

Coloproctologie

Prehabilitatie colorectale kanker patiënten leidt tot verbeterde disease-free-survival.

Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery. M. Trépanier et al. *Annals of Surgery*, August 2019, Volume 270, Issue 2, p 493-501.

Pubmed ID: 31318793.

OBJECTIVE: The objective of this study was to investigate the effect of prehabilitation on survival after colorectal cancer surgery.

BACKGROUND: Preoperative multimodal exercise and nutritional programs (prehabilitation) improve functional capacity and recovery following colorectal surgery. Exercise may also affect cancer outcomes by mediating the systemic inflammatory response. The effect of prehabilitation on cancer outcomes is unknown.

METHODS: Pooled data from 3 prehabilitation trials (2 randomized controlled trials, 1 cohort) in patients undergoing elective, biopsy-proven, primary non-metastatic colorectal cancer surgery from 2009 to 2014 within an enhanced recovery program were analyzed. Patients were grouped into +prehab or –prehab. The primary outcomes were 5-year disease-free (DFS) and overall survival (OS). DFS and OS were analyzed using Kaplan-Meier curves and multiple Cox regression.

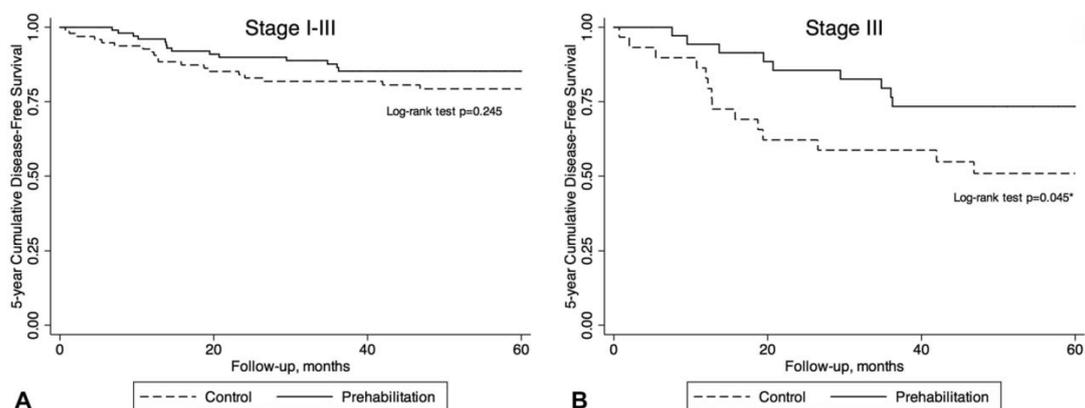


FIGURE 2. Kaplan-Meier survival curves of 5-year disease-free survival in patients undergoing prehabilitation vs control for (A) all stages and (B) stage III disease.

RESULTS: A total of 202 patients were included (+prehab 104, –prehab 98). Median prehabilitation duration was 29 days (interquartile range 20–40). Patient and tumor characteristics were well-balanced (33% stage III). Postoperative complications and time to adjuvant chemotherapy were similar. Mean duration of follow-up was 60.3 months (standard deviation 26.2). DFS was similar for the combined group of stage I–III patients ($P = 0.244$). For stage III patients, prehabilitation was

associated with improved DFS (73.4% vs 50.9%, $P = 0.044$). There were no differences in OS ($P = 0.226$). Prehabilitation independently predicted improved DFS (hazard ratio 0.45; 95% confidence interval, 0.21–0.93), adjusting for stage and other confounders. Prehabilitation did not independently predict OS.

CONCLUSION: In this report, prehabilitation is associated with improved 5-year DFS in stage III colorectal cancer. This finding should be confirmed in future trials.

Marker voor het voorspellen van response na neoadjuvante chemoradiatie van rectumcarcinoom.

Immunogenomic profiles associated with response to neoadjuvant chemoradiotherapy in patients with rectal cancer. T Akiyoshi et al. *BJS*, Sept 2019 – Volume 106 – Issue 10, pages 1381-1392.

Pubmed ID: 31197828.

BACKGROUND: Accumulating evidence suggests that radiotherapy success has an immune-associated component. The immunogenomic profiles associated with responses to chemoradiotherapy (CRT) were assessed in patients with locally advanced rectal cancer in this study.

METHOD: CD8+ tumour-infiltrating lymphocyte (TIL) and stromal lymphocyte densities were assessed by immunohistochemistry using pretreatment biopsies from patients with advanced rectal cancer who had preoperative CRT. Whole-exome sequencing and gene expression microarray analysis were conducted to investigate the genomic properties associated with the response to CRT and CD8+ TIL density. Response to CRT was determined based on Dworak tumour regression grade (TRG); tumours with complete (TRG 4) or near-complete (TRG 3) regression were grouped as good responders, and those with TRG 1 as non-responders.

RESULTS: Immunohistochemical examinations (275 patients) showed that pre-CRT CD8+ TIL density was associated with better response to CRT and improved recurrence-free survival, whereas pre-CRT stromal CD8+ cell density was not associated with either response to CRT or recurrence-free survival. Whole-exome sequencing (74 patients) showed that the numbers of single-nucleotide variations (SNVs) and neoantigens predicted from SNVs were higher in good responders than in non-responders, and these correlated positively with CD8+ TIL density ($r_s = 0.315$ and $r_s = 0.334$ respectively). Gene expression microarray (90 patients) showed that CD8A expression correlated positively with the expression of programmed cell death 1 (PDCD1) ($r_s = 0.264$) and lymphocyte-activation gene 3 (LAG3) ($r_s = 0.507$).

CONCLUSION: Pre-CRT neoantigen-specific CD8+ T cell priming may be a key event in CRT responses where immune checkpoint molecules could be useful targets to enhance tumour regression.

d RFS by CD8+ TIL density

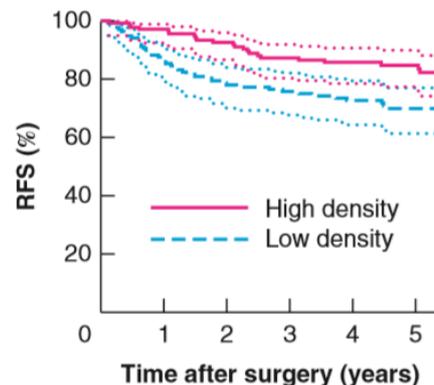


Fig 1d Kaplan-Meier estimates for recurrence-free survival (RFS) according to CD8+ TIL density. Dotted lines represent 95 per cent confidence intervals. $P=0.013$

UPPER GI

Invloed neoadjuvante chemoradiatie op longfunctie

Effect of neoadjuvant chemoradiation on preoperative pulmonary physiology, postoperative respiratory complications and quality of life in patients with oesophageal cancer. A Elliott et al. BJS, Sept 2019 – Volume 106 – Issue 10, pages 1341-1351.

Pubmed ID: 31282584.

BACKGROUND: It remains controversial whether neoadjuvant chemoradiation (nCRT) for oesophageal cancer influences operative morbidity, in particular pulmonary, and quality of life. This study combined clinical outcome data with systematic evaluation of pulmonary physiology to determine the impact of nCRT on pulmonary physiology and clinical outcomes in locally advanced oesophageal cancer.

METHOD: Consecutive patients treated between 2010 and 2016 were included. Three-dimensional conformal radiation was standard, with a lung dose–volume histogram of V20 less than 25 per cent, and total radiation between 40 and 41.4 Gy. Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) were assessed at baseline and 1 month after nCRT. Radiation-induced lung injury (grade 2 or greater), comprehensive complications index (CCI) and pulmonary complications were monitored prospectively. Health-related quality of life was assessed among disease-free patients in survivorship.

RESULTS: Some 228 patients were studied. Comparing pulmonary physiology values before with those after nCRT, FEV1 decreased from mean(s.d.) 96.8(17.7) to 91.5(20.4) per cent (–3.6(10.6) per cent; $P < 0.001$), FVC from 104.9(15.6) to 98.1(19.8) per cent (–3.2(11.9) per cent; $P = 0.005$) and DLCO from 97.6(20.7) to 82.2(20.4) per cent (–14.8(14.0) per cent; $P < 0.001$). Five patients (2.2 per cent) developed radiation-induced lung injury precluding surgical resection. Smoking ($P = 0.005$) and increased age ($P < 0.001$) independently predicted percentage change in DLCO. Carboplatin and paclitaxel with 41.4 Gy resulted in a greater DLCO decline than cisplatin and 5-fluorouracil with 40 Gy ($P = 0.001$). On multivariable analysis, post-treatment DLCO predicted CCI ($P = 0.006$), respiratory failure ($P = 0.020$) and reduced physical function in survivorship ($P = 0.047$).

CONCLUSION: These data indicate that modern nCRT alters pulmonary physiology, in particular diffusion capacity, which is linked to short- and longer-term clinical consequences, highlighting a potentially modifiable index of risk.

Extranodale tumor deposities bij maagkanker voorspellen een slechtere prognose. Incluseren in TNM stadiering?

Impact of extranodal tumor deposits on prognosis and N stage in gastric cancer. Yuexiang Liang et al. Surgery: September 2019 – Volume 166 – Issue 3 – p 305-313

Pubmed ID: 31221435.

BACKGROUND AND OBJECTIVE: Extranodal tumor deposits have been reported to be associated with a poor prognosis in many malignancies and are also included in the tumor, node, and metastasis staging system for colorectal cancer.

METHODS: We reviewed retrospectively a total of 2,344 gastric cancer patients who underwent gastrectomy with curative intent at the Tianjin Medical University Cancer Institute and Hospital (Hexi District, Tianjin, China) and the First Affiliated Hospital of Hainan Medical University (Longhua District, Haikou, China). Patients were categorized into 2 groups based on extranodal tumor deposit status: a positive group, including those with extranodal tumor deposits, and a negative group composed of those with no extranodal tumor deposits. Clinicopathologic factors were correlated with extranodal tumor deposits, and their individual prognoses were analyzed. In addition, a pathologically modified node classification system was proposed by incorporating the extranodal tumor deposit status into the 8th ed of the N staging system. The superiority of prognostic prediction between the modified node classification and node stage was compared.

RESULTS: A total of 645 (27.5%) patients had extranodal tumor deposits. The presence of extranodal tumor deposits was associated with a larger tumor size, Borrmann type III and IV, a deeper depth of invasion, and an advanced node stage. In the multivariate analysis, extranodal tumor deposits were an independent prognostic factor for gastric cancer patients after curative resection. Gastric cancer patients with extranodal tumor deposits demonstrated a lesser 5-year overall survival than those with no extranodal tumor deposits (31.9% vs 61.4%, $P < .001$). With the strata analysis, statistically significant prognostic differences between the two groups were only observed in patients at the N0-N2 stage. The modified node classification was found to be more appropriate for predicting the overall survival of gastric cancer patients after curative resection than node stage, and the -2 log likelihood of the modified node classification (16,042.890) was smaller than the value of node stage (16,150.811).

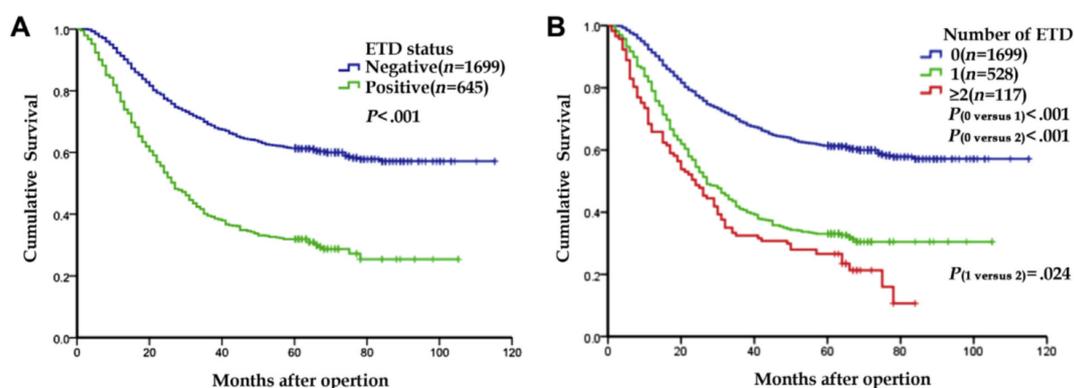


Fig 1. Overall survival curves after curative resection. (A) Patients with or without an ETD ($P < .001$, log-rank test). (B) Patients grouped according to the number of ETDs ($P < .001$).

CONCLUSION: Extranodal tumor deposits in gastric cancer patients indicate aggressive characteristics and a poorer prognosis of gastric cancer. We maintain that extranodal tumor deposits should be incorporated into the N staging system to enhance the accuracy of the prognostic prediction of patients with gastric cancer.

HPB

Adjuvante therapie bij papilcarcinoom gebaseerd op histologisch subtype?

Role of Adjuvant Multimodality Therapy After Curative-Intent Resection of Ampullary Carcinoma.

BL Ecker et al. JAMA Surg. 2019;154(8):706-714.

Pubmed ID: 31141112.

IMPORTANCE: Ampullary adenocarcinoma is a rare malignant neoplasm that arises within the duodenal ampullary complex. The role of adjuvant therapy (AT) in the treatment of ampullary adenocarcinoma has not been clearly defined.

OBJECTIVE: To determine if long-term survival after curative-intent resection of ampullary adenocarcinoma may be improved by selection of patients for AT directed by histologic subtype.

DESIGN, SETTING, AND PARTICIPANTS: This multinational, retrospective cohort study was conducted at 12 institutions from April 1, 2000, to July 31, 2017, among 357 patients with resected, nonmetastatic ampullary adenocarcinoma receiving surgery alone or AT. Cox proportional hazards regression was used to identify covariates associated with overall survival. The surgery alone and AT cohorts were matched 1:1 by propensity scores based on the likelihood of receiving AT or by survival hazard from Cox modeling. Overall survival was compared with Kaplan-Meier estimates.

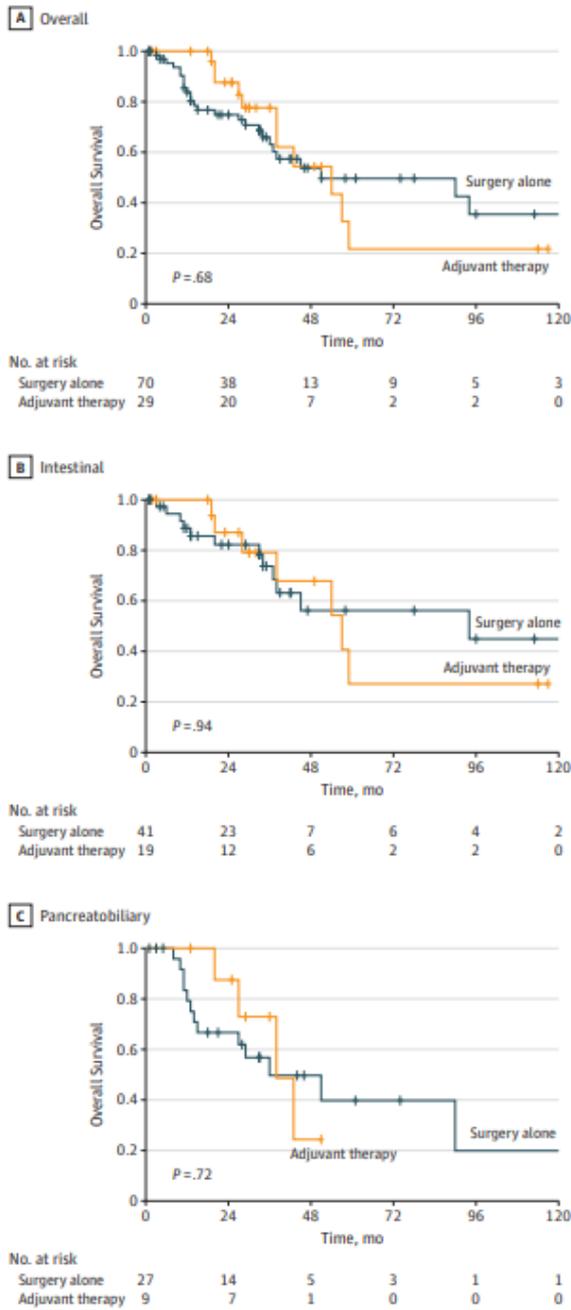
EXPOSURES: Adjuvant chemotherapy (fluorouracil- or gemcitabine-based) with or without radiotherapy.

MAIN OUTCOMES AND MEASURES: Overall survival.

RESULTS: A total of 357 patients (156 women and 201 men; median age, 65.8 years [interquartile range, 58-74 years]) underwent curative-intent resection of ampullary adenocarcinoma. Patients with intestinal subtype had a longer median overall survival compared with those with pancreatobiliary subtype (77 vs 54 months; $P = .05$). Histologic subtype was not associated with AT administration (intestinal, 52.9% [101 of 191]; and pancreatobiliary, 59.5% [78 of 131]; $P = .24$). Patients with pancreatobiliary histologic subtype most commonly received gemcitabine-based regimens (71.0% [22 of 31]) or combinations of gemcitabine and fluorouracil (12.9% [4 of 31]), whereas treatment of those with intestinal histologic subtype was more varied (fluorouracil, 50.0% [17 of 34]; gemcitabine, 44.1% [15 of 34]; $P = .01$). In the propensity score–matched cohort, AT was not associated with a survival benefit for either histologic subtype (intestinal hazard ratio, 1.21; 95% CI, 0.67-2.16; $P = .53$; pancreatobiliary: hazard ratio, 1.35; 95% CI, 0.66-2.76; $P = .41$).

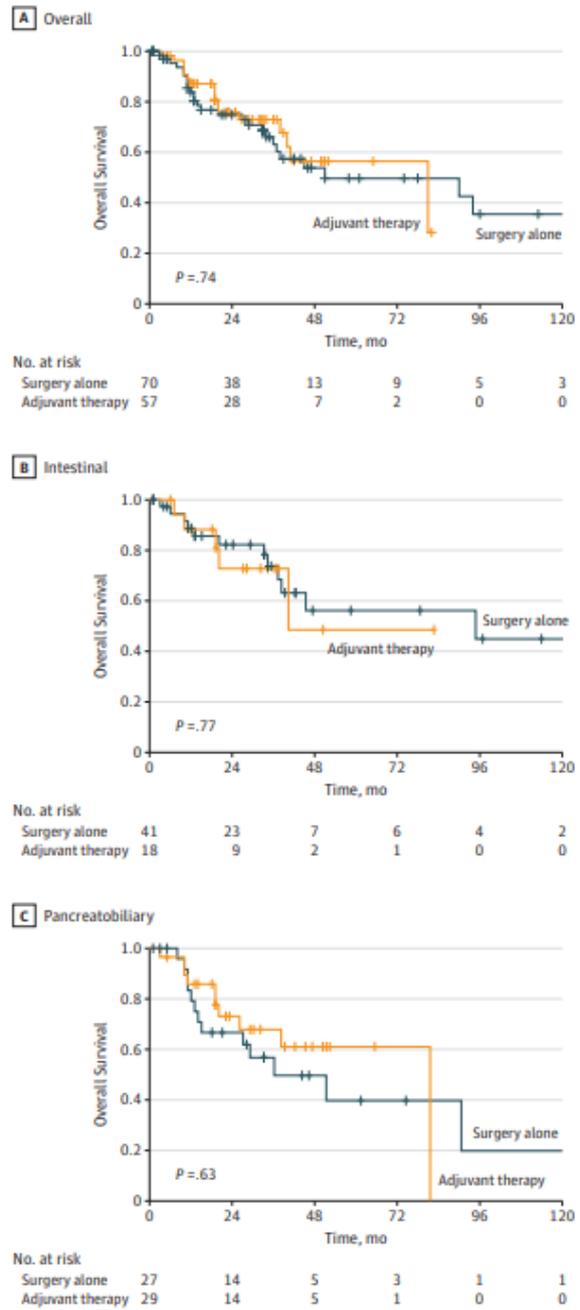
CONCLUSIONS AND RELEVANCE: Adjuvant therapy was more frequently used in patients with poor prognostic factors but was not associated with demonstrable improvements in survival, regardless of tumor histologic subtype. The value of a multimodality regimen remains poorly defined.

Figure 2. Association of Fluorouracil-Based Chemotherapy and Overall Survival in the Propensity Score-Matched Cohort



A, Overall cohort (n = 100). B, Intestinal histologic subtype (n = 61). C, Pancreatobiliary histologic subtype (n = 36).

Figure 3. Association of Gemcitabine-Based Chemotherapy and Overall Survival in the Propensity Score-Matched Cohort



A, Overall cohort (n = 127). B, Intestinal histologic subtype (n = 59). C, Pancreatobiliary histologic subtype (n = 54).

Opiaat- en insulín-gebruik na totale pancreatectomie met eilandjes autotransplantatie bij chronische pancreatitis

Efficacy of total pancreatectomy with islet autotransplantation on opioid and insulin requirement in painful chronic pancreatitis: A systematic review and meta-analysis. MA Kempeneers et al. *Surgery*: September 2019 – Volume 166 – Issue 3 – p 263-270.

Pubmed ID: 31085044.

BACKGROUND AND OBJECTIVE: The rationale for total pancreatectomy in painful, treatment refractory, chronic pancreatitis is pain control. Concomitant islet cell autotransplantation can prevent the loss of islet cell function. This study aimed to systematically examine the impact of total pancreatectomy with islet cell autotransplantation on pain and quality of life.

METHODS: This meta-analysis was conducted according the Meta-analyses of Observational Studies in Epidemiology guideline. The Cochrane Library, PubMed, and Embase were searched for the following terms (1990 through April 2018): total pancreatectomy and chronic pancreatitis. Studies were included when addressing total pancreatectomy with islet cell autotransplantation for chronic pancreatitis in adults. Studies that reported no data on pain, endocrine function, or quality of life were excluded. Quality was assessed using the Newcastle-Ottawa scale for evaluation of all studies.

RESULTS: We included 15 observational studies evaluating 1,255 patients, of whom 28% had had endoscopic and 23% operative therapy. One year after total pancreatectomy with islet cell autotransplantation, the opioid-free rate had improved from between 0% and 15% to 63% (95% CI 46–77), and the insulin-free rate had decreased from between 89.5% and 100% to 30% (95% CI 20–43). An alcoholic etiology was associated with a lesser insulin-free rate after total pancreatectomy with islet cell autotransplantation. Quality of life improved statistically after total pancreatectomy with islet cell autotransplantation. Publication bias was present for both opioid and insulin outcomes.

CONCLUSIONS: In selected patients with painful, treatment refractory, chronic pancreatitis, evidence shows that total pancreatectomy with islet cell autotransplantation is effective for pain control in almost two-thirds of patients, whereas the insulin-free rate is relatively low.

LEVERCHIRURGIE

RCT: Betere health-related QoL na laparoscopische dan open leverresectie bij colorectale levermetastasen

Quality of life from a randomized trial of laparoscopic or open liver resection for colorectal liver metastases. AA Fretland et al; BJS, Sept 2019 – Volume 106 – Issue 10, pages 1372-1380.

Pubmed ID: 31322735.

BACKGROUND: Most treatments for cancer cause a decline in patients' health - related quality of life (HRQoL). Limiting this decline is a universal goal for healthcare providers. Using minimally invasive instead of open surgical techniques might be one way to achieve this. The aim of this study was to compare postoperative HRQoL after open and laparoscopic liver resection.

METHOD: This was a predefined substudy of an RCT comparing open with laparoscopic liver resection. Patients with colorectal liver metastases were assigned randomly to open or laparoscopic parenchyma - sparing liver resection. HRQoL was assessed with the Short Form 36 questionnaire at baseline, and 1 and 4 months after surgery.

RESULTS: A total of 280 patients were randomized, of whom 273 underwent surgery (129 laparoscopic, 144 open); 682 questionnaires (83.3 per cent) were available for analysis. One month after surgery, patients in the laparoscopic surgery group reported reduced scores in two HRQoL domains (physical functioning and role physical), whereas those in the open surgery group reported reduced scores in five domains (physical functioning, role physical, bodily pain, vitality and social functioning). Four months after surgery, HRQoL scores in the laparoscopic group had returned to preoperative levels, whereas patients in the open group reported reduced scores for two domains (role physical and general health). The between - group difference was statistically significant in favour of laparoscopy for four domains after 1 month (role physical, bodily pain, vitality and social functioning) and for one domain after 4 months (role physical).

CONCLUSIONS: Patients assigned to laparoscopic liver surgery reported better postoperative HRQoL than those assigned to open liver surgery. For role limitations caused by physical health problems, patients in the laparoscopic group reported better scores up to 4 months after surgery. Registration number: NCT01516710 (<http://www.clinicaltrials.gov>).

	Between-groups difference in changes from baseline to 1 month	P	Between-group difference in changes from baseline to 4 months	P
Physical functioning	-1.4 (-6.1, 3.3)	0.564	-1.8 (-6.7, 3.2)	0.484
Role physical	-13.1 (-21.1, -5.1)	0.001	-9.9 (-18, -1.6)	0.019
Bodily pain	-11.6 (-19.4, -3.8)	0.003	-6.3 (-14.4, 1.7)	0.124
General health	0.4 (-3.2, 3.9)	0.837	-1.8 (-7.0, 3.3)	0.490
Vitality	-6.8 (-12, -1.0)	0.023	-3.2 (-9.3, 2.8)	0.295
Social functioning	-8.1 (-15.3, -1.0)	0.026	-5.1 (-12.5, 2.2)	0.174
Role emotional	-2.0 (-9.5, 5.4)	0.59	-2.3 (-10.0, 5.4)	0.553
Mental health	0.64 (-3.8, 5.1)	0.78	-1.2 (-5.9, 3.4)	0.604

Values in parentheses are 95 per cent confidence intervals. The analysis included only patients who completed at least one Short Form 36 questionnaire (laparoscopic, 127; open, 143). Values were estimated by a linear mixed model.

RCT: vroege cholecystectomie versus opname bij voorspelde milde biliaire pancreatitis

Gallstone Pancreatitis: Admission Versus Normal Cholecystectomy—a Randomized Trial (Gallstone PANC Trial). KM Mueck et al. *Annals of Surgery*: August 2019, Volume 270, Issue 2, p 519-527.

Pubmed ID: 31415304.

INTRODUCTION: Early cholecystectomy shortly after admission for mild gallstone pancreatitis has been proposed based on observational data. We hypothesized that cholecystectomy within 24 hours of admission versus after clinical resolution of gallstone pancreatitis that is predicted to be mild results in decreased length-of-stay (LOS) without an increase in complications..

METHODS: Adults with predicted mild gallstone pancreatitis were randomized to cholecystectomy with cholangiogram within 24 hours of presentation (early group) versus after clinical resolution (control) based on abdominal exam and normalized laboratory values. Primary outcome was 30-day LOS including readmissions. Secondary outcomes were time to surgery, endoscopic retrograde cholangiopancreatography (ERCP) rates, and postoperative complications. Frequentist and Bayesian intention-to-treat analyses were performed.

RESULTS: Baseline characteristics were similar in the early (n = 49) and control (n = 48) groups. Early group had fewer ERCPs (15% vs 29%, P = 0.038), faster time to surgery (16 h vs 43 h, P < 0.005), and shorter 30-day LOS (50 h vs 77 h, RR 0.68 95% CI 0.65 – 0.71, P < 0.005). Complication rates were 6% in early group versus 2% in controls (P = 0.613), which included recurrence/progression of pancreatitis (2 early, 1 control) and a cystic duct stump leak (early). On Bayesian analysis, early cholecystectomy has a 99% probability of reducing 30-day LOS, 93% probability of decreasing ERCP use, and 72% probability of increasing complications.

CONCLUSIONS: In patients with predicted mild gallstone pancreatitis, cholecystectomy within 24 hours of admission reduced rate of ERCPs, time to surgery, and 30-day length-of-stay. Minor complications may be increased with early cholecystectomy. Identification of patients with predicted mild gallstone pancreatitis in whom early cholecystectomy is safe warrants further investigation.

TABLE 3. Negative Binomial Regression for Length of Stay and Number of Procedures

	Control Group, n = 48	Early Group, n = 49	IRR	95% CI	P Value
Preoperative LOS, h	43 (34–63)	16 (13–21)	0.34	0.32–0.37	<0.005
Postoperative LOS, hours	19 (11–43)	23 (10–54)	0.99	0.93–1.05	0.641
Index Hospital LOS, h	77 (52–111)	45 (26–72)	0.67	0.64–0.70	<0.005
Number of procedures at 30 d, n	1 (1–1)	1 (1–2)	0.82	0.58–1.17	0.282
Total 30 d Length of stay, h	77 (52–111)	50 (27–82)	0.68	0.65–0.71	<0.005

Adjusted for American Society for Gastrointestinal Endoscopy Risk of Choledocholithiasis classification.

BARIATRISCHE CHIRURGIE

Bariatrische chirurgie leidt tot minder colorectale laesies?

Bariatric surgery is independently associated with a decrease in the development of colorectal lesions. M Kwak et al. *Surgery*: September 2019 – Volume 166 – Issue 3 – p 322-326.

Pubmed ID: 31097317.

BACKGROUND AND OBJECTIVE: Obesity is a risk factor for colorectal cancer and possibly the formation of precancerous, colorectal polyps. Bariatric surgery is very effective for long-term weight loss; however, it is not known whether bariatric surgery decreases the risk of subsequent colonic neoplasia. We hypothesized that bariatric surgery would decrease the risk of developing colorectal lesions (new cancer and precancerous polyps).

METHODS: We reviewed all patients (n = 3,676) who underwent bariatric surgery (gastric bypass, sleeve gastrectomy, or gastric banding) at the University of Virginia (Charlottesville, VA) 1985–2015. Obese, nonoperative patients (n = 46,873) from an institutional data repository were included as controls. Cases and controls were propensity score matched 1:1 by demographics, comorbidities, body mass index, and socioeconomic factors. The matched cohort was compared by univariate analysis and conditional logistic regression.

RESULTS: A total of 4,462 patients (2,231 per group) with a median follow-up of 7.8 years were well-matched with no statistically significant baseline differences in initial body mass index (48 vs 49 kg/m²), sex, and age in addition to other comorbidities (all P > .05). The operative cohort had more weight loss (55.5% vs –1.4% decrease in excess body mass index, P < .0001). The operative cohort developed fewer colorectal lesions (2.4% vs 4.8%, P < .0001). We observed no differences in polyp characteristics or staging for patients who developed cancer (all P > .05). After risk adjustment, bariatric surgery was independently associated with a decrease in new colorectal lesions (OR 0.62, 95% CI 0.42–0.91, P = .016).

CONCLUSION: Bariatric surgery was associated with lesser, risk-adjusted incidence of new colorectal lesions in this large population of propensity matched patients undergoing bariatric surgery compared with a control group not undergoing bariatric surgery. These results suggest the benefits of bariatric surgery may extend beyond weight loss and mitigation of comorbidities
