

# Wetenschapsdag Chirurgie 2019



## Programma- en Abstract boek

Vrijdag 15 november 2019  
De Rode Hoed  
Amsterdam

## Voorwoord

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Beste collegae,

Hartelijk welkom bij de eerste Wetenschapsdag van de afdeling Chirurgie Amsterdam UMC voor de opleidingsregio's 1 en 2. Wetenschappelijk onderzoek uit de gezamenlijke Amsterdamse regio wordt op 15 november 2019 gepresenteerd. De Rode Hoed, waar kritische en nieuwsgierige denkers en doeners samenkomen, vormt de perfecte entourage om wetenschappelijke bevindingen te delen, nieuwe ideeën op te doen en de onderlinge band te versterken. Er staat ons een inspirerende dag te wachten die wordt afgesloten met een stijlvol galadiner ter viering van de verbondenheid binnen de chirurgie. We wensen u een heel geslaagde Wetenschapsdag Chirurgie 2019 toe!



Jaap Bonjer

Olivier Busch

## Welkomstwoord van de commissie

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Wij zijn zeer verheugd u allen te mogen verwelkomen op de allereerste Wetenschapsdag Chirurgie van regio I & II, in de Rode Hoed te Amsterdam!

Met deze dag hopen we de samenwerking tussen de regio's te stimuleren en elkaar op de hoogte te brengen van lopend wetenschappelijk onderzoek.

Vandaag zullen interessante presentaties over de meest uiteenlopende onderwerpen ter sprake komen. We hopen met de huidige sessie-indeling iedereen een interessant en divers podium te bieden. De parallelsessies geven u de mogelijkheid om de enorme diversiteit aan onderzoek uit de regio's te ontdekken. Met presentaties en pitches zullen studenten, onderzoekers, ANIOS, AIOS en chirurgen uitkomsten, protocollen of zelfs proefschriften aan u presenteren. De dag wordt afgesloten met de best abstract sessie. De winnaar wordt door u gekozen middels een elektronische stemming en krijgt een prachtige, door OLYMPUS gesponsorde, prijs.

Daarnaast zijn wij vereerd dr. Matthijs Botman te mogen verwelkomen als keynote speaker. Als voorzitter van Global Surgery Amsterdam zal hij een interessante voordracht geven over (chirurgisch) wetenschappelijk onderzoek in ontwikkelingslanden en innovaties om de zorg (aldaar) betaalbaar te houden.

Wij hopen van harte dat u zich laat inspireren op, maar met name geniet van, de eerste Wetenschapsdag Chirurgie van regio I & II.

Veel dank aan eenieder die heeft geholpen deze dag een succes te maken.

Veel plezier!

De organisatie Wetenschapsdag Chirurgie 2019

Congrescommissie: Jaap Bonjer, Olivier Busch, Marjolein van Egmond, Ron de Hoon, Paul van Amstel, Lotte Blonk, Anouk Emmen, Marie-Louise Loos, Dorien Salentijn, Maxime Slooter, Daan Voeten, Nina Wesdorp



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## Programma

Tijd	Sessie		Zaal	Verdieping
8:30-09:00	Inloop			
09:00-10:15	<b>Sessie 1</b>	Waking up the brain	Oosterhuiszaal	BG
10:15-10:45	Pauze 1			Balkon 1e en 2e verdieping
10:45-12:00	<b>Sessie 2a</b>	Experimental	Oosterhuiszaal	BG
10:45-12:00	<b>Sessie 2b</b>	Survival after surgery	Zwanenzaal	1e verdieping
12:00-13:00	Lunch pauze			Balkon 1e en 2e verdieping
13:00-14:10	<b>Sessie 3a</b>	New surgical techniques	Oosterhuiszaal	BG
13:00-14:10	<b>Sessie 3b</b>	Image-guided Diagnostics & Surgery	Zwanenzaal	1e verdieping
13:00-14:10	<b>Sessie 3c</b>	To cut or not to cut	Vrijburgzaal	2e verdieping
14:10-14:40	Pauze 2			Balkon 1e en 2e verdieping
14:40-15:45	<b>Sessie 4a</b>	The vulnerable patient	Oosterhuiszaal	BG
14:40-15:45	<b>Sessie 4b</b>	Centralisation & interhospital variation	Zwanenzaal	1e verdieping
14:40-15:45	<b>Sessie 4c</b>	Wound healing	Vrijburgzaal	2e verdieping
15:45-16:15	Pauze 3			Balkon 1e en 2e verdieping
16:15-16:45	<b>Sessie 5</b>	Global Surgery - Frog Leap	Oosterhuiszaal	BG
16:45-17:30	<b>Sessie 6</b>	Best abstracts	Oosterhuiszaal	BG
17:30	<b>Afsluiting</b>	Award ceremonie and remarks	Oosterhuiszaal	BG
17:40	Borrel		Foyer	BG

Omkleedruimte dames

Groenzaal

(BG)

Omkleedruimte heren

Banningzaal

(2e verdieping)

## Regio 1 & 2

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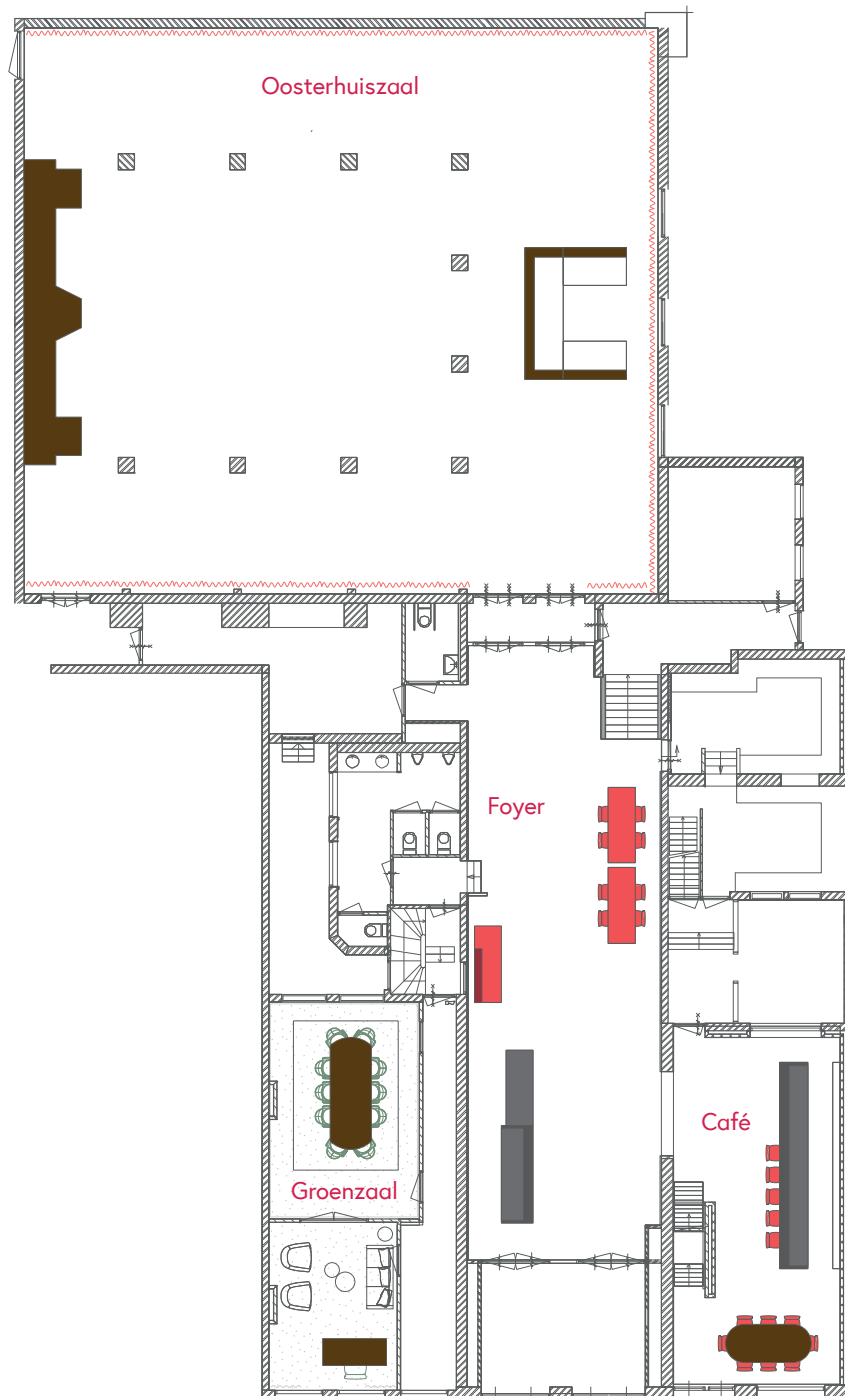






# Rode Hoed

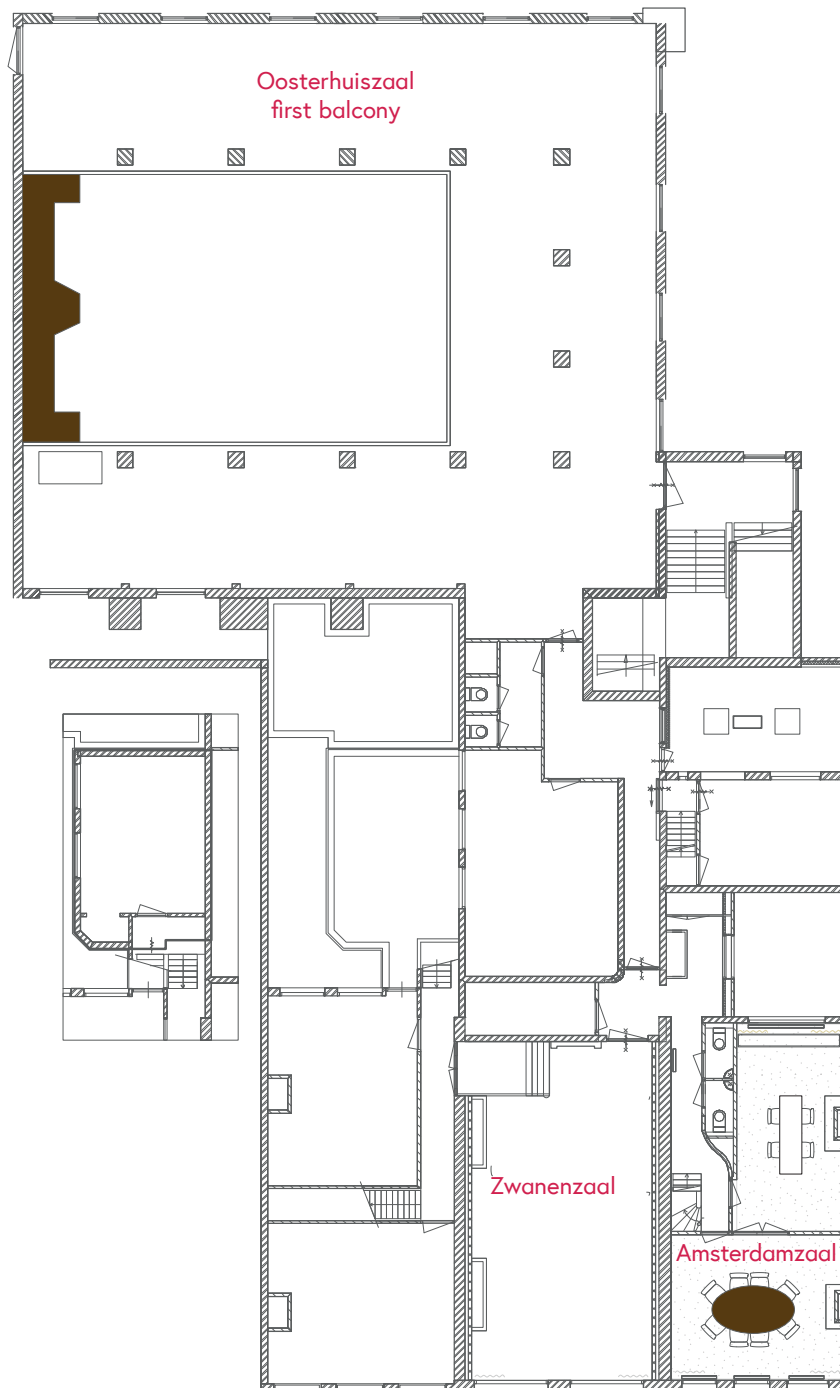
Ground floor





# Rode Hoed

First floor

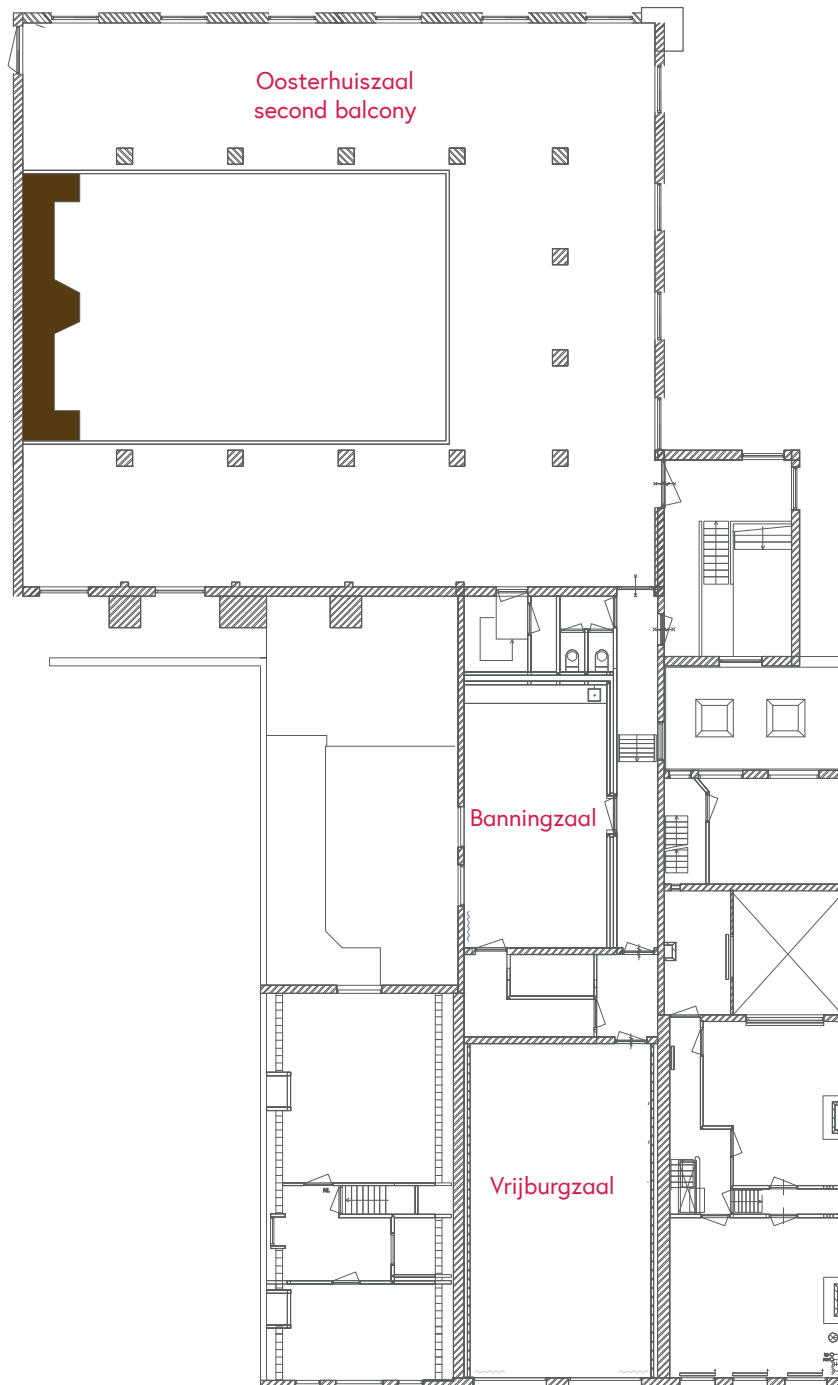






# Rode Hoed

Second floor



# OLYMPUS

# 100 YEARS

Endeavor for Better

## 1919



Founding of **Olympus** by Takeshi Yamashita under the company name **Takachiho Seisakusho**; established in Tokyo, Japan, for domestic production of microscopes.



Sales launch of **Asahi** microscope.

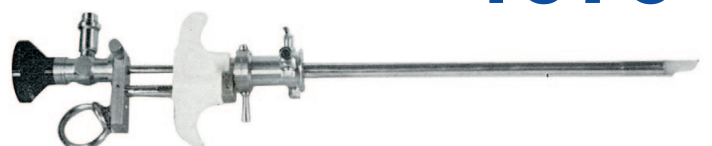
## 1920

## 1936



Launch of first Olympus camera, the **Semi-Olympus I**, after development of Zuiko photographic lenses.

Acquired Winter & Ibe GmbH to establish Olympus Winter & Ibe for the production and supply of **surgical endoscopes and instruments**.



## 1979

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# Waking up the brain

## Sessie 1

1	Wouter Bom	<u>Appendicitis during daytime versus at night; are they the same?</u>
2	Victoria Tedjawirja	<u>Difference in comorbidity between women and men, can it explain the higher risk of mortality in women treated for asymptomatic aortic aneurysms?</u>
3	Kelly Dreuning	<u>One-stop-surgery: An efficient and effective innovation in paediatric inguinal hernia repair</u>
4	Fenne van den Bunder	<u>The Dutch incidence of infantile hypertrophic pyloric stenosis and the influence of seasons</u>
5	Charlotte Heidsma	<u>Long-term Quality of Life after surgery for pancreatic neuroendocrine tumors</u>
6	Ester Barsom	<u>Using video consultation in healthcare: A national patient survey exploring perceptions and conditions for receiving medical specialist care at home</u>
7	Chantal den Bakker	<u>Electronic health program to empower patients in returning to normal activities after surgery: The results of a multicenter, single-blind, randomized, placebo-controlled trial</u>
8	Fay Sanders	<u>Malpractice claims in foot/ankle surgery, can we learn from our mistakes?</u>
9	Charlotte Lameijer	<u>Proefschrift 'Perspectives on outcome following hand and wrist injury in non-osteoporotic patients'</u>

## Appendicitis during daytime versus at night; are they the same?

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Wouter J. Bom, Joske de Jonge, Jochem C.G. Scheijmans, Anna A.W. van Geloven, Sara L. Gans, Marja A. Boermeester, Willem A. Bemelman, Charles C. van Rossem; on behalf of the SNAPSHOT collaborators

**Introduction** Not much is known about the patient with appendicitis who presents at night. The aim of this study is to compare patients with an appendicitis between presentation at night and in the daytime, and to correlate the time of presentation to the number of postoperative complications. It is hypothesized that patients presented at night more often have a complicated appendicitis and therefore develop more complications.

**Methods** In this study data was used from the nationwide, prospective SNAPSHOT study appendicitis, which included 1975 patients with appendicitis. For the current analysis only adult patients were included. Primary outcome was the number of patients presenting at night, developing a complication, compared to the number of patients who present at daytime. Analysis for both complicated and uncomplicated appendicitis was performed and a multivariable model was used to correct for baseline characteristics and time to surgery.

**Results** Thirteen hundred sixty one patients with an appendicitis were analyzed. Both at night and in the daytime, 34% had a complicated appendicitis. In patients with an uncomplicated appendicitis who presented at daytime, 7.7% developed a postoperative complication compared to 11.8% for presentation at night ( $p = 0.09$ ). For complicated appendicitis this was 20.5% vs 31.6%, respectively ( $p = 0.032$ ). In a multivariable analysis the risk for a post-operative complication when presenting at night was not significantly increased, for both complicated and uncomplicated appendicitis (OR 1.56, 95%CI 0.86–2.80 and OR 1.71, 95%CI 0.90–3.22, respectively). Surgery within eight hours after presentation does not seem to lower this risk for both complicated and uncomplicated appendicitis (OR 1.47, 95%CI 0.92–2.36 and OR 1.16, 95%CI 0.69–1.98, respectively).

**Conclusion** The ratio between complicated and uncomplicated is the same for presentation in the daytime and at night. For patients with a complicated appendicitis who present at night the risk of a postoperative complication is higher, as compared to presentation in the daytime. Surgery within 8 hours after presentation does not evidently influence the postoperative complication rate.

# Difference in comorbidity between women and men, can it explain the higher risk of mortality in women treated for asymptomatic aortic aneurysms?

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Victoria N. Tedjawirja, M.C.J. de Wit, R. Balm, M.J.W. Koelemay

**Introduction** An abdominal aortic aneurysm (AAA) is a dilatation of the abdominal aorta that can be fatal when rupture occurs. Elective open surgical repair (OSR) or endovascular aneurysm repair (EVAR) may prevent death from AAA rupture. The risk of mortality after elective AAA repair is higher in women than in men. We hypothesized that the higher surgical risk might be related to differences in baseline comorbidities.

**Methods** A systematic review and meta-analysis was conducted in accordance with the PRISMA Statement (PROSPERO registration CRD42019133314). The EMBASE, MEDLINE and CENTRAL databases were queried to identify studies with patients who underwent elective AAA repair (final search July 25th, 2019). Included studies reported comorbidities in absolute numbers for women and men separately. Comorbidities were categorised into 17 groups and for each comorbidity, the pooled prevalence was calculated. Meta-analyses were performed to compare the pooled prevalence between women and men. Statistical analyses were conducted with RStudio, version 3.5.1.

**Results** From a total of 1681 studies, 21 were included, comprising 199,394 women and 478,819 men. From a total of 17 comorbidities, smoking, diabetes, ischemic heart disease, cardiac disease, liver disease, and cancer were less prevalent in women compared with men. In contrast, hypertension and pulmonary disease were more prevalent in women. Women were significantly older than men at the time of surgery. The risk of 30-day/in-hospital mortality after OSR and EVAR was 2% lower in men compared to women.

**Conclusion** The hypothesis that higher mortality rates in women are caused by more comorbidities is refuted. Women undergoing elective AAA repair had fewer comorbidities than men. However, in the majority of the included papers, it was unclear if standardised definitions for reporting comorbidities were used. Standardised reporting comorbidities is mandatory to increase the ability to interpret data across studies.

# One-stop-surgery: An efficient and effective innovation in paediatric inguinal hernia repair

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Kelly M.A. Dreuning, J.P.M. Derikx, A. Ouali, L.M.J. Janssen, M.W. van Tulder, H.A. van Oers, L. Haverman, L.W.E. van Heurn

**Introduction** One-stop-surgery allows for same-day outpatient clinic visit, preoperative assessment and surgical repair; however, it is not or rarely done in children. This study assessed the efficiency, (cost-)effectiveness and parental satisfaction of one-stop paediatric inguinal hernia surgery.

**Methods** A prospective comparative study was performed in patients (aged 3 months–18 years, ASA I–II) with inguinal hernia diagnosed by general practitioner or paediatrician, and eligible for regular day-care surgery. Consecutive patients referred between 1 May 2017 and 1 November 2018 were screened and, if willing to participate, scheduled for one-stop-surgery (intervention). Patients scheduled for regular treatment were included in the control group. Parent-reported satisfaction and cost-effectiveness were evaluated using the PedsQL Healthcare Satisfaction (divided into six different categories) and iProductivity Cost Questionnaire (iPCQ).

**Results** Ninety-one patients (intervention  $n = 54$ , control  $n = 37$ ) were included. Following one-stop-surgery, 53 patients (98.1%) (median [IQR] age: 5 [3–6] years) were first seen at our outpatient clinic and discharged at the same day. Postoperative complication rates (1.9% vs 2.7%,  $p = 1.000$ ) and recurrence rates (0% vs 2.7%,  $p = 0.407$ ) were equivalent in the intervention and control group. General satisfaction (median [IQR]) (87.5 [81.3–100] vs 81.3 [73.4–89.1],  $p = 0.007$ ), and also satisfaction regarding communication (88.9 [75–100] vs 75 [67.9–78.5],  $p = 0.001$ ), inclusion of family (91.7 [75–100] vs 75 [75–83.3],  $p = 0.002$ ) and technical skills (91.7 [75–100] vs 75 [75–83.3],  $p = 0.021$ ) was higher after one-stop-surgery. Satisfaction about information (81.3 [71.9–100] vs 75 [68.8–81.3],  $p = 0.113$ ) and emotional needs (81.3 [75–100] vs 75 [73.4–82.8],  $p = 0.076$ ) were equal between the groups. Median [IQR] number of hospital visits was reduced in the intervention group (1 [1–1] vs 3 [2–3.5],  $p < 0.001$ ), leading to a decrease in healthcare costs.

**Conclusion** One-stop inguinal hernia repair in children is safe and feasible. One-stop-surgery increases treatment efficiency and parental satisfaction, and decreases direct healthcare and productivity costs.

# The Dutch incidence of infantile hypertrophic pyloric stenosis and the influence of seasons

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Fenne .A.I.M. van den Bunder, M. den Dulk, J.B.F. Hulscher, J.H. Allema, C.M.G. Keyzer-Dekker, M.J. Witvliet, I. de Blaauw, L.W.E. van Heurn, J.P.M. Derikx

**Introduction** Infantile hypertrophic pyloric stenosis (IHPS) is a common disease in newborns. Yet the exact etiology is still unknown. Some studies report seasonal variation in the presentation of infants with IHPS and that the incidence of IHPS is decreasing. However other studies show contradicting results. The aim of this study is to assess the incidence of IHPS in the Netherlands and to determine whether seasonal variation is present in a large cohort.

**Methods** All infants with IHPS hospitalized in the Netherlands between January 2007 and December 2017 were included in this retrospective cohort study. Incidence rates per 1000 livebirths (LB) were calculated by using total number of live births during the matched month, season or year respectively. Seasonal variation in month of presentation and month of birth were calculated using one-way ANCOVA analysis. Trend analysis over time was performed by logistic regression analysis.

**Results** 2481 infants were included for analysis, of which the majority was male (75.9%). Median [IQR] age at procedure was 34 [18] days. Incidence rates varied from 1.09 per 1000 LB to 1.48 per 1000 LB during the study period. The incidence showed an increasing trend during 2007–2012 ( $p = 0.074$ ) and decreased significantly since 2012 ( $p = 0.015$ ). Highest incidence was present in summer (1.33 per 1000 LB; 95%CI 1.18–1.48) and lowest in winter (1.22 per 1000 LB; 95%CI 1.06–1.37). However, differences between months and seasons were not significant ( $p = 0.985$  and  $p = 0.737$  respectively).

**Conclusion** We found an average incidence of 1.28 per 1000 LB in the Netherlands in the past 10 years. The incidence of IHPS is after a moderate increase from 2007 to 2012, decreasing again. Contrary to prior publications, we did not find evidence for seasonal variation.



# Long-term Quality of Life after surgery for pancreatic neuroendocrine tumors

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Charlotte M. Heidsma, A.P. Jilesen, K.M.A. Dreijerink, H.J. Klumpen, C.H.J. van Eijck, M.G.H. Besselink, A.F. Engelsman, E.J.M. Nieveen van Dijkum

**Introduction** Pancreatic surgery is associated with a considerable risk of short- and long term post-operative complications including pancreatic fistula, hemorrhage, pancreatic exocrine and endocrine insufficiency. These complications may negatively impact quality of life (QoL), which is especially relevant in the case of pancreatic neuroendocrine tumors (pNET). PNETs have long survival rates (up to 90% 10-year survival) and potential options for a wait-and-see policy. Additionally, some institutions opt for parenchyma preserving resections such as enucleations instead of pancreatoduodenectomy or distal pancreatectomy when treating pNETs. Therefore, the aim of this study is to evaluate long-term complications and QoL after all types of pancreatic surgery for pNET.

**Methods** All surviving patients after resection of pNET between 1993–2018 were included in this cross-sectional retrospective cohort study. QoL was assessed using the generic EQ-5D-5L questionnaire and disease-specific QLQ C.30 and QLQ GI.NET.21 questionnaires. Patients were split into 3 groups based on type of surgery (pancreatoduodenectomy (PD), distal pancreatectomy (DP), parenchyma preserving pancreatectomy (PPP). Sensitivity analyses included complications Clavien-Dindo grade <3 vs  $\geq 3$ , follow-duration (<5, 5–10,  $\geq 10$  years) and tumor size <2 vs  $\geq 2$  cm.

**Results** 93 of 138 (67%) patients responded to the questionnaires. Median follow-up after surgery was 99 (5–307) months. 30 patients (33.7%) underwent PD, 29 patients (32.6%) DP, and 29 patients (32.6%) PPP. Twenty-five (28.0%) patients had major post-operative complications (Clavien-Dindo grade  $\geq 3$ ), 20% developed new onset diabetes, and 40% patients required pancreatic enzymes. Mean daily health status and index scores (EQ-5D-5L) were significantly lower for pNETs than the general population ( $p = <0.05$ ). The QLQ-C30 questionnaire identified lower QoL in all functional and symptom scales with the exception of pain, when compared to the Dutch population ( $p = <0.05$ ). QoL was worse in almost all domains for PD patients, while PPP patients reported the highest QoL. No differences in QoL were seen in the sensitivity analyses.

**Conclusion** QoL after resection of pNET significantly lower as compared to the general Dutch population and this reduction remains stable until more than 10 years after surgery. Patients who underwent PPP had better QoL than those who underwent other types of resections. PD patients had the lowest QoL and the highest long-term complications.

# Using video consultation in healthcare: A national patient survey exploring perceptions and conditions for receiving medical specialist care at home

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Ester Z. Barsom, A. Rauwerdink, R. de Haan, W.A. Bemelman, M.P. Schijven

**Introduction** Video consultation is increasingly gaining attention as an alternative to out-patient clinic visits. However, little is known in terms of attitude, preferences and obstacles of patients towards receiving medical specialist care using video consultation.

**Methods** A total of 1202 patients were invited via the National Dutch Healthcare Consumer Panel of the Dutch Patient Federation for this prospective survey study. The survey consisted of two parts. First, patient characteristics such as age, gender, level of education, type of disease and travelling details were collected. The second part consisted of statements regarding the use of technology, the intention to use VC, factors influencing future use of VC and questions regarding the possibilities of replacing regular outpatient appointments using VC.

**Results** A total of 962 (80% response rate) patients completed the survey. Almost half of the patients express a positive attitude towards using VC for future outpatient visits. Saving physical energy was rated as the most important benefit of VC. Only 10% of patients believe not to be able to set up a video call themselves. Patients are most likely to choose a VC in case of a regular follow-up outpatient appointment, the first appointment after hospital discharge or for consultations of diagnostic results with anticipated outcome. The majority of patients opposed to the option of replacing consultations with possible bad news for a VC, or when they fear the same quality of care could not be provided with VC. Under these circumstances, patients prefer personal face-to-face contact with their healthcare provider.

**Conclusion** Patients express a strong wish to have the possibility to consult their medical specialist via VC in regular follow up, for discussing diagnostic results with anticipated good outcome and to replace first check-up appointment after clinical discharge. The results of this study may support healthcare professionals, hospital management and policymakers in their joined effort to provide such care for situations deemed fit to their patients in the near future.

# Electronic health program to empower patients in returning to normal activities after surgery: The results of a multicenter, single-blind, randomized, placebo-controlled trial

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Chantal M. den Bakker, J.A.F. Huirne, F.G. Schaafsma, H.J. Bonjer, J.R. Anema

**Introduction** Due to strong reduction in length of hospital stay, postoperative care is provided only in a limited way which hampers recovery. Instructing and guiding patients after surgery is essential for successful recovery. The aim of this study was to evaluate whether a personalized eHealth care program may improve return to normal activities after surgery.

**Methods** A multicenter, single blind, randomized controlled trial was performed in twelve teaching hospitals in the Netherlands. Patients aged 18–75 years who were scheduled for laparoscopic or open colectomy or hysterectomy were recruited and were randomized to the intervention or control group. Participants in the intervention group had access to a perioperative, personalised, eHealth-care program, which managed recovery expectations and provided postoperative guidance tailored to the patient. The control group received usual care and access to a placebo website containing standard recovery advice. Participants were asked to complete questionnaires at seven timepoints during the 12-months period postoperative. The primary outcome was time between surgery and return to normal activities, measured using personalised patient-reported outcome measures. Intention-to-treat and per-protocol analyses were done. This trial is registered in the Netherlands National Trial Register, number NTR5686.

**Results** Between February 2016 and June 2017, 355 participants were enrolled and randomly allocated to either the intervention ( $n = 178$ ) or control ( $n = 177$ ) group. 13 participants (3.7%) were lost to follow-up, with 342 participants included in the primary outcome analysis. Preliminary results show a median time until return to normal activities of 52 days (95%CI 46.5–80.4) in the intervention group and 65 days (95%CI 38.2–65.8) in the control group (hazard ratio 1.29, 95%CI 1.02–1.62  $p = 0.032$ ).

**Conclusion** Using a personalized eHealth intervention in abdominal surgery speeds up the return to normal activities compared with usual care. This eHealth program should be considered to be implemented in the perioperative period of several commonly applied abdominal surgical procedures.

# Malpractice claims in foot/ankle surgery, can we learn from our mistakes?

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Fay R.K. Sanders, P. Wimmer-Boelhouwers, O.X. Dijt, G.M.M.J. Kerkhoffs, T. Schepers

**Introduction** Orthopedic foot/ankle surgery is a high risk specialty when it comes to the chance of receiving a malpractice claim. However, research on risk factors and causality is sparse within this area. Identifying the most common reasons for claims in a specific field can lead to healthcare improvements to avoid patient damages and claims in the future. This study aims to evaluate the incidence, characteristics and outcome of claims related to orthopedic foot/ankle surgery, in order to identify bottlenecks in treatment.

**Methods** This study retrospectively analyzed all claims related to foot ankle surgery filed with MediRisk (medical liability insurer) between 2007 and 2016. Data was acquired from MediRisk's anonymous database, searching for afflicted areas "lower leg", "ankle", "foot", "toes" and treating specialist being an (orthopedic) surgeon. Baseline claim/claimant characteristics were collected, including outcome, consequences and costs of the claim.

**Results** Analyzing 460 claims in total, we found that claimants were on average 46.5 y/o, female patients with a fracture. The claim was often related to a delay in/wrong diagnosis or to (complications of) an elective surgical procedure. The chance for a claim to be settled seemed only to be related to the type of injury (fracture) and the type of claim (diagnostic mistake). The median amount in euros disbursed in settled claims was €12,549 with a maximum of €322,149. The overall number of claims did not increase with the years.

**Conclusion** In agreement with previous literature most claimants in this cohort were young, female patients. Missed fracture diagnosis and "failed"/disappointing results of elective surgical procedures were the most common causes for claims. Although not all medical errors can be avoided, sufficient knowledge in the assessment of foot/ankle trauma and clear communication/expectation management before elective procedures could help to improve quality of healthcare and patient satisfaction.

# Proefschrift 'Perspectives on outcome following hand and wrist injury in non-osteoporotic patients'

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Charlotte M. Lameijer

Little emphasis has been put on reporting hand and wrist injuries in young non-osteoporotic patients with high demands of their hand and wrist and with a long active and working life ahead of them.

The aims of this thesis were to report on several outcomes following hand and wrist injuries in this young group and putting them in a clinical perspective. Firstly, we described radiological measurements, Clinician Reported Outcomes (CROs) and Patient Reported Outcomes (PROs) following distal radius fractures (DRFs) and perilunate (fracture) dislocations (PLD/PLFDs) in young non-osteoporotic patients. Furthermore, the association between these outcomes was analysed. Finally, we explored the validity of several PROs that might be used to analyse consequences of hand and wrist injuries.

From our systematic review we concluded that prevalence of PA reported in all included studies was 50% and 37% when analysing the 10 studies with open source data. PA seemed to progress over time with a statistically significant higher prevalence of PA of 64% after follow-up > 36 months versus a prevalence of 31% with follow-up duration ≤ 36 months. In our cohort study, PA had a prevalence of 32% and was statistically significantly associated with longer radial length, diminished flexion/extension and ulnar/radial deviation. Grip strength was not associated with the presence of PA. Regarding the PROs, multiple statistically significant associations with PA were found. In regression analyses the Disability of Arm Shoulder and Hand questionnaire (DASH), Patient Reported Wrist Evaluation (PRWE) subscale 'function' and the total score of the PRWE were statistically significantly associated with flexion/extension.

Regarding CROs following DRFs, flexion/extension, ulnar/radial deviation and pro/supination of the injured wrist were all significantly diminished compared to the uninjured wrist. Only MIC for flexion/extension and grip strength had been reported. The flexion/extension difference of 11.2° with the uninjured wrist exceeded MIC, while grip strength differences did not. MICs for DASH and PRWE have been reported in patients following DRFs, but not for MHQ nor for the SF36. Residual articular incongruency seemed to be associated with diminished range of motion. Also, a diminished SF36 'mental component score' seemed to be statistically significantly associated with residual articular incongruency. Further research is mandatory on MICs when reporting outcome following DRFs, to be able to interpret clinically relevant outcomes.

Patients following perilunate (fracture) dislocations (PLD/PLFDs) experienced a significant impact on everyday life with diminished range of motion (flexion/extension and ulnar/radial deviation), pain, diminished physical functioning, diminished satisfaction and they reported a lower general health status than healthy controls. Interestingly, no consequences for work participation were found in this small study.

Although several PROs are commonly used in reporting on outcomes following hand and wrist injuries, the interpretability and clinical relevancy are challenging. There is some variation in the psychometric properties of these instruments and the concepts measured are not always well defined. We evaluated structural validity and construct validity using Confirmatory Factor Analysis (CFA) of the Dutch version of the DASH (DASH-DLV) for 370 patients with isolated hand or wrist injury. This study suggested that the DASH-DLV reflects a unidimensional trait. Thus, reporting on subscale scores is of very limited value and should be avoided.

Completing (several) PROs is time-consuming for patients. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed a series of item banks, including the PROMIS® Physical Function – Upper Extremity (UE) v2.0. The item bank will be used as a Computerized Adaptive Test (CAT) system using an algorithm that selects questions from the item bank based on patients' response to previous questions. When a predefined precision is reached, the system automatically stops asking questions which reduces the number of questions that need to be asked.

We validated the Dutch-Flemish PROMIS UE v2.0 (DF-PROMIS-UE v2.0) item bank in 303 patients with upper extremity injuries by reporting on structural validity and construct validity using CFA. We showed that the DF-PROMIS-UE v2.0 item bank measures a unidimensional trait. Sufficient structural validity, internal consistency and construct validity were found.

To be able to use the DF-PROMIS-UE v2.0 CAT, successful validation and calibration with Item Response Theory (IRT) was conducted in a cohort of 521 patients with upper extremity injuries. Therefore, the DF-PROMIS UE v2.0 item bank is considered to show sufficient evidence for unidimensionality, had negligible local dependence, good Graded Response Model (GRM) fit and demonstrated sufficient measurement invariance. The DF-PROMIS-UE v2.0 is now ready for use as CAT in research and clinical practice. CAT reduces the number of questions that need to be answered and therefore diminishes the burden for patients.

We have shown that hand and wrist injuries can evolve in major life events for patients, due to possible impairment in daily life. We advise a 'lean' version of the described core set of measures for clinical practice with known MICs to interpret clinical relevant change; flexion/extension, ulnar/radial deviation and either the DASH or PRWE. We advise to validate the Dutch translated version of the MHQ and SF36 and to report on MICs for the DASH, quickDASH, PRWE, MHQ, SF36 and DF-PROMIS-UE v2.0 item bank for young non-osteoporotic patients following hand and wrist injury. This will enable implementation of low burden PROs in 'lean' core sets to interpret outcome in clinical practice.



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# Experimental

## Sessie 2a

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# Efficient expansion and tumor reactivity of TILs from late stage NSCLC metastases

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Rosa de Groot, Koen Hartemink, Kim Monkhorst, Egbert Smit, Monika Wolkers

**Introduction** Non-small cell lung cancer (NSCLC) is the second most occurring type of cancer. Because of the high mortality rates with the current treatments, novel therapeutic approaches are warranted. Autologous T cell therapy can be an effective treatment for NSCLC because of high mutational rates of tumors and high levels of T cell infiltrates. We have shown that tumor infiltrating lymphocytes (TILs) from treatment naïve, stage I/II NSCLC tumors can be effectively expanded and reprogrammed into tumor-reactive T cells for T cell therapy. However, both treatment strategies and metastatic lesions may affect the TIL content and functionality in late stage patients. Little is known about the effect of treatment and location of metastasis on the functionality and expansion of TILs.

**Methods** Using flowcytometry, we compared the immune infiltrates in metastatic NSCLC lesions (n = 25) both therapy-naïve (n = 5) and pretreated (n = 20) with chemotherapy, immunotherapy or targeted therapy and early stage primary NSCLC lesions (n = 25). From metastatic lesions of patients with progressive disease, we assessed the efficiency of TILs to expand and tested functionality after expansion by stimulation with autologous tumor cells, medium or PMA/Iono.

**Results** Although the immune infiltrate phenotype differed strongly between patients, overall, we found a very high content of regulatory T cells, and PD1 or CD137-expressing T cells in metastatic lesions compared to early stage primary lesions. TILs were efficiently expanded from tumor material of all patients. Neither TIL phenotype nor their expansion rate correlated with organ of origin or treatment-type. Upon stimulation with autologous tumor digest, a proportion of T cells became activated (10–20%) and produced pro-inflammatory cytokines (0.3–15%).

**Conclusion** In conclusion, T cells can be efficiently expanded from late stage NSCLC resection material into tumor reactive T cells, independent of prior treatment or organ of origin. Therefore, autologous T cell therapy should be considered as treatment for NSCLC patients.

# In-depth immune profiling of peripheral blood mononuclear cells in pancreatic cancer patients

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Eline S. Zwart, E. Rodriguez, J. Verhoeff, L.L. Meijer, T.Y.S. Le Large, J.J. García Vallejo, R.E. Mebius, Y. van Kooyk and G. Kazemier

**Introduction** Pancreatic adenocarcinoma still has a dismal prognosis. In order to develop new diagnostic tests and new treatment strategies, such as immunotherapy, it is essential to understand which cells and ligands play an important role in the carcinogenesis and maintaining of pancreatic ductal adenocarcinoma (PDAC). Therefore, we aim to identify different immune subsets in PBMCs of patient with pancreatic ductal adenocarcinoma and correlate these with clinical outcome.

**Methods** Patients with pancreatic adenocarcinoma and benign diseases like cholecystolithiasis or pancreatitis were included between July 2017 and January 2019. Peripheral blood mononuclear cells (PBMCs) were collected from buffy coats by a lymphoprep gradient. All PDAC diagnosis were confirmed by a pathologist. Four age and sex matched groups were formed, consisting of patients with resectable stage I–III PDAC (n = 20), patients with non resectable stage IV PDAC (n = 20), patients with benign diseases (n = 20) and healthy controls (n = 20). Barcoded PMBCs will be stained with two antibody panels, one for myeloid cells and one for lymphoid cells, each consisting of 39 markers. Cells will be acquired with the CyTOF and analyzed using unsupervised clustering with the viSNE algorithm in Cytobank and R. With this method, different immune populations will be identified and correlated to clinical parameters such as disease, stage and survival.

**Conclusion** In depth immune profiling using CyTOF will help identify different immune subsets in PBMCs of patient with pancreatic ductal adenocarcinoma.

## The microbiome-immune contexture axis in colorectal cancer and its relation with clinical outcome

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J. Reinder D. Reuvers, S.J. Oosterling, H.B.A.C. Stockmann, G. Kazemier, M. van Egmond

**Introduction** The composition of the immune cells around tumors is correlated with oncological outcome, as patients with a 'hot' tumor immune infiltrate have a better oncological outcome compared to patients with a less favorable 'cold' infiltrate. Furthermore, there is mounting evidence that the microbial composition of the intestine is correlated with post-operative infection and even recurrence rates after colorectal surgery. We anticipate that analyzing the microbial composition from rectal swabs, immune cell infiltrate in CRC tissue samples, combined with clinical data from the same colorectal cancer patients we will be able to get more insight into these interactions.

**Methods** Rectal swabs and tissue samples have been collected from 196 patients that were included in the Selective decontamination of the digestive tract in ELective Colorectal cancer patients Trial (SELECT). Composition of the microbiome on the swabs was determined using interspace-region-based profiling (IS-PRO). Tissue samples will be analyzed with multispectral immunofluorescence staining, with two 7-color panels looking into different immune cells and endothelial trafficking markers.

**Results** IS-pro analysis has been performed for all patients. Additionally, the first multispectral 7-color panel has been established and optimized, containing markers for T-cell and macrophage subsets. Tissue slides from the first patients have been stained.

**Conclusion** This project studies the role of the microbiome and its possible effect on the immune contexture in colorectal cancer in human patients. Combining these with long-term follow-up data it will gain more insight on how these two interact and its effect on clinical outcome.

# Targeting tumour vessels to improve leukocyte trafficking for immunotherapy

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Niels Heemskerk

**Introduction** This project addresses a very important scientific question; the ability to overcome tumours ability to evade the immune system. There have been many advancements in the field of cancer immunotherapy as an answer to treating cancer. However, there is still a major problem in that tumours are able to evade the immune system and so more work is needed to overcome this issue and allow immunotherapy techniques to provide their full benefit. Tumour blood vessels display distorted cell adhesion molecule expression patterns that exclude immune cells from entering tumour tissue, thereby limiting anti-cancer immune responses. The aim of my project is therefore to improve the entry of immune cells into tumours by enhancing the trafficking of leukocytes across tumour endothelial cells.

**Methods** I will use targeted delivery of TNF/IL1 $\beta$  to increase leukocyte adhesion receptors on tumour endothelial cells. With the use of a state-of-the-art 3D perfusion model to mimic tumour blood vessels on a chip and a unique triple-colour phagocyte reporter mouse for multi-colour intravital imaging, I will identify how tumour endothelial cells contribute to cancer immune escape.

**Results** My preliminary data shows that tumour vasculature has downregulated ICAM-1, limiting leukocyte infiltration. However, expression of some tumour endothelial-specific surface proteins were increased. These molecules, often involved angiogenesis, are ideal for local drug delivery to tumour vasculature. Importantly, I successfully cultured tumour spheroids in the 3D perfusion model for microscopy, and established 6-colours intravital imaging to examine leukocyte trafficking in the triple-colour phagocyte reporter mouse in real-time.

**Conclusion** Breaking tumour immune-exclusion has the potential, to improve the efficacy of antibody therapy and other cancer immunotherapies, to induce tumour regression and lasting and potentially permanent protection against cancer recurrence.

# Breaking innate immune exclusion in established tumors using antibody-cytokine fusion proteins

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Dennis Gout, Niels Heemskerk, Kees Tuk, Marjolein van Egmond

**Introduction** Neutrophils are an underestimated leukocyte subset in cancer immunotherapy. It is the most abundant leukocyte in circulation and possesses strong tumor-killing capabilities when stimulated with IgA anti-tumor antibodies. Stimulation of the IgA receptor FcαRI induced strong neutrophil recruitment to the edge of the tumor, but tumor-infiltration by recruited neutrophils was negligible. This strongly suggests an innate immune excluded tumor phenotype, comparable to the more well-known T-cell excluded phenotype ('a cold tumor').

**Methods** In order to break this innate immune exclusion, I will develop antibody-cytokine fusion proteins, which will target the tumor with one of its arms and bind a cytokine receptor with the cytokine fused to its other arm. Primary targets for cytokine binding are the chemokine receptor CXCR2, in order to stimulate neutrophil chemotaxis into the tumor, and the TNF receptor TNFR2, in order to increase the inflammatory status in the tumor and (re-)activate nearby leukocytes.

**Conclusion** I anticipate that combining this treatment with targeting FcαRI will break the innate immune exclusion, leading to lytic tumor killing by neutrophils, which will drive the adaptive immune response in return.

# MicroRNAs as predictive biomarkers for response to systemic treatment in patients with pancreatic ductal adenocarcinoma

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Lenka N.C. Boyd, Laura L. Meijer, Ingrid Garajová, Tessa Y.S. Le Large, Enrico Vasile, Geert Kazemier and Elisa Giovannetti

**Introduction** Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy and commonly diagnosed at an advanced disease stage. Treatment options for patients with advanced PDAC consist of combination therapy with 5-fluorouracil, oxaliplatin and irinotecan (FOLFIRINOX), gemcitabine combined with NAB-paclitaxel (gem-nab-pac), or gemcitabine monotherapy. Although patients can benefit from these therapies, drug resistance notoriously hampers the success of treatment. MicroRNAs (miRNAs) have recently emerged as important players in therapy resistance in PDAC. The aim of this study is to identify miRNAs that could predict response to treatment with FOLFIRINOX or gem-nab-pac, in order to select the best therapeutic strategy for patients with advanced PDAC.

**Methods** Microarray-based profiling was used to discover deregulated miRNAs in pre- and post-chemotherapy plasma samples from patients based on their progression-free survival after FOLFIRINOX. Nine candidate plasma miRNAs were validated in an independent cohort (n = 43). The most discriminative plasma miRNA was investigated in a small cohort of patients treated with gem-nab-pac (n = 25). Plasma samples and clinical data are currently available for 54 patients treated with FOLFIRINOX and 33 patients treated with gem-nab-pac. A discovery cohort of 10 patients of both treatment arms will be investigated for miRNA expression prior to treatment using next generation sequencing. Significantly differentially expressed miRNAs will be identified and validated in the remaining samples by RT-qPCR and digital droplet PCR.

**Conclusion** Decline in plasma miR-181a-5p was associated with better prognosis after FOLFIRINOX, whereas no such correlation was found in patients treated with gem-nab-pac, and may be useful for guiding therapeutic choices. However, further analysis of miRNA expression profiles of PDAC patients treated with FOLFIRINOX or gem-nab-pac might improve our understanding of molecular mechanisms involved in therapy resistance and unravel innovative tools to overcome such resistance.



# Circulating tumour DNA as prognostic marker for colorectal cancer patients with peritoneal metastasis: A clinical feasibility study

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Nina R. Sluiter\*, Jamie J. Beagan\*, Sander Bach, Paul Eijk, Stijn L. Vlek, Daniëlle A.M. Heideman, Miranda Kusters, D. Michiel Pegtel, Geert Kazemier, Nicole C.T. van Grieken, Bauke Ylstra<sup>^</sup>, Jurriaan B. Tuynman<sup>^</sup>

**Introduction** Colorectal cancer (CRC) patients diagnosed with peritoneal metastases (PMs) may benefit from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC), which has a curative intent. Unfortunately, limitations in diagnostic techniques often result in detection of PMs at an advanced stage, reducing the chance of curation. Circulating tumor (ct)DNA analysis has the potential to quantify the extent of PMs to select patients for CRS-HIPEC, serve as a preoperative prognostic marker and monitor recurrence during routine follow-up.

**Methods** Thirty patients eligible for CRS-HIPEC were included. Blood was sampled from 24 patients who underwent CRS-HIPEC and six who had an open-close procedure. Targeted next generation sequencing (NGS) of DNA from PMs was performed and somatic variants were tested in corresponding plasma cell-free (cf)DNA samples using droplet digital (dd)PCR. Detection of ctDNA preoperatively was correlated with clinico-pathological variables and disease-free survival (DFS). Detection in follow-up samples was compared to the timing of recurrence.

**Results** CtDNA was detected in preoperative plasma samples from 8/24 (33%) CRS-HIPEC and 2/6 (33%) open-close patients. Preoperative detection could not determine the extent of PMs, but was significantly associated with a worse median DFS (6.0 months vs not reached,  $p = 0.016$ ). None of the samples taken initially after CRS-HIPEC had detectable levels of ctDNA, except for one patient that had a systemic recurrence diagnosed within 6 months after CRS-HIPEC. CtDNA was detected in follow-up samples from 4/4 (100%) patients with a systemic- and 1/8 (13%) with a loco-regional recurrence.

**Conclusion** Preoperative ctDNA detection is associated with a reduced DFS after CRS-HIPEC which supports its feasibility as a prognostic marker, however, it is not suitable as a quantitative measure of PMs. Detection of ctDNA during follow-up could help diagnose recurrence. Larger prospective studies are needed to confirm the clinical utility of ctDNA detection to select patients for CRS-HIPEC and to monitor recurrence.

# Detection of colorectal cancer in urine: A novel liquid biopsy

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Sander Bach, I. Paulis, N.R. Sluiter, S.E. van Oostendorp, L.J.H. Smits, J.B. Tuynman, I. Bahce, R.D.M. Steenbergen, G. Kazemier

**Introduction** Colorectal cancer (CRC) is the second leading cause for cancer-related death globally. Prognosis is heavily influenced by cancer stage at diagnosis, hence the importance of early detection. Liquid biopsies, the analysis of bodily fluids, could facilitate personalized oncologic diagnostics. Urine, as a liquid biopsy, contains CRC-specific hypermethylated DNA (hmDNA) fragments. Furthermore, urine allows for extramural collection and is of limitless supply. In this study, the potential of urinal hmDNA for non-invasive CRC detection was determined.

**Methods** First, a systematic literature search according to PRISMA-guidelines was performed, categorizing CRC methylation markers in blood. Next, urine samples of a total of 59 CRC patients and 48 healthy volunteers were analyzed for the presence of selected hmDNA markers. DNA methylation levels were determined through use of quantitative methylation specific PCR (qMSP).

**Results** From the literature study, six CRC-specific hmDNA markers were selected based on accuracy for cancer detection. Urine of CRC patients showed statistically significant increased levels of DNA methylation for two hmDNA markers X1 and X3 ( $p = 0.047$  and  $0.011$ ). Through use of an alternative urine DNA isolation method, a larger difference between groups was observed for marker X1 ( $p = 0.000$ ).

**Conclusion** CRC patient urine samples show elevated levels of DNA methylation. This potentially allows for non-invasive cancer detection. Furthermore, as a confirmed liquid biopsy, urine DNA could also play a role in clinical decision making and assist in prognostication and monitoring of oncologic patients.

# Bioengineering patient-specific 3D vascular scaffolds for the investigation of smooth muscle cell and extracellular matrix dysfunction in aortic aneurysms

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Natalja Bogunovic, J.P. Meekel, J. Majolée, M. Hekhuis, J. Pyszkowski, S. Jockenhövel, M. Kruse, E. Rieseboos, D. Micha, J.D. Blankensteijn, P.L. Hordijk, S. Ghazanfari\*, K.K. Yeung\*

**Introduction** Abdominal aortic aneurysms (AAA) are associated with overall high mortality in case of rupture. The pathophysiology is unclear, but smooth muscle cells (SMC) dysfunction and extracellular matrix (ECM) degradation have been proposed as key underlying causes. We aimed to create a patient-specific 3D vascular model for translational studies of SMC-ECM interactions and their role in AAA pathophysiology.

**Methods** SMC isolated from the aortic wall of controls and AAA patients were seeded on electrospun poly-lactide-co-glycolide scaffolds and cultured for five weeks, after which endothelial cells were added. Cell morphology, orientation, mechanical properties and ECM production were quantified for validation and comparison between controls and patients.

**Results** We show that cultured SMC proliferated into multiple layers after five weeks in culture and produced ECM proteins. Endothelial cells attached to multilayered SMC, mimicking layer interactions. The bioengineered scaffolds exhibit visco-elastic properties comparable to biological vessels and cytoskeletal organization increases during the five weeks in culture. Increased cytoskeletal alignment and decreased ECM production indicate different organization of scaffolds seeded with AAA patients' cells compared to healthy controls.

**Conclusion** In conclusion, our 3D bioengineered scaffolds are robust, patient-specific models of SMC-endothelial cell organization and ECM production. We demonstrate a valuable preclinical model of AAA with applications in both translational research and therapeutic developments.

# Survival after surgery

## Sessie 2b

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22	Alma Moekotte	The benefit of adjuvant chemotherapy in the subtypes of resected ampullary adenocarcinoma
23	Stijn van Roessel	Evaluating the added value of adjuvant therapy following pancreatic cancer surgery after preoperative treatment with FOLFIRINOX chemotherapy
24	Julia Henneman	Prognostic value of disease-free interval on overall survival after repeat local treatment for recurrent colorectal cancer liver metastases
25	Ted van Schaik	Predicting mortality and secondary interventions after open and endovascular aneurysm repair
26	Tara van Merrienboer	Investigating the metformin pathway in patient-specific aortic smooth muscle cells as a potential therapy for abdominal aortic aneurysms
27	Louise Blankensteijn	Survival and amputation risk in patients with diabetic foot ulcers

# The association of perioperative quality-of-care parameters (textbook outcome) with long term outcome after esophagectomy for esophageal cancer

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Marianne Kalff, I. Vesseur, W. Eshuis, D. Heineman, F. Daams, D.L. van der Peet, S.S. Gisbertz, M.I. van Berge Henegouwen

**Introduction** Despite current improvements in the multimodal treatment of esophageal cancer, surgery remains the key component. Therefore, it is essential to optimize the surgical procedure and to pursue the highest surgical quality. TO is a composite measure of ten perioperative parameters reflecting the quality of surgical care concerning esophagectomy. The objectives of this study were to confirm the association of textbook outcome (TO) and overall long-term survival after esophagectomy for esophageal cancer, to investigate the relationship of TO and recurrence rates and to identify clinicopathological predictors for not achieving TO.

**Methods** All patients with esophageal cancer who underwent a transthoracic or transhiatal esophagectomy with curative intent in two tertiary referral centers in The Netherlands between 2007–2016 were included. Patients with a carcinoma in situ, patients undergoing salvage or emergency procedure and patients that applied for opt-out were excluded. Clinicopathological predictors for not achieving TO were identified using univariate and multivariate logistic regression. Survival was compared using Kaplan-Meier life-table estimates and cox regression.

**Results** In total, 1057 patients were included. Over time, the percentage of patients who achieved TO increased from 28.9% in 2007 to 37.5% in 2016. BMI under 18.5, ASA score above one and age above 65 years were associated with a worse TO rate (OR 2.72 [1.02–7.24], ASA 2 OR 1.57 [1.13–2.17] and ASA 3+4 OR 2.33 [1.56–3.48], OR 1.387 [1.06–1.81], respectively), whereas neoadjuvant treatment predicted a better TO rate (OR 0.58 [0.41–0.81]). The median overall survival was 53 months (95%CI 42 – 63) for patients with TO and 35 months (95%CI 29 – 41) for patients without TO; resulting in an overall survival benefit of 18 months (HR 0.759, 95%CI 0.636 – 0.906,  $p = 0.002$ ). The recurrence rates between TO and no-TO differed, but was not statistically significant (47.1% vs 42.8%,  $p = 0.177$ ).

**Conclusion** BMI less than 18.5, ASA-score higher than one and age older than 65 were characteristics associated with not achieving TO. Neoadjuvant therapy was associated with a better TO rate. Achieved TO resulted in a better overall five-year survival indicating the importance of pursuing TO.

# Conditional survival after curative treatment of esophageal cancer

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Eliza R.C. Hagens, M.L. Feenstra, M.I. van Berge Henegouwen, W.J. Eshuis, M.C.C.M. Hulshof, H.W.M. van Laarhoven, S.S. Gisbertz

**Introduction** Conditional survival accounts for the time already survived after surgery and may be of additional informative value. The aim was to assess conditional survival in esophageal cancer patients and to design a nomogram predicting the conditional probability of survival after surgery.

**Methods** This retrospective study included consecutive patients with esophageal cancer who received neoadjuvant chemoradiation followed by an esophagectomy between January 2004 and 2019 in Amsterdam University Medical centers, location AMC, The Netherlands. Conditional survival was defined as the probability of surviving “y” years after already surviving for “x” years. The used formula was:  $CS(x|y) = S(x+y)/S(x)$  with  $S(x)$  representing the overall survival at “x” years. Cox proportional hazard models were used to evaluate predictors for overall survival. A nomogram was constructed to predict 5-year survival directly after surgery and given 1-, 2-, 3- and 4-years survival after surgery.

**Results** 660 patients were included. The median overall survival was 46.4 months (95%CI 39.1–53.8). The probability to achieve 5-year overall survival after resection increased from 46% directly after surgery to 55%, 67%, 79% and 88% per additional year survived. Cardiac comorbidity, ypT-stage, ypN-stage and pulmonary complications were independent predictors for survival. The nomogram predicted 5-year survival using these predictors and number of years already survived.

**Conclusion** The probability to achieve 5-year overall survival after esophagectomy for cancer increases per additional year survived. The proposed nomogram predicts survival in patients after esophagectomy, taking the years already survived into account. This nomogram can be helpful in counselling patients during follow-up after surgery.

# An immunosuppressive PD-L1 positive tumour microenvironment marks oesophageal adenocarcinomas refractory to neo-adjuvant chemoradiotherapy

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Willem Koemans, J. van Dieren, J. van den Berg, M. Chalabi, F. Voncken, G. Meijer, J. van Sandick, L. Kodach

**Introduction** In the Netherlands oesophageal adenocarcinoma (OAC) patients are treated with neo-adjuvant chemoradiotherapy (nCRT) followed by oesophageal resection. However, not all patients respond to nCRT, and the mechanisms of poor response is not understood. An effective antitumour immune response is critical for a successful tumour elimination. Therefore, an immunosuppressive tumour microenvironment (TME) may play an important role in failure of nCRT. This study aims to characterise TME and immune infiltrate in OAC patients in relation to response to nCRT.

**Methods** Surgical resection specimens were used from 125 patients with OAC treated with nCRT: 63 responders (Mandard TRG 2) and 62 non-responders (Mandard TRG 4 or 5). Tumour sections were stained with pSTAT1, CD3, CD8, FOXP3 and PD-L1 antibodies. Immunostained slides were scanned and digital image analysis was performed using Halo software. Group differences were analysed using the chi-square test or the Mann-Whitney U test.

**Results** Both responders and non-responders displayed active interferon gamma signalling in the tumour cells as judged by positive pSTAT1 staining, suggesting that tumour antigen presentation on MHC class I and tumour-specific stimulation of the immune system were common in both groups. Surprisingly, a significantly higher amount of CD3+ (mean 2354 versus 1299 cells/mm<sup>2</sup>;  $p < 0.001$ ) and CD8+ (mean 1175 versus 761 cells/mm<sup>2</sup>;  $p < 0.001$ ) tumour infiltrating lymphocytes was seen in non-responders as compared to responders. Thus, differences cannot solely be explained by induction of T-cell infiltration in responders compared to non-responders. Also, the amount of FOXP3+ regulatory T-cells was similar in both groups (mean 257 versus 182 cells/mm<sup>2</sup>;  $p = 0.185$ ). Significantly more non-responders were found to have PD-L1 expression in the tumour stroma than responders (60% versus 23%;  $p < 0.001$ ).

**Conclusion** In tissue samples of OAC patients treated with nCRT, the presence of an immunosuppressive TME was associated with absence of treatment response, suggesting that cancer immunotherapy may be a valuable alternative treatment option for this group of patients.



# The benefit of adjuvant chemotherapy in the subtypes of resected ampullary adenocarcinoma

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Alma L. Moekotte, Giuseppe Malleo, Stijn Van Roessel, Morgan Bonds, Asif Halimi, Laura Zarantonello, Niccolò Napoli, Stephan Dreyer, Ulrich Wellner, Louisa Bolm, Vasileios K. Mavroeidis, Stuart Robinson, Khalid Khalil, Daniele Ferraro, Matthew C. Mortimer, Scott Harris, Bilal Al-Sarireh, Giuseppe K. Fusai, Keith J. Roberts, Martina Fontana, Steven A. White, Zahir Soonawalla, Nigel B. Jamieson, Ugo Boggi, Adnan Alseidi, Alaaeldin Shablak, Johanna W. Wilmink, John N. Primrose, Roberto Salvia, Claudio Bassi, Marc G. Besselink, Mohammed Abu Hilal

**Introduction** At present, it is unclear whether patients with ampullary adenocarcinoma (AAC) gain a survival benefit from adjuvant chemotherapy and whether treatment effect differs between the histopathologic subtypes. The aim of this study was to compare overall survival between patients who did or did not receive adjuvant chemotherapy after resection of the various subtypes of AAC.

**Methods** An international multicenter cohort study was conducted, including patients who underwent pancreatoduodenectomy for AAC (2006–2017) in 13 centers in six countries. Propensity scores were used to match patients who received adjuvant chemotherapy to those who did not; both in the entire cohort and in two subgroups (pancreaticobiliary/mixed and intestinal subtype). Survival was assessed using the Kaplan-Meier method and Cox regressions.

**Results** Overall, 1163 patients underwent pancreatoduodenectomy for AAC. After excluding 179 patients, median survival in the resulting 976 patients was 67 months (95%CI 56–78). A total of 520 patients received adjuvant chemotherapy and 456 patients did not. In the matched cohort (194 vs 194 patients), median survival was not reached in patients receiving adjuvant chemotherapy group vs 60 months in the group without adjuvant chemotherapy,  $p = 0.05$ . In the pancreaticobiliary/mixed subtype a survival benefit was seen; median survival was not reached in patients receiving adjuvant chemotherapy vs 32 months in the group without chemotherapy,  $p = 0.02$ . The intestinal subtype did not show a survival benefit from adjuvant chemotherapy.

**Conclusion** Patients with resected AAC of the pancreaticobiliary/mixed subtype may demonstrate a survival benefit with adjuvant chemotherapy whereas no benefit seems present in resected AAC of the intestinal subtype.

# Evaluating the added value of adjuvant therapy following pancreatic cancer surgery after preoperative treatment with FOLFIRINOX chemotherapy

Stijn van Roessel, E. van Veldhuisen, S. Klompmaker, Q.P. Janssen, M. Abu Hilal, C. Bassi, O.R. Busch, M. del Chiaro, J.W. Wilmink, I.Q. Molenaar, M. Lesurtel, T. Keck, J. Kleeff, R. Salvia, O. Strobel, B. Groot Koerkamp<sup>^</sup>, M.G. Besselink<sup>^</sup>; on behalf of the scientific committee of the European-African Hepato-Pancreato-Biliary Association

**Introduction** The added value of adjuvant chemotherapy following resection of pancreatic cancer after neoadjuvant chemotherapy remains unknown. The aim of the present study was to assess the treatment effect of adjuvant chemotherapy on overall survival in different subgroups who underwent pancreatic surgery following neoadjuvant FOLFIRINOX chemotherapy for borderline resectable pancreatic cancer and locally advanced pancreatic cancer.

**Methods** Retrospective cohort study within the European-African Hepato-Pancreato-Biliary-Association (E-AHPBA) on pancreatic cancer resection after neoadjuvant FOLFIRINOX chemotherapy (2012–2016). A multivariable Cox model was used to assess the prognostic significance of traditional histopathologic parameters on overall survival (OS) and points were assigned to create a clinical prediction rule based on the hazard ratios. The survival benefit of adjuvant chemotherapy was evaluated in different risk groups. Patients who died within 6 months after surgery were excluded to minimize immortal-time bias.

**Results** We included 515 patients from 29 centers in 22 countries, with a median OS of 37 months (95%CI 35–42 months). Using a Cox model, points were assigned to the different pathological predictors (positive resection margin, 1 point; moderately tumor differentiation 2 points; poor tumor differentiation, 3 points; N1 disease, 1 point; N2 disease, 2 points) with a total sum score ranging from 0 to 6. Two risk groups were created based on a total score of < or ≥4 points. The low and high-risk group consisted of 320 (62%) and 195 (38%) patients with a median OS of 30 and 50 months, respectively (log-rank  $p < 0.001$ ). Whereas in the low risk-group adjuvant therapy did not demonstrate a survival benefit (49 vs. 55 months for adjuvant vs. no adjuvant therapy, log-rank  $p = 0.79$ ), prolonged survival was noted for patients who received adjuvant therapy in the high risk-group (30 vs. 22 months for adjuvant vs. no adjuvant therapy, log-rank  $p = 0.013$ ).

**Conclusion** This large European series in 515 patients who received preoperative FOLFIRINOX chemotherapy evaluated the added value of adjuvant therapy following pancreatic cancer surgery. A clinical prediction rule was created and a subgroup with unfavorable histopathologic parameters was identified who might benefit from adjuvant chemotherapy. Reproducibility of these findings should be assessed by external validation.

# Prognostic value of disease-free interval on overall survival after repeat local treatment for recurrent colorectal cancer liver metastases

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Julia J. Henneman, T. Hellingman, C.J.A. Haasbeek, M.R. Meijerink, M.P. van den Tol, J.J. van der Vliet, J.J.J. de Vries, J.H.T.M. van Waesberghe, B.M. Zonderhuis, G. Kazemier

**Introduction** The potential benefit of repeat local treatment in patients with early recurrence of colorectal cancer liver metastases (CRLM) has not been established yet. Therefore, treatment strategy in patients suffering from early recurrence of CRLM is frequently debated during multidisciplinary team meetings. The aim of this study is to assess whether disease-free interval after initial local treatment of CRLM is associated with overall survival after repeat local treatment of patients with recurrent CRLM.

**Methods** Patients with recurrent CRLM, that underwent repeat local treatment in a tertiary referral hospital between 2009–2019, will be retrospectively identified in this historic cohort study. All patients that underwent resection or local ablation techniques qualify for this study. Patients with experimental local treatment strategies are excluded from analysis. Patient and tumor characteristics, including disease-free interval after initial local treatment, will be collected from prospectively maintained electronic medical records.

**Results** The primary and secondary outcome will be overall and progression-free survival after repeat local treatment of CRLM. These results will be estimated for various disease-free intervals by the Kaplan-Meier method, using log-rank test to compare. If possible, a multi-variable Cox regression analysis will be performed to correct for relevant confounders.

**Conclusion** We hypothesize that patients with short disease-free interval have poor prognosis after repeat local treatment of CRLM. Nevertheless, repeat local treatment remains the only treatment with curative intent. Therefore, repeat local treatment seems justifiable in patients with early recurrence of CRLM.

# Predicting mortality and secondary interventions after open and endovascular aneurysm repair

---

Ted G. van Schaik, K.K. Yeung, J.L. de Bruin, J.D. Blankensteijn

**Introduction** The influence of hostile aneurysm neck anatomy on outcomes after aneurysm repair has been argued before, however, only limited studies debate the long-term consequences on reinterventions and survival. Therefore, long-term effects of neck morphology after endovascular and open repair for infrarenal abdominal aortic aneurysms were investigated in patients enrolled in the DREAM-trial.

**Methods** A post hoc on-treatment analysis was performed in patients enrolled in the DREAM-trial. The aneurysm severity grading (ASG)-score, classifying the aneurysm neck morphology, was calculated based on pre-operative CT-angiography images, and was used to predict the risk for secondary interventions and death. Freedom from reinterventions and overall survival were compared for patients with low (<5) and high (>5) ASG-scores using Kaplan-Meier methods, differences were calculated with log-rank tests. With use of ROC analysis the positive predicting value and likelihood-ratios were calculated.

**Results** In the DREAM-trial 174 patients underwent open and 173 endovascular repair, 17% were considered high risk (ASG >5). The likelihood ratio for secondary reinterventions in patients at high risk is 3.3 after endovascular repair. Twelve year after randomisation the rates free from reintervention was 88.5% in the low-risk group and 59.9% in the high-risk group after EVAR (difference 28.6%, 95%CI 2.9 to 54.3;  $p = .001$ ). The overall survival after EVAR showed no differences on the long-term ( $p = .15$ ), however, after open repair overall survival rates were 30.7% in the low-risk group and 52.8% in the high-risk group (difference 22.1%, 95%CI, 7.5 to 36.7;  $p = .02$ ), twelve years after randomisation.

**Conclusion** The ASG was not only predictive for reinterventions after endovascular repair, it also increased the risk of death in patients undergoing open repair. In other words, patients unsuitable for endovascular repair have increased mortality on the long-term, which might render endovascular repair a better choice.

# Investigating the metformin pathway in patient-specific aortic smooth muscle cells as a potential therapy for abdominal aortic aneurysms

---

Tara A.R. van Merrienboer, Natalija Bogunovic, Jorn P. Meekel, Kak K. Yeung

**Introduction** Ruptured abdominal aortic aneurysms (AAA) are associated with overall mortality rates up to 90%. SMC are the predominant cell type in the aorta, and defects in SMC are emerging as key underlying causes. Diabetes Mellitus (DM), is a strong cardiovascular risk factor. However, multiple epidemiological studies have confirmed that a negative relationship exists between DM and AAA presence, growth and rupture. In fact it is possible that DM medication is responsible for the protective effects. The aim of this study is to examine the metformin mechanism of action in smooth muscle cells (SMC) of AAA patients and investigate its potential as an AAA therapy.

**Methods** Smooth muscle cells of healthy controls and AAA patients were seeded on plastic and in 3D scaffolds to investigate the effect of metformin on their gene expression and extracellular matrix production. SMC were treated with 10mM glucose, to mimic diabetes, and with 2mM, 5mM and 10mM metformin and a selection left untreated as negative control. After one week and after three weeks, RNA was isolated and samples were fixated for immunofluorescence staining.

**Results** Pilot results indicate that metformin has a different effect on SMC of controls and AAA patients. A dose response to metformin was observed in both groups. In healthy controls, metformin stimulation affects the insulin pathway (IRS1) and decreases cell proliferation (Ki67) compared to untreated and glucose. In SMC of AAA patients, metformin decreases the gene expression of inflammatory markers (IL6 and MCP1) and decreases pro-apoptotic markers (TP53) compared to both untreated and SMC treated with glucose.

**Conclusion** Smooth muscle cells of controls and AAA patients responded differently to metformin stimulation. Metformin treatment may have beneficial effect on SMC of AAA patients by acting anti-inflammatory and preventing cell death. Further research is needed to explicate the exact pathway and identify therapeutic targets of metformin in AAA.

# Survival and amputation risk in patients with diabetic foot ulcers

---

Matthijs J. Scheltema, Claudia Staats, Louise L. Blankensteijn, Laurens Huisman, Martine Willems, Mare Lensvelt

**Introduction** The prevalence of obesity and diabetes has increased over the last years and is expected to continue rising in the near future. As a result, we expect a growing number of patients presenting with diabetic foot ulcers; a complex problem that requires prompt and adequate assessment and treatment.

**Methods** Our goal was to evaluate the five-year survival and amputation rate in patients with diabetic foot ulcers and to define predictive patient characteristics at presentation. The primary outcome was the five-year survival rate. Secondary outcomes included rates of cured ulcers, new ulcers, amputation and predictive patient characteristics. Mortality data was extracted from the national population registry, other patient parameters were extracted from the electronic patient files. The Charlson comorbidity index score was used to summarise patient frailty at presentation.

**Results** 114 patients were included (median age 65 years). The five-year survival was 64% (73/114). Only 5% (2/41) of deaths was directly related to the diabetic foot ulcer. The Charlson comorbidity index score was a significant predictor for mortality (HR 1.253, 95%CI 1.074 – 1.460,  $p = 0.004$ ). A similar trend was observed for patients with an impaired renal function (HR 2.275, 95%CI 0.905–5.715,  $p = 0.080$ ). Patients with a high comorbidity score ( $>5$ ) and an impaired renal function had a one-, two- and five-year survival rate of 68%, 38% and 18%, respectively. During follow-up 24% (27/114) of patients underwent a minor amputation, 11% (12/114) a major amputation and 9% (10/114) a contralateral amputation.

**Conclusion** Patients with diabetic foot ulcers have a high five-year mortality risk. The Charlson comorbidity index score (frailty) and/or impaired renal function are predictive for mortality. Prospective studies are necessary to further define the optimal care within these patient populations with preservation of quality of life.



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# New surgical techniques

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# Valuation of the learning curves for technical skills in laparoscopic training

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Sem F. Hardon, L.A. van Gastel, T. Horeman, F. Daams, D.L. van der Peet

**Introduction** The need for simulation training for minimally invasive surgery has been widely acknowledged. However, residents still gain most of their experience and technical skills set in the operating room operating on real patients under direct supervision. The aim of the study was to evaluate implementation and objectively assess outcomes of a novel remote training program for technical skills in laparoscopic training.

**Methods** In this prospective cohort study, a three-week training program for technical skills in laparoscopy was developed, validated and implemented. Novice surgical residents from eight centers participated. A mobile box trainer was equipped with a state-of-the-art tracking system to sense tissue manipulation forces and instrument movement during every trial. Six FLS-like tasks for basic laparoscopy were trained. Learning curves for eighteen parameters were established, visualized and analyzed. A pre- and post-course comparison indicated overall progression of the cohort. Learning curves were statistically analyzed by using linear regression test. A survey was distributed to support the validity evidence of this course.

**Results** In total, 4268 trials, executed by 24 residents were captured and assessed successfully. Significant reduction of maximum exerted forces was observed for five out of six tasks ( $p \leq 0.009$ ). A significant reduction of path length and time to complete task was observed for all tasks (resp.  $p \leq 0.001$  and  $p < 0.001$ ). Mean overall progression in technical skills was 31.67% (SD  $\pm$  11.58%) for tissue manipulation (MaxForce) and respectively 49.83% (SD  $\pm$  9.67%) and 60.50% (SD  $\pm$  10.52%) for instrument handling (Path Length) and efficiency of movements (Time).

**Conclusion** A novel skills training program was developed, validated and implemented successfully. Individual learning patterns have been visualized. Tissue manipulation and instrument handling skills for laparoscopy have been objectively assessed before entering the OR. Therefore, competency was assured before operating on real patients.

# Open versus minimally invasive total gastrectomy after chemotherapy: Results of a European randomized trial

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Nicole van der Wielen, J. Straatman, F. Daams, M.A. Cuesta, D.L. van der Peet

**Introduction** Minimally invasive techniques have been implemented in oncological resections with improvement of short-term outcomes whilst maintaining similar oncological results. With regard to gastric cancer, mainly Asian studies showed comparable oncological and short-term postoperative outcomes. The reproducibility of these results in the Western population remains to be investigated.

**Methods** A randomized trial was performed in several hospitals in Europe. Patients with an indication for total gastrectomy who received neo-adjuvant chemotherapy were eligible for inclusion. Primary outcomes were the number of resected lymph nodes and radicality. Secondary outcomes were postoperative complications and recovery.

**Results** Between January 2015 and June 2018, 110 patients were included in this trial. After exclusion of fourteen patients, forty-nine patients were randomized to an open and forty-seven to a minimally invasive procedure. The mean number of resected lymph nodes was  $44.3 \pm 16.7$  in the open group and  $40.7 \pm 16.3$  in the minimally invasive group ( $p = 0.209$ ). There was no significant difference in radicality. Four patients had positive resection margins, one in the open group and three in the minimally invasive group. No significant differences were found regarding postoperative complications and recovery.

**Conclusion** Minimally invasive total gastrectomy for gastric cancer is safe regarding oncological outcomes in the Western population. Additionally, no differences in postoperative complications and recovery were seen between the open and minimally invasive groups.

# Long-term oncological results after transanal total mesorectal excision for rectal carcinoma

---

Jeroen C. Hol, Stefan E. van Oostendorp, Jurriaan B. Tuynman, Colin Sietes

**Introduction** Transanal total mesorectal excision (TaTME) for mid and low rectal cancer has shown to result in benefits in short-term outcomes, mostly reflected by lower conversion rates and with improved quality of the specimen. However, robust long-term oncological data supporting the encouraging clinical and pathologic outcomes are lacking.

**Methods** All consecutive patients undergoing TaTME with curative intent for mid- or low rectal cancer in two reference centers in the Netherlands with a complete and minimum follow-up interval of 36 months from date of surgery were included. Primary outcome was local recurrence rate. Secondary outcome were disease free survival, overall survival and development of metastasis.

**Results** In this series of 159 consecutive patients operated between January 2012 to April 2016, the 3 years local recurrence rate was 2.0% and the 5 years local recurrence rate was 4.0%. Median time to local recurrence was 19.2 months. Disease free survival at 3 years was 92% and at 5 years was 81%. Overall survival at 3 years was 83.6% and at 5 years was 77.3%.

**Conclusion** The long-term follow-up of the current cohort confirms the oncological safety and feasibility of TaTME in two high volume reference centers for rectal carcinoma. However, further robust and audited data must confirm current findings before widespread implementation of TaTME.

# Increased multifocal local recurrences after TaTME during implementation of the technique within a structured training pathway

---

Stefan E. van Oostendorp, B.T. Bootsma, J.C. Hol, H.J. Belgers, E.J.T.H. Belt, W. Bleeker, F.C. Den Boer, A. Demirkiran, M.S. Dunker, H.F.J. Fabry, E.J.R. Graaf, G.D. Slooter, A.K. Talsma, H.L. Van Westreenen, D.J.A. Sonneveld, M. Kusters, R. Hompes, H.J. Bonjer, C. Sietses, J.B. Tuynman

**Introduction** Transanal Total Mesorectal Excision (TaTME) has been implemented worldwide for treatment of rectal cancer with the promise to improve the quality the pelvic dissection and subsequently improve clinical outcomes for patients with mid and low rectal cancer. Due to the high complexity and associated learning curve the procedure is introduced in the Netherlands within a structured training pathway including on site proctoring. The aim was to evaluate the long term oncological outcome of the patients within this training curriculum.

**Methods** Long term outcomes of the first ten TaTME procedures in 12 participating centers in the Netherlands within the national structured training pathway were evaluated. Consecutive patients operated for rectal carcinoma with curative intent were included and data of long term follow up was collected with external audit. Primary outcome was the incidence of local recurrence (LR). A logistic regression model was used to identify potential risk factors in univariate analysis. Secondary outcomes were disease free survival, overall survival and long-term stoma status. A case matched cohort of laparoscopic TME (lapTME) surgery from the COLORII trial was identified for comparative analysis.

**Results** This cohort of 120 patients that underwent TaTME within the structured training program had a mean follow up of 23.4months. The overall LR rate was 10%, with a mean interval to LR of 15.2 ( $\pm 7$ ) months. Potential predisposing factors were Pelvic Sepsis (17.5%) with Odds ratio (OR) 4.107 ( $p$  0.029), (y)pT3 stage (49.2%) with OR 6.020 ( $p$  0.025) and a positive CRM (5.0%) with OR 11.667 ( $p$  0.006). A multifocal local recurrence was seen in 8 of the 12 cases (66.7%). Case matched analysis of TaTME to the COLOR II lapTME arm showed a 24 months local recurrence free survival of 91.2% and 99.0% respectively ( $p$  0.001).

**Conclusion** The increased risk of local recurrence of 10% is higher than expected when considering the pathology. Especially the high rate of multifocal pelvic recurrence is concerning and might be technique and learning curve dependent which warrants further investigation. Before TaTME can be considered as a valid approach for rectal cancer on a broad scale, data from high quality-controlled trials must be awaited to allow thorough evaluation of the long term consequences.

## Local recurrence after Transanal Total Mesorectal Excision for rectal cancer: A multicenter cohort study

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Sapho X. Roodbeen, A. Spinelli, W.A. Bemelman, F. Di Candido, M. Cardepont, Q. Denost, A. D'Hoore, B. Houben, J.J. Knol, B. Martín-Pérez, E. Rullier, D. Sands, I. Setton, K. van de Steen, P.J. Tanis, S.D. Wexner, R. Hompes, and A.M. Wolthuis

**Introduction** Transanal total mesorectal excision (TaTME) is a relatively new surgical procedure for mid- and low rectal cancer. Recently, concerns have been raised on the oncological safety in light of reported high local recurrence (LR) rates with a multifocal pattern. This study aimed to determine LR rate and pattern after TaTME for rectal cancer.

**Methods** This was a multicenter observational cohort study in six tertiary referral centres. All consecutive TaTME cases for primary rectal adenocarcinoma from the first TaTME case in every center until December 2018 were included for analysis. Patients with benign tumours, malignancies other than adenocarcinoma and recurrent rectal cancer, as well as exenterative procedures, were excluded. The primary endpoint was two-year rate of LR. Secondary endpoints included patterns and treatment of LR and histopathological characteristics of the primary surgery.

**Results** A total of 767 patients were eligible for analysis. After a median follow-up of 25.5 months, 24 patients developed LR (crude LR rate of 3.1%), with an actuarial cumulative two-year LR rate of 3.3%. In none of the patients, a multifocal pattern of LR was observed. Thirteen patients had isolated LR (without systemic disease) and 10/13 could be managed by salvage surgery of whom eight were disease-free at end of follow-up. After primary TaTME, resection margins were involved in 8.0% and optimal pathological outcome was achieved in 86.0% of patients.

**Conclusion** This study shows good loco regional control after TaTME when performed at a tertiary referral center and does not indicate an inherent oncological risk of the surgical technique.

## Added value of 3D-robotic surgery in biotissue pancreatico- and hepaticojejunostomy (LAEBOT 3D2D): A randomized controlled cross-over trial

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M.J.W. Zwart, Leia R. Jones, A. Balduzzi, K. Takagi, A. Vanlander, P.B. van den Boezem, F. Daams, C. Rosman, D.J. Lips, A.J. Moser, M.E. Hogg, O.R.C. Busch, M.W.J. Stommel, M.G. Besselink; on behalf of the Dutch Pancreatic Cancer Group

**Introduction** Robotic surgery has the advantage of articulating instruments and 3D-vision. Consensus is lacking on the added value of 3D-vision during laparoscopic surgery. Given the improved dexterity with robotic surgery, the benefits of 3D-vision could be less than in regular laparoscopic surgery. Objective: We tested the added value of 3D-vision on procedure time and surgical performance during robotic biotissue pancreaticojejunostomy (PJ) and hepaticojejunostomy (HJ) as created during robotic pancreatoduodenectomy.

**Methods** Design: Randomized controlled cross-over trial in 2018 and 2019. Setting: Experimental. Participants: 20 surgeons and surgical residents from 5 countries. Intervention: Participants were randomized to perform robotic pancreaticojejunostomy (PJ) and hepaticojejunostomy (HJ) in a biotissue organ model using either 2D or 3D as initial visualization in the da Vinci® system. Main outcome and Measures: Primary endpoint was the time required to complete both anastomoses. Secondary endpoint was the objective structured assessment of technical skill (OSATS; range 12–60) rating; which was scored by three observers blinded to 3D/2D.

**Results** 20 participants completed 80 robotic PJs and HJs. Robotic 3D-vision reduced the combined operative time from 78.1 to 57.3 minutes (24.6%,  $p < .001$ ; 20.8 min, 95% confidence intervals 12.8–28.8 min). This reduction was consistent for both anastomoses,  $p < .001$  (11.4 and 10.0 min, inter group significance  $p = .163$ ). The reduction in operative time with 3D did not differ significantly between experts and residents ( $p = .279$ ). Robotic 3D-vision improved OSATS performance by 6.1 points (20.8%,  $p = .003$ ) compared to 2D (39.4 to 45.1 points,  $SD \pm 5.5$ ).

**Conclusion** In this randomized trial, 3D-robotic surgery, as compared to 2D-robotic surgery, reduced operative time by 25% and improved surgical performance by 21% during PJ and HJ biotissue anastomoses. New robotic systems are advised to include 3D-vision.

## ACT guided heparin administration in elective open abdominal aortic aneurysm repair: Results of a pilot study

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Orkun Doganer, A.M. Wiersema, M. Pierie, J.D. Blankensteijn, K.K. Yeung, V. Jongkind

**Introduction** Most vascular surgeons use a bolus of 5 000 IU of unfractionated heparin (UFH). However, its dose-response and elimination curves are non-linear. The activated clotting time (ACT) is used to measure the level of anticoagulation. The purpose of this study was to evaluate the incidence of arterial thrombo-embolic complications (ATEC) and bleeding complications in patients undergoing elective open abdominal aortic aneurysm repair (AAA). Results of a bolus of 5 000 IU of UFH was compared to an ACT guided additional UFH dose protocol.

**Methods** All consecutive patients that underwent primary elective open AAA repair were included in this multicentre study. During the first part of the study patients received a bolus of 5 000 IU. During the second part of the study patients received an initial bolus of 5 000 IU or 100 IU/kg and additional UFH dosages were administered, with a target ACT of 200–250 sec. The primary study endpoints were ATEC, bleeding complications and mortality, during the procedure or 30 day follow-up.

**Results** 46 primary elective open AAA procedures were included, 18 patients in the standard dose group and 28 patients in the additional dose group. In the standard dose group 28% of patients reached an ACT of 200 sec. compared to 100% in the additional dose group. In the additional dose group the mean total periprocedural UFH dose administered was  $9874 \pm 2909$  IU. ATEC occurred in 27.8% of patients in the standard dose group versus 14.3% in the additional dose group ( $p = 0.26$ ). Bleeding complications did not increase in the additional dose group (38.9 versus 35.7%,  $p = 0.83$ ). In both groups no patient died during 30 day follow-up.

**Conclusion** Higher dosing of UFH, aiming at an ACT of 200–250 sec. is safe, does not lead to increased bleeding, and potentially leads to a reduction in ATEC.

# The safety and efficacy of improvised tourniquets in life-threatening hemorrhage: A systematic review

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Maarten P. Cornelissen, A. Brandwijk, L. Schoonmade, G. Giannakopoulos, S. van Oostendorp, L. Geeraedts Jr.

**Introduction** The increased incidence of mass casualty incident (MCI) with penetrating injuries in the civilian setting creates a call for implementing devices, such as a tourniquet (TQ), in civilian first aid. Bystanders could act as immediate responders after an MCI in order to prevent a victim from exsanguination using direct pressure or commercial tourniquets (C-TQ). Reports have shown that immediate access to C-TQs was not available and bystanders used objects available at the trauma scene to make an improvised tourniquet (I-TQ). The aim of this systematic review of literature was to summarize the existing literature on designs, efficacy and safety of I-TQs.

**Methods** A systematic review of the literature was performed. Bibliographic databases PubMed, EMBASE.com and Cochrane Library were searched. All types of original studies about I-TQ's were included. Review studies, excerpts from textbooks or studies with TQs applied during elective surgeries were excluded.

**Results** Twenty studies were included. In both simulated experiments and real-life situations, I-TQs outperformed commercial TQs (C-TQ) regarding success rate. Of the I-TQs, the band and windlass design performed most consistently. Although lacking any statistical analysis, there was no reported difference in adverse events between I-TQs and C-TQs.

**Conclusion** The use of and training in I-TQ by civilian immediate responders is not recommended because of limited efficacy and safety concerns; direct pressure is a viable alternative. However, I-TQs may save lives when applied correctly with proper objects; therefore, future studies regarding the best design and training in application of effective and safe I-TQs should be encouraged.



# Image-guided diagnostics & surgery

## Sessie 3b

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# Optimization of wire-guided technique with bracketing reduces resection volumes in breast-conserving surgery for early breast cancer

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Yasmin A. Civil, Katya M. Duvivier, Paola Perin, Astrid H. Baan, S. van der Velde

**Introduction** Wire-guided localization (WGL) of early breast cancer can be facilitated using multiple wires, which is called bracketing wire-guided localization (BWL). The primary aim of this study is to compare BWL and WGL regarding minimization of resection volumes without compromising margin status. Secondly, BWL is evaluated as an alternative method for intra-operative ultrasound (US) guidance in poorly definable breast tumors on ultrasound.

**Methods** In this retrospective cohort study, patients with preoperatively diagnosed breast cancer undergoing wide local excision between January 2016 and December 2018 were analyzed. Patients with multifocal disease or neoadjuvant treatment were excluded from this study. In BWL, the number of wires to be inserted depended on the location of the tumor relative to the pectoral muscle and the skin. Optimal resection with minimal healthy breast tissue removal was assessed using the calculated resection ratio (CRR). A CRR of 1 is considered an ideal resection, and higher values indicate more healthy breast tissue removal.

**Results** BWL was performed in 17 (9%) patients, WGL in 44 (22%) and US in 139 (70%). The rate of negative margins was comparable in all three groups. CRR was significantly smaller for BWL (0.6) than WGL (1.3) in tumors larger than 1.5 cm ( $p = 0.008$ ). Additionally, BWL (0.8) led to smaller CRRs than US (1.7) ( $p = 0.015$ ). This could be explained by the high number of small tumors ( $\leq 1.5$  cm) in the US group for which greater CRRs are obtained than for large tumors ( $> 1.5$  cm) (1.9 versus 1.4,  $p = 0.005$ ).

**Conclusion** For breast tumors larger than 1.5 cm, BWL achieves more optimal resection volumes without compromising margin status compared to WGL. Moreover, BWL seems a suitable alternative to US in patients with poorly ultrasound-visible breast tumors and patients with a small tumor in a (large) breast.

# Image-guided de-escalation of neoadjuvant chemotherapy in HER2-positive breast cancer: The TRAIN-3 study

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Anna van der Voort, Mette S. van Ramshorst, Ritse Mann, Vincent O. Dezentjé, Wim A. van der Steeg, Gonneke A.O. Winter-Warnars, Robert-Jan Schipper, Astrid N. Scholten, Jelle Wesseling, Erik D. van Werkhoven, Frederique van Duijnhoven, Marie-Jeanne T.F.D. Vrancken Peeters, Gabe S. Sonke

**Introduction** Pathologic complete response rates (pCR) after neoadjuvant therapy are increased drastically since the addition of pertuzumab to trastuzumab containing chemotherapy for HER2-positive breast cancer. Achieving a pCR is associated with a favorable long-term outcome. In addition, a radiologic complete response (rCR) is predictive of the pathologic response in HER2-positive tumors. Therefore it is hypothesized that image-guided evaluation to detect the early occurrence of rCR can be used to tailor the number of chemotherapy cycles before surgery.

**Methods** This is a single arm, multicenter study evaluating the efficacy of image-guided de-escalation of neoadjuvant treatment with paclitaxel, Herceptin®, carboplatin, and pertuzumab (PTC-ptz). Response evaluation with MRI and ultrasound of the axilla is performed every 3 cycles of treatment. In case of a rCR after 3 or 6 cycles, early surgery will be performed. If residual tumor is present at surgery, patients complete 9 cycles of PTC-ptz. All patients receive adjuvant Herceptin® and pertuzumab. The primary endpoint is event-free survival (EFS) at 3 years. Secondary endpoints are overall survival, rCR, concordance between rCR and pCR (ypT0/is, ypN0), percentage radical resections, differences in EFS and OS following pCR between patients who received 3, 6, or 9 cycles, and toxicity. Eligible patients have stage II/III HER2-positive breast cancer and can be HR-positive or negative. This is a single-arm study. Statistics will be performed for each hormone receptor subgroup separately. Stopping rules are based EFS-rates described in literature (88% for HR– and 90% for HR+ tumors). The 3-year EFS-estimate will be calculated using Kaplan-Meier statistics. Accrual Target accrual is 462 patients. The study is currently enrolling in 18/50 hospitals and 57 patients are included.

**Conclusion** The TRAIN-3 is a multidisciplinary study with the aim to evaluate the efficacy of image-guided de-escalation of neoadjuvant chemotherapy in HER2-positive breast cancer.

# Axillary staging with supine 18F-FDG PET/CT is useful in breast cancer patients undergoing tailored axillary treatment after neoadjuvant systemic treatment according to the MARI protocol

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Ariane A. van Loevezijn, M.P.M. Stokkel, E. van Werkhoven, F.H. van Duijnhoven, M.T.F.D. Vrancken Peeters

**Introduction** Staging in breast cancer patients with neoadjuvant systemic therapy (NST) can be performed with 18F-FDG PET/CT in supine position. In the MARI protocol (Marking Axillary lymph nodes with Radioactive Iodine seeds), PET/CT is used to tailor axillary treatment post-NST. The number of positive axillary nodes (ALNs) on PET/CT pre-NST determines MARI strategy:  $\geq 4$  ALNs is followed by axillary node dissection (ALND) in case of a tumor-positive MARI. We aim to assess the value of the additional prone position scan for axillary staging.

**Methods** MARI patients with PET/CT in both supine and prone position from 2014–2017 were selected. One hour after administration of 180–240 MBq 18F-FDG, images in prone position were acquired using a mock-up coil. Subsequent whole body PET/CT scan was performed in supine position along with a low-dose CT scan (2 mm CT slices). Both sets of images (prone and supine) were separately assessed (>7 day interval) by a nuclear medicine physician.

**Results** 153 patients had FDG-PET/CT in supine and prone position. At assessment of supine images there were 114 patients with <4 positive ALNs and 39 patients with  $\geq 4$  positive ALNs. Addition of prone position images categorized 9/153 patients (6%) in a different ALN category. Five patients were downstaged to <4 ALNs (3.3%, 95%CI: 1.1–7.5) and 4 patients were upstaged to  $\geq 4$  ALNs (2.6%, 95%CI: 0.7–6.6). There were 34 patients with  $\geq 4$  ALNs in both assessments: 18/34 patients (53%) had a tumor-positive MARI and underwent ALND. A median of 7 lymph node metastases (4–17) were removed at ALND. Three out of 4 upstaged patients had a positive MARI of which 2 patients underwent ALND, with 2 and 5 lymph node metastases.

**Conclusion** FDG-PET/CT for axillary staging according to the MARI protocol can be adequately performed with supine images alone or in combination with prone position images.

# Depth of invasion in patients with early stage oral cancer staged by sentinel node biopsy

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Inne J. den Toom, Luuk M. Janssen, Robert J.J. van Es, K. Hakki Karagozoglu, Bart de Keizer, Stijn van Weert, Stefan M. Willems, Elisabeth Bloemena, C. René Leemans, Remco de Bree

**Introduction** To investigate if depth of invasion (DOI) can predict occult nodal disease in patients with cT1-2N0 (7th TNM) oral squamous cell carcinoma (OSCC) staged by sentinel lymph node biopsy (SLNB).

**Methods** In two Dutch Head and Neck centers SNLB was performed in 199 OSCC patients and retrospectively analyzed. DOI of the primary tumor was considered to be the actual mass beneath the mucosal surface, or in case of ulceration or exophytic lesions the theoretical reconstruction of the mucosal surface. Patients with a positive SLN and patients with regional metastasis during follow-up in case of a negative SLNB (false-negatives), were considered as patients with metastases.

**Results** Metastases were found in 64 of 199 patients (32%). Of these 64 patients, the mean DOI was 6.58 mm compared to 4.69 mm in patients without metastases ( $p = 0.003$ ). In univariate logistic regression analysis, DOI showed an odds ratio of 1.15 (95%CI 1.05 – 1.26) progressive per 1 mm ( $p = 0.002$ ). The ROC-curve showed an area under the curve of 0.65 with a most optimal cut-off point of 3.4 mm DOI (sensitivity 83%, specificity 45%). Regional metastases were found in 15% of patients with DOI  $\leq 3.4$  mm. Median follow-up was 19 months (range 1–104).

**Conclusion** DOI seems to be a poor predictor for regional metastasis in patients with cT1-2N0 OSCC. Therefore, staging of the neck using SLNB in patients with early stage oral cancer should also be performed in tumors with limited DOI and probably in T3 (8th TNM) OSCC  $\leq 4$  cm diameter.

# Navigation during EVAR: Improvement of operative workflow with image fusion and automatic navigation based on preoperative CTA

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Stefan P.M. Smorenburg, Maarten Truijers, Kakkhee Yeung and, Arjan W.J. Hoksbergen

**Introduction** During endovascular aortic repair (EVAR), the surgeon guides it's catheter/guidewire through the femoral artery into the aorta with real-time X-ray guidance (fluoroscopy). A recently introduced technique is image fusion, which enables navigation of the guidewire using a 3D vascular roadmap based on preoperative CTA. The 3D vascular roadmap is superimposed on the fluoroscopy, making navigation more easy and exact. Additional advantages are optimal positioning of C-arm angles to visualize renal/iliac arteries, which reduces the use of nephrotoxic contrast and radiation dose/exposure. However, image fusion is still operator-dependent, potentially hampering accuracy, and without experience relatively time-consuming. The aim of this study was to improve perioperative planning and workflow and to validate a new registration algorithm (Philips, Best, The Netherlands) which automatically fuses pre-operative CTA and live fluoroscopy.

**Methods** Patients who underwent elective EVAR were analyzed with this new automatic fusion software (n = 10). Pre-operative CTA and fluoroscopy images of the procedure were collected and automatically fused, based on the vertebral column. Accuracy of fusion was determined by measuring the distance between an identical bone location in both CTA and fluoroscopy in mm. Additionally, the vascular accuracy after fusion was determined by measuring potential mismatch of renal arteries (mm) between the vascular roadmap and the live images after contrast injection.

**Results** Automatic fusion was successful in 7 out of 10 patients. Manual registration help was needed in 3 patients. Average vertebral column mismatch after fusion was  $0.5 \pm 0.6$  mm. The average vascular mismatch however was  $9.0 \pm 5.8$  mm.

**Conclusion** Automatic fusion on bone was possible in most cases and very accurate. The vascular mismatch was relatively high due to vessel displacement after insertion of stiff guidewires and stentgrafts. Future development of image fusion should be focused on solving the vascular mismatch to further decrease nephrotoxic contrast and radiation use.

# 18FDG PET scanning in locally advanced gastric carcinoma

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Tim Verhaak, C.J. Hoekstra, R. Verhoeven, O.S. Hoekstra, K. Bosscha

**Introduction** 2-[18F]fluoro-2-deoxy-D-glucose (FDG)-PET is widely used for initial staging, restaging, assessment of early treatment response, evaluation of metastatic disease response and prognostication of various malignant tumours. FDG-PET's clinical value in gastric cancer remains debatable as some gastric cancers are not 18FDG-avid. Recent studies show that 18FDG avidity in gastric cancer seems to correlate with certain clinicopathologic parameters.

**Methods** In total 52 patients with histologically proven locally advanced gastric adenocarcinoma were prospectively included in five hospitals in the southern part of the Netherlands. All patients underwent FDG PET/CT scans prior to the initiation of neoadjuvant chemotherapy. FDG PET imaging was performed using the NEDPASS protocol based on guidelines by the European Association of Nuclear Medicine (EANM). Clinicopathologic parameters were collected after standardised surgery.

**Results** Total incidence of 18FDG avid gastric carcinoma was 70.3%. Predictors of FDG-avidity included large tumour size and non mucinous and signet-ring cell carcinoma type. Proximal tumour site versus distal tumour site was not associated with 18FDG avidity.

**Conclusion** 18F-FDG avidity can be predicted by certain clinicopathologic parameters. These parameters can be used to form a prediction model of 18FDG avidity in patients with gastric cancer. Leading to the use of 18FDG-PET as a tool for early treatment response in selected patients with locally advanced gastric cancer.

# Lateral region sentinel node biopsy of low rectal cancer guided by indocyanine green

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Vittoria Bellato

**Introduction** Lateral Lymph Node Dissection (LLND) in COLORECTAL SURGERY is nowadays a topic of debate, in fact there remains a lack of international consensus on the appropriate management of lateral node disease. The incidence of LLN metastases reaches as high as 10/25% and 27% of rectal cancer patients who undergo Total Mesorectum Excision (TME) without LLND would develop recurrence. Japanese 2014 guidelines for treatment of colorectal cancer recommend that patients with stages II-III rectal cancer below the peritoneal reflection undergo regular TME+LLND. Accounting that LLND involves higher intraoperative and postoperative complication, West Countries aims to eradicate small-volume disease with neoadjuvant chemoradiotherapy alone, followed by TME. Therefore American NCCN and European ESMO guidelines recommended single TME for rectal cancer but, if necessary, LLND is added when MRI show evidence of LLN metastases. Many studies are investigating the role of MRI in detecting suspect nodal disease after chemoradiotherapy to select which patients might benefit from an LLND. Recent studies showed that in patients with shrinkage of later nodes from an Short Axis (SA) node size of >7 mm on primary MRI to an SA node size of  $\leq$ 4mm on restating MRI, LLND can be avoided. Still no indications are available for restaged regional lymph node on MRI with SA >4mm. The feasibility of application of indocyanine green enhanced near-infrared fluorescence-guided imaging in laparoscopic lateral pelvic lymph node dissection combined with lateral region sentienel node biopsy was proved by Noura S. et all, although the population sample examined was small. The aim of this trial is to assess the efficacy and safety of indocyanine green lateral region sentinel biopsy followed by laparoscopic LLND+ TME. A combined trial between Japan and Europe countries aim to define which patients would benefit of LLND selected by lateral region sentinel node indocyanine green guided biopsy would solve the debate avoiding almost 85% of regional local recurrence and unnecessary LLND complication. No running trials are investigating this topic. The results of this trial can change the standard of care of rectal cancer treatment.



## Surgical navigation in rectal cancer surgery

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Esther Kok, Roeland Eppenga, Koert Kuhlmann, Harald Groen, Ruben van Veen, Jolanda van Dieren, Thomas van Wijkerslooth, Doenja Lambregts, Wout Heerink, Nikie Hoetjes, Oleksandra Ivashchenko, Monique van Leerdam, Geerard Beets, Arend Aalbers, Theo Ruers and Jasper Nijkamp

**Introduction** Surgery of rectal tumors can be challenging due to disrupted anatomical planes caused by tumor in-growth, fibrosis or radiation effects. The number of positive margins in rectal surgery mount up to 5–10%. To improve surgical margins, intraoperative surgical navigation can be beneficial. This study explores the application an in-house developed electromagnetic (EM) navigation system with real-time tumor tracking for rectal cancer surgery.

**Methods** This was a prospective feasibility study. Preoperatively, patients received fiducial markers close to the rectal tumor by endoscopic ultrasonography and a patient specific 3D-model of tumor and surrounding structures was created. During surgery, a cone beam CT scan was acquired and matched to the 3D model based on the bony structures and fiducials. EM patient trackers and an EM-sensor on the rectal tumor continuously determined the real-time position of the tumor and surrounding structures. A tracked pointer was used for intraoperative anatomical guidance. The primary endpoint was feasibility. Secondary endpoints were safety and accuracy.

**Results** In total 31 patients were included, of which 29 patients (93.5%) were operated using the navigation system. Real-time tracking of the tumor was feasible in 24 patients (82.5%). No intraoperative navigation-related complications occurred but one patient suffered from a rectal perforation related to the fiducial placement. Accuracy was validated by placing surgical clips on the proximal tumor border based on the navigation system intraoperatively and correlating the position of these clips to the pathological proximal tumor border. The median distance between the surgical clips and the pathological proximal tumor border was 4 mm (IQR: 2 – 12 mm).

**Conclusion** Application of real-time tumor tracking using an intraoperative navigation system during rectal cancer surgery is feasible, safe and accurate. Further research is necessary to investigate the impact of surgical navigation on resection margins in rectal cancer surgery.

## Imaging for preoperative assessment of vascular involvement in perihilar cholangiocarcinoma

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Lotte C. Franken, R.J. Coelen, J.I. Erdmann, R.J. Swijnenburg, J. Verheij, M. Kop, T.M. van Gulik, S.S. Phoa

**Introduction** Approximately 40% of patients with perihilar cholangiocarcinoma (PHC) is still deemed unresectable at laparotomy, often due to vascular involvement. On imaging, occlusion, narrowing, irregularity of the wall and circumferential tumor-vessel contact of >180 degrees have been suggested to predict vascular involvement in patients with PHC. In this study, preoperative CT images were compared to intraoperative and histopathological findings, in an attempt to improve assessment of vascular involvement and identify reliable criteria for vascular invasion.

**Methods** Patients undergoing exploration in a single tertiary center between March 2015–April 2018 were included. Tumor-vessel relation of the portal vein and hepatic artery were blindly scored by two independent radiologists (eg. circumference and length of contact, irregularity of vessel wall and stenosis/occlusion). Intraoperative/pathological findings were derived from the operation and pathology reports. As of January 2018, intraoperative vascular involvement was scored prospectively in theatre.

**Results** A total of 42 CT-scans were evaluated. Radiological findings could be correlated to intraoperative/pathological findings for 116 vessels. Occlusion of the portal vein on imaging had a positive predictive value (PPV) for involvement of 1 and the PPV of an irregular wall with narrowing was 0.83. For the hepatic artery, the PPV for occlusion and stenosis was also 1, whilst all other criteria resulted in a PPV <0.70. Combining potential criteria for vascular involvement (>180°/irregularity/narrowing/occlusion) resulted in a PPV of 0.85 for the portal vein and 0.53 for the hepatic artery, respectively. Sensitivity, however, of all criteria was low. Cohens kappa for assessment of tumor-vessel contact between the two radiologists was 0.265 (SE 0.062), indicating fair interobserver agreement.

**Conclusion** On imaging, occlusion or an irregular wall of the portal vein accurately predict invasion. CT criteria for vascular involvement of the hepatic artery, other than occlusion, seem unreliable and should not preclude exploration.

# To cut or not to cut

## Sessie 3c

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# The role of surgery for stage I non-small cell lung cancer in octogenarians in the era of stereotactic body radiotherapy in the Netherlands

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Julianne C. de Ruiter, David J. Heineman, Johannes M.A. Daniels, Judi van Diessen, Ronald A.M. Damhuis, Koen J. Hartemink

**Introduction** Surgical resection is the standard treatment for stage I non-small cell lung cancer (NSCLC) in medically operable patients. Stereotactic body radiotherapy (SBRT) is recommended for inoperable patients. A shift from surgery to SBRT is expected in elderly patients due to increased frailty and competing risks. We assessed the current influence of age on treatment decision-making and survival.

**Methods** Data from patients with clinical stage I NSCLC diagnosed in 2012–2016 and treated with lobectomy, sublobar resection, or SBRT were retrieved from the nationwide Netherlands Cancer Registry. Patient characteristics and five-year overall survival were compared between SBRT and (sub)lobar resection.

**Results** 8764 patients with clinical stage I NSCLC treated with lobectomy (n = 4648), sublobar resection (n = 394), or SBRT (n = 3722) were included. Between 2012 and 2016, the use of SBRT increased for patients aged 18–79 and  $\geq 80$  years from 30.8% to 43.2% and from 75.3% to 83.7%, respectively. Octogenarians received less systemic adjuvant therapy following postsurgical pathological upstaging compared to patients aged 18–79 years (3.3% versus 12.5%). Five-year overall survival in the whole population was 70% after surgery versus 38% after SBRT and 50% versus 26% in octogenarians.

**Conclusion** SBRT has become the prevailing treatment in octogenarians with stage I NSCLC. Although surgery was associated with better survival than SBRT, an important selection bias may be present since comorbidity, poor pulmonary function and poor performance score are more common among SBRT patients. The wider application of SBRT and poor survival in octogenarians likely reflect the frailty of this population. Registries and trials are required to identify key determinants of frailty in this specific population to improve patient selection.

# Lateral nodal recurrence in rectal cancer: Results from a multicenter study and proposal of LaNoReC prospective study

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Noor S.F. Boogerd, A. Ogura, D.P. Schaap, R. Hompes, P.J. Tanis, J.B. Tuynman, M. Kusters

**Introduction** Distal cT3/4 rectal cancers have the tendency to spread to lateral lymph nodes (LLN). Despite neoadjuvant (chemo)radiotherapy (CRT) and total mesorectal excision (TME) some patients still develop lateral lymph node recurrences (LLR). Japanese studies suggest that addition of a lateral lymph node dissection (LLND) could reduce the number of LLR. In a retrospective multicenter study it was studied which cut-off sizes of LLNs pose a risk for LLR, what the role of restaging MRI is and whether a LLND results in fewer LLR.

**Methods** Data from 1216 patients with a cT3/T4 rectal cancer up to 8cm from the anal verge who underwent surgery in a 5-year period were selected. MRI's were re-evaluated with a standardized protocol to assess LLN features.

**Results** Of all 1216 patients, 108 patients developed a local recurrence (5-year LR rate 10%), of which 59 (54%) a LLR (LLR rate 5.5%). LLNs with a short axis of  $\geq 7$ mm resulted in significantly higher risk of LLR than LLNs  $< 7$ mm ( $p = 0.045$ ). 5-year LLR was 19.5% in patients with LLNs  $\geq 7$ mm who underwent CRT+TME but decreased to 5.7% in patients who underwent (C)RT+TME+LLND ( $p = 0.042$ ). In 741 patients with restaging MRI with shrinkage of the short axis of a LLN from  $\geq 7$ mm on primary MRI to  $\leq 4$ mm on restaging MRI, LLR-rate was zero and a LLND can thus be avoided. Persistently enlarged nodes in the internal iliac compartment resulted in a high risk of LLR (52.3%).

**Conclusion** LLR is still a significant problem after (C)RT+TME in LLNs with a short axis of at least 7mm on pretreatment MRI. After (C)RT, measurements of LLNs on restaging MRI are important for clinical decision making. The addition of a LLND significantly lowers the LLR rate. The next step is the LaNoReC study, in which standardized CRT and surgery is offered.

# Rectal preserving treatment for early rectal cancer. A multicenter randomized trial of radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer; an update on the TESAR trial

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Presented by Lisanne J. Smits

**Introduction** The implementation of a screening program for colorectal cancer has led to an increasing incidence of rectal cancer and a shift towards detection of earlier oncological stages. According to the Dutch guideline, local excision (e.g. TEM/TAMIS/ESD/EMR) is sufficient in the earliest stage of rectal cancer. However, for most patients the current treatment standard is a completion total mesorectal excision (cTME), which is accompanied by high morbidity and ostomy rates. In intermediate risk early rectal cancer, lymph node involvement is estimated at 5–20%. Therefore, additional surgery may lead to a substantial overtreatment of this population. The balance between treatment related morbidity and oncological outcome may be optimized by rectal preserving treatment options, such as adjuvant chemoradiotherapy (aCRT) after local excision.

**Methods** In this multicenter, randomized, non-inferiority trial, patients with intermediate risk T1-2N0M0 rectal cancer who underwent local endoluminal excision will be randomized between cTME and aCRT. To evaluate outcomes of patients who underwent local excision only based on their own preference, a prospective cohort side arm has been added. The primary outcome is three year local recurrence rate. The secondary outcomes are morbidity, disease free- and overall survival, quality of life, functional outcomes and cost-effectiveness. Next to this, local recurrence rates for T1-2 carcinomas treated by cTME, aCRT and close surveillance after local excision were evaluated in a meta-analysis.

**Results** Results of the TESAR trial have to be awaited. Currently, 157 patients are included. Eighty-eight patients of the total sample size of 302 patients have been randomized. The preliminary results of the meta-analysis show that local recurrence rates for close surveillance after local excision are 10% for T1 and 32% for T2 tumors. After cTME local recurrence rates are 6% for T1 and 9% for T2 tumors. The local recurrence rates in the aCRT group are 9% for T1 and 16% for T2 tumors.

**Conclusion** If the TESAR trial shows non-inferiority of adjuvant chemoradiotherapy compared to completion TME, it might be a promising treatment option in rectal preserving treatment for patients with intermediate risk rectal carcinoma, causing better functional outcomes within oncological safe margins.

# Long term oncological outcomes of rectal cancer patients with a complete response followed in a wait-and-see approach, is there an increased risk for metastasis?

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Hester E. Haak, Marit E. van der Sande, Doenja M.J. Lambregts, Regina Beets-Tan, J. Melenhorst, Geerard L. Beets, Monique Maas and the Dutch Watch-and-Wait Consortium

**Introduction** Patients with a local regrowth(LR) in a Watch and Wait(W&W) program are reported to have a higher risk for metastases, but it is unclear if these are arising from the LR, or if they were already present subclinically at initial diagnosis and are merely a manifestation of more unfavorable disease. The aim of this study was to evaluate oncological outcomes in W&W patients, and to evaluate the risk of distant metastasis in patients with a LR.

**Methods** Patients were included in a W&W-program between 2004 and 2018 when a three modality approach with digital rectal examination, endoscopy and MRI with Diffusion-Weighted-Imaging(MRI-DWI) showed a (near)cCR. Patients were followed with frequent endoscopy and MRI every 3 months during the first year, and 6-monthly thereafter. Oncological outcomes was assessed with Kaplan-Meier curves and compared with a log rank test. Multivariate analysis was done with a Cox proportional hazard test.

**Results** We analyzed 304 patients with a median FU of 40 months(range 2–158) of which the majority(n = 191) were prospectively analyzed. 16.7% developed a LR within 3 years (n = 50, 43 luminal, 3 nodal, 4 both luminal and nodal). 7 patients with LR developed distant metastasis (3-year rate of 83.7%) compared to 10 patients with distant metastasis without LR (3-year rate of 96.7%) ( $p = 0.001$ ). 6/7 patients developed a LR first and 1 patient developed both simultaneously. 3-year overall survival in patients with LR was 92.7% versus 96.9% without LR ( $p = 0.260$ ).

**Conclusion** Rectal cancer patients selected for a W&W-program who develop a regrowth have a higher risk of distant metastasis. It is hypothesized that this is related to the tumour biology but it remains unsure if metastasis arise from a regrowth. Overall survival outcomes in patients with and without regrowth did not differ significantly.

# Survival benefit of local treatment in patients suffering from early recurrence of colorectal cancer liver metastases

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Tessa Hellingman, L.M. Buffart, C.J.A. Haasbeek, M.R. Meijerink, M.P. van den Tol, K.S. Versteeg, J.J. van der Vliet, J.J.J. de Vries, J.H.T.M. van Waesberghe, B.M. Zonderhuis, G. Kazemier

**Introduction** Consensus on treatment strategy in patients suffering from early recurrence of colorectal cancer liver metastases (CRLM) is lacking. Patients with early recurrence of CRLM are believed to have an aggressive tumor biology and may therefore benefit from systemic treatment, while local treatment is the only curative option. This study assessed the potential survival benefit of local treatment compared to systemic treatment of patients with early recurrence of CRLM.

**Methods** In this historic observational cohort study, patients with early recurrence of CRLM treated in a tertiary referral hospital between 2009–2019 were retrospectively identified. Early recurrence was defined as new CRLM diagnosed within twelve months after initial local treatment with curative intent. Demographic and tumor characteristics were collected from prospectively maintained electronic patient files. Overall and progression-free survival were assessed from time of recurrence by univariable and multivariable Cox-regression analysis.

**Results** Over a ten-year period, 109 patients qualified for this study. Local treatment significantly improved overall survival in patients with recurrence after 4 months following initial treatment with curative intent, resulting in a median overall survival of 53 months compared to 29 months in patients subjected to systemic treatment (HR = 3.612, [95%CI: 1.692–7.711];  $p < 0.001$ ). Local treatment was considered an independent prognostic factor for overall survival in these patients (aHR = 2.835 [95%CI: 1.219–6.594];  $p = 0.016$ ). No significant difference in overall survival was observed between local and systemic treatment of patients with recurrence within 4 months. Progression-free survival did not differ significantly between local and systemic treatment strategy.

**Conclusion** Local treatment is considered treatment of choice in patients with recurrence of CRLM after 4 months following initial treatment with curative intent. Further research should be conducted to establish optimal treatment strategy in patients suffering from recurrence within 4 months.



# The role of a staging laparoscopy in gastric cancer. A population-based cohort study

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Alexander B.J. Borgstein, M.I. van Berge Henegouwen, W. Lameris, W.J. Eshuis, S.S. Gisbertz

**Introduction** The value of a staging laparoscopy in gastric cancer is unclear. This study investigates the unnecessary laparotomy/laparoscopy rate (detecting metastases or local irresectability during gastrectomy) in patients with and without a staging laparoscopy.

**Methods** This population-based cohort study included all patients with a potentially curable gastric adenocarcinoma, operated between 2011 and 2016, registered in the Dutch Upper GI Cancer audit. Patients with or without a staging laparoscopy were compared. The primary outcome was the unnecessary laparotomy/laparoscopy rate, secondary outcome was (y)pTNM stage.

**Results** 2946 patients who underwent surgery with the intent of gastrectomy were included. 433 of 2946 patients underwent a staging laparoscopy before initiation of treatment. The unnecessary laparotomy/laparoscopy rate was 18.0% in the staging laparoscopy group, compared to 9.3% in the non-laparoscopy group ( $p = <0.001$ ), negative predictive value being 81.9. Main reason for unnecessary laparotomy/laparoscopy was distant metastases (in 54 [12.5%] in the laparoscopy and 151 [6.0%] in the non-laparoscopy patients,  $p < 0.001$ ). cT and cN stage were higher in patients who underwent a staging laparoscopy, as was pT  $\geq$  T3 stage: 226 (67.5%) versus 1220 (53.3%;  $p = <0.001$ ) and pN+ stage: 221 (62.3%) versus 1153 (50.6%;  $p = <0.001$ ).

**Conclusion** The staging laparoscopy group showed a higher cTN and pTN stage, suggesting selection of patients with a higher disease stage for staging laparoscopy. Despite the staging laparoscopy, a higher percentage of UL was found, suggesting a low sensitivity for detecting distant metastases in this patient group.

# Conservative treatment of appendicitis in the Netherlands

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Simone Augustinus, T.H. Geerdink, B.C. Vrouenraets, S.M.M. de Castro

**Introduction** Acute appendicitis is one of the most common surgical diseases worldwide. Current Dutch guidelines advise an appendectomy. Recent international research shows that conservative treatment with antibiotics is a safe and effective alternative for uncomplicated acute appendicitis, with a 35% chance of recurrence in 5 years. The aim of this article is to map the effectivity of conservative treatment of uncomplicated appendicitis in the Netherlands and to compare this to the international literature.

**Methods** Retrospectively we found 54 patients in the OLVG hospital between 2012 and 2017 with an uncomplicated acute appendicitis treated conservatively. In this cohort, we measured the effectivity of the conservative treatment defined as the chance of recurrence and the number of complications that occurred. Additionally, we reviewed parameters that can predict successful conservative treatment.

**Results** Recurrence of appendicitis was seen in 11 (20.4%) of 54 patients, in 8 of these 11 patients an appendectomy was performed. A complication occurred in 2 (3.7%) of 54 patients, either an appendicular abscess or mass. A complication was associated with a prolonged length of stay in the hospital. Namely, 11 days (SD 3) compared to an uncomplicated conservative treatment of 2 days (SD 0). No parameters that can predict successful conservative treatment were found.

**Conclusion** The effectivity of conservative treatment for appendicitis in the Netherlands can be considered similar to international literature. Further research should be performed to identify parameters that can predict successful conservative treatment and to examine the cost-effectivity.

# Long-term outcome after non-operative treatment of simple appendicitis in children: 5 year median follow-up

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Max Knaapen, R. Bakx, J.H. van der Lee, L.W.E. van Heurn, H.A. Heij, R.R. Gorter

**Introduction** Non-operative treatment of simple appendicitis with antibiotics instead of appendectomy has been the subject of many recent research. Because of a relatively low prevalence of complicated appendicitis the paediatric population is of special interest for non-operative treatment. Pilot studies show that appendectomy can be averted in more than 9 out of 10 children. However, this success rate declines over time as a result of recurrent appendicitis. So far there is very limited information on recurrence rates after more than 2 years post-treatment. In this study we present the long-term outcomes of children with simple appendicitis that were treated with antibiotics in a prospective cohort study.

**Methods** Between September 2012 and November 2015 children aged 7–17 years with a radiologically confirmed simple appendicitis were invited to participate in a multicentre prospective cohort study. They were treated with intravenous antibiotics for 48–72 hours, daily blood tests and ultrasound follow-up. Antibiotic treatment was continued orally at home for 5 days. Children with a faecalith on imaging studies were excluded. In October 2019 their rates of complications and subsequent appendectomies will be assessed by telephone follow-up. Rate of subsequent appendectomy will be presented as a Kaplan-Meijer curve. Secondary outcomes are recurrent appendicitis with complications, infertility or bowel obstruction due to abdominal adhesion or other appendicitis related complications.

**Results** We will be presenting the results of 49 children; median (range) of follow-up is 5.3 years (3.9–7.1). Follow-up will be completed on November 1st 2019.

# The vulnerable patient

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## Sessie 4a

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# Good survival and ambulatory state after ruptured aneurysm repair in octogenarians

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Liliane C. Roosendaal, A.M. Wiersema, K.K. Yeung, Ç. Ünlü, R. Metz, W. Wisselink, V. Jongkind

**Introduction** Octogenarians increasingly present themselves with a ruptured aneurysm of the abdominal aorta (rAAA). However, little is known about the postoperative outcomes and ambulatory state after rAAA repair in octogenarians. In order to make an informed shared decision, it is important that information is available about the expected postoperative outcomes.

**Methods** A retrospective study was performed in general and university hospitals in the Netherlands. Patients with an age above 80, operated for a rAAA between January 2013 and October 2018, were included. The primary outcomes were postoperative ambulatory state, 1-year mortality, and comparison in outcome after EVAR or OR.

**Results** 110 patients were included, with a mean age of 84. The 1-year mortality was 50.0%, without a significant difference between endovascular aneurysm repair and open aneurysm repair. 65.2% of the survivors were discharged home, 34.8% went to a nursing home for rehabilitation. After rehabilitation, 82.6% of the surviving patients went back to living in their pre-existing home situation.

**Conclusion** Overall treatment outcomes are positive for octogenarians suffering from rAAA. Half of the octogenarians that undergo treatment are still alive 1 year after rAAA repair. In addition, over 80% of those are living in their own home after rehabilitation.

# Mortality after falls in the Netherlands; data from a retrospective cohort study

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Nadia A.G. Hakkenbrak, W.P. Zuidema, Q.G.H. Rikken, J.A. Halm, T. Dorn, U.J.L. Reijnders, G.F. Giannakopoulos

**Introduction** Annually, approximately 3,600 people die as a result of a fall in the Netherlands, according to the Statistics Netherlands. The aim of this study is to evaluate the demographic parameters, fall characteristics and resulting injury patterns of this group in the region of Amsterdam.

**Methods** All patients deceased as a result of injury due to a fall in the period July 1st 2013 until July 1st 2018 in the region of Amsterdam were included. Data were collected from the database (Formatus) of the Department of Forensic Medicine (Public Health Service Amsterdam).

**Results** During the study period 1,258 patients died after a fall. The mean age was 83 years (0–103 years) and 41% was male. A psychiatric disease was diagnosed or suspected in 44% of the population of which cognitive impairment, including dementia, occurred most of the cases (82%). The majority of the falls happened at home (47%) or at nursing facilities. A minority (1.3%) was work related. Over 81% of the falls were from standing position, 17.6% were not from standing position of which 80.1% regarded falls from stairs, the majority was male. Multitrauma patients accounted for 17.1% of the population. From the remaining 1,040 patients, 61.7% sustained one or more injuries to the pelvis or extremities. Injury of the central nervous system (CNS) was described in 31.3% of the patients. Mortality was in 26.8% of the cases due to CNS injury, 62.3% was due to complications of which clinical deterioration (58.7%) and infection (17.1%) were most common.

**Conclusion** In the region of Amsterdam the majority of deaths due to a fall regards the geriatric population. Fall from standing position and mortality due to complications, mainly clinical deterioration, accounted for the majority of deaths. Intervention to prevent falls and complications need more awareness to reduce mortality.

# Older patients returning to the ED: Root causes and potential preventability

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Babiche E.J.M. Driesen, Hanneke Merten, Cordula Wagner, Prabath W.B. Nanayakkara

**Introduction** Increasing use of Emergency Departments (ED) among older patients is causing a heavy burden on the acute care chain. This complex group of patients frequently returns to the ED resulting in negative consequences for both the patient and healthcare policy. The aim of this study was to provide insight in the root causes and potentially preventability of unplanned return presentations (URP) to the ED within 30 days of the initial presentation in patients aged 70 years and older.

**Methods** A prospective observational study was conducted from February 2018 to November 2018 in an academic hospital in Amsterdam. We included 83 patients, aged 70 years and older, with an URP to the ED within 30 days of the initial ED presentation. Patients, GPs and doctors at the ED were interviewed by trained interviewers and basic administrative data were collected. A root cause analysis was conducted using the PRISMA-method and classification was done according the Eindhoven Classification Model.

**Results** In more than half of the total URPs, the patients returned to the ED within 7 days and in the majority of patients (77%) the URP was related to the initial presentation. The mortality rate was 13% after 6 months follow-up and the deceased patients had a high need and use of care in the last period of their live. 151 Root causes were identified and almost half (49%) of them were disease-related. In none of the cases, there was an overall agreement on the judgement that a URP was potentially preventable between the patient, the doctor at the ED and the GP.

**Conclusion** This study shows that almost half of the URPs of older patients at the ED within 30 days are disease-related. Older patients returning to the ED are in a fragile state, having a higher risk of functional decline or mortality. Healthcare workers should be aware of this and screen the patient and identify their needs and preferences involving the complete acute care chain. This way, in an early stage, it can be advisable to adjust the care plan.

# Algorithm for the treatment of proximal humeral fractures: Solving the unsolved fracture!

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Leanne S. Blaas, T. Alta, C.M. Lameijer, A. van Noort, R.J. Derksen

**Introduction** Proximal humeral fractures (PHF) have an incidence of 3–5%. However, the optimal treatment of the PHF, especially dislocated fractures, remains debated. Therefore, the aim was to develop a treatment algorithm based on expert opinion and a literature review. This algorithm will provide the necessary support to the day-to-day decision making of the treatment of the PHF.

**Methods** In this multicenter study a treatment algorithm was developed. Two orthopaedic surgeons, two trauma surgeons and a researcher PhD-candidate/resident, all specialised in the upper extremity region, used the latest literature and their practical experiences to develop an algorithm for the primary treatment of the PHFs.

**Results** The algorithm includes seven decision-making steps. The first step distinguishes non-dislocated fractures, for which conservative treatment is opted, from dislocated fractures. For dislocated fractures the age of the patients is differentiating; this is the second step. For patients younger than 70 years of age, head-preserving surgery is recommended by either open or closed reduction and internal fixation. An exception is made for patients between 50–60 years of age with a head-split fracture or shoulder dislocation (step 3). For this patient group a hemiarthroplasty is preferred and for patients over 60 years of age, a reverse shoulder arthroplasty (RSA) is advised. The fourth, fifth and sixth step addresses the number of fracture fragments of the PHF, ASA classification and presence of osteoporosis respectively. Combined these three steps determined the treatment options for people >60. A seventh step, surgical or anatomical head fractures, is added to differentiate between closed reduction and fixation, open reduction and fixation and RSA.

**Conclusion** The developed algorithm can be used as an aid for decision-making for the treatment of the PHF. To further substantiate this, a systematic review and a cohort study will be conducted based on this algorithm.



# Validation of the Dutch-Flemish translation of the PROMIS V2.0 Physical Function Upper Extremity item bank in Dutch patients with musculoskeletal disorders of the upper extremity

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Suus G.J. van Bruggen, C.M. Lameijer, C.B. Terwee

**Introduction** Aim of this study was to validate the Dutch-Flemish Patient-Reported Outcomes Measurement Information System Physical Function – Upper Extremity version 2.0 item bank in patients with upper extremity injuries.

**Methods** Cross-sectional study. Structural validity was assessed using Confirmatory Factor Analysis examining unidimensionality. In addition, a bi-factor model was fitted. Internal consistency was assessed by Cronbach's alpha. Construct validity was examined by assessing correlations with legacy instruments Disability of Arm Shoulder and Hand, Patient Reported Wrist Evaluation and Michigan Hand Questionnaire subscale Activities in Daily Life.

**Results** A total of 303 patients (144 female) with mean age of 50 years (standard deviation 18) were included. Confirmatory Factor Analysis showed Comparative Fit Index of 0.94, a Tucker Lewis Index of 0.93, a Root Mean Square Error of Approximation of 0.12 and a Standardized Root Mean Residual of 0.09. Factor loadings were all above 0.70. Bifactor analysis showed an omega-H of 0.79 and Explained Common Variance of 0.67. The correlations with the legacy instruments were as expected or higher than expected.

**Conclusion** The Dutch-Flemish Patient-Reported Outcomes Measurement Information System Physical Function – Upper Extremity version 2.0 item bank measures a unidimensional trait and sufficient construct validity was found.

# A mixed psychiatric and somatic care unit for trauma patients: A ten year experience in an urban level I trauma center in the Netherlands

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Lisette Dekker, Hansje M. Heller, Jessica E. van der Meij, Annelies E.J. Toor,  
Leo M.G. Geeraedts jr.

**Introduction** A Medical-Psychiatric Unit (MPU) is a special ward where staff is trained in caring for patients with psychiatric or behavioural problems that need hospitalisation for physical health problems. It is well-known that these patients are at higher risk of complications, have a longer length of stay resulting in higher costs than patients without psychiatric comorbidity. The objective of this study was to analyse the trauma patient population of the first ten years of existence of the MPU in a level I trauma center.

**Methods** A retrospective analysis was performed in two-year cohorts from 2006 through 2016. All trauma patients admitted to the MPU were compared with the overall trauma patient population in VUmc. Data (psychiatric diagnosis, substance abuse, trauma scores, surgical interventions, complications, mortality) were extracted from individual patient notes and the Regional Trauma Registry.

**Results** 258 patients were identified. 36% of all patients had a history of previous psychiatric admission and 30% had attempted suicide at least once in their lifetime. Substance abuse was the most common psychiatric diagnosis (39%), with psychotic disorder (28%) in second place. The median hospital stay was 21 days. Median MPU length of stay was 10 days (range 1–160). Injuries were self-inflicted in 57%. The most common mechanism of injury was fall from height with intentional jumping in second place. Penetrating injury rate was 24% and 33% had an ISS > 16, compared to 5% and 15% respectively in the overall trauma patient population. The most common injuries were those of the head and neck. Complication rate was 49%.

**Conclusion** Trauma patients that were admitted to the MPU of an urban level I trauma center had serious psychiatric comorbidity as well as high injury severity. Penetrating injury was much more common than in the overall trauma patient population. A high complication rate was noted. The high psychiatric comorbidity and the complicated care warrants combined psychiatric and somatic (nursing) care for this subpopulation of trauma patients. This should be taken into account in the prehospital triage to a trauma center. The institution of a MPU in level I trauma centers is recommended.

# ERAS-APPtimize: Improving patient participation in colorectal surgery by using a patient-centred mobile application

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M. Jansen, Sebastiaan L. van der Storm, A. Rauwerdink, C.I. Buskens, M.P. Schijven

**Introduction** Enhanced Recovery After Surgery (ERAS) is a multidisciplinary and multimodal protocol focusing on perioperative care, which has been successful in improving clinical outcomes for patients undergoing colorectal resection. Adequate compliance to the elements of the ERAS protocol is multifactorial and is associated with improved clinical outcomes. There are still opportunities to improve compliance by actively involving the patient. The main objective of this study is to investigate whether compliance of selected items in the ERAS protocol can be improved through actively involving patients in the ERAS care pathway by using a patient-centred mobile application.

**Methods** A multicentre randomized controlled trial is being conducted. Patients undergoing elective colorectal surgery, who are 18 years or older and in possession of an eligible smartphone, will be included. Patients assigned to the intervention group will install the mobile application to be guided through the ERAS care pathway. Patients in the control group will receive care as usual. Both groups will wear an activity tracker. The primary outcome is overall compliance to selected active elements of the ERAS protocol, as registered by the patient. Secondary outcomes include Patient Reported Outcome Measures (PROMs) such as health-related quality of life, physical activity, and patient satisfaction. Length of hospital stay, number of complications, re-intervention, and readmission rates, will also be assessed. The enrolment of patients started in August 2019. No data has been analysed yet.

**Conclusion** We hypothesize that the compliance to the active elements of ERAS protocol can be improved by providing patients with a patient-centred mobile application, resulting in an increased health-related quality of life, physical activity, and patient satisfaction.

## Medium Care observation after colorectal surgery in high-risk patients

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Carla C.M. Marres, C.J. Buskens, T.M. Mackay, S. van Dieren, R. Sentjens, A.W.H. van de Ven

**Introduction** The aim of this study is to investigate the effect of postoperative 24 hour Medium Care (MC) surveillance after colorectal surgery on severe complications in high-risk patients.

**Methods** The study was designed as a historically controlled interventional study. Patients who underwent colorectal resection between 2015–2018 were included and compared to 704 patients from a historical database (2009–2014). The Groningen Frailty Index (GFI) was scored preoperatively through a questionnaire in patients. Frailty was defined as GFI>4.

**Results** In total, 601 patients underwent colorectal resections. In 491 patients GFI was scored; 79 had GFI>4, of which 67 (85%) were monitored on the MC. The major complication (Clavien-Dindo > 3b) and mortality rate decreased significantly (18.3% vs. 12.5%,  $p = 0.005$  and 5.7% vs. 1.3%,  $p < 0.001$ , respectively). Median length of hospital stay decreased from 8 (IQR 5–14) to 5 days (IQR 3–8) ( $p < 0.001$ ) and the number of emergency ICU admission from 9.5% to 5.8% ( $p < 0.001$ ). Multivariate analyses showed that surgery after 2015 was a strong independent predictor for less major complications (OR:0.59, 95%CI 0.39–0.86).

**Conclusion** A significant decrease in major complications and mortality was observed after introducing a 24 hour observation on the MC in high-risk patients.

# Evaluation of risk factors associated with a prolonged hospital stay and readmissions in patients after a primary bariatric surgery

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Leontien M.G. Nijland, H. Marsman, W.F. van Tets, S.M.M. de Castro, R.N. van Veen

**Introduction** The introduction of enhanced recovery after surgery (ERAS) has resulted in a decrease in length of hospital stay of patients after bariatric surgery. The general length of hospital stay is two days. Some bariatric patients stay longer after an uncomplicated procedure for varying reasons. The aim of the present study is to identify risk factors associated with prolonged hospital stay.

**Methods** A total of 1,669 patients who underwent a primary laparoscopic gastric bypass (70.7%) or sleeve gastrectomy (29.3%) were included. The median length of stay was 2 days (range 2–70 days). One hundred thirty three patients (7.8%) were diagnosed with a postoperative complication and 89 patients were readmitted (5.3%) within 30 days after discharge. Overall, the hospital stay of 348 patients (20.9%) was longer than 2 days. Univariate analysis showed that Depression, ASA III, Sleeve gastrectomy and perioperative and postoperative complication were significantly associated with a prolonged stay. Multivariate analysis showed that Depression and Sleeve gastrectomy were independent risk factors for prolonged hospital stay. Univariate analysis of factors associated with readmission were Depression, perioperative and postoperative complications. Multivariate analysis for readmission showed that only presence of a postoperative complication was an independent risk factor.

**Conclusion** Depression and Sleeve gastrectomy seem to be important independent risk factors for prolonged hospital stay. More research is needed to address the underlying causes of these factors to be able to improve perioperative care and implement new strategies to further reduce hospital stay.

# Centralisation & interhospital variation

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# The effect of a multidisciplinary outpatient team approach on outcomes in diabetic foot care: A single center study

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Eline Huizing, Michiel A. Schreve, Willemijn Kortmann, Jan P.J. Bakker, Jean-Paul P.M. de Vries, Çağdaş Ünlü

**Introduction** Recent studies showed no reduction in major amputation rates after introduction of a multidisciplinary team (MDT) approach for the treatment of diabetic foot ulcer. The efficacy of MDTs in the current standard of care is being questioned. This retrospective single-center study evaluated the efficacy of an outpatient MDT approach on limb salvage and ulcer healing in treating diabetic foot ulcers.

**Methods** Patients with a diabetic foot ulcer treated before (2015) and after (2017) implementation of an MDT in a single center were compared. The MDT met weekly and consisted of a vascular surgeon, physiatrist, internist, shoe technician, wound care nurse, nurse practitioner, cast technician, and podiatrist. The primary outcome was limb salvage at 1 year. Secondary outcomes were ulcer healing, amputation-free survival, freedom from any amputation, and overall survival. Multivariable Cox regression models were used to assess predictors for major amputation.

**Results** A vascular surgeon treated 104 patients with 148 ulcers in 2015, and the multidisciplinary team treated 133 patients with 188 ulcers in 2017. Limb salvage (90.9% vs. 95.5%,  $p = 0.050$ ), freedom from any amputation (56.5% vs. 78.0%,  $p < 0.001$ ), and ulcer healing (48.3% vs. 69.2%,  $p < 0.001$ ) were significantly lower in the non-MDT group than in the MDT group. Amputation-free survival and overall survival did not differ significantly between the groups. Predictors for major amputation were University of Texas Wound Classification 3D (hazard ratio, 2.8; 95% confidence interval, 1.17–6.45) and being treated in the non-MDT group (hazard ratio, 3.7; 95% confidence interval, 1.25–11.08).

**Conclusion** This retrospective study found an MDT dedicated to diabetic foot care was highly effective in increasing limb salvage and ulcer healing. We advise that such an MDT is an integrated part of the patient's chain-based care.

# Optimizing oncological referrals in the north west region of the Netherlands

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Merijn E. de Swart, B.M. Zonderhuis, T. Hellingman, G. Kazemier

**Introduction** Centralization of specialized care has led to an improvement of outcome for oncological patients. Due to centralization, patients are referred to specialized hospitals. Health information exchange (HIE) between hospitals takes place to share acquired clinical information and diagnostics in order to determine treatment strategy. Despite digital innovations, HIE takes mainly place by fax and CD-ROMs in the Netherlands. This creates a potential loss of patient information, due to manual selection. The aim of this study is to analyze the available patient information during MDT meetings of oncological patients referred to a tertiary care center in order to improve care.

**Methods** A prospective cohort study was performed in Amsterdam UMC, location VUmc. All eleven oncological MDT meetings were attended for six weeks. All patients who were referred from other hospitals were included. Primary outcome was completeness of patient reports for referral. Completeness was defined as presence of a letter of referral, imaging, imaging reports, laboratory results and pathology reports. Secondary outcome was repeat diagnostics. An independent MD scored outcomes and consulted an expert MD in case of ambiguity.

**Results** During 84 MDT meetings, 169 out of 843 discussed patients (20.0%) were included for analysis. Data collection and discussion with a second MD has completed 3/11 MDT meetings (24 patients). In this subgroup, complete clinical information was provided in 16.6% (4/24). In 60.9% (14/23), diagnostic imaging was shared completely. Imaging reports were shared in 90.9% (20/22). Laboratory results were shared in 70.8% (17/24). Complete pathology reports were shared in 43.8% (7/16). In 25.0% (6/24), repeat diagnostics was conducted.

**Conclusion** For the majority of tertiary referrals discussed in oncological MDT meetings, patient data were shared incompletely. This leads to repeat diagnostics. Innovations in data exchange could improve availability of patient information.



# Impact of second opinions in breast cancer diagnostics and treatment: A retrospective analysis

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Erik Heeg, Y.A. Civil, M.A. Hillen, C.H. Smorenburg, L.A.E. Woerdeman, E.J. Groen, H.A.O. Winter-Warnars, M.T.F.D. Vrancken Peeters

**Introduction** Breast cancer care is becoming increasingly complex and patients with breast cancer are increasingly aware of the different treatment options resulting in requests for second opinions (SOs). The current study investigates the impact of breast cancer SOs on final diagnosis and treatment in the Netherlands Cancer Institute (NCI) using a newly designed Breast Cancer Second Opinion (BCSO) classification system.

**Methods** Patients who visited the NCI for an SO between October 2015 and September 2016 were included. Demographics, diagnostics, and treatment proposals were compared between first and SO. Discrepancy was categorized using our BCSO-classification system, categorizing SOs into 1) noncomparable, 2) identical, 3) minor and 4) major discrepancy. The category 'minor' means the discrepancy had most likely little impact on the treatment plan and prognosis. A discrepancy is called major when the impact was clinically relevant.

**Results** The majority of SOs ( $n = 591$ ) were patient-initiated (90.7%). 121 patients underwent treatment prior to their SO, leaving 470 patients for assessment of discrepancies according to our BCSO-classification system. More than 45% of these SOs resulted in at least one discrepancy with comparable rates in physician-initiated SOs as in patient-initiated SOs (42.5% versus 45.6%,  $p = 0.708$ ). Significantly more discrepancies were observed in patients with additional imaging (51.3% vs. 37.2%,  $p = 0.002$ ) and biopsies (53.7% versus 40.3%,  $p = 0.005$ ). Almost 60% of all discrepancies were categorized as major (neoadjuvant systemic treatment (NST) instead of primary surgery, breast-conserving surgery (BCS) instead of mastectomy and proposing postmastectomy immediate breast reconstruction (IBR)).

**Conclusion** Our findings show substantial differences in diagnostic and treatment options in breast cancer patients visiting the NCI for an SO, thereby emphasizing more consensus for the indication of these treatment modalities. The new BSO-classification can be used in future studies to assess the clinical impact of SOs in a reproducible way.

# Centralization of lung cancer surgery in the Netherlands: Differences in care and survival of patients with stage I non-small cell lung cancer between hospitals with and without in-house lung cancer surgery

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Julianne C. de Ruiter, David J. Heineman, Adrianus J. de Langen, Max Dahele, Ronald A.M. Damhuis, Koen J. Hartemink

**Introduction** We hypothesized that centralization of lung cancer surgery might lead to treatment variation between hospitals with and without in-house lung cancer surgery and to different survival in hospitals without in-house surgery for patients with stage I non-small cell lung cancer (NSCLC).

**Methods** Information about patients with clinical stage I NSCLC diagnosed between 2012 and 2016 and treated with radiotherapy or surgery was retrieved from the Netherlands Cancer Registry. Parameters predictive of treatment choice were assessed by tabulations and multivariable analysis. Variation in five-year overall between in hospitals with and without lung cancer surgery was tested for significance by logrank testing.

**Results** Between 2012 and 2016, 9630 patients were treated with a resection ( $n = 5488$ ) or radiotherapy ( $n = 4142$ ) for stage I NSCLC. In Dutch hospitals with and without in-house lung cancer surgery, 59% and 51% were treated by surgical resection, respectively (OR 1.25; 95%CI 1.01–1.54;  $p = 0.04$ ). In hospitals with in-house lung cancer surgery, between 41 and 75% of patients were operated on and in hospitals without lung cancer surgery, the proportion of operated patients varied between 18 and 71%. Postoperatively, 23% of tumors were pathologically upstaged to stage II or a higher stage. Five-year overall survival (OS, for curative-intent surgery and radiotherapy combined) did not differ between hospitals with and without in-house lung cancer surgery (56% and 57%, respectively;  $p = 0.26$ ).

**Conclusion** Centralization of lung cancer surgery may be associated with differences in patterns of care. In this population-based analysis, absence of lung surgery facilities in hospitals influenced treatment choice, but did not lead to worse OS. The relationship between centralization, treatment selection, and OS merits further investigation.

# Completeness of lymph node dissection in patients undergoing minimally invasive or open surgery for non-small cell lung cancer: A nationwide study

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Lisa van der Woude, Michel W.J.M. Wouters, David J. Heineman, Ad F.T.M. Verhagen, Koen J. Hartemink

**Introduction** In patients with NSCLC, lymph node metastases are an important prognostic factor. Despite an accurate pre-operative work up, for optimal staging an intrapulmonary and mediastinal lymph node dissection (LND) as part of the operation is mandatory. The aim of this study is to assess the completeness of LND in patients undergoing an intended curative resection for NSCLC in the Netherlands and to compare performance between open surgery and minimally invasive surgery (MIS).

**Methods** In this retrospective national cohort study, the intraoperative LND was evaluated in 7461 patients who had undergone a lobectomy for clinically staged N0-1 NSCLC between 2013 and 2018. The LND was considered complete, when at least three mediastinal (N2) lymph node stations, always including station 7, were sampled or dissected, in addition to the intrapulmonary (N1) lymph nodes from station 10 and 11. A comparison was made between open surgery and MIS.

**Results** Of 5154 patients, who had MIS, a sufficient intrapulmonary LND was performed in 47.9% and a sufficient mediastinal LND in 58.6%. A complete LND of both N1 and N2 stations was performed in 31.6%. For 2307 patients who had an open resection, these numbers were 45.0%, 59.0%, and 30.6%, respectively. The overall between-hospital variation in a complete LND ranged between 0 and 72.5%.

**Conclusion** A complete LND of both intrapulmonary and mediastinal lymph nodes, in concordance with international guidelines, is performed only in a minority of patients in the Netherlands, with substantial between-hospital variation. No differences were seen between open surgery and MIS.

# Nationwide practice and outcomes of endoscopic biliary drainage in resectable pancreatic head cancer

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**Introduction** International guidelines advise self-expanding metal stent (SEMS) placement over plastic stent placement for preoperative endoscopic biliary drainage (EBD) in resectable pancreatic head or periampullary cancer. This study assessed the relation between SEMS, EBD-related complications, and postoperative outcomes in a nationwide, population-based cohort.

**Methods** All patients diagnosed with pancreatic head or periampullary cancer who underwent EBD before pancreaticoduodenectomy between January 2017 and December 2018 were included from the Dutch Pancreatic Cancer Audit, a nationwide mandatory audit including all 17 Dutch pancreatic centers. Multivariable logistic and linear regression models were performed.

**Results** Of 1056 patients undergoing pancreaticoduodenectomy, 575 (62.0%) underwent EBD of whom 246 (42.8%) with a SEMS. The use of SEMS varied from 0 to 77.1% between pancreatic centers ( $p < 0.001$ ). The majority of plastic stents (69.6%) was placed before the MDT of a pancreatic center. EBD-related complications (17.9% vs. 19.5%,  $p = 0.607$ ) including pancreatitis (8.9% vs. 7.6%,  $p = 0.387$ ) were comparable between SEMS and plastic stents, respectively. EBD-related cholangitis however occurred in 4.1% vs. 9.7% ( $p = 0.043$ ) of patients, respectively. Major postoperative complications did not differ (23.6% vs. 27.4%,  $p = 0.316$ ). Mean hospital stay was 14.0 days vs. 17.4 days ( $p = 0.005$ ). The proportion of patients with postoperative pancreatic fistula was lower in patients with a SEMS compared to plastic stents (9.8% vs. 18.5% respectively,  $p = 0.004$ ), but this difference disappeared in multivariable analysis. In multivariable analyses, SEMS placement was associated with lower odds of cholangitis (OR 0.36 95%CI 0.15–0.88,  $p = 0.026$ ) and a shorter postoperative hospital stay (B -2.75 days, 95%CI -4.94–-0.56,  $p = 0.014$ ).

**Conclusion** In this population-based study, SEMS placement was associated with a lower risk of cholangitis and shorter postoperative hospital stay without an increased risk of pancreatitis, and should therefore be preferred. A nationwide implementation strategy seems indicated.

# Somatostatin analogues for the prevention of pancreatic fistula after pancreaticoduodenectomy: A retrospective, nationwide analysis of the Dutch Pancreatic Cancer Audit

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Boukje T. Bootsma, Victor D. Plat, Daitlin E. Huisman, Barbara M. Zonderhuis, Geert Kazemier, Freek Daams – on behalf of the Dutch Pancreatic Cancer Group

**Introduction** A postoperative pancreatic fistula (POPF) is a severe complication following pancreaticoduodenectomy for patients with malignant tumors of the pancreatic head or periampullary region. Somatostatin analogues (SA) are currently in use to prevent development of POPF. Aim of this study was to evaluate the effect of the different SA protocols in the Netherlands on the incidence of POPF, by using nationwide data of the Dutch Pancreatic Cancer Audit (DPCA).

**Methods** DPCA data was queried for patients undergoing elective pancreaticoduodenectomy for pancreatic cancer between 2013 and 2017. Patients were divided into four groups: octreotide, lanreotide, pasireotide protocol or no protocol, based on the SA protocol of use in the operating hospital. The updated alternative Fistula Risk Score (ua-FRS) was used to analyse the incidence of POPF across various risk scenarios.

**Results** The final analysis included 1089 patients. 401 patients were treated without SA protocol, 326 according to octreotide protocol, 222 according to lanreotide protocol and 140 patients according to pasireotide protocol. A clinically relevant POPF occurred more often when pasireotide (16.4%) or octreotide (14.4%) was used, as patients treated according to lanreotide protocol (6.8%) or no protocol (12.0%) had lower incidences of POPF ( $p = 0.019$ ). Regression analysis, controlling for ua-FRS, demonstrated that administration of lanreotide decreases the risk of severe POPF development (OR 0.46, 95%CI 0.25–0.85).

**Conclusion** This retrospective cohort study evaluated POPF development across various risk scenarios in the Netherlands. Perioperative use of lanreotide appears to be beneficial in preventing POPF.

# The Snapshot Strengileus: A prospective nationwide audit of the management of adhesive small bowel obstruction

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Merel Pape, F.C. den Boer

Nationwide research led by: P. Krielen, M. Stommel, P. Tanis, H. van Goor, R. ten Broek

**Introduction** Adhesion formation after surgical operations in the abdominal and pelvic region is the most common cause for long-term postoperative complications, such as adhesive small bowel obstruction (ASBO). These adhesions are often causing abdominal pain, distention, vomiting and obstipation and frequently result in admission to the hospital. Sometimes there is a need for adhesiolysis performed during an emergency laparotomy. Remarkably, little is known about the optimal management of ASBO, despite the huge morbidity. Guidelines are not universally implemented and often based on expert opinions rather than evidence-based medicine. In this nationwide audit in the Netherlands, we will study the differences in the management and outcome of patients admitted with ASBO and define new research questions to improve the diagnosis and treatment.

**Methods** A nationwide prospective cohort will be observed over a period of six months in 2019, from May 1st to November 1st, in as many as hospitals in the Netherlands. The goal is to include at least 500 patients with a clinical suspicion of ASBO. During participation, a digital snapshot questionnaire for each patient will be sent to provide the research team with characteristics and patient data about symptoms, diagnosis, imaging, risk factors and treatment. The database will be finished in Castor. The analysis will include regression analysis for variation in clinical management and outcome of ASBO treatment. The METC of the Radboud UMC has given approval for this study. This study is not WMO-compulsory.

**Results** During writing of this abstract, patients are still being included. Thus far, a total of 130 patients has been included, of which ten in the Zaans Medisch Centrum.

**Conclusion** The background hypotheses on adhesive small bowel obstruction and the current literature on this topic will be discussed. We will present the audit methodology and the most important outcome measures.

# Wound healing

## Sessie 4c

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## Towards better outcomes in necrotizing soft tissue infections

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Jaco Suijker, Anouk Pijpe, Paul van Zuijlen, Annebeth de Vries

**Introduction** Necrotizing Soft-Tissue Infections (NSTI) are severe bacterial infections with a high morbidity and mortality. Intensive care and extensive operations are often needed. Outcomes of disease and care may depend on multiple factors, like age, comorbidities, type of NSTI, time to diagnosis, time to surgery and volume of the centre. NSTI have a long-term impact resulting in patients reporting lower (physical) Quality of Life. In order to improve NSTI care and outcomes more knowledge on various relevant disease and treatment aspects is needed.

**Methods** All patients diagnosed with NSTI between the 1st of January 2013 and 31st of December 2017 will be identified in all participating hospitals in three provinces (NH, ZH, GR). All relevant patient, disease and treatment characteristics as well as data on outcome (morbidity, complications, mortality) will be collected. Data collection was started in the three dedicated DutchBurn Centres and will be followed by the other hospitals.

**Results** In the three Dutch Burn Centres 67 patients have been identified. Data are currently being extracted and results will be presented at the conference. Of the total of 33 hospitals located in the three provinces, 11 have been contacted including the five academic medical centres and all agreed to participate. In nine of them local approval has been obtained. We anticipate to include at least 300 patients.

**Conclusion** We encourage participation of all centres in order to establish a complete, detailed and representative retrospective cohort on NSTI. This will reveal starting points for improving NSTI care and outcomes.



# A systematic review and meta-analysis of closed incision negative pressure wound therapy in the groin after arterial surgery: Need for reporting standards

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Julia Peltenburg, L. Schoonmade, I. Thomassen, A. Hoksbergen, M. Truijers

**Introduction** Post-operative wound complications are common after arterial procedures involving the groin. Negative pressure wound therapy (NPWT) on closed surgical incisions is suggested to reduce wound complications. We systematically reviewed current literature and conducted a meta-analysis to study the effect of NPWT on closed groin incisions following arterial surgery.

**Methods** The meta-analysis was performed in accordance with the PRISMA guidelines. The databases of PubMed, Embase and the Cochrane Library were used to identify relevant studies. Study quality, risk of bias and data extraction were performed by two independent researchers. The primary outcome was surgical site infection. Secondary outcomes were clinically relevant parameters including readmission and reoperation rates, length of hospital stay and cost-effectiveness.

**Results** The initial search identified 1046 records, after screening and quality assessment six randomized controlled studies were identified and used for meta-analysis. Significantly fewer wound infections were found in the NPWT group compared to the control group (11.8% versus 29.6%). The number needed to treat to prevent one severe infection involving the arterial reconstruction is 37. Reporting of the studies on the impact on specific risk factors and secondary outcome measures including re-admission and reoperation rates were too heterogeneous or poorly reported to be included in the analysis.

**Conclusion** NPWT significantly reduces the incidence of surgical site infections. The effect of NPWT on the prevention of severe infections involving the arterial reconstruction seems limited. The clinical relevance remains unclear, as data secondary outcomes is limited. Due to heterogeneous reporting on risk factors for the development of wound complications, the meta-analysis did not allow the identification of patients that might benefit most from NPWT. The use of reporting standards on outcome and confounding risk factors could improve the quality of future systematic reviews and increase the level of evidence in favor or against the routine use of NPWT following vascular surgery.

# A systematic review and meta-analysis of hyperbaric oxygen therapy for diabetic foot ulcers with arterial insufficiency

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Robin Brouwer, Rutger Laliu, Rigo Hoencamp, Rob van Hulst, Dirk Ubbink

**Introduction** Diabetic foot ulcers (DFU) are frequently associated with peripheral arterial occlusive disease (PAOD) and may ultimately lead to amputations of the lower extremity. Adjuvant hyperbaric oxygen treatment (HBOT) might foster better wound healing and lower amputation rates in patients with DFU and PAOD. A systematic review was conducted to assess the effects of HBOT as an adjunctive therapy to standard treatment for patients with DFUs with PAOD.

**Methods** Systematic review using the MEDLINE, EMBASE and Cochrane CENTRAL databases (from inception to October 2018). All original, comparative studies on the effect of HBOT on DFUs with PAOD were eligible. The primary outcome measures were amputation rate, amputation-free survival, complete ulcer healing and mortality.

**Results** Eleven studies, totaling 729 patients, were included for analysis, including seven randomized clinical trials, two controlled clinical trials, and two retrospective cohorts. Four were used for quantitative synthesis. Meta-analysis showed a significantly fewer major amputations in the HBOT group (10.7% vs. 26.0%; RD = -15%, 95%CI -25 to -6,  $p = 0.002$ , NNT = 7, 95%CI 4–20). No difference was found for minor amputations (RD = 8%, -13 to 30,  $p = 0.46$ ). Three studies reporting on complete wound healing showed contrasting results. No significant difference was found for mortality or amputation-free survival.

**Conclusion** Current evidence shows that adjuvant HBOT improves major amputation rate, but not wound healing, in patients with DFUs and PAOD. Given the wide range of patients included in the trials, better patient selection may help define which patients with DFUs and PAOD benefit most from HBOT as standard adjunctive treatment.

# Prescribing antiplatelet and anticoagulation therapy after endovascular and surgical interventions for lower extremity peripheral arterial disease: Results of a survey

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Jetty Ipema, A.R.T. Brand, G.J. de Borst, J.P.P.M. de Vries, Ç. Ünlü

**Introduction** Prescribing antiplatelet therapy after endovascular and surgical interventions for peripheral arterial disease (PAD) of the lower limb is common practice. However, local and international guidelines differ. This paper shows the results of a survey about antiplatelet and anticoagulation prescription after lower extremity endovascular and surgical interventions by surgeons and interventional radiologists in The Netherlands.

**Methods** 307 surgeons or surgical residents and 328 interventional radiologists or radiologic residents from The Netherlands were asked to participate. Prescribing patterns of antiplatelet and anticoagulation therapy for percutaneous and surgical procedures of the whole iliac, femoral, popliteal and below the knee tract were asked. Choices of medications were: aspirin, clopidogrel, vitamin-K antagonists, direct oral anticoagulants and combinations of the aforementioned. Duration of therapy and the use of tests for antiplatelet effectiveness were also asked.

**Results** 45% of the vascular surgeons completed the survey. Mean practicing duration was 12.7 years ( $\pm 8.6$ ). Clopidogrel was the most prescribed drug after iliac percutaneous transluminal angioplasty (PTA) (77%), femoral PTA (77%), femoral PTA with drug coated balloon (66%), and femoropopliteal (80%) and femorocrural (51%) prosthetic bypasses. Dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel was most often prescribed after femoral PTA with stent (56%) and crural PTAs (55% without stent, 73% with stent), but clopidogrel monotherapy was also prescribed often. DAPT duration varied with the majority preferring 12 weeks. Vitamin-K antagonists were most often prescribed after venous bypasses ( $\geq 80\%$ ). Only 7% of the interventional radiologists completed the survey. Many answered that they only advise in medication prescription.

**Conclusion** Prescribing patterns of antiplatelet and anticoagulation use after certain endovascular and surgical interventions of the lower limb in PAD patients vary among Dutch surgeons. Randomized trials are needed to fill in the gap in knowledge of what is the best medical treatment and optimal duration to improve patency and limb salvage.

# Neurodevelopment of patients with gastrointestinal congenital malformations: A systematic review and meta-analysis

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Daniëlle Roorda, M. Königs, L.D. Eeftinck Schattenkerk, A.F.W. van der Steeg, L.W.E. van Heurn, J. Oosterlaan

**Introduction** Children with gastrointestinal congenital malformations may be at risk of neurodevelopmental impairment due to challenges to the developing brain, including perioperative hemodynamic changes, exposure to anesthetics and post-operative immuno-inflammatory influences. This study aimed to summarize neurodevelopmental outcomes of patients with gastrointestinal congenital malformations, hypothesizing their neurodevelopment may be impaired compared to normative populations.

**Methods** Pubmed, Embase and Web of Science were searched for peer-reviewed articles published until October 2018. Out of the 4578 unique articles that were identified, 40 studies met selection criteria and were included. Standardized mean differences (Cohen's d) between cognitive, motor and language outcomes of patients with gastrointestinal congenital malformations and normative populations were aggregated across studies using random-effects meta-analysis. The value of (clinical) predictors was studied using meta-regression and diagnostic subgroups were compared.

**Results** The 40 included studies represented a total of 1,839 children. Patients with gastrointestinal congenital malformations had small-sized overall neurodevelopmental impairment ( $d = -0.421$ ,  $p < 0.001$ ; 95%CI  $-0.525$  to  $-0.316$ ), which was explained by small-sized cognitive impairment ( $d = -0.393$ ,  $p < 0.001$ ; 95%CI  $-0.506$  to  $-0.281$ ), small to medium-sized motor impairment ( $d = -0.483$ ,  $p < 0.001$ ; 95%CI  $-0.628$  to  $-0.338$ ) and medium-sized language impairment ( $d = -0.597$ ,  $p < 0.001$ ; 95%CI  $-0.893$  to  $-0.302$ ). Effects were not moderated by gestational age or birthweight. Cognitive impairment decreased with higher age ( $r = 0.004$ ;  $p = 0.03$ ). Our findings were limited by the impossibility to assess the attributive risk of other potential important etiological factors of neurodevelopmental impairment.

**Conclusion** This study shows that children with gastrointestinal congenital malformations exhibit small to medium-sized impairments in neurodevelopmental outcomes. This highlights the need for routine screening of patients with gastrointestinal congenital malformations in follow-up.

# CRP as a predictor for anastomotic leakage; beware of a decline in C-Reactive Protein for anastomotic leakage after colonic surgery

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Yongbo An, V. Bellato, C.C.M. Marres, A.W.H van de Ven

**Introduction** Over the past few years the predictive value of C-reactive Protein (CRP) for early detection of anastomotic leakage in colorectal surgery is extensively investigated, but it remains an area of debate. The aim of this study was to investigate the predictive value of CRP for anastomotic leakage after colorectal surgery and the relation with patient characteristics.

**Methods** All patient files of patients who underwent a colorectal oncological resection between 2009 and 2018 were reviewed. All patients with a primary anastomoses were identified. Patient characteristics, clinical outcome (including all available CRP measurements) were collected. In our hospital CRP was routinely measured on day two and day four and compared. From 2015 to 2018 CRP was routinely measured on day 3.

**Results** 1230 patients were identified who underwent colorectal surgery with primary anastomoses. We found no significant difference in CRP levels in patients with a preoperative infectious cause or patients with higher BMI. Overall leakage percentage was 5.5% (n = 68). Out of these patients, difference between two measuring points in the first four days postoperatively was obtainable for 35 patients. We found a decline in CRP in 19 out of these 35 patients (54%). There was a significant difference between days until re-intervention between the groups with a decline in CRP (mean 4.9, median 5) and a rise in CRP (mean 7.7, median 7). ( $p = <.000$ ). Basing on our data, we set the PCR threshold at 200. CRP levels were then associated with a diagnosis of anastomotic leakage (O.R. = 1.0008;  $p = <0.001$ ). The CRP cutoff point 200 showed a sensitivity of 64% and a Specificity of 75% with an Area under ROC curve of 0.737 and a Youden Index (j) of 0.40.

**Conclusion** Elevated CRP in combination with clinical symptoms is a usable predictor for anastomotic leakage and CT should be performed. A decline of CRP should not be reassuring.

# Anastomotic leakage after cytoreductive surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

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Tim M. Feenstra, C.J. Verberne, A.G.J. Aalbers

**Introduction** Anastomotic leakage (AL) after colorectal surgery is well-researched, yet the effect of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) after Cytoreductive Surgery (CRS) on anastomotic integrity is unclear. Assessment of risk factors of AL in these patients may assist surgeons during pre- and intraoperative decision making.

**Methods** A review of a prospective database of patients undergoing CRS-HIPEC for colorectal peritoneal metastasis was conducted in the Netherlands Cancer Institute between January 1, 2010 and December 31, 2018. Outcomes were anastomotic leakage, associated morbidity, and its effect on overall survival (OS) and disease-free survival (DFS).

**Results** Anastomotic leakage was observed in 17 of 165 (10.3%) patients and 17 of 237 (7.2%) anastomoses. Gastrointestinal and ileo-ileal anastomoses leaked once in 92 anastomoses (1.1%), while ileocolic, colo-colic, and colorectal anastomoses leaked in 10.3%, 20%, and 9.3% respectively. There were no statistically significant associations between anastomotic leakage and patient factors, tumor characteristics, and previous therapies. Risk of anastomotic leakage did not accumulate when more anastomoses were created, and decreased from 10.3% to 5.8% in patient who received diverting stomata. There was no association between anastomotic leakage and DFS and OS in this study cohort.

**Conclusion** Risk of anastomotic leakage in CRS-HIPEC is comparable to regular colorectal surgery. Colon anastomoses lead to anastomotic leakage more often than gastrointestinal anastomoses, yet additional anastomoses do not result in cumulative risk of leakage. Diverting stomata are protective for anastomotic leakage, but are only reversed in half of the cases due to disease progression. We therefore advocate that it is safe to create multiple anastomoses, if necessary combined with a diverting stoma, in patients undergoing CRS-HIPEC.

# LekCheck: The first prospective study to identify perioperative modifiable risk factors for anastomotic leak in colorectal surgery

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Daitlin E. Huisman, M. Reudink, S.J. van Rooijen, B.T. Bootsma, W. Bleeker, C. Feo, A. Jongen, L.P.S. Stassen, N. Komen, H.M. Kroon, T. Sammour, E. Lagae, K.A. Talsma, J.A. Wegdam, T.S. de Vries Reilingh, B. van Wely, E. Sonneveld, S.C. Veltkamp, E.G.G. Verdaasdonk, R.M.H. Roumen, G.D. Slooter, F. Daams

**Introduction** Colorectal anastomotic leakage (CAL) remains a severe complication following surgery. To improve this outcome, there is increased awareness we should focus on perioperative modifiable risk factors. Both surgical and anesthesiological intraoperative risk factors may contribute to leakage and enhanced recovery after colorectal surgery.

**Methods** A consecutive series of adult patients undergoing elective colorectal surgery with primary anastomosis were enrolled from January 2016 to December 2018. 14 hospitals (Europe and Australia) collected perioperative data by carrying out the LekCheck, an additional time-out procedure to check perioperative values on 1) general condition 2) local perfusion and oxygenation, 3) surgery related factors. Univariate and multivariate logistic regression analysis were performed to identify associations between perioperative potential modifiable factors and leakage.

**Results** A total of 1562 patients were included in this study. CAL was reported in 132 (8.5%) of the patients. Anaemia (OR 5.21,  $p < 0.001$ ), contamination of the operative field (OR 3.14,  $p < 0.001$ ), hyperglycaemia (OR 3.05,  $p = 0.002$ ), inotropic support (OR 1.78,  $p = 0.010$ ), inadequate administration of preoperative antibiotic prophylaxis (OR 1.57,  $p = 0.047$ ) and administration of epidural analgesia were all associated with CAL (OR, 1.75,  $p = 0.014$ ).

**Conclusion** This study identified six potential modifiable risk factors for CAL. This need and potential for improvement urge us to develop multimodal and multidisciplinary strategies that strives optimal perioperative values.

# Gluteal turnover flap for closure of the perineal wound after abdominoperineal resection for rectal cancer, BIOPEX 2 study

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Sarah Sharabiany, R. Hompes, W.A. Bemelman, P.J. Tanis, G.D. Musters

**Introduction** In the Netherlands, approximately 600 patients undergo abdominoperineal resection (APR) for rectal cancer per year. Morbidity after APR is substantial and mainly consists of perineal wound problems. In a previous randomised study we investigated whether pelvic floor reconstruction with a biological mesh improves primary perineal wound healing compared to primary closure of the perineum after APR (BIOPEX study). The percentage of uncomplicated perineal wound healing was comparable: 63% (30/48) after using a biological mesh and 66% (33/50) after primary closure ( $p = 0.7177$ ). The hypothesis for the negative primary outcome is the fact that a biological mesh does not fill the soft tissue defect. Filling the perineal defect after an APR should preferably meet the following requirements: little extra surgery time, no necessary deployment of a plastic surgeon, no extra morbidity or scar of the donor site, and no impediment to mobilise and restore the flap postoperatively. A gluteal turnover flap seems to meet these requirements.

**Methods** 14 hospitals will participate in this multicenter trial, four of which are academic centers. A total of 160 patients will be included. Patients undergoing APR for primary or recurrent rectal carcinoma, with or without prior radiotherapy, are candidates for the study. The included patients will be randomised between standard care with primary perineum closure, and perineal closure with the gluteal turnover flap. The primary outcome measure is the percentage of uncomplicated perineal wound healing.

**Results** The percentage of patients with uncomplicated wound healing is expected to rise from 65% to 85% with the gluteal turnover flap.

**Conclusion** A multicenter trial to investigate whether a gluteal turnover flap for closure of the perineal wound improves primary perineal wound healing after APR for rectal cancer.





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# Best abstract session

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79	Simone Rottier	Systemic neutrophil activation products as biomarker in patients with acute abdominal pain, a hypothesis forming study
80	Dennis Schaap	The role of peroperative CEA-specific fluorescence imaging during CRS-HIPEC surgery in peritoneally metastasized colorectal cancer
81	Anna Geraedts	Observing a decade of yearly standardised surveillance in EVAR-patients with ultrasound or CT-scan: Preliminary analysis within 5 centres
82	Kelly Kwa	Enzymatic debridement is selectively effective in burn wounds depending on the thermal damage of the collagen: An ex vivo burn wound experiment

# Systemic neutrophil activation products as biomarker in patients with acute abdominal pain, a hypothesis forming study

Simone J. Rottier, L.C. Dreuning, J.J. Vrolijk, G. van Mierlo, S.T. van Dijk, H.J. Doodeman, J. van Pelt, A.A.W. van Geloven, W.H. Schreurs, S.S. Zeerleder, M.A. Boermeester

**Introduction** Acute abdominal pain remains a diagnostic challenge, particularly when differentiating between uncomplicated and complicated causes. Currently used biomarkers such as C-reactive protein (CRP) are usually elevated during inflammation but are of little diagnostic value. The aim of this study was to assess the potential of neutrophil activation products as (early) biomarkers in patients with acute abdominal pain.

**Methods** Patient data and samples from a prospective case-control study including patients with acute abdominal pain at the emergency department were used. Neutrophil activation products were compared to those of healthy volunteers. The diagnostic accuracy for uncomplicated and complicated cases of abdominal infection was compared to currently used biomarkers such as CRP and WBC.

**Results** A total of 145 patients with acute abdominal pain were included and compared to 19 healthy volunteers. Patients with abdominal pain had significantly higher concentrations of HNE-A1ATc ( $p < 0.001$ ) and nucleosome levels ( $p = 0.002$ ) (median [IQR]: 58.3 [39.75–96.45] ng/ml and 22.8 [14.25–37.03] u/ml) when compared to healthy volunteers (25.0 [19.00–35.00] ng/ml and 15.0 [7.10–20.00] u/ml, respectively). Both biomarkers were able to differentiate between uncomplicated and complicated abdominal infections, HNE-A1ATc (median [IQR]) 53.5 [43.4–87.6] versus 99.9 [51.7–199.7] ( $p = 0.002$ ) and nucleosome levels 20.5 [12.8–30.8] versus 37.2 [21.7–61.1] ( $p < 0.001$ ), respectively. These markers had a slightly higher specificity when compared to CRP and white blood cell count (WBC), being 80.8% for CRP and 51.9% for WBC (leukocytes) versus 88.7% for nucleosome levels, 86.8% for HNE-A1ATc. Overall nucleosome levels had the highest accuracy.

**Conclusion** This study showed that neutrophil activation products are elevated in patients with acute abdominal pain. Increased concentrations of these markers seem to be associated with the severity of the abdominal infection and yielded the highest specificity and accuracy when compared to currently used biomarkers. Results are promising, however, future studies are needed to determine the true potential of these markers.

# The role of peroperative CEA-specific fluorescence imaging during CRS-HIPEC surgery in peritoneally metastasized colorectal cancer

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Dennis P. Schaap, Kim S. de Valk, Marion M. Deken, Ruben P.J. Meijer, Francoise Cailler, Jacobus Burggraaf, Alexander L. Vahrmeijer, Miranda Kusters, on behalf of the SGM-101 study group

**Introduction** Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) is the standard treatment for patients with peritoneally metastasized (PM) colorectal carcinoma. The detection of tumour tissue is pivotal to determine the extent of peritoneal disease and acquire a complete cytoreduction, but can be challenging with traditional visual and tactile feedback. This study assessed the value of fluorescence imaging with SGM-101, a fluorescent anti-CEA monoclonal antibody, for the intraoperative detection of PM of colorectal origin.

**Methods** In this open-label pilot study, 14 patients with PM from colorectal origin who were scheduled for CRS and HIPEC were included between January 2017 and January 2019. SGM-101 was administered in dosages ranging from 10 to 15 mg, four to six days prior to surgery. After abdominal exposure, the peritoneal carcinomatosis index (PCI) was determined with standard visual and tactile feedback and thereafter with fluorescence imaging. Both clinically suspected malignant lesions and fluorescent lesions were resected and evaluated with histopathological examination. Changes in the PCI, surgical plan and the concordance between clinical detection and fluorescence imaging were carefully noted.

**Results** A total of 103 lesions were resected, of which 66 were malignant. Fluorescent imaging was able to identify 88 lesions, resulting in an accuracy of 85.4%. The sensitivity was 98.5%, specificity was 53.5% and the positive and negative predictive values were 76.5% and 95.8%, respectively. Fluorescence imaging resulted in a correct PCI increase in four patients (28.6%), leading to the resection of lesions that were otherwise left behind. In three patients, a moderate to severe adverse event occurred, which were not related to the administration of SGM-101.

**Conclusion** The use of fluorescence imaging with SGM-101 is safe, feasible and has the ability to detect peritoneal deposits. This technique has the capacity to aid in a more accurate assessment of the PCI and subsequently a more complete cytoreduction.

# Observing a decade of yearly standardised surveillance in EVAR-patients with ultrasound or CT-scan: Preliminary analysis within 5 centres

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Anna C.M. Geraedts, S. Mulay, S.M.L. de Mik, M.J.W. Koelemay, R. Balm, on behalf of the ODYSSEUS study group

**Introduction** Yearly imaging surveillance is recommended to all patients following endovascular aortic repair (EVAR) to detect complications requiring re-intervention. EVAR is currently the predominant technique for elective infrarenal abdominal aortic aneurysm (AAA) repair in the Netherlands. Consequently, a cumulative amount of hospital visits for imaging surveillance will arise. This causes a burden on both patients and the healthcare system. We therefore aimed to study the re-intervention free survival and survival stratified for patients with and without yearly imaging surveillance.

**Methods** Patients with an asymptomatic infrarenal AAA that underwent elective EVAR between January 2007 and January 2012 were included in this study with long-term follow-up till December 2018. Patients were excluded if abnormalities were shown at their first postoperative computed tomography angiography (CTA). We retrospectively collected data in 5 medical centres from their medical record and categorized patients as compliant versus non-compliant. Compliance was defined as undergoing imaging surveillance at least every 16 months. Survival plots were generated with the Kaplan-Meier method.

**Results** Five hundred and nineteen consecutive patients with a CTA without abnormalities were analysed. One hundred ninety-three patients were compliant to follow-up, whereas 326 patients were non-compliant to follow-up according to our definition. There was no difference between the groups in terms of gender, ASA-classification, type of endograft, and neck length. Age and AAA diameter varied between the two groups. Re-intervention free survival was not significantly different between the compliant and non-compliant group ( $p = 0.579$ ). The difference in cumulative re-intervention free survival at five years between the compliant (20%) and non-compliant (25%) group is five percent. Overall survival was significantly different between the compliant and non-compliant group ( $p = 0.010$ ).

**Conclusion** Imaging surveillance after EVAR appears not to protect against mortality and may even lead to unnecessary re-interventions, which can cause complications. We conducted this study as a pilot prior to a multicentre national study among 2000 patients with long-term follow-up in which we hope to conclude that the revenues of the proposed scheduled follow-up are minimal if the initial CTA shows no abnormalities.

# Enzymatic debridement is selectively effective in burn wounds depending on the thermal damage of the collagen: An ex vivo burn wound experiment

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Kelly A.A. Kwa, Ludo van Haasterecht, Esther Middelkoop, Roelf S. Breederveld, Marloes L. Groot, Paul P.M. van Zuijlen, Bouke K.H.L. Boekema

**Introduction** The treatment of burn wounds with enzymatic debridement using bromelain in our burn center has shown promising results. However, inadequate debridement occurred in some cases with low temperature burns. We hypothesized that bromelain is ineffective in burns in which collagen denaturation, which occurs at  $>65^{\circ}\text{C}$ , has not taken place. Our objective was to assess whether there is a relationship between the denaturation of collagen and the ability of bromelain to debride acute scald burn wounds of different temperatures.

**Methods** Scald burns were induced to ex vivo human skin samples of 1x1 cm by water immersion in temperatures of  $40^{\circ}\text{C}$ ,  $50^{\circ}\text{C}$ ,  $60^{\circ}\text{C}$ ,  $70^{\circ}\text{C}$  and  $100^{\circ}\text{C}$  for twenty minutes. Denaturation of collagen was assessed using histology, with hematoxylin and eosin staining, picrosirius red staining and a fluorescently labelled collagen hybridizing peptide (CHP), and with second harmonic generation (SHG) microscopy. Burned samples and one control sample (room temperature) were weighed before and after application of enzymatic debridement to assess the efficacy of bromelain.

**Results** Unfolding of collagen, loss of basket weave arrangement, and necrosis was seen in samples heated to  $70^{\circ}\text{C}$  or higher. Evident CHP fluorescence, indicative of collagen denaturation, was seen in samples of  $70^{\circ}\text{C}$  and  $100^{\circ}\text{C}$ . SHG intensity, signifying intact collagen, was significantly lower in the  $70^{\circ}\text{C}$  and  $100^{\circ}\text{C}$  group ( $p < 0.0001$ ) compared to the other groups. After enzymatic debridement, a weight reduction of 80% was seen in the samples of  $70^{\circ}\text{C}$  and  $100^{\circ}\text{C}$ , the other samples showed a reduction of 20%.

**Conclusion** The status of collagen denaturation in skin samples, which occurred between  $60^{\circ}\text{C}$  and  $70^{\circ}\text{C}$ , is strongly correlated with the efficacy of enzymatic debridement. Therefore, enzymatic debridement with the use of bromelain of burn wounds caused by temperatures up to and including  $60^{\circ}\text{C}$  is ineffective.



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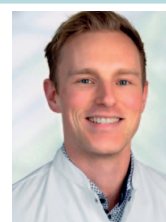
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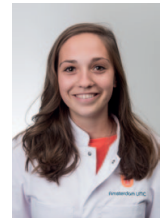
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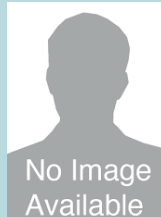
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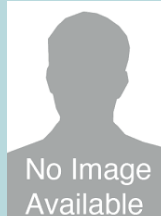
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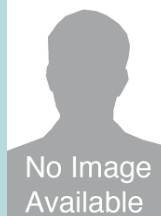
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