mucinous cysts (281.45 ng/ml; n=27). CEA measurements and pathology were both of value to predict a mucinous cyst (for CEA OR 2.4 95% CI: 1.4-4.0;p = 0.001; for cytology OR 7.1, 95% CI: 1.7-28.6; p = 0.006). Using a cut-off level of >192 ng/ml, CEA had an accuracy of 63%, and pathology an accuracy of 66%. In a multivariable logistic regression, both tests contributed significantly to the model (CEA: p = 0.002; pathology: p = 0.032). Combination of both tests (with a CEA cut-off >30 ng/mL) resulted in the highest accuracy of 78.1%.

Conclusions: Both CEA measurement and pathological background analysis of pancreatic cysts contribute independently to the diagnosis of mucinous cysts (IPMN or MCN). Our study is in concordance with previous reports suggesting that the highest sensitivity, specificity, predictive value and accuracy of EUS-FNA are achieved by the combination of both tests.

Serous cystadenoma; a single center experience

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Neoplastic cystic lesions are increasingly detected in daily clinical practice. In general serous cystadenomas can be recognized by their characteristic appearance, a typical honeycomb multi-microcystic tumor, and low levels of amylase and CEA in cyst fluid. However not all serous cystadenomas have this characteristic appearance and practice of the diagnosis can be difficult. Also there is little consensus on the presentation, symptomatology, natural course of history and its outcomes, resulting in variety in the management of serous cystadenomas.We set out to define the natural history and optimal management of serous cystadenoma of the pancreas.Methods Retrospectively all patients that underwent an endoscopic ultrasonography from 1990-2013 in our centre, in which the possible diagnosis of serous cystadenomas was mentioned in the report, were included. Data on patient characteristics, diagnostics, treatment and outcome have been ascertained from hospital records.Results In total 31 patients were diagnosed with a serous cystadenoma of the pancreas. Of all patients 84 % was female, with an age range of 37-91 (mean 66) years. Most serous cystadenomas were found incidentally (66%) and were asymptomatic, 28% presented themselves with nonspecific abdominal pain and 7% presented themselves with pancreatic abdominal pain. Mean tumor diameter was 34 mm with a range of 11-80 mm, located in the head, body, body & tail and tail in 61%; 26% ; 10% and 3% respectively. In 43% a fine needle aspiration was performed. Pathology confirmed the diagnosis serous cystadenoma in 2 cases, but only after resection. Pathology showed wide cysts covered with cubic epithelia, with little to no atypical cells nor mitotic activity. The cysts were filled with serous fluid. Two patients underwent surgery, both to relieve nonspecific abdominal pain. At the end of follow-up with a mean 15,3 months (range 0-60 months) all but two patients were alive. One patient died due to cardiovascular disease. The cause of death of the other patient is unknown. Three patients developed malignancies: colorectal carcinoma, renal carcinoma and thyroid cancer.
Conclusion: Serous cystadenoma is a rare neoplastic cystic lesion of the pancreas with a benign course. Its diagnosis is often fortuitous and can be made upon characteristic morphology, preferentially by two cross-sectional imaging modalities, and is supported by cyst fluid analysis on CEA (<5ng/L). FNA rarely contributes to the diagnosis. Surgery is generally not indicated and should only be performed when there is rapid growth (> 1 cm/year) or severe symptoms.

Diagnostic value of a pancreatic mass on computed tomography in patients undergoing pancreatoduodenectomy for presumed pancreatic cancer

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Some patients undergoing pancreatoduodenectomy for suspected malignancy are ultimately diagnosed with benign disease. We aimed to determine the diagnostic value of a pancreatic mass on computed tomography (CT) in patients with presumed pancreatic cancer and the additional value of reassessment by expert-radiologists.We performed a multicenter retrospective cohort study in 1629 consecutive patients undergoing pancreatoduodenectomy for suspected malignancy (2003-2010). All patients with unexpected benign disease at postoperative pathological diagnosis were included in a 1:3 ratio with random patients with (pre)malignant disease. The preoperative CT scan was reassessed by two expert-radiologists separately and subsequently (after defining a mass as 'a measurable space occupying soft tissue density, except for an enlarged papilla or focal steatosis') in consensus.86 patients with benign and 258 patients with (pre)malignant disease were included. A mass was reported in the original CT report in 66% of patients versus 48% and 50% on reassessment by the two expert-radiologists, respectively. Interobserver agreement among expert-radiologists was moderate (kappa=0.47, 95%CI 0.38-0.56); they disagreed on the presence of mass in 29% of patients. The incidence of mass decreased to 44% after consensus reading (P<0.001 vs. original report). 167/212 (79%) masses identified in the original report proved to be malignant after pancreatoduodenectomy versus 139/150 (93%) masses identified by expert-radiologists in consensus (P<0.001). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of masses identified in the original CT report were 68%, 42%, 79%, 7%, and 67%, respectively. For masses identified by expert-radiologists in consensus these were 54%, 87%, 98%, 12%, and 56%, respect-tively. Conclusions: In patients with presumed pancreatic cancer, expertradiologists less frequently identified a pancreatic mass on CT as compared to the original CT reports, with doubled specificity for malignancy. As interobserver agreement, even among expert-radiologists, is only moderate, the use of a uniform definition for pancreatic mass is recommended.

Comparison of Incidence Rates of Acute Pancreatitis and Pancreatic Cancer among the general population and type 2 Diabetes Mellitus patients between different Databases in the SAFEGUARD project

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Background: Incidence rates (IRs) of pancreatic diseases, such as acute pancreatitis (AP) and pancreatic cancer (PC) increased over the last decades in Western countries. This may be explained by increasing prevalence of alcohol use, gallstones or comorbid diseases, such as type 2 diabetes mellitus (T2DM). Use of health care databases (DBs) may help understanding the increasing IRs across countries and permit comparative analyses that may elucidate the epidemiology of AP and PC. Aim: To compare IRs of AP and PC diagnoses in the general population and T2DM patients in Western countries. Methods: Data was retrieved from nine databases (DBs), from five European countries and United States of America (USA): Italy (HSD, UNIMIB, CMNS), Spain (BIFAP), the Netherlands (IPCI, PHARMO), Germany (GePaRD), United Kingdom (CPRD) and USA (Medicare). BIFAP, CPRD, HSD and IPCI are general practice DBs, the others are administrative DBs. Each DB covers a study period between 2000 and 2012. Code mapping and harmonization was performed to develop common definitions that accounted for differences in disease coding systems (ICD-9, ICD-10, READ or ICPC codes). A subcohort of T2DM patients was identified using antihyperglycemic drug prescriptions and T2DM diagnoses codes. Age and sex stratified IRs for AP and PC per 100,000 person-years (PYs) were calculated in the general population and in the T2DM subcohort. Results: From a source population of 42,097,819 patients, 64,103 incident AP and 43,539 incident PC events were identified. In all DBs an increase in IRs with increasing age was observed, for AP a steady increase, for PC a steep increase after age 60-64 years. IRs were higher for males than females across all age groups: 1-1.5 times for AP and 1-3 times for PC. IRs overall ranged from 7-160 per 100,000 PYs for AP and from 9-83 per 100,000 PYs for PC. In the T2DM population of 1,764,072 subjects 5867 incident AP and 5867 incident PC events occurred. Notably, IRs increased in younger age groups; for AP from 20-24 years, for PC from 40-44 years. As in the general population, IRs were higher for males than females across all age groups, 1-3 for AP and 1-2.5 times for PC. IRs overall ranged from 36-120 per 100,000 PYs for AP and from 71-216 per 100,000 PYs for PC. Conclusions: The pattern of increasing IRs of AP and PC diagnoses in Western countries with increasing age was similar across DBs. Differences in IRs between countries may in part be explained by differences in database types (general practice or hospital data).The observation that IRs for AP and PC are higher in T2DM than in the overall population may reflect differences in risk factors and comorbidity.

Introduction of laparoscopic minor liver surgery in a HPB unit: not necessarily associated with a "learning curve

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Although laparoscopic minor liver surgery (LMLS(as defined by The Louisville Statement, 2008)) is considered the standard for several types of minor liver resection, some HPB units have not yet adopted it, potentially because of concerns of a learning curve effect.
A retrospective monocenter study, including all consecutive patients undergoing LMLS during a 4 year period (May 2009-Augustus 2013). Primary outcome: Clavien-Dindo >II complication rate. Secondary outcomes: operative time, conversion rate, need for blood transfusion, postoperative hospital stay, in-hospital mortality, and radicality. A potential learning curve was assessed by comparing the initial 50% (period A) with the last 50% of patients (period B). All operations were performed or supervised by 2 experienced liver surgeons who each had completed a fellowship in open liver surgery, had experience with advanced laparoscopic gastrointestinal surgery and had taken two courses on LMLS. Resections were performed with ultrasonic dissector and/or staplers. In total, 47 patients underwent LMLS of whom 31 (66%) for a malignancy, including 8 (17%) hepatocellular carcinoma. LMLS comprised 12% of all liver resections (period A, 10% versus period B, 14% (p=0.25)). The procedures performed were metastasectomies (segments 2,3,4,5,6,7 and 8; 74%) or left lateral sectionectomies (26%). Clavien-Dindo >II complications occurred in 5/47 (11%), median operative time was 152 minutes (interquartile range (IQR) 95-183), conversion rate 1/47 (2%), blood transfusion in 2/47 (4%) patients, median postoperative hospital stay 6 days (IQR 4-6), in-hospital mortality 2% (one cirrhotic, diabetic patient with hepatorenal syndrome) and 86% R0 resections in malignant cases. There was no apparent learning curve as complications, operative time, conversion rate, need for transfusion, and radicality were satisfactory already in period A without improvement in period B.
Conclusion: Introduction of LMLS for is not necessarily associated with a learning curve effect if these procedures are performed by surgeons with experience in both open liver and advanced laparoscopic gastrointestinal surgery and LMLS courses.

Overexpression of HOXA13 in Barrett's esophagus is a potential mediator of its posterior phenotype

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Barrett's Esophagus (BE) is a metaplastic and precancerous condition, induced by bile and acid reflux and defined by the presence of intestinal-type tissue in the esophagus. The morphology of this tissue resembles a posterior phenotype, as observed in the colon. Identifying the cause of this positional misspecification can lead to a better understanding of BE pathophysiology. The mammalian Hoxa cluster encodes master regulators of embryonic anterior to posterior specification, making it a potential effector of positional misspecification. The 3' to 5' sequence of genes in the Hoxa cluster, corresponds to the sequence in which they act along the anterior to posterior axes of the body. Acquired deregulation of Hoxa genes during adulthood can be linked to carcinogenesis and HOXA13 overexpression to poor survival in gastric cancer. However, Hoxa cluster expression has never been thoroughly investigated in the gastrointestinal (GI) tract, nor in BE. Therefore, our aim was to study the expression of Hoxa genes along the GI tract and characterize Hoxa cluster gene expression in BE. Firstly, we collected biopsy specimens from nine places along the GI tract in patients who underwent double balloon enteroscopy for unexplained symptoms. Secondly, we collected biopsy specimens of BE and adjacent squamous epithelium from other patients. RT-qPCR was used to quantify the expression of HOXA1, 2, 3, 4, 5, 6, 7, 9, 10, 11 and 13, and data were analyzed using the efficiency^â^†â^†Ct method. In this study Hoxa cluster gene expression differed significantly along the GI tract. Expression of Hoxa genes in the proximal part of the GI tract, from the esophagus to the proximal ileum, revealed a downward trend with anterior genes having a higher expression compared to posterior genes. The expression of posterior genes HOXA11 and 13 was low or absent. From the terminal ileum to the rectum, expression of Hoxa genes revealed an upward trend. Notably, expression of HOXA11 and 13 was only found in the colon, with HOXA13 showing the highest expression of all Hoxa genes in the GI tract. Furthermore, in BE, Hoxa genes revealed an upward trend of expression with a very high expression of HOXA13 whereas the expression of HOXA13 in squamous epithelium is undetectable.
Conclusion: Our data reveal position-dependent Hoxa coding along the GI tract, suggesting a prominent role of this gene cluster in mediating locational genetic identity. The expression of Hoxa cluster genes in BE resembles colonic Hoxa cluster expression. The high overexpression of HOXA13 found in BE is a potential mediator of posterior phenotype in this disease and may play a role in neoplastic progression.

Comprehensive profiling of plasma microRNAs reveals potential biomarkers for Barrett's esophagus and esophageal adenocarcinoma

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Circulating microRNAs (miRNAs) have been suggested as promising novel markers for various diseases. Their stability and predictive value make them ideal to be tested in plasma samples and provide the possibility of direct measurement and surpasses the need for invasive procedures, such as upper endoscopy. The goal of this study was to identify circulating miRNAs that were able to distinguish Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) patients from negative controls (NC). miRNA expression profiling was performed by qPCR using plasma samples from 10 BE and 10 EAC patients, and 10 NC. A specific plasma focus PCR panel (Exiqon, Denmark) containing miRCURY LNA™ Universal RT miRNA PCR assays for miRNAs found in plasma was used. Subsequent validation was performed by analyzing the expression of 6 miRNAs (and an extra 5 miRNAs for normalization) selected from the initial profiling study by quantitative RT-PCR in plasma of 41 BE and 59 EAC patients, and 15 NC. Area under the curve (AUC) analysis was used to evaluate diagnostic accuracy.Of the panel of 175 miRNAs, we identified 6 miRNAs that were EAC specific, 4 miRNAs that were BE specific and 10 miRNAs that were specific for NC. Further validation in a total of 115 patients and NC, showed that miRNA-382 ($p<0.05$) was increased in plasma from EAC and miRNA-133a ($p<0.05$) was decreased in EAC compared to BE and NC. miRNA-194 ($p<0.05$) and miRNA-451 ($p<0.05$) were increased, and miRNA-136 ($p<0.01$) was decreased in plasma from BE patients compared to NC. The combination of 3 or more miRNAs showed a good diagnostic performance with an AUC of 0.832 in discriminating BE from NC, an AUC of 0.846 in discriminating EAC from NC and an AUC of 0.797 in discriminating BE from EAC.This study showed promising diagnostic performance characteristics for the detection of BE and EAC compared to NC by analysing the expression of plasma miRNA-95, -133a, -136, -194, -382 and -451. These plasma miRNAs may potentially function as non-invasive molecular markers for BE and EAC screening and surveillance. The next step is to replicate our findings in a large prospective population-based study.

Trans-ethnic association study of IBD identifies 14 new disease loci and demonstrates pervasive sharing of genetic risk factors and phenotypic features between Europeans and Non-Europeans

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Previous studies in inflammatory bowel disease (IBD) patients of European descent identified 163 genetic susceptibility loci. Although the incidence of IBD is rising across Asia as well as in developing countries, there is little knowledge on the genetic background and phenotypic presentation in IBD patients of non-European descent. A new cohort of 9,359 individuals of East Asian (Japan, South Korea, Hong Kong-China and UK individuals from South Asia), Indian and Indo-European (Iran) descent were genotyped using the Immunochip with dense coverage of immune related genes. Stringent quality control was performed. A linear mixed model (MMM) was used for case-control association tests. These data were combined with a cohort of 79,584 individuals of European descent (Jostins et al. Nature 2012) to perform a trans-ethnic meta-analysis, as implemented in Mantra, allowing heterogeneity in effect sizes to be correlated to geographical distance between populations. For each known IBD locus, we investigated whether differences in the variance explained in Europeans vs non-Europeans were due to differences in effect size or allele frequency. Phenotype data were collected including the Montreal classification. We identified 14 novel IBD loci at genome wide significant levels ($p < 5x10^{-8}$) harbouring genes previously reported for other immune-mediated disease (including CD28, TNFRSF1A, CTLA4, IRF4, PRKCQ, UBASH3A, NFKBIZ,and CD44) and genes not reported for immune-mediated disease (e.g. ZEB2, ZNF366, TSPAN32, CD27, and CCL20). The majority of genetic risk factors, including these 14 novel loci, were common to both European and non-European IBD. However, the amount of phenotypic variance explained by these loci between populations was clearly heterogeneous, driven by a combination of differences in effect size and allele frequency. Phenotype data was available for 3,986 non-European and 47,799 European patients. There was a male predominance for Crohn's disease (69% vs 45%), more ileocolonic disease (54% vs. 39%) and lower colectomy rates in UC (4% vs 18%) in non-European than European populations. In this largest study to date of genetic risk factors underlying non-European IBD, we identified 14 novel IBD loci increasing the total number of IBD loci to 177. There is pervasive sharing of genetic risk factors between different ethnicities; however, the relative contributions for individual genes to the variance explained differ between ethnicities. The clinical characteristics are remarkably similar between different ethnicities. The presented similarities and dissimilarities between populations add to the heterogeneity of IBD.

Interleukin-10 inhibits human IFNγ-secreting effector T cells indirectly by controlling antigen-presenting cell function

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Chronic inflammation of the gastrointestinal tract, as seen in inflammatory bowel disease, arises from abnormal reactivity of T cells to commensal microbiota. Interleukin-10 (IL-10) plays a crucial role in suppressing microbiota-specific T cell responses. However, it is unknown how IL-10 prevents reactivation of effector T cells in the human intestine. We have recently identified a homozygous loss-of-function mutation in the IL-10RI gene of a pediatric patient with early-onset colitis. In contrast to recently reported cases, disease remission could be achieved without stem-cell transplantation, allowing in-depth analysis of the mechanism by which IL-10 controls human effector T cells. Lesional intestinal tissue taken at onset of disease contained high numbers of IL-17+ and T-bet+ cells. In agreement, IL-10 failed to control IFNγ and IL-17 production by activated T cells derived from the IL-10RI-deficient patient in vitro. By coculturing $CD4^+$ T cells and monocyte-derived dendritic cells (DC) from the IL-10R1-deficient patient and a healthy control, we revealed that IL-10R expression on DC, and not on T cells, is important for controlling IFNγ production, and to a lesser extent IL-17 production, by effector T cells. Importantly, we demonstrated that IL-10 plays a pivotal role in controlling the differentiation of immature monocyte-derived DC into inflammatory DC with a disease promoting phenotype. Taken together, our study demonstrates that IL-10 is essential to limit IFNγ and IL-17 secretion by human effector T cells and reveals that IL-10 exerts its suppressive function on IFNγ-secreting effector T cells mainly indirectly by controlling antigen-presenting cell function.

The role of microRNA-142-5P in experimental colitis

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Background and aim: MicroRNAs are non-coding posttranscriptional regulators of gene expression and control in that way over 60% of all protein coding genes, especially in the immune response. This indicates an important role for microRNAs in IBD and therefore they may be potential new therapeutic 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. 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 colon 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 for miR-142-5p in the colon are related to diverse signalling pathways (PPAR, TLR), early stage of cancer and metalloproteases and some of them are found to be down regulated in IBD.To translate this finding to a human situation we are currently testing human cell lines (macrophages and epithelial cells) that are overexpressing miR-142-5P. Target genes, identified in microarray on mice, are determined at mRNA and protein levels.
Conclusion: Various potential interesting pathways are involved in the diminution of chronic experimental colitis after blocking miR-142-5P.

Identification of novel non-transcriptionally acting glucocorticoid receptor ligands that suppress T cell activation but lack adipogenic activity

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Background: The use of glucocorticoids as immunosuppressives is limited by important side effects such as loss of bone mass, muscle atrophy and adipogenesis. Glucocorticoids bind to the glucocorticoid receptor (GR) that translocates from the cytosol to the nucleus and regulates transcription of target genes. In addition to this transcriptional regulation, there are also more rapid, non-transcriptionally mediated effects of glucocorticoids. We have previously shown that the GR is part of the T cell receptor (TCR) complex and that ligand binding results in dissociation of the GR from this complex and inhibition of canonical TCR signalling through LCK-PLCg. The dissociation of this complex appears to play an important role in glucocorticoid mediated inhibition of T cell activation as we found that stimuli that bypass LCK-PLCg signalling render T lymphocytes glucocorticoid resistant. Here we aimed to develop a GR ligand that inactivates LCK-PLCg signalling without resulting in transcriptional regulation. We examined if this approach could separate the anti-inflammatory effects of glucocorticoids from some of their side effects. Methods: Potential steroidal and nonsteroidal candidates were identified using an in silico docking assay to predict GR affinity. Selected compounds where screened in in vitro for glucocorticoid response element (GRE) mediated transcriptional regulation and their capacity to inhibit phytohemagglutinin (PHA) or Staphylococcus aureus enterotoxin B induced T cell activation. Two lead compounds were examined for GR binding, their capacity to inhibit canonical LCK-PLCg mediated TCR signalling and ability to induce adipogenesis and muscle fiber atrophy. Results: In the first in silico screening round, we screened 9.2 million compounds and selected 20,000 steroidal and non-steroidal compounds based on similarity to the structure of cortisol. In the second round these compounds were virtually docked in the binding pocket of the GR in two conformations and assigned a score that reflected their predicted affinity. The top 100 compounds were further screened for their capacity to inhibit T cell proliferation. This approach led to the discovery of compounds S3.1 and S3.4, which lack a generic cortisol structure but bind the GR in T lymphocytes and inhibit LCK-PLCg dependent T cell proliferation without causing transcriptional modulation of GR target genes. In contrast to classical glucocorticoids, S3.1 and S3.4 do not induce adipogenesis or cause muscle cell atrophy in vitro. Conclusion: Our data show that it is possible to develop nonsteroidal GR ligands that dissociate transcriptional from non-transcriptional effects and may have reduced side effects.

Differential induction of dendritic cell-mediated T cell tolerance in the small and large intestine

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Intestinal antigen-presenting cells continuously sample harmless antigens from the lumen and migrate via efferent lymph to draining lymphoid tissues to induce tolerance. We previously demonstrated that administration of ovalbumin (OVA) to the colon leads to DC-mediated antigen presentation in the iliac lymph nodes (ILN), while orally applied antigen is exclusively presented in the mesenteric lymph nodes (MLN). Despite the difference in draining site, both small intestinal and colonic OVA administration induced tolerance to the antigen via the induction of Foxp3+ Treg cells. The aim of this study was to investigate whether tolerance in the small and large intestine is imposed by distinct local regulatory mechanisms. At steady state, the ILN-derived DC comprised two main DC subsets, CD103+CD11b- DC and CD103-CD11b+ DC. The CD103+CD11b+ DC subset known to be present in the MLN was strikingly absent. After feeding OVA, CD103+CD11b+ DC actively migrated from the small intestine to MLN. These MLN-derived CD11c+ DC preferentially expressed RALDH2, a vitamin A-converting enzyme important for Foxp3 induction. In contrast, colonic antigen application increased the CD103+CD11b- DC population in the ILN. The ILN-derived CD11c+ DC expressed low levels of RALDH2, enhanced levels of IL-10 and cyclooxygenase-2, an enzyme involved in prostaglandin-mediated Foxp3 expression. Despite the differences in DC subsets and the low RALDH2 expression, ILN-derived CD11c+ DC were effective in driving TGFβ-mediated differentiation of Foxp3+IL-10+ Treg cells in vitro.
Taken together, our study reveals that different DC subtypes drive small intestinal and colonic tolerance and may imply that RALDH-independent processes are operative in colonic tolerance.

Efficacy of a novel JAK1-specific inhibitor in a mouse model of acute and chronic colitis

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Interferon (IFN) signaling via Janus Tyrosine Kinases (JAK1-3 and TYK2) reflects an important inflammatory pathway in inflammatory bowel diseases (IBD). The inhibition of JAK has been shown to ameliorate clinical symptoms in different auto-immune diseases, such as IBD [1]. However, the currently available JAK-inhibitor on the market has broad JAK inhibition properties, often leading to secondary undesirable effects. JAK1i is a selective JAK1 inhibitor (formerly known as GLPG0555; in-licensed by GSK from Galapagos) that was shown to have potent selective JAK1 inhibitory effects in vitro, while genome-wide transcriptional studies demonstrate its potential to down-regulate genes associated with chronic inflammatory response and NF-kB signaling. Our aim was to investigate the effect of JAK1 signal blockade in mouse models of acute and chronic Dextran Sodium Sulphate (DSS)-induced colitis using the JAK1-specific inhibitor JAK1i. For that purpose C57/Bl6 mice were daily given 2% DSS in drinking water ad libitum during 7 days and then sacrificed (acute) or received DSS for 5 days and sacrificed at day 20 (chronic). Mice were dosed daily (or every second day in the chronic model) by oral gavage with three different concentrations of JAK1i in a 1% Methylcellulose solution: 3, 10 and 30 mg/kg. Micro-colonoscopies and clinical inflammation scoring were performed. Total RNA and protein were isolated from colon specimens. In the chronic model, mice treated with the lowest dose of JAK1i had a significantly better recovery in their body weight (bw) (103.6% of initial bw (p=1) as compared to 95.6% (p=0.011) for vehicle treated, at day 14; p values as compared to non-DSS vehicle treated mice), as well as reduced levels of mIL-6 (protein and mRNA) and increased levels of mIL-10 (protein) compared to vehicle-treated mice. In acute DSS-induced colitis, JAK1 inhibition worsened clinical disease scores in a dose dependent fashion when compared with vehicle control. Animals treated with DSS plus vehicle had lost on average 4.7% of their initial bw while animals treated with DSS plus 3, 10 or 30 mg/Kg JAK1i had lost 5.4, 8.4 and 8.4% of initial bw, respectively. Oral dosing of Jak1i was effective in reducing colitis symptoms and mucosal inflammation in mice subject to chronic but not acute DSS-induced colitis. Mice treated with 3mg/kg JAK1i had improvement of clinical parameters of chronic colitis, in particular body weight recovery. In addition, both protein and mRNA levels of mIL-6 were reduced, while mIL-10 levels were increased.

Gluten degrading enzyme effectively digests gluten in the stomach and small intestine of healthy volunteers

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A significant proportion of the population does not tolerate dietary gluten intake. Aspergillus niger prolyl endopeptidase (AN-PEP) enzyme efficiently degrades gluten molecules into non-immunogenic peptides in a dynamic, multi-compartmental gastrointestinal simulation model but its efficacy in vivo remains to be established. Aim of our study was to assess the efficacy of AN-PEP on gastrointestinal breakdown of gluten in healthy subjects, as well as the effect of meal caloric density on AN-PEP efficiency.In this double-blind, randomized, placebo-controlled cross-over study 12 healthy subjects attended to four test days in random order. On each occasion they received a low (143 kCal) or high (405 kCal) caloric meal, containing 4g gluten, with AN-PEP or placebo via a triple-lumen nasoduodenal catheter. Acetaminophen was added to measure gastric emptying rate. One lumen, positioned in the stomach, was used for administration of the test meal and collection of gastric fluid. A second lumen was used for the continuous injection of polyethylene glycol 3350 (PEG-3350) to enable the calculation of meal dilution by endogenous secretions, with the injection port positioned just distal to the pylorus. A third lumen, located at the tube tip 10 cm distal to the second port, was used for collection of duodenal content. Fluid samples were taken regularly during 4 hours after meal infusion. The presence of α3-gliadin was quantified using the Gluten-Tec® ELISA assay. Degradation of intact gluten proteins was measured by Western-Blot analysis. Duodenal PEG-3350 concentrations and gastric acetaminophen concentrations were determined by HPLC. The effect on gluten degradation was measured by the difference in 240-min Area Under the Curve (AUC) of gluten exposure between AN-PEP and placebo. Differences between combinations of treatment and meal were assessed using linear mixed models. Compared to placebo, AN-PEP significantly lowered the gliadin concentration and absolute output (as 240-min AUCs) from low and high caloric meals in stomach and duodenum fluid ($p < .005$). The high caloric meal containing placebo showed a significantly lower 240-min AUC of duodenal gliadin concentration compared to the low caloric meal with placebo ($p = .001$). No differences were observed between gliadin concentrations of a low or high caloric meal containing AN-PEP. The gastric emptying time of the high caloric meal was longer compared to the low caloric meal, both in the presence of placebo ($p = .014$) and AN-PEP ($p = .100$).AN-PEP significantly enhances gluten digestion in healthy volunteers. Meal caloric density does not affect the efficacy of AN-PEP on gluten degradation.

High frequency of concomitant immune-mediated diseases in celiac disease in a large Dutch cohort

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Celiac disease (CD) is a chronic immune-mediated disease with an inflammatory response induced by dietary exposure to gluten. CD is characterized by a clinical heterogeneity with increased morbidity attributable to frequent concomitant disorders. While much is known of associated conditions, there are few good cohort descriptions of proven celiac patients. This study provides an overview of CD patients in a large Dutch cohort with a focus on the presenting symptoms and co-occurrence of immune mediated diseases. We performed a retrospective study in a university and non-university medical centre. Patient identification was based on financial codes (DBC) and the national pathology database (PALGA) from Jan 2003 to Sept 2013. All records were screened and patients were only included in case of a duodenal biopsy with a Marsh 1 classification with positive antibodies against tissue transglutaminase, gluten, gliadin or endomysium or a Marsh 2 classification or higher. Patients with an alternative diagnosis for intraepithelial lymphocytosis were excluded. 389 patients were included, 67.6% women, mean age at diagnosis was 36,5 yrs. 233 of the CD patients (60%) had positive auto-antibodies and 364 (94%) patients a Marsh 2 or higher at presentation. The most frequent presenting symptoms are anaemia (36%, men 47%, women 31%), (recurrent) diarrhea (35%), fatigue (33.7%), weight loss (32.1%) and abdominal pain (30.9%). Other, less frequent (10-20%), but regular reported symptoms are abdominal distension, abdominal cramps, nausea, poor appetite or even constipation and pyrosis.Neurologic symptoms occurred in 13.1%, 1 (0.26%) patient had epilepsy with microcalcifications. Depression was reported in 6.8%.117 patients (30.8%) had one or more immune-mediated disease, in particular thyroid disease (12.3%), rheumatic disorders (5.7%), insulin dependent diabetes (5.4%) and microscopic colitis (4.9%). Inflammatory bowel disease (1.3%) skin disorders (2.6%), associated autoimmune liver diseases (2.1%) and other (4.2%) were also reported. Malignancies occurred in 54 patients (14%), of which 8 (2.1%) patients had an Enteropathy Associated T-Cell Lymphoma. Conclusion CD is a very heterogeneous disease, it is noteworthy that only a third of the patients present with the classic symptoms (anaemia, diarrhea, fatigue and weight loss). Over 30% had a co-occurrence of an immune-mediated disease, which is much higher than reported in the literature (~15%), in particular autoimmune thyroid diseases. This is the first study describing a CD cohort in such detail in the Netherlands and shows the importance of screening and awareness of related immune mediated diseases in CD patients.

Relapse rates of type 1 and 2 autoimmune pancreatitis: long-term outcome

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Autoimmune pancreatitis (AIP) is a distinct type of chronic pancreatitis, which responds dramatically to steroid therapy. Two subtypes are described: type 1 and 2, with type 2 being more rare, not IgG4 related, and less likely to relapse. However, little is known about differences in the long-term disease course between the two types. Therefore, we compared the clinical profile and long-term outcomes of type 1 and type 2 AIP. From our AIP database registry, we included patients with a minimum follow-up of 2 years. Type 1 AIP patients fulfilled either the HISORt criteria or the ICDC. Patients with type 2 AIP (either definite or probable) were diagnosed as proposed by Maire et al. (Am J Gastroenterol 2011;106:151-6). Information was subtracted from the database regarding base characteristics, (treatment) response, and relapses. Potential risk factors for relapse were evaluated; age, gender, AIP type, other organ involvement, serum IgG4 levels, steroid dose, and pancreatic surgery. Hundred-and-seven patients were included (90% type 1; 87% male, median age 71 years), with a median follow-up of 82 months (IQR 52-118). At presentation, patients with type 1 AIP were older (63 years (IQR 53-70), versus 42 (IQR 27-52) in type 2; $p<0.001$) and had a higher male predominance (90%, versus 64% in type 2; $p=0.036$). Eighty-nine patients were treated with steroids (83%), with a 100% initial success rate. Overall, 55 patients experienced a relapse (52%). The first relapse occurred a median of 31 months (IQR 11-85) after diagnosis and most frequently involved the pancreas (51%) or biliary tract (62%). Furthermore, almost 80% of the relapses occurred within 2 years after diagnosis. Relapses were observed more frequently in type 1 patients (55%, versus 27% in type 2), but this difference did not reach statistical significance ($p=0.11$). Of note, type 2 patients never relapsed more than once. The only risk factor for relapse was the presence of IgG4-associated cholangitis (OR 5.3; 95% CI 2.3-12.4). Relapses occurred most often in unrecognized and therefore untreated patients (60%), or following the first two months of steroid cessation (31%). Subsequently, in 27% of these patients, azathioprine was added as maintenance therapy.

Conclusion: In this large cohort of AIP patients, relapses were common for both disease types and typically occurred in the first 2 years after diagnosis. Although clinical profiles of type 1 and 2 AIP are distinct, we found no significant differences in relapse rates. Therefore, clinicians should observe all AIP patients carefully in the first years after tapering steroids.

Incidence of Microscopic Colitis in the Netherlands. A Nationwide Population-Based Study from 2000-2012

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The incidence rates of microscopic colitis (MC) seem to vary between countries. However, the number of epidemiological studies is limited and generally based on regional data in relatively small populations, which makes it hard to draw firm conclusions on the geographical distribution and changes over time. Therefore, we aimed to assess the mean annual incidence rate of MC in the Netherlands in a nationwide population-based cohort from 2000-2012. A retrospective search was performed in the Dutch national pathology registry (PALGA), covering all pathology records of approximately 16.5 million inhabitants since 1991. The search included all pathology conclusions with the diagnosis microscopic, collagenous (CC), or lymphocytic colitis (LC) between January 2000 and December 2012 in the Netherlands. A subepithelial collagen layer ≥10µm had to be present for CC and an increased number of intra-epithelial lymphocytes (>20/100 epithelial cells) for LC. Cases were classified as undefined MC (uMC) if specific features for CC or LC were not noted. Incident cases were defined as subjects with a first diagnosis of CC, LC, or uMC between 2000 and 2012. In total, 6,863 incident cases were identified. The overall mean annual incidence rate for all MC cases was 3.2 per 100,000 person years. We found 3,724 cases of CC (75.6% females) and 2,385 cases of LC (70.5% females) with an overall mean annual incidence rate of 1.7 and 1.1 per 100,000 person years, respectively. Remaining 754 cases were described as uMC. From 2000 to 2012, the incidence rates increased significantly from 1.2 to 2.5 per 100,000 person years ($p<0.001$) in CC and from 0.3 to 2.3 per 100,000 person years ($p<0.001$) in LC. Compared to CC, the incidence rate of LC increased significantly more over time. The total number of MC cases per 1,000 colonoscopies increased as well, from 2.3 to 2.9 between 2004 and 2011. For both CC and LC the median age at diagnosis was 61 years. Females above 65 years of age had a 3.6 and 3.3 times increased risk of CC and LC, respectively, compared to those below 65 years. Conclusion: In this Dutch, nationwide population-based study the CC and LC mean annual incidence rates were considerably lower than the incidence rates published so far. However, both CC and LC incidence rates increased significantly over time with a clear predominance for elder females. The increase can only partially be explained by the raise in annually performed colonoscopies. Further research on environmental and lifestyle risk factors may reveal explanations for the discrepancy in international MC incidence rates and changes over time.

Immunoglobulin-bound bacteria in pediatric IBD patients

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Incidence of pediatric Inflammatory Bowel Diseases (IBD), encompassing Crohn Disease (CD) and Ulcerative Colitis (UC), has increased recently, especially in Canada and Northern Europe. Alterations in host-bacterial interactions are important factors for disease pathogenesis. A key component for maintaining a homeostatic balance between microbiota and the host-immune system is the production of immunoglobulins (Ig). Since both bacteria and Ig have the potential to influence each other and affect inflammation in the gut, our hypothesis was that children with IBD have more Ig-bound bacteria compared to controls and that the composition of these Ig-bound microbes differ, possibly including more virulent bacteria. The aim of the study was to determine the proportion of Ig-bound bacteria, and to assess major changes in composition of (Ig-bound) bacteria in pediatric patients between children with CD, UC and non-IBD controls. Intestinal aspirates from children with IBD and non-IBD controls were collected from the terminal ileum during endoscopy using sa washes. Ig-bound bacteria were identified using immunofluorescent staining and quantified and sorted by flow cytometry. Total amounts of (Ig-bound) bacteria within aspirates were measured by qPCR using 16S rDNA universal primers. Dominant bacterial groups, including; Bacteroides-Prevotella-Porphyromonas group, Clostridium cluster XIVa, Clostridium cluster IV, Bifidobacterium spp., Lactobacillus-Pediococcus-Leuconostoc group, and Enterobacteriaceae family were further quantified by qPCR. Our results showed no difference in the total amount of bacteria in gut washes between non-IBD, CD and UC patients; however, compositional analyses of 6 major bacterial groups showed differences in the relative abundance of the studied bacterial groups, with Lactobacillus- Pediococcus-Leuconostoc group showing a significantly higher relative abundance in UC than non-IBD controls ($p<0.05$). In addition, IBD patients displayed distinct IgA and IgG-bound microbiota when compared to non-IBD Ig-bound bacteria. Enterobacteriaceae family were over-represented in Ig-bound bacteria in IBD patients. In conclusion, these results suggest that the microbiota composition in terminal ileum washes differs based on disease phenotype. More importantly, we showed that Ig-bound microbiota differed between IBD and non-IBD patients. Among them, over-representation of Enterobacteriaceae family in Ig-bound microbiota in IBD patients suggested that this bacterial group, which includes many virulent bacteria, plays an important role in the host-microbiota interactions.

Lower abundance of Uncultured Clostridiales in PSC patients

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Primary sclerosing cholangitis (PSC) is a cholestatic liver disease, strongly associated with a particular phenotype of inflammatory bowel disease (IBD) with right-sided colonic involvement. The aim of our study was to characterize the intestinal mucosal microbiota at the level of the terminal ileum and coecum in PSC patients. We included PSC-, UC-patients and non-inflammatory controls. The microbiota composition based the on 16S rRNA diversity was determined on ileal and cecal biopsies per patient using the Human Intestinal Tract Chip (HITChip). We prospectively included 34 patients; 14 patients in the PSC group, 11 patients in the UC group and 9 non-inflammatory controls. In the PSC group, median age was 37.5 years (IQR 25-55), 86% of the patients were male, median PSC disease duration was 4.5 years (range 0-17) and 12 of these PSC patients (86%) had concomitant IBD; 4 Crohn's disease (CD) and 8 ulcerative colitis (UC). In the UC group, median age was 50 years (IQR 37-67) and 82% of the patients were male. In non-inflammatory controls, median age was 65 years (IQR 50-70) and 78% were male. Samples did not cluster by disease group. In the non-inflammatory control group, where the potential effect of inflammation on the microbiota composition per segment is eliminated: no significant differences were found in the comparison of 22 phylum/order-like and 130 genus-like groups included in HITChip analyses in ileal versus colonic mucosal biopsies. The average Pearson correlation for intra-individual comparisons was: r=0.88±0.13. Ileal and colonic biopsies were comparable according to: diversity, eveness and richness in colon vs ileum respectively, justifying analyzing pooled ileal-cecal biopsies for further analyses. Similarity of the profiles within the PSC cohort was different compared to non-inflammatory controls (p=0.03). At genus-like level, the relative abundance of Uncultered Clostridiales was lower in PSC (0.24%±0.10) compared to IBD (0.41%±0.29) and controls (0.49%±0.25) (False discovery rate: 0.038; p=<0.001). No significant differences in diversity and evenness were found, but the richness differed across the groups and was lowest in the PSC patients: 685±181 in PSC, 746±210 in IBD and 821±175 in controls (p=0.02).
In conclusion: the mucosal adherent microbiota at the ileocecal level in PSC patients shows significantly reduced richness. At genus-like level, the relative abundance of Uncultured Clostridiales is significantly lower as compared to IBD- and healthy controls. The reduced amounts of the Uncultured Clostridiales in PSC biopsies can be considered as an indication for a compromised gut as we have recently observed that this group of not yet cultured Firmicutes correlates significantly with health.

High Infliximab trough levels are associated with impaired quality of life in IBD patients in clinical and biochemical remission on maintenance IFX therapy

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Preliminary evidence suggests a therapeutic window for infliximab (IFX) trough levels (TL's) in patients with inflammatory bowel disease (IBD). It remains unknown if higher or presumably 'supra-therapeutic' TL's are associated with adverse effects. The aim of this study was to identify an association between high TL's, side effects of IFX treatment and quality of life.We performed a cross-sectional study in IBD patients in clinical and biochemical remission. Clinical remission was defined as HBI<5 for Crohn's disease (CD) and CCAI<5 for ulcerative colitis (UC). Biochemical remission was defined as a fecal calprotectine < 250 microgram/gram. IFX TL's and biochemical markers to rule out alternative diagnosis for fatigue were assessed (Hb, Ht, TSH, CRP and vitamin D). Quality of life was assessed by IBDQ and SF-36. Fatigue and joint pain were measured by VAS scores and for skin lesions a skin questionnaire was completed. The patient cohort was separated in patients with 'therapeutic' (IFX TL 3-7 ug/ml) and 'supra-therapeutic' (IFX TL >7 ug/ml) drug levels. Patients were unaware of their TL when they completed the questionnaires.Thirty-seven out of 81 screened IBD patients (26 CD and 11 UC) met all the criteria for clinical and biochemical remission. The median CRP, fecal calprotectine and haemoglobin concentration was 0.7 mg/l, 63 microgram/gram and 8.7 mmol/l, respectively, while median IBDQ was 180. Therapeutic TL's were found in 29 out of 37 (78%) patients, whereas 8 out of 37 (22%) patients had supra-therapeutic TL's. Antibodies to IFX were undetectable in all patients. Inverse correlations between TL concentrations and quality of life determinants were found for IBDQ (-0.370, P<0.05) and the following domains of the SF-36 questionnaire: social (-0.359, P<0.05), pain (-0.406, P<0.05) and perception (-0.380, P<0.05). Patients with supra-therapeutic TL's had lower SF-36 scores, compared to the therapeutic TL group, in 5 out of 9 domains, of which two were significant: social (50 versus 70; P<0.05) and pain (67.5 vs. 88; P<0.05). The two groups scored equally for the remaining 4 SF-36 domains. Although not statistically significant, patients with supra-therapeutic TL's reported a somewhat lower quality of life by IBDQ (175 vs. 185; P=0.30) and more joint pain (13.5 vs. 6.0; P=0.33).
Conclusions: IBD patients who were in clinical and biochemical remission with supra-therapeutic IFX TL's had an impaired quality of life compared to those with therapeutic IFX TL's. Future trials should determine whether dose de-escalation would abolish these side effects.

Low dose naltrexone in therapy resistant IBD, a case series

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Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing bowel disorders. Several established drug therapies exist, but some patients become resistant to these. For these patients, new treatments are urgently needed. Small studies have suggested that the immune system can be influenced by modulating the opioid receptors in the gut using low dose naltrexone (LDN). Here, we report our experience with LDN in patients resistant to conventional therapies.A case series of all IBD outpatients treated with LDN (5mg/day) were identified and investigated. Patients with at least 1 follow-up visit were included. Clinical and endoscopic response were analyzed where available. Clinical response was defined as clinical remission after 3 months of treatment. Endoscopic response was defined as a reduction of the endoscopic Mayo score to ≤ 1.From June 2010 until June 2013, 40 patients (43% male, median age 40 years, IQR 28 – 52 years) were treated with LDN. Previous treatments included anti-TNF in 36 patients, immunomodulators in 39 patients and corticosteroids in 40 patients. At time of LDN start, 8 patients were on anti-TNF treatment, 12 received immunomodulators and 18 patients received corticosteroids. Follow-up is ongoing in 27 patients, the other 13 patients were followed for a median of 6 months (IQR 4 – 13 months). 22 patients had a diagnosis of CD and 18 had UC. Clinical response was achieved in 12 patients (30%), 8 CD (36%) and 4 UC (22%). 22 other patients (55%) had a response of limited duration (1 to 3 months), whereas 6 patients (15%) showed no response at all. Endoscopic data was available in 8 responders, with 7 showing endoscopic response. Endoscopic data of 13 non-responders was available, with none showing endoscopic improvement.Amongst long term responders, remission was sustained for a median of 21 months (IQR 15 – 26 months). 9 patients are still in remission, the other 3 patients relapsed at 11, 21 and 21 months. In total, 11 patients underwent surgery (28%), 5 CD (4 subtotal colectomies, 1 partial small bowel resection) and 6 UC patients (all subtotal colectomies). Corticosteroids could be stopped in 13 patients. In total, 5 patients (12%) reported side-effects (headache, nightmares, dizziness), 1 patient stopped LDN treatment because of these. Our data shows that for IBD patients refractory to conventional treatment, LDN may be a promising application - 30% of these severe cases responded to treatment, with 20% of patients showing lasting benefits. The relatively mild side-effects of LDN justify the consideration of this treatment for therapy-resistant IBD or as a bridge to surgery.

Interspace microbiome profiling (IS-pro) enables to differentiate IBD subclasses and disease activity by specific loss of bacterial diversity

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Aim Supposedly, intestinal microbiota plays a major role in IBD-pathogenesis. Differences in its composition have been observed between and within patients with Crohn's disease (CD) and ulcerative colitis (UC), varying with disease activity. This opens diagnostic potential in IBD. To date no standard laboratory techniques for microbiota analysis, suitable for daily clinical practice, are available, the more when using sample types like faeces and mucosal biopsies. As sampling method, storage and processing of samples have been shown to affect microbiota analysis, limitations in standardisation and accessibility arise. Therefore, we aimed to collect rectal swabs from IBD-patients during consultation in an outpatient clinical setting and analyse these with IS-pro. Methods Rectal swabs were collected from consecutive IBD-patients at a referral, third-IBD outpatient clinic. Disease activity was determined with clinical indices. Total DNA was isolated by standard laboratory isolation procedures. Subsequently, microbial DNA was analysed with IS-pro, a within 8 hours performed, automated, high-throughput molecular fingerprinting method identifying composition of intestinal microbiota based on the ribosomal DNA (rDNA) interspace (IS) region combined with phylum specific sequence variation of the 16S rDNA. Combined with the proprietary IS-pro software suite, final output consists of profiles giving relative quantification of bacterial species within the most prominent phyla, Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia. From these data, Shannon diversity indices were calculated for all samples. ResultsIn total 144 rectal swabs were collected (CD n=85; UC n=59). Lower species diversity in the Firmicutes/Actinobacteria phyla was observed in CD as compared to UC (p0.02).Species diversity in the Proteobacteria phylum was lower in active disease, both for CD (p0.02) and UC (p0.05). Loss of species in Bacteroidetes phylum in active CD versus quiescent CD was observed (p<0.01).Total species diversity was lower in active disease, both in CD and UC (p0.05 and p0.05, respectively). Within each phylum no specific species was typically associated with disease type or degree of activity.
Conclusion Rectal swabs analysed with IS-pro is a feasible means of microbiota determination in an outpatient clinical setting. Differences in species diversity were observed in IBD; disease subtype differed when analysing diversity in the Firmicutes/ Actinobacteria phyla whereas disease activity was associated with lower diversity in Proteobacteria (in IBD) and in Bacteroidetes (in CD). These data suggest that diagnosis and stratification of IBD by microbial profiling (IS-pro) may be feasible.

Preconception care in IBD women leads to less disease relapses during pregnancy

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Background Preconception care is important for all women with a reproductive wish. Preconception care in IBD patients (pts) is besides health promotion and risk behavior reduction, also important to increase knowledge on the effects of IBD and drugs on pregnancy outcomes. We assessed whether preconceptional care in IBD pts affects pregnancy outcome. Methods From 2008 till 2013, all pts visiting the preconception and pregnancy outpatient clinic (POC) were prospectively followed. For the purpose of this study we compared pts who received preconception care prior to pregnancy (study group), to pts visiting the POC when already pregnant (control group). Patient characteristics, disease,-and obstetric history and medication were documented. Number of relapses, folate intake, medication changes, smoking behaviour and pregnancy outcomes were noted. Results In the study group (76 CD, 25 UC, 6 IBDU), 107 out of 152 pts got pregnant, resulting in 82 live births, 16 miscarriages, 1 stillbirth and 8 still pregnant at time of analysis. In the control group (71 CD, 30 UC, 2 IBDU), 103 pregnancies resulted in 82 live births, 9 miscarriages, 1 stillbirth, 1 elective abortion, 8 still pregnant at time of analysis and 2 lost to follow-up. The groups were comparable in terms of marital status (p=0.898), education level (p=0.265), smoking 3 months before pregnancy (p=0.498), 5-ASA use (p=0.1244), corticosteroids use during pregnancy (p=0.1543) and previous bowel surgery (p=0.329). Pts in the study group were more often nulliparous (p=0.007) and more often used thiopurines (p=0.0011) and anti-TNF (p=0.0001) during pregnancy. Compared to the control group, pts in the study group more often used folate (44 vs 99, p=0.0005) and more often quit smoking during pregnancy (3 vs 13 p=0.0013). In the control group, 8 pts discontinued IBD medication due to fear of side effects on the child, which lead to disease relapse in 1 pt. In the study group, none of the pts discontinued IBD medication at own initiative. Preconception care had a protective effect on disease activity during pregnancy, independent of smoking status, disease duration and peri-conceptional disease activity (Crude OR= 0.441 95% CI: 0.232-0.838, Adjusted OR= 0.455 95%CI: 0.211-0.979).
Conclusion: Preconception care in IBD women is associated with smoking cessation, folate intake and adequate intake of IBD medication during pregnancy and prevents disease relapse.

Anti-TNF is safe to stop in the second trimester of pregnancy in IBD women in remission

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Background. Anti-TNF is relatively safe during pregnancy in Inflammatory Bowel Disease (IBD) females. Continuation of anti-TNF during pregnancy is related to high anti-TNF in the newborn and might have immunological consequences. We earlier reported that stopping around week 24 seems feasible and safe. In this study, we further evaluated the maternal safety of discontinuing anti-TNF in the 2nd trimester and compared relapse between females that stopped and continued anti-TNF. Methods. Out of a prospective cohort of 210 pregnant IBD patients (pts), all pts on anti-TNF were selected. IBD pts in remission around gestational week 20 stopped anti-TNF before gestational week 25 (study group), and IBD pts not in remission around week 20 continued anti-TNF until at least week 30 (control group). Disease activity and pregnancy outcomes were compared between the study and the control group. Results. The study and control group were drawn from a population of 210 pregnant IBD pts. Anti-TNF was used in 74 pregnancies (44 infliximab (IFX), 30 adalimumab (ADA)), resulting in 59 live births, 12 miscarriages, 1 elective abortion and 2 pts were still pregnant at the time of analysis. In the study group, 32 pts stopped anti-TNF before week 25 and in the control group 22 pts continued anti TNF until at least week 30. Reasons for continuation included disease activity around week 20 (n=6), anti-TNF start in first trimester (n=1) and difficult to control disease (n=15). Median gestational week of anti-TNF cessation was 22 weeks (IQR: 12-29). A total of 8 pts in the study group had concomitant drugs (aminosalicylates (n=2), corticosteroids (n=1), azathioprine (n=5)) , compared to 6 women in the control group (azathioprine (n=6) combined with aminosalicylates (n=1) and corticosteroids (n=1)) (p=1.000).In the study group, 2 pts relapsed in week 30 and 36 after anti-TNF cessation in week 22, while in the control group 1 pt relapsed (p=1.000). There were no significant differences in birth weight, gestational term, congenital abnormalities and APGAR scores between the study and the control group. As reported previously, the anti-TNF levels in the cord blood from children from females that stopped anti-TNF prior to week 25 were significantly lower compared to females that continued anti-TNF until the 3rd trimester (1.48 µg/ml vs 8.65 µg/ml, p>0.0001).
Conclusion: Anti-TNF is safe to stop in the 2nd trimester in IBD women in sustained remission. Anti-TNF cessation before gestational week 25 is not associated with a higher risk of relapse compared to women who continue anti-TNF treatment.

Decision-making, counselling and course of pregnancy in female inflammatory bowel disease patients

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Inflammatory bowel disease (IBD) often affects women in their reproductive years. The influence of their disease on pregnancy outcome is of great concern to IBD patients. This study aimed to assess decision-making and outcome of pregnancy in women with IBD treated in a general hospital. All female IBD patients from two general hospitals were asked to complete a survey regarding decision-making, counselling and pregnancy outcome. Clinical records were also reviewed. From a total of 760 women with IBD, 385 (51%) completed the survey: 185 (48%) patients had Crohn's disease, 197 (51%) had ulcerative colitis and 3 (1%) had unclassified IBD. Median age of respondents was 44 years (IQR 33-56). Median age at diagnosis of IBD was 30 years (IQR 21-40). In total, 115 patients (30%) had received counselling on pregnancy of whom 5 (4%) thought the quality was poor. Of those who were not counselled, 15 (6%) were dissatisfied about this. In total, 113 women (29%) had never been pregnant, in most cases (n=78, 69%) this was a conscious decision, unrelated to the presence of IBD. In 20 women (18%) the decision not to become pregnant was partly related to their disease.Of 275 women that had been pregnant, 99 women had a total of 156 pregnancies after IBD diagnosis. Median time between diagnosis and subsequent pregnancy was 5 years (IQR 3-8). Having IBD had no influence on the wish to become pregnant in 113 of 156 pregnancies (72%). Immunosuppressive drugs were used before pregnancy in 36 cases (23%), of which anti-TNF agents were used in 7 (5%). In 9 cases (6%), immunosuppressive therapy was stopped before pregnancy. Disease activity increased during pregnancy in 30 cases (19%), requiring immunosuppressive drugs in 9 cases. Pregnancy-related complications such as preeclampsia occurred in 18 cases (12%). The frequency of pregnancy-related complications did not differ significantly between women with or without immunosuppressive medication (17% vs 10%, respectively, p=0.249). The number of preterm births was higher (24% vs 11%, p=0.090) and mean birth weight was lower (3047 vs, 3310 grams, p=0.034) in patients on immunosuppressive drugs.
Conclusions. In female IBD patients from a general hospital, counselling on pregnancy seems satisfactory and having IBD does not have a great impact on women's decision-making regarding pregnancy. The outcome of pregnancies after IBD diagnosis is generally good. However, preterm birth and lower birth weight are more frequent in IBD patients using immunosuppressive drugs. These latter patients are likely to have more severe disease and, therefore require active monitoring by a gastroenterologist and gynaecologist during pregnancy.

The Pharmacokinetics of Infliximab and Markers for Response to Induction Therapy in Patients with moderate to severe Ulcerative Colitis

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Insufficient serum concentrations have been suggested as a cause of lack of response to infliximab (IFX) in Ulcerative Colitis (UC) and associated with a high inflammatory load. Nevertheless early pharmacokinetics (PK) of IFX and markers for response to induction therapy have been poorly studied. We studied the PK of IFX induction therapy and inflammatory makers for response in patients with moderate-to-severe UC.In this multicenter prospective observational study patients with moderate-to-severe UC (endoscopic Mayo 2/3) starting on IFX were included. Serum IFX concentrations, antibodies to IFX, CRP and albumin and fecal samples (calprotectin and IFX concentration) were collected at 10 serial time points during the first 6 weeks of therapy. Endoscopic response was defined as improvement at week 6-8 endoscopy. Absence of response was defined as the need for higher dose infusion during induction or colectomy within 3 months.Fifteen UC patients were included. All but one patient received IFX according to the regular induction regime of 5mg/kg at week 0,2,6. 8/15 patients had no endoscopic improvement. At day 4 median (IQR) serum CRP was 59 (30-96) mg/l for patient with absence of response (n=3) compared to 3.8 (1.3-11.3) for responders (n=12), P=0.01, with CRP>25mg/l as cut-off (OR:175, 95%CI:2.9-10520, P<0.01) for predicting absence of response. Median (IQR) CRP at day 7 was 15 (2-35) mg/l for endoscopic non-responders (n=8) compared to 2 (1-3) mg/l for endoscopic responders (n=7), P=0.06, CRP>5mg/l had an (OR:23, 95%CI:0.99-556, P=0.02) for predicting lack of endoscopic response. Both serum albumin and fecal calprotectin discriminated less or later between clinical and endoscopic response. At week 6 antibodies to IFX were present in 4 patients and median 'trough' level was 2.5 ug/ml for endoscopic non-responders versus 8.2 ug/ml for responders (P=0.03). Serum IFX≤7ug/ml at week 6 was defined as a cut-off (OR:36, 95%CI 1.8-719, P=0.03) to predict endoscopic non-response. Fecal IFX at day 1 was significantly higher (P=0.02) for non-responders compared to responders. Average post-hoc area under the IFX concentration versus time curve (AUC) was 1204 mg/L/day in the non-responders compared to 1417 mg/L/day for the responders (p=0.42). Conclusions: A wide variation in early serum concentrations of IFX was observed. Primary non-responders have lower serum concentrations IFX at induction compared to responders, increased fecal concentrations in the first days of treatment and in some instances early development of antibodies to IFX. Serum CRP is a better early marker for response to IFX therapy compared to fecal calprotectin or serum albumin in patients with UC.

Large variation in infliximab trough levels is associated with disease activity in pediatric Inflammatory Bowel Disease

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Background: Low serum trough levels (TL) of infliximab (IFX) and the formation of antibodies to IFX (ATI) are associated with the loss of therapeutic response in adults with inflammatory bowel disease (IBD). Until now, pediatric data are scarce. Therefore, we aimed to investigate the association between ATI and IFX TLs, and clinical and biochemical disease activity (DA) in children receiving maintenance treatment with IFX for IBD. Methods: All children aged <18 years receiving scheduled IFX infusions for Crohn's disease (CD) or ulcerative colitis (UC) in 3 hospitals in the Netherlands where asked to participate. Prior to two consecutive IFX infusions, IFX TL and ATI were measured. Therapeutic range of IFX was considered 3-7 Furthermore, biochemical DA was assessed by CRP and fecal calprotectin (FC) (Bühlman ELISA). Clinical DA was determined by PCDAI and PUCAI, for CD and UC, respectively. Clinical remission was defined as a score of <10 for PCDAI and PUCAI. A score of >30 or 65 was considered severe DA for PCDAI and PUCAI, respectively. Results: Between December 2012 and February 2013 33 patients were included (26 CD, 7 UC), with a median age of 14 years [IQR 12-16]. All TL measurements combined (n=66) the median IFX TL was 3 µg/mL [IQR 1-6]. Subtherapeutic, therapeutic and supratherapeutic TLs were found in 42.4%, 39.4% and 18.2% of measurements, respectively. ATI were detected in 3 patients but our assay does not allow antibody detection in the presence of drug. Median FC and CRP was 394.5 µg/g and 2.4 mg/L, respectively. At both time points, the majority of patients were either in clinical remission (56.9%) or had mild to moderate clinical DA (41.2%). At the first measurement, no significant correlation between IFX TL and clinical or biochemical DA was found, although a trend was observed for FC (r=-0.33, p=0.08) and CRP (r=-0.33, p=0.06). At the second measurement, a significant correlation was found between IFX TL and clinical DA grading (r=-0.48, p=0.01) and FC (r=-0.49, p=0.01). Patients with therapeutic IFX TLs (≥3 µg/mL) were more likely to be in clinical remission (p=0.01). At both measurements, a significant correlation between clinical DA and FC was observed (r=0.53, p<0.01; r=0.50, p=0.02), whereas no correlation was found between CRP and clinical DA (p=0.16; p=0.44). No difference was found in IFX TLs between children receiving IFX monotherapy or concomitant immunosuppression.
Conclusion: IFX TLs appear to be related to both clinical and biochemical DA (the latter measured by FC), which provides a rationale for therapeutic drug monitoring in children receiving IFX for IBD. Furthermore, a large variation in IFX TLs was found.

Top-down versus step-up treatment in newly diagnosed Crohn: no difference in long-term outcome

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Background: Early combined immunosuppression ('top-down' (TD)) is more effective than conventional management ('step-up' (SU)) for induction of remission and reduction of corticosteroid use in newly diagnosed Crohn's disease (CD). However, it remains unknown whether short-term benefits are sustained long-term and thus the natural history of CD can be altered. Therefore, we aimed to investigate the long-term effects of TD (induction IFX and maintenance azathioprine (AZA)) vs. conventional SU treatment in CD. Methods: Long-term follow-up data was retrospectively collected from patients who participated in a randomized controlled trial evaluating TD vs. SU in patients with newly diagnosed Crohn's disease (1). Data collection was performed in 12 of the 18 participating centers. For 16 semesters following the original trial follow-up, the following was abstracted from patients' medical records: clinical disease activity by global assessment, medication use, hospitalization, surgery, and the occurrence of new fistulas and significant flares. Comparisons were done by intention-to-treat analysis. Time to event data was evaluated using the Kaplan-Meier and log-rank test. To compare the proportions of time in remission, Fisher's exact test was used. Algorithm failure was considered any of the following: surgery, start of adalimumab, ciclosporin or experimental therapy. Results: 112 patients (SU n=57) were included in the analysis. At the start of follow-up, 81.6% (57.1% AZA, 24.5% methotrexate (MTX)) vs. 66.7% (54.2% AZA, 12.5% MTX) of patients used an immunomodulator, and 20.4% vs. 16.7% received IFX in TD and SU, respectively. No difference in the proportion of semesters that patients were in clinical remission during follow-up was found between TD and SU (66.6% vs. 68.3%; p=0.52). Mean time to first hospitalization was 13.9 vs. 13.1 semesters (p=0.46), mean time to first new fistula was 15.1 vs. 14.5 semesters (p=0.53) and mean time to algorithm failure was 11.7 vs. 10.5 semesters (p=0.27). The median time to Crohn-related surgery was similar in both groups (15.0 vs. 14.1; p=0.28). A trend towards a difference between TD and SU was observed for time to significant flare (median time 6 vs. 8 semesters; p=0.09).
Conclusion: No difference in long-term outcome was found between top-down versus step-up treatment algorithms for newly diagnosed Crohn's disease. A potential explanation may be that top-down induction was restricted to only 3 IFX infusions. Furthermore, an early start of immunomodulation and/or IFX in the SU group, could have lead to a reduced contrast between patient groups. (1) D'Haens, GR et al. Lancet 2008;371:660–7.

Skewed thiopurine metabolism leads to early therapeutic failure in the majority of patients with inflammatory bowel disease

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Background The conventional thiopurines azathioprine and 6-mercaptopurine are considered maintenance immunosuppressive drugs of choice in the treatment of inflammatory bowel disease (IBD). Unfortunately, treatment is often discontinued due to 6-methylmercaptopurine ribunucleotide (6-MMPR) metabolite associated adverse events or refractoriness. Patients with an aberrant thiopurine metabolism may be particularly at risk for therapy failure. We determined the predictive value of this pharmacological phenomenon in IBD patients during regular thiopurine therapy. Methods Clinical effectiveness and tolerability of weight-based thiopurine therapy were determined in all IBD patients displaying a skewed metabolism (ratio 6-MMPR/6-thioguaninenucleotide (6-TGN) >20). All samples were routinely assessed between 2008-2012, being part of standard clinical follow-up after initiation of conventional thiopurines. Results Fourty-one (84%) out of 49 included IBD patients discontinued thiopurines (55% female and 53% with Crohn's disease) with a median duration of 14 weeks (IQR 10-29). The majority of patients with a skewed metabolism discontinued thiopurines due to adverse events (55%) or refractoriness (12%). The most commonly observed adverse event was hepatotoxicity (18 patients, 37%). Median 6-TGN level was 159 pmol/10e8RBC (IQR 113-218 pmol/10e8RBC), median 6-MMPR level was 11020 pmol/10e8RBC (IQR 7210-20340 pmol/10e8RBC) and the median 6-MMPR/6-TGN ratio was 72 (IQR 43-114). Thiopurine therapy failure was associated with a ratio above 50 ($p< 0.03$). Hepatotoxicity occurred more frequent in patients with an extreme skewed metabolism (6-MMPR/6-TGN ratio >100) ($p<0.01$).
Conclusions This study demonstrates that a skewed metabolism is a major risk factor for early thiopurine failure in IBD patients. These observations implicate that routine thiopurine metabolite measurements may be used as a prognostic tool to identify those patients with an aberrant metabolism in an early stage, possibly benefitting from therapy adjustments.

Early assessment of thiopurine metabolites predicts thiopurine-induced leukopenia in inflammatory bowel disease patients

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The most important and potentially lethal adverse event of azathioprine (AZA) and mercaptopurine (6MP) treatment in inflammatory bowel disease (IBD) patients is leukopenia, which occurs mostly during the first months of treatment. Leukopenia has been mainly attributed to low thiopurine S-methyltransferase (TPMT) activity, resulting in high cytotoxic 6-thioguanine nucleotides (6TGN) concentrations. Our aim was to study the predictive value of 6TGN and/or 6-methylmercaptopurine ribonucleotides (6MMPR) metabolite concentrations, assessed one week after thiopurine therapy initiation, for the development of leukopenia during the first 8 weeks of treatment. The study was performed in thiopurine-naïve IBD patients who started thiopurine treatment as part of the Dutch randomised multi-centre trial TOPIC (ClinicalTrials.gov NCT00521950). Development of leukopenia was defined by leukocyte counts below 3.0x10*9/L. Blood samples for 6TGN and 6MMPR analysis were collected one week after thiopurine therapy initiation (T1). For comparison, all patients without leukopenia were selected from the first 272 included patients in the TOPIC trial, who completed the follow-up period of 8 weeks without any thiopurine dose adjustments. Thirty-two patients with leukopenia and 162 patients without leukopenia were analysed. Both 6TGN and 6MMPR metabolites were correlated with the occurrence of leukopenia: areas under the Receiver Operating Characteristic curves were 0.73 (95% CI: 0.63-0.84; p<0.0001) and 0.72 (95% CI: 0.61-0.83; p<0.0001), respectively. In addition, patients with leukopenia were more frequently treated with 6MP than AZA (Odds Ratio (OR) = 7.3 (95% CI: 3.1-17.0)) and were more often co-treated with anti-TNF agents (OR 5.1 (95% CI: 1.6-16.4)). At T1 threshold values of ~213 pmol/8x10*8 red blood cells (RBC) for 6TGN and ~3525 pmol/8x10*8 RBC for 6MMPR, patients with elevated 6TGN or 6MMPR levels at T1 were at increased risk of leukopenia during week 1-8: ORs were 6.2 (95% CI: 2.8-13.8) and 5.9 (95%CI: 2.7-13.3), respectively. Logistic regression analysis of the T1 6TGN and 6MMPR thresholds, thiopurine type and concurrent anti-TNF therapy at baseline, revealed that patients with elevations of both T1 6TGN and 6MMPR had the highest risk of developing leukopenia, followed by patients exceeding only the T1 6MMPR or T1 6TGN predictive threshold level.

In conclusion, both T1 6TGN and 6MMPR were independently associated with the occurrence of leukopenia during the first 8 weeks of thiopurine therapy. Assessment of 6TGN and 6MMPR metabolite concentrations one week after thiopurine initiation identifies patients at risk of developing thiopurine-induced leukopenia.

FcR-mediated effector function contributes to the therapeutic response of anti-TNF monoclonal antibodies in a mouse model of IBD

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Anti-TNF monoclonal antibodies (infliximab, adalimumab) are effective in the treatment of Crohn's disease while a TNF receptor fusion protein (etanercept) is not effective and an anti-TNF F(ab')2 fragment (certolizumab) shows a very low rate of complete mucosal healing. In contrast, all four TNF neutralizing drugs have demonstrated efficacy in the treatment of rheumatoid arthritis. These clinical observations suggest that factors other than neutralization of TNF may contribute to the clinical outcomes for TNF inhibitors in Crohn's disease. Here we tested the hypothesis that Fc receptor (FcR)-mediated effects may contribute to the therapeutic response of anti-TNF antibodies in inflammatory bowel disease.We modified an IgG2c mouse anti-TNF antibody that effectively binds the high affinity FcRs to generate an IgG1 isotype with strongly diminished binding to the high affinity FcRs. We examined the therapeutic effects with both antibodies in the T cell transfer model of inflammatory bowel disease and the collagen-induced arthritis model. The IgG2c anti-TNF antibody had a significant effect in preventing colonic inflammation in the T cell transfer model of colitis while the IgG1 anti-TNF did not elicit a significant effect. Differences in the anti-inflammatory response for each antibody could not be explained by differences in TNF potency or antibody pharmacokinetics. Conversely, both the IgG2c and IgG1 anti-TNF were similarly effective in reducing the severity of articular inflammation in mouse collagen-induced arthritis.
Conclusion: These data suggest that the mechanism of action for TNF neutralizing biologics may differ across immune mediated diseases and, potentially, between therapeutics within a particular disease. Our data suggest a specific role of Fc-mediated immune regulation in the resolution of intestinal inflammation by anti-TNF monoclonal antibodies.

Interrater reliability of the Chicago Classification in pediatric high-resolution esophageal manometry recordings

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The Chicago Classification (CC) of esophageal motility facilitates the interpretation of high resolution esophageal manometry (HRIM) recordings. Application of the CC and related software tools to the pediatric population requires validation. We aimed to assess interrater reliability of interactive CC analysis software for diagnosis of pediatric esophageal motility disorders.A database of 30 solid state HRIM recordings in children referred for manometry (13M; mean age at study 12.1 SD 5.1 years) was created and 10 liquid swallows per patient were analyzed by 10 raters (6 experts, 4 non-experts). Raters were blinded to clinical profile and recordings were provided in a randomized order. Analysis was performed using interactive software (MMS version 8.23) which populated each swallow tracing with analysis landmarks, which observers were required to manually adjust or remove. Swallow metrics (Integrated Relaxation Pressure (IRP4s), Distal Contractile Integral (DCI), Contractile Front Velocity (CFV), Distal Latency (DL) and Break size (BS)) as well as an overall CC diagnosis per study were automatically generated. In addition, all raters provided their CC diagnosis based on personal opinion. Fleiss' kappa (κ) was used for agreement of categorical data and the intraclass correlation coefficient (ICC) for continuous data. Metrics were excluded from analysis if not uniformly retained by all observers. Overall interrater reliability for IRP4, DCI and BS was almost perfect (κ =0.941, κ =0.967, κ =0.927 respectively). Reliability for CFV and DL (κ =0.523, κ = 0.464, respectively) was moderate and depended on level of experience (κ =0.629, κ =0.787 respectively amongst experts and κ =0.282 and κ =0.375 amongst non-experts). Interrater reliability for the software-generated CC diagnosis was substantial (κ =0.65) and moderate (κ =0.53) when based on the raters' personal opinion. Overall, raters changed software-generated diagnoses in 10%-53% of patient studies. Agreement across all raters on diagnosis of normal motility, EGJ outflow obstruction (IRP4-dependent) and weak peristalsis with large breaks was substantial (κ=0.77, 0.76, and 0.65 respectively). Agreement for weak peristalsis with small breaks and distal esophageal spasm (DL-dependent) was fair (κ=0.43, 0.41 respectively).
Conclusion: Interrater reliability of CC-based diagnosis of pediatric HRIM recordings was substantial when software generated, however changes introduced by personal opinion reduced reliability. Moderate agreement for CFV and DL requires caution when diagnosing motility disorders dependent on these metrics in pediatric patients.

The effect of oral vitamin B_{12} supplementation on fatigue in patients with irritable bowel syndrome or inflammatory bowel disease

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Many patients with irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) suffer from fatigue. In non-conventional treatment, Vitamin B_{12} supplementation is used to treat fatigue. However, there is insufficient evidence to support this approach in IBS and IBD patients. The objective of this study is to investigate the effect of additional oral vitamin B_{12} supplementation on fatigue in patients with IBS or IBD. This randomized double-blind, placebo-controlled trial included 95 out-clinic IBS and IBD patients with normal vitamin B_{12} blood levels aged 18 - 65 years. The participants were randomly assigned to receive 1000 µg vitamin B_{12} daily or a placebo supplement for 8 weeks. The primary outcome measure was fatigue (Checklist Individual Strength [CIS], Fatigue Impact Scale [FIS], Visual Analogue Scale [VAS]). In addition, measures of quality of life (36-item Short Form Health Survey [SF-36], short form World Health Organisation Quality of Life Assessment [WHOQOL-BREF]) and depression (Center for Epidemiologic Studies Depression [CES-D], Hospital Anxiety and Depression Scale [HADS]) were examined. No increase was found in scores of the CIS subscale 'subjective fatigue' when comparing the intervention group and the control group with a mean change of -8.1 (± 9.5) and -8.0 (± 10.6), respectively. We observed significantly improved scores on the CIS subscale 'motivation' with a difference in change of -2.2 (95% CI -4.4 to -0.4, P=0.046) in the intervention group compared to the placebo group. No significantly increased scores were found concerning depression using the CES-D questionnaire in the intervention group or in the control group (-1.4 ± 6.5 and -1.9 ± 4.9, respectively) Furthermore, scores on depression were not improved using the HADS questionnaire with a mean change of 0.0 ± 2.4 in the intervention group compared to a mean change of 0.0 ± 1.9 in the control group. In addition, no difference was observed in any subgroup on quality of life between the intervention group and the control group after the intervention period. The present study showed no confirmation of the expected effect on fatigue after oral vitamin B_{12} supplementation in IBS or IBD patients. In addition, no positive effect was found on depression or quality of life. However, significantly improved scores were indicated on the CIS subscale 'Motivation'.

Comprehensive nutritional status of patients with (refractory) coeliac disease and EATL at diagnosis

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Nutritional deficiencies, malnutrition and diarrhoea are common in patients with newly diagnosed (CD) and complicated coeliac disease. A small minority of patients does not show clinical improvement upon a strict gluten free diet (GFD). These patients are diagnosed with Refractory Coeliac Disease II (RCDII) or Enteropathy associated T-cell lymphoma (EATL) may develop in (R)CD patients. Nutritional status of patients with RCDII and EATL at diagnosis is compared with that of newly diagnosed CD patients. Nutritional status was assessed by anthropometrics (and considered 'poor' according to definition between brackets); Body Mass Index (BMI<18.5 kg/m^2)), percentage unintentional weight loss (>10%/past 6 mo), handgrip strength (HGS<85% of reference value), Fat Free Mass Index (FFMI<16.7 (male)/<14.6 kg/m^2 (female)). Intestinal absorption was defined as the difference in nutritional intake (energy, fat, protein and carbohydrate) calculated from a 4D accurately weighted food record) and faecal losses (3D faecal production; energy and macronutrients) expressed as %. Malabsorption was classified as <85% absorption. Besides, Resting Energy Expenditure (REE) was measured (kcal/D by indirect calorimetry) and compared with the estimated REE by Harris and Benedict ± 10%. CD patients (45.6±14.8y, n=43) were younger than RCDII (64.1±8.2y, n=26) or EATL (62.2±5.6y, n=26) patients (p=0.01). A 'poor' HGS and FFMI were detected in approximately 1/3 of all patient groups. 'Poor' BMI was more often observed in RCDII patients than in CD or EATL patients (in 35% vs 11.5%, p=0.033) and BMI was lower in RCDII than in CD patients (20.8±2.5 and 23.4±4.3 kg/m^2, p=0.007), whereas the EATL patients had more frequently weight loss than CD or RCDII patients (60, 40 and 20%, resp; p<0.001). Energy malabsorption was detected in 38.9% and 33.3% of the RCDII and EATL patients, vs 21.6% in CD patients. Faecal energy loss was higher in RCDII and EATL than in CD patients (571±445, 506±704 vs 242±185 kcal/D, p=0.023). An increased REE was found in 60% of RCDII, 90% of EATL, and 38% in CD patients (p=0.006).

In conclusion, although nutritional status of newly diagnosed CD patients is negatively affected at diagnosis, it is 'poorer' in patients with RCDII and EATL. Both increased faecal losses as well as elevated REE contributed to malnutrition at diagnosis.

Taurine and major surgical trauma, role of the route of nutrition

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Background Early postoperative nutrition is imperative for postoperative recovery. However it is still unclear which nutrients have a key role directly after major surgery. Because postoperative ileus is a frequent and common problem after major abdominal surgery, artificial feeding strategies are used to deliver nutrients. In a randomized study investigating whether early enteral nutrition, as a bridge to a normal diet, can reduce postoperative ileus, amino acids with antioxidant targets such as taurine were correlated with outcome. Methods Patients undergoing major rectal surgery for locally advanced primary or recurrent rectal carcinoma were externally randomized to early enteral nutrition by nasojejunal tube (EEN, n=61) or early parenteral nutrition (EPN, n=62) in addition to an oral diet. Early nutrition was started eight hours after surgery. Early parenteral nutrition was given as control nutrition to obtain caloric equivalence and minimize confounding. The primary endpoint was time to first defecation; as secondary outcomes amino acids were measured preoperatively and on day 1 and 5 after surgery. SPSS was used for statistical analysis, p value of < 0.05 was considered significant. Data given is the 95% Confidence interval for mean, lower and upper bound. Results Base characteristics were similar for both groups. In intention to treat analysis, less early postoperative ileus occurred in the enteral nutrition arm compared to the control group (p=0.04). Anastomotic leakage was significantly less in the enteral group (1 patient) compared to parenteral supplementation (9 patients, p=0.009). L-taurine plasma concentrations were not significant different in time or between the two nutritional interventions (rANOVA, p= 0.062). Glycine plasma levels were significantly lower in the EEN group at both POD 1 (EEN 137.9 – 163.1 µmol/l vs. EPN 162.5- 186.6 µmol/l, p=0.003) and POD 5 (EEN 133.4-157.0 µmol/l vs. EPN 161.0 – 196.4 µmol/l, p=0.005) in comparison to EPN.
Conclusions Early enteral nutrition is associated with less anastomotic leakage in patients undergoing extensive rectal surgery. After major surgery, plasma amino acid concentrations drop. Major determinants for surgical trauma were blood loss en extension of operation. Plasma amino acid levels with antioxidant properties were not of influence; the route of feeding could be of more importance.

Unimpaired anabolic response to oral meal feeding in patients with pancreatic cancer cachexia

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Pancreatic cancer is often accompanied by cachexia, a syndrome of severe weight loss and muscle wasting. A suboptimal response to nutritional support may further aggravate cachexia. The influence of nutrition on protein kinetics in these patients is poorly understood. This study investigates the effect of feeding on protein kinetics in cachectic pancreatic cancer patients using amino acids labelled with stable isotopes. Eight cachectic pancreatic cancer patients and seven control patients received a primed continuous intravenous infusion of L-[ring-$^{2}H_5$]-phenylalanine and L-[3,3-$^{2}H_2$]-tyrosine for eight hours. After four hours, oral feeding was started (0.083g protein/kg/h). Whole body protein breakdown was measured as total rate of appearance (Ra) of phenylalanine corrected for exogenously administered phenylalanine. Protein synthesis was calculated as total phenylalanine Ra minus rate of phenylalanine hydroxylation. Net protein balance was calculated by subtracting protein breakdown from protein synthesis. Results are given as median with interquartile range (IQR) in µmol/kg lean body mass/h. Base protein breakdown and protein synthesis were higher in cachectic patients compared with controls (breakdown: 67.1, IQR=48.1-79.6 versus 45.8, IQR=42.6-46.3, p=0.049; and synthesis: 63.0, IQR=44.3-75.6 versus 41.8, IQR=37.6-42.5; p=0.021). During feeding, protein breakdown decreased significantly to 34.4 (IQR=11.7-44.8; p=0.012) in the cachexia group and to 14.0 (IQR=6.72-26.3; p=0.018) in the control group. This decrease did not differ between groups (p=0.487). Protein synthesis was not affected by feeding in cachectic patients (58.4, IQR=46.5-76.1; p=1.000), but was stimulated in controls (47.9, IQR=41.8-56.7; p=0.018). Both groups achieved a positive net balance during feeding: 26.8, IQR=15.9-39.7 (cachexia) and 33.5, IQR=26.3-36.1, p=0.487. Conclusions Cachectic pancreatic cancer patients have a higher basal protein turnover which correlates with inflammation. Both cachectic patients and controls are able to achieve a comparable positive net balance during feedings. In cachectic patients this is primarily related to reduced protein breakdown, whereas in controls both protein breakdown and protein synthesis alterations are involved. Though anabolism is not impaired in cachectic patients, interventions stimulating protein synthesis may increase the efficacy of nutritional support in cancer cachexia.

Enteral glutamine administration increases urea production

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The virtually undisputed perception that glutamine benefits ICU patients was recently challenged by the REDOXS trial, showing increased mortality in ICU patients receiving glutamine supplementation. The explanation for this finding that contradicts current scientific evidence and clinical guidelines is unclear. In the REDOXS trial, patients received glutamine by parenteral and enteral route simultaneously, whereas positive effects of supplemental glutamine in critically ill patients are particularly described after parenteral administration. Glutamine is more avidly metabolized after enteral than after parenteral administration. Consequently, effects of enteral glutamine supplementation may vary greatly from those of parenteral glutamine supplementation. Enteral glutamine administration leads to lower systemic glutamine availability but may also increase urea formation, which may be a detrimental side-effect of enteral glutamine supplementation. Aim of this study was to assess the formation of urea from exogenous glutamine during enteral and parenteral administrationSixteen surgical patients received α-15N-glutamine via intravenous (n=8) or enteral (n=8) infusion. The infusion rate (15.7 μmol/kg/h) was similar in both groups. Systemic 15N-urea enrichments were measured in arterial blood by LCMS as a measure of the irreversible loss of nitrogen from α-15N-glutamine by transamination processes. After 5 hours, mean±SEM 15N-urea enrichment was 10.7±4.8% in the intravenous group vs. 33.9±4.4% in the enteral group ($p<0.001$, 2-way ANOVA).The REDOXS trial has confused current opinions on glutamine supplementation in the ICU. Its design however hampers comparability with other studies since the metabolic fate of enteral administered glutamine differs from that of parenteral administered glutamine. Instead of discarding previous literature on glutamine supplementation in the light of the results of the REDOXS trial as suggested by some, it may be more appropriate to explore (patho-)physiological explanations for the intriguing different outcomes of old and new studies. Here we show that a substantial amount of enteral administered glutamine is transaminated and converted to urea, leading to low systemic glutamine availability, increased blood-urea nitrogen levels and an unfavorable nitrogen balance. We hypothesize that high-dosed enteral glutamine supplementation in critical illness is deleterious by deteriorating nitrogen balance without exerting the potential beneficial effects of enhancement of systemic glutamine availability.

Alfabetische lijst van standhouders tijdens het Voorjaarscongres, 20-21 maart 2014 te Veldhoven

G = Genderzaal, D = Diezezaal, K = Kempenhal, M = Meijerijfoyer	***Standnummer***
AbbVie	K1
AbbVie (HCV)	K19
Alvleesklliervereniging	MF4
Aquilant Nederland Pyramed	D5
Astellas Pharma BV	D9
Boston Scientific Nederland BV	G2
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Cablon Medical BV	K6
Campro Scientific	K17
CCUVN	MF1
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Colopolast BV	G7
COOK Nederland BV	K4
Covidien Nederland	G11
Dr. Falk Pharma Benelux BV	G1
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Endoss BV	G15
Endotechniek	G12
Erbe Nederland BV	K8
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Ferring BV	K10
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