De Leestafel

December 2020

Een Maandelijkse Selectie van Wetenschappelijke GE-nieuws

Coloproctologie

De langverwachte RAPIDO trial!

Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. RR Bahadoer, EA Dijkstra et al. Lancet Oncology: 2021 Jan;22(1):29-42.

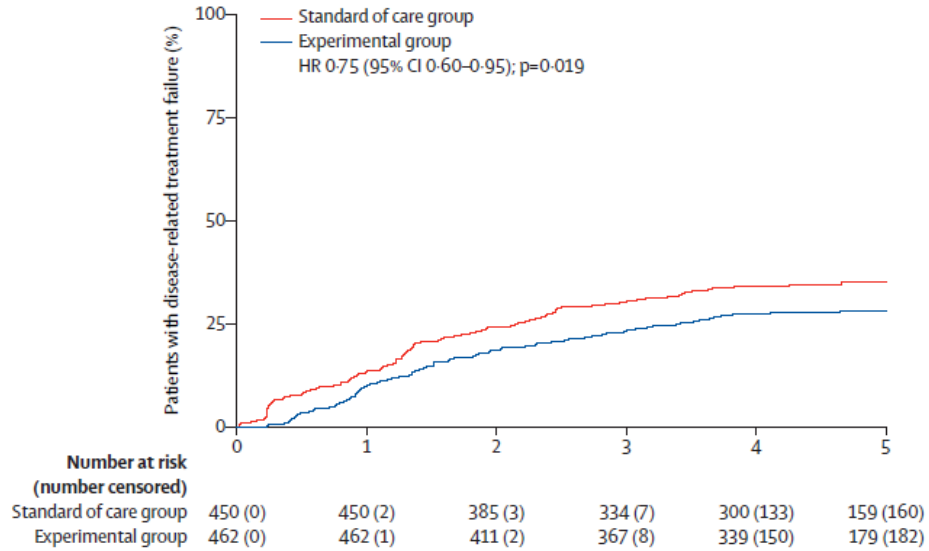
Pubmed ID: 33301740.

Background: Systemic relapses remain a major problem in locally advanced rectal cancer. Using short-course radiotherapy followed by chemotherapy and delayed surgery, the Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial aimed to reduce distant metastases without compromising locoregional control.

Methods: In this multicentre, open-label, randomised, controlled, phase 3 trial, participants were recruited from 54 centres in the Netherlands, Sweden, Spain, Slovenia, Denmark, Norway, and the USA. Patients were eligible if they were aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, had a biopsy-proven, newly diagnosed, primary, locally advanced rectal adenocarcinoma, which was classified as high risk on pelvic MRI (with at least one of the following criteria: clinical tumour [cT] stage cT4a or cT4b, extramural vascular invasion, clinical nodal [cN] stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes), were mentally and physically fit for chemotherapy, and could be assessed for staging within 5 weeks before randomisation. Eligible participants were randomly assigned (1:1), using a management system with a randomly varying block design (each block size randomly chosen to contain two to four allocations), stratified by centre, ECOG performance status, cT stage, and cN stage, to either the experimental or standard of care group. All investigators remained masked for the primary endpoint until a prespecified number of events was reached. Patients allocated to the experimental treatment group received short-course radiotherapy (5 × 5 Gy over a maximum of 8 days) followed by six cycles of CAPOX chemotherapy (capecitabine 1000 mg/m2 orally twice daily on days 1-14, oxaliplatin 130 mg/m2 intravenously on day 1, and a chemotherapy-free interval between days 15-21) or nine cycles of FOLFOX4 (oxaliplatin 85 mg/m2 intravenously on day 1, leucovorin [folinic acid] 200 mg/m2 intravenously on days 1 and 2, followed by bolus fluorouracil 400 mg/m2 intravenously and fluorouracil 600 mg/m2 intravenously for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3-14) followed by total mesorectal excision. Choice of CAPOX or FOLFOX4 was per physician discretion or hospital policy. Patients allocated to the standard of care group received 28 daily fractions of 1·8 Gy up to 50·4 Gy or 25 fractions of 2·0 Gy up to 50·0 Gy (per physician discretion or hospital policy), with concomitant twice-daily oral capecitabine 825 mg/m2 followed by total mesorectal excision and, if stipulated by hospital policy, adjuvant chemotherapy with eight cycles of CAPOX or 12 cycles of FOLFOX4. The primary endpoint was 3-year disease-related treatment failure, defined as the first occurrence of locoregional failure, distant metastasis, new primary colorectal tumour, or treatment-related death, assessed in the intention-to-treat population. Safety was

assessed by intention to treat. This study is registered with the EudraCT, 2010-023957-12, and ClinicalTrials.gov, NCT01558921, and is now complete.

Findings: Between June 21, 2011, and June 2, 2016, 920 patients were enrolled and randomly assigned to a treatment, of whom 912 were eligible (462 in the experimental group; 450 in the standard of care group). Median follow-up was 4·6 years (IQR 3·5-5·5). At 3 years after randomisation, the cumulative probability of disease-related treatment failure was 23·7% (95% CI 19·8-27·6) in the experimental group versus 30·4% (26·1-34·6) in the standard of care group (hazard ratio 0·75, 95% CI 0·60-0·95; p=0·019). The most common grade 3 or higher adverse event during preoperative therapy in both groups was diarrhoea (81 [18%] of 460 patients in the experimental group and 41 [9%] of 441 in the standard of care group) and neurological toxicity during adjuvant chemotherapy in the standard of care group (16 [9%] of 187 patients). Serious adverse events occurred in 177 (38%) of 460 participants in the experimental group and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy. Treatment-related deaths occurred in four participants in the experimental group (one cardiac arrest, one pulmonary embolism, two infectious complications) and in four participants in the standard of care group (one pulmonary embolism, one neutropenic sepsis, one aspiration, one suicide due to severe depression).



Interpretation: The observed decreased probability of disease-related treatment failure in the experimental group is probably indicative of the increased efficacy of preoperative chemotherapy as opposed to adjuvant chemotherapy in this setting. Therefore, the experimental treatment can be considered as a new standard of care in high-risk locally advanced rectal cancer.

CRP betrouwbaar in het diagnosticeren van een naadlekkage na colorectale chirurgie?

C‐reactive protein trajectory to predict colorectal anastomotic leak: PREDICT Study. BD Stephensen et al. BJS, Dec 2020 – Volume 107 – Issue 13, pages 1832-1837.

Pubmed ID: 32671825.

Background: Anastomotic leak is a common complication after colorectal surgery, associated with increased morbidity and mortality, and poorer long‐term survival after oncological resections. Early diagnosis improves short‐term outcomes, and may translate into reduced cancer recurrence. Multiple studies have attempted to identify biomarkers to enable earlier diagnosis of anastomotic leak. One study demonstrated that the trajectory of C‐reactive protein (CRP) levels was highly predictive

of anastomotic leak requiring intervention, with an area under the curve of 0·961. The aim of the present study was to validate this finding externally.

Methods: This was a prospective international multicentre observational study of adults undergoing elective colorectal resection with an anastomosis. CRP levels were measured before operation and for 5 days afterwards, or until day of discharge if earlier than this. The primary outcome was anastomotic leak requiring operative or radiological intervention.

Results: Between March 2017 and July 2018, 933 patients were recruited from 20 hospitals across Australia, New Zealand, England and Scotland. Some 833 patients had complete CRP data and were included in the primary analysis, of whom 41 (4·9 per cent) developed an anastomotic leak. A change in CRP level exceeding 50 mg/l between any two postoperative days had a sensitivity of 0·85 for detecting a leak, and a high negative predictive value of 0·99 for ruling it out. A change in CRP concentration of more than 50 mg/l between either days 3 and 4 or days 4 and 5 after surgery had a high specificity of 0·96–0·97, with positive likelihood ratios of 4·99–6·44 for a leak requiring intervention.

Table 4 Diagnostic indices for ability of daily C-reactive protein change exceeding 50 mg/l to predict anastomotic leak requiring intervention

Timing of CRP increase > 50 mg/l	Sensitivity	Specificity	PLR	NLR	PPV	NPV
Between any 2 days	0·85	0·51	1·75	0·29	0·08	0·99
From day 1 to day 2	0·63	0·57	1·48	0·64	0·07	0·97
From day 2 to day 3	0·32	0·90	3·10	0·76	0·14	0·96
From day 3 to day 4	0·20	0·96	4·99	0·84	0·21	0·96
From day 4 to day 5	0·17	0·97	6·44	0·85	0·25	0·96

CRP, C-reactive protein; PLR, positive likelihood ratio; NPR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Conclusion: This study confirmed the value of CRP trajectory in accurately ruling out an anastomotic leak after colorectal resection.

Kans op recidief diverticulitis wordt kleiner met de tijd.

Conditional risk of diverticulitis after non‐operative management. R Garfinkel et al. BJS, Dec 2020 – Volume 107 – Issue 13, pages 1838-1845.

Pubmed ID: 32876945.

Background: The objective of this study was to describe conditional recurrence‐free survival (RFS) of patients after an index episode of diverticulitis managed without surgery, and to estimate the difference in conditional RFS for diverticulitis according to specific risk factors.

Methods: This was a multicentre retrospective cohort study including all patients managed without surgery for acute sigmoid diverticulitis at two university‐affiliated hospitals in Montreal, Quebec, Canada. Conditional RFS for diverticulitis was estimated over 10 years of follow‐up. A Cox proportional hazards model was performed at the index episode and again 2 years later.

Results: In total, 991 patients were included for analysis. The 1, 2‐ and 3‐year actuarial diverticulitis RFS rates were 81·1, 71·5 and 67·5 per cent respectively. Compared with the 1‐year actuarial RFS rate of 81·1 per cent, the 1‐year conditional RFS increased with each additional year survived recurrence‐free, reaching 96·0 per cent after surviving the first 4 years recurrence‐free. A similar phenomenon was observed for 2‐year diverticulitis conditional RFS. Lower age (hazard ratio (HR) 0·98, 95 per cent c.i. 0·98 to 0·99), Charlson Co‐morbidity Index score of 2 or above (HR 1·78, 1·32 to 2·39) and immunosuppression (HR 1·85, 1·38 to 2·48) were independently associated with recurrence of diverticulitis from the index episode. At 2 years from the index episode, immunosuppression was no longer associated with diverticulitis recurrence (HR 1·02, 0·50 to 2·09).

Conclusion: The conditional RFS of patients with diverticulitis improved with each year that was survived recurrence‐free. Although several factors at index presentation may be associated with early recurrence, the conditional probability of recurrence according to many of these risk factors converged with time.

UPPER GI

De waarde van endoscopische biopten in de pre-SANO trial.

Residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer: locations undetected by endoscopic biopsies in the preSANO trial. BJ van der Wilk et al. BJS, Dec 2020 – Volume 107 – Issue 13, pages 1791-1800.
Pubmed ID: 32757307.

Background: Active surveillance has been proposed for patients with oesophageal cancer in whom there is a complete clinical response after neoadjuvant chemoradiotherapy (nCRT). However, endoscopic biopsies have limited negative predictive value in detecting residual disease. This study determined the location of residual tumour following surgery to improve surveillance and endoscopic strategies.

Methods: The present study was based on patients who participated in the prospective preSANO trial with adenocarcinoma or squamous cell carcinoma of the oesophagus or oesophagogastric junction treated in four Dutch hospitals between 2013 and 2016. Resection specimens and endoscopic biopsies taken during clinical response evaluations after nCRT were reviewed by two expert gastrointestinal pathologists. The exact location of residual disease in the oesophageal wall was determined in resection specimens. Endoscopic biopsies were assessed for the presence of structures representing the submucosal layer of the oesophageal wall.

Results: In total, 119 eligible patients underwent clinical response evaluations after nCRT followed by standard surgery. Residual tumour was present in endoscopic biopsies from 70 patients, confirmed on histological analysis of the resected organ. Residual tumour was present in the resection specimen from 27 of the other 49 patients, despite endoscopic biopsies being negative. Of these 27 patients, residual tumour was located in the mucosa in 18, and in the submucosa beneath tumour‐free mucosa in eight. One patient had tumour in muscle beneath tumour‐free mucosa and submucosa.

Conclusion: Most residual disease after nCRT missed by endoscopic biopsies was located in the mucosa. Active surveillance could be improved by more sampling and considering submucosal biopsies.

Betere overall survival met adjuvante chemotherapie na slokdarmresectie, met name in patiënten zonder response op neoadjuvante chemotherapie.

Adjuvant therapy following oesophagectomy for adenocarcinoma in patients with a positive resection margin. RK Bott et al. BJS, Dec 2020 – Volume 107 – Issue 13, pages 1801-1810.
Pubmed ID: 32990343.

Background: The role of adjuvant therapy in patients with oesophagogastric adenocarcinoma treated by neoadjuvant chemotherapy is contentious. In UK practice, surgical resection margin status is often used to classify patients for receiving adjuvant treatment. The aim of this study was to assess the survival benefit of adjuvant therapy in patients with positive (R1) resection margins.

Methods: Two prospectively collected UK institutional databases were combined to identify eligible patients. Adjusted Cox regression analyses were used to compare overall and recurrence‐free

survival according to adjuvant treatment. Recurrence patterns were assessed as a secondary outcome. Propensity score‐matched analysis was also performed.

Results: Of 616 patients included in the combined database, 242 patients who had an R1 resection were included in the study. Of these, 112 patients (46·3 per cent) received adjuvant chemoradiotherapy, 46 (19·0 per cent) were treated with adjuvant chemotherapy and 84 (34·7 per cent) had no adjuvant treatment. In adjusted analysis, adjuvant chemoradiotherapy improved recurrence‐free survival (hazard ratio (HR) 0·59, 95 per cent c.i. 0·38 to 0·94; P = 0·026), with a benefit in terms of both local (HR 0·48, 0·24 to 0·99; P = 0·047) and systemic (HR 0·56, 0·33 to 0·94; P = 0·027) recurrence. In analyses stratified by tumour response to neoadjuvant chemotherapy, non‐responders (Mandard tumour regression grade 4–5) treated with adjuvant chemoradiotherapy had an overall survival benefit (HR 0·61, 0·38 to 0·97; P = 0·037). In propensity score‐matched analysis, an overall survival benefit (HR 0·62, 0·39 to 0·98; P = 0·042) and recurrence‐free survival benefit (HR 0·51, 0·30 to 0·87; P = 0·004) were observed for adjuvant chemoradiotherapy versus no adjuvant treatment.

Conclusion: Adjuvant therapy may improve overall survival and recurrence‐free survival after margin‐positive resection. This pattern seems most pronounced with adjuvant chemoradiotherapy in non‐responders to neoadjuvant chemotherapy.

HPB

Mag de drain eruit?

Drain Management Following Distal Pancreatectomy: Characterization of Contemporary Practice and Impact of Early Removal. TF Seykora et al. Annals of Surgery, December 2020, Volume 272, Issue 6, p1110-1117.

Pubmed ID: 30943185.

Objective: To explore contemporary drain management practices and examine the impact of early removal following distal pancreatectomy (DP).

Background: Despite accruing evidence supporting its benefit following pancreatoduodenectomy, early drain removal after DP has yet to be explored.

Methods: The American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) was queried for elective DPs from 2014 to 2017. When possible, data were linked to survey responses regarding drain management from hepato-pancreato-biliary (HPB) surgeons in the ACS-NSQIP HPB Collaborative conducted in 2017. The independent association between timing of drain removal and patients' outcomes was investigated through multivariable analyses and propensity-score matching.

Results: Of 5581 DPs identified, 4708 (84.4%) patients received intraoperative drains and early removal (≤ POD3) was performed in 716 (15.2%). Drain fluid amylase was recorded on POD1 for 1285 (27.3%) patients who received drains. The overall rates of death or serious morbidity (DSM) and clinically-relevant fistula (CR-POPF) were 19.5% and 17.0%. Early removal demonstrated significantly better outcomes when compared to late removal and no drain placement for: DSM, CR-POPF, delayed gastric emptying, percutaneous drainage, length of stay, and readmission. On multivariable analysis, early removal demonstrated reduced odds of developing DSM (OR = 0.41, 95% CI = 0.26-0.65) and CR-POPF (OR = 0.33, 95% CI = 0.18-0.61) compared to no drain placement, while late removal displayed increased odds for CR-POPF (OR = 2.15, 95% CI = 1.27-3.61) when compared to no drain placement. After propensity-score matching, early removal was associated with reduced odds for CR-POPF (OR = 0.35, 95% CI = 0.17-0.73).

Conclusion: Although not yet widely implemented, early drain removal after distal pancreatectomy is associated with better outcomes. This study demonstrates the potential benefits of early removal and provides a substrate to define best practices and improve the quality of care for DP.

TABLE 3. Early and Late Drain Removal Outcomes Stratified by DFA-1 Level

Outcome n (%)	DFA-1 ≤ 2000 IU n = 744 (57.9%)			DFA-1 > 2000 IU n = 541 (42.1%)		
	Early ≤ POD3 n = 250 (33.6%)	Late > POD3 n = 494 (66.4%)	*P* Value	Early ≤ POD3 n = 86 (15.9%)	Late > POD3 n = 455 (84.1%)	*P* Value
DSM	26 (10.4)	100 (20.2)	**<0.001**	8 (9.3)	94 (20.7)	**0.01**
CR-POPF	10 (4.0)	75 (15.2)	**<0.001**	3 (3.5)	135 (29.7)	**<0.001**
DGE	5 (2.0)	20 (4.0)	0.14	2 (2.3)	23 (5.1)	0.40
Percutaneous drain placement	18 (7.2)	54 (10.9)	0.10	8 (9.3)	60 (13.2)	0.32
Reoperation	4 (1.6)	22 (4.4)	0.05	4 (4.7)	17 (3.7)	0.76
Median LOS (IQR)	4 (4–6)	6 (5–8)	**<0.001**	4 (3–5)	5 (4–7)	**<0.001**
Readmission	26 (10.4)	86 (17.4)	**0.01**	7 (8.1)	85 (18.7)	**0.02**

DFA-1 indicates postoperative day 1 drain fluid amylase; DGE, delayed gastric emptying; DSM, death or serious morbidity; IU, international units; LOS, length of stay.
Bold indicates statistically significant *P*-value

Een brug naar resectie van pancreastumoren bij betrokkenheid van de vms.

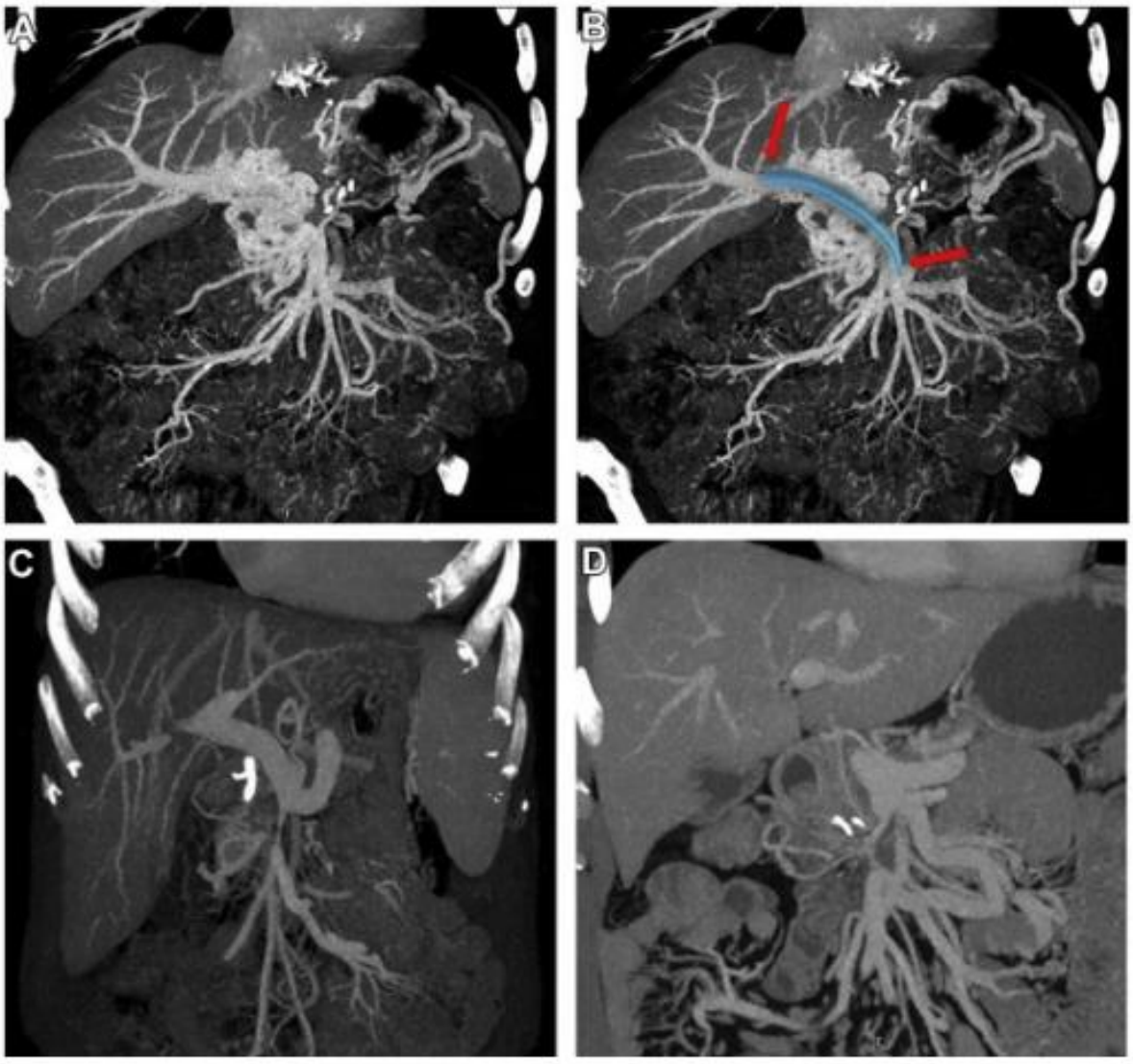
Mesoportal bypass, interposition graft, and mesocaval shunt: Surgical strategies to overcome superior mesenteric vein involvement in pancreatic cancer. B Kinny-Köster et al. Surgery: December 2020 – Volume 168 – Issue 6 – p 1048-1055.
Pubmed ID: 32951905.

Background: In pancreatic cancer, extensive tumor involvement of the mesenteric venous system poses formidable challenges to operative resection. Such involvement can result from cavernous collateral veins leading to increased intraoperative blood loss or long-segment vascular defects of not only just the superior mesenteric vein but also even jejunal/ileal branches. Strategies to facilitate margin-free resection and safe vascular reconstruction in pancreatic surgery are important, particularly because systemic control of the tumor is improving with multi-agent chemotherapy regimens.

Methods: We describe a systematic, multidisciplinary assessment for patients with pancreatic cancer that involves the superior mesenteric vein, as well as the preoperative planning of those undergoing operative resection. In addition, detailed descriptions of operative approaches and technical strategies, which evolved with increasing experience at a high-volume center, are presented.

Results: For the preoperative evaluation of tumor-free, vascular locations for potential reconstruction and collateralization, computed tomographic imaging with high-resolution of vascular structures (used with 3-dimensional or cinematic rendering) allows a precise calibration of radiographic data with intraoperative findings. From an operative perspective, we identified 5 potential strategies to consider for resection: collateral preservation, mesoportal bypass (preresection), mesoportal interposition graft (postresection), mesocaval shunt, and various combinations of these strategies. Many of these techniques use interposition grafts, making it essential to assess autologous veins (preferred conduit for reconstruction) or to prepare cryopreserved vascular allografts (an alternative conduit, which must be thawed and should be matched for size and blood type).

Conclusion: Herein we share operative strategies to overcome involvement of the superior mesenteric vein in pancreatic cancer. Improvements in preoperative planning and operative technique can address common barriers to resection with curative intent.



Three-dimensional renderings based on venous-phase computed tomography scan in patients with SMV involvement as a result of pancreatic cancer. (A) SMV occlusion with right-sided dominant collateralization and a patent-appearing distal SMV. (B) Schematic demonstration of a mesoportal bypass/interposition graft that was planned in this case. (C) Severe SMV narrowing without substantial collateralization. A pancreatoduodenectomy with an interposition graft was performed in this patient. (D) SMV obliteration with left-sided dominant collaterals and a tumor-free appearing IMV-SV-PV axis. A pancreatoduodenectomy with a permanent mesocaval shunt was performed in this patient. IMV, inferior mesenteric vein; PV, portal vein; SMV, superior mesenteric vein, SV, splenic vein.

LEVERCHIRURGIE

De weg naar personalised treatment planning: dubbelmutatie *APC* en *PIK3CA* is een predictor voor kortere ziektevrije en algehele overleving voor patiënten met colorectale levermetastasen.

APC and PIK3CA Mutational Cooperativity Predicts Pathologic Response and Survival in Patients

Undergoing Resection for Colorectal Liver Metastases. S Yamashita et al. Annals of Surgery, December 2020, Volume 272, Issue 6, p1080-1085.
PMID: 28379870.

Objective: The aim of the study was to determine the prognostic impact of co-existence of APC and PIK3CA mutations in patients undergoing preoperative chemotherapy and resection for colorectal liver metastases (CLM).

Background: Co-occurring genetic events have been shown to drive carcinogenesis in multiple malignancies.

Methods: We identified 396 patients with primary colorectal cancer and known somatic mutation status by next-generation sequencing who underwent hepatectomy for CLM (2005-2015). Survival after hepatectomy in patients with double mutation of APC and PIK3CA and others was analyzed. Predictors of pathologic response and survival were determined. The prognostic value of double mutation was evaluated with a separate cohort of 157 patients with CLM undergoing chemotherapy alone.

Results: Forty-five patients had double mutation of APC and PIK3CA; 351 did not. Recurrence-free survival (RFS) and overall survival (OS) after hepatectomy were worse in patients with double mutation (3-year RFS, 3.1% vs 20% [P < 0.001]; 3-year OS, 44% vs 84% [P < 0.001]). Independent predictors of major pathologic response were bevacizumab use (odds ratio [OR] 2.22; P = 0.001), tumor size <3 cm (OR 1.97; P = 0.004), wild-type RAS (OR 2.00; P = 0.003), and absence of double mutation (OR 2.91; P = 0.002). Independent predictors of worse OS were primary advanced T category (hazard ratio [HR] 2.12; P = 0.021), RAS mutation (HR 1.74; P = 0.015), and double mutation (HR 3.09; P < 0.001). In the different medical cohort, patients with double mutation had worse 3-year OS of 18%, compared with 35% without double mutation (P = 0.023).

Conclusions: Double mutation of APC and PIK3CA predicts inferior response to preoperative chemotherapy and poor survival in patients with CLM.

	RFS		OS	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Primary tumor T3/4 vs. T1/2	NS		2.12 (1.11–4.60)	0.021
Multiple liver metastases	1.47 (1.14–1.91)	0.003	NS	
RAS mutation	1.75 (1.34–2.27)	<0.001	1.74 (1.11–2.70)	0.015
Double *APC* and *PIK3CA* mutations	1.63 (1.11–2.31)	0.013	3.09 (1.72–5.27)	<0.001

CLM indicates colorectal liver metastases; HR, hazard ratio; CI, confidence interval; NS, not significant on univariable analysis; OS, overall survival; RFS, recurrence-free survival.

Multivariable Cox Regression Models for RFS and OS Among 396 Patients After Resection of CLM

BARIATRISCHE CHIRURGIE

Bariatrische chirurgie als preventiemaatregel tegen borstkanker?

Bariatric Surgery is Associated With Reduced Risk of Breast Cancer in Both Premenopausal and Postmenopausal Women. HS Feigelson et al. Annals of Surgery, December 2020, Volume 272, Issue 6, p1053-1059.

Pubmed ID: 30998538.

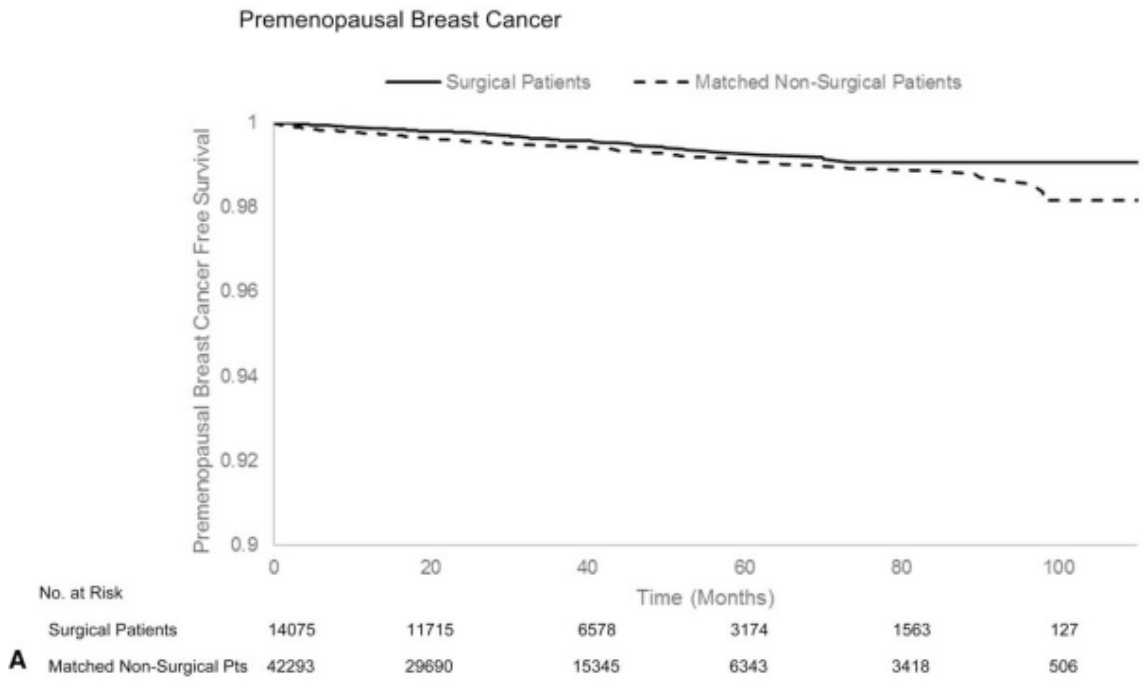
Objective: This retrospective cohort study examined whether bariatric surgery is associated with reduced risk of breast cancer among pre- and postmenopausal women.

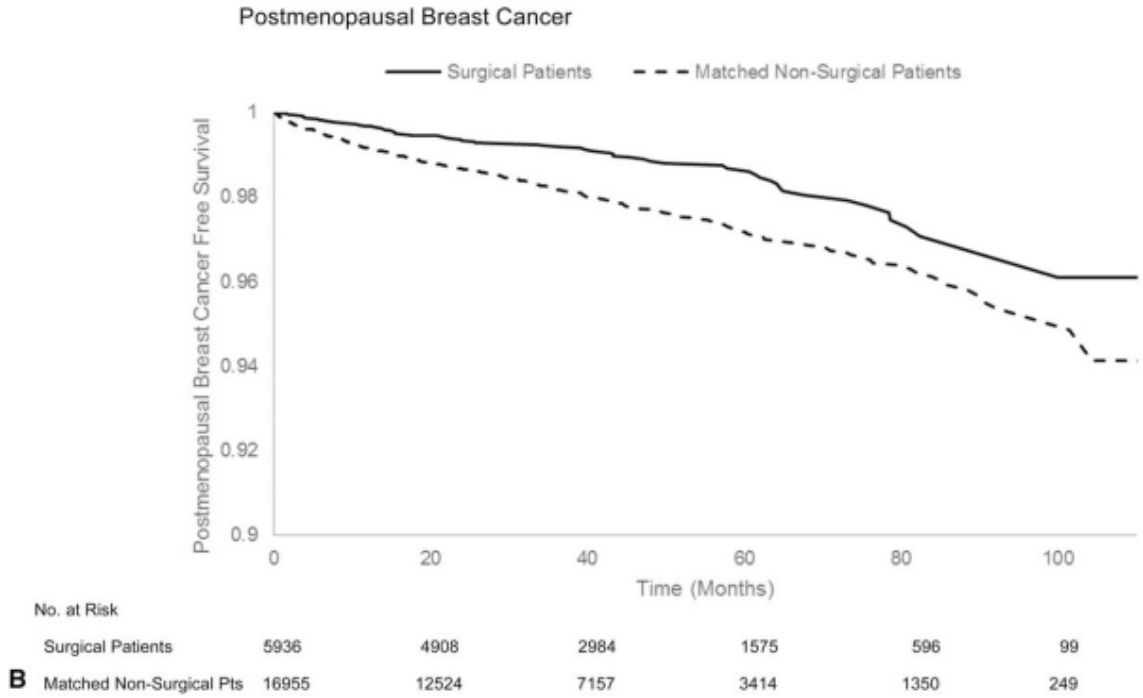
Background: Obesity is associated with increased risk of breast cancer, but the impact of weight loss on breast cancer risk has been difficult to quantify.

Methods: The cohort included obese (body mass index ≥35 kg/m) patients enrolled in an integrated health care delivery system between 2005 and 2012 (with follow-up through 2014). Female bariatric surgery patients (N = 17,998) were matched on body mass index, age, study site, and comorbidity index to 53,889 women with no bariatric surgery. Kaplan-Meier curves and Cox proportional hazards models were used to examine incident breast cancer up to 10 years after bariatric surgery. Pre- and postmenopausal women were examined separately, and further classified by estrogen receptor (ER) status.

Results: The analysis included 301 premenopausal and 399 postmenopausal breast cancer cases. In multivariable adjusted models, bariatric surgery was associated with a reduced risk of both premenopausal (HR = 0.72, 95% CI, 0.54-0.94) and postmenopausal (HR = 0.55, 95% CI, 0.42-0.72) breast cancer. Among premenopausal women, the effect of bariatric surgery was more pronounced among ER-negative cases (HR = 0.36, 95% CI, 0.16-0.79). Among postmenopausal women, the effect was more pronounced in ER-positive cases (HR = 0.52, 95% CI, 0.39-0.70).

Conclusions: Bariatric surgery was associated with a reduced risk of breast cancer among severely obese women. These findings have significant public health relevance because the prevalence of obesity continues to rise, and few modifiable breast cancer risk factors have been identified, especially for premenopausal women.





Kaplan–Meier estimated cancer-free survival for premenopausal breast cancer (A), and postmenopausal breast cancer (B). In panel A, there were 65 cancers in the bariatric surgery group and 236 cancers in the nonsurgical group. The Wilcoxon rank-sum test had a P value of 0.004. In panel B, there were 68 cancers in the bariatric surgery group and 331 cancers in the nonsurgical group. The Wilcoxon rank-sum test had a P value of <0.001.

***