

# DE LEESTAFEL

## DECEMBER 2018

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*Een Maandelijkse Selectie van Wetenschappelijke GE-nieuws*

### Coloproctologie

#### **Watch and wait veilig voor de behandeling van het rectumcarcinoom? Een systematic review**

*Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Systematic Review and Pooled Analysis.* Dattani et al. *Ann Surg* 2018; 268 (6); 955 – 967.

Pubmed ID: 29746338

**OBJECTIVE:** The aim of this study was to evaluate the oncological and survival outcomes of a Watch and Wait policy in rectal cancer after a clinical complete response (cCR) following neoadjuvant chemoradiotherapy.

**BACKGROUND:** The detection of a cCR after neoadjuvant treatment may facilitate a nonoperative approach in selected patients. However, the long-term safety of this strategy remains to be validated.

**METHOD:** This is a systematic review of the literature to determine the oncological outcomes in Watch and Wait patients. The primary outcome was the cumulative rate of local regrowth, success of salvage surgery, and incidence of metastases. We also evaluated survival outcomes. A pooled analysis of manually extracted summary statistics from individual studies was carried out using inverse variance weighting.

**RESULTS:** Seventeen studies comprising 692 patients were identified; incidence of cCR was 22.4% [95% confidence interval (CI), 14.3-31.8]. There were 153 (22.1%) local regrowths, of which 96% (n = 147/153) manifested in the first 3 years of surveillance. The 3-year cumulative risk of local regrowth was 21.6% (95% CI, 16.0-27.8). Salvage surgery was performed in 88% of patients, of which 121 (93%) had a complete (R0) resection. Fifty-seven metastases (8.2%) were detected, and 35 (60%) were isolated without evidence of synchronous regrowths; 3-year incidence was 6.8% (95% CI, 4.1-10.2). The 3-year overall survival was 93.5% (95% CI, 90.2-96.2).

**CONCLUSION:** In rectal cancer patients with a cCR following neoadjuvant chemoradiotherapy, a Watch and Wait policy appears feasible and safe. Robust surveillance with early detection of regrowths allows a high rate of successful salvage surgery, without an increase in the risk of systemic disease, or adverse survival outcomes.

# Machine learning in het voorspellen van nabloeding na colorectale chirurgie

*Postoperative bleeding risk prediction for patients undergoing colorectal surgery.* Chen et al. *Surgery* 2018; 164 (6); 1209 – 1216.

Pubmed ID: 30033185

**BACKGROUND:** There is limited consensus regarding risk factors for postoperative bleeding. The objective of this work was to investigate the capability of machine learning techniques in combination with practice-based longitudinal electronic medical record data for identifying potential new risk factors for postoperative bleeding and predicting patients at high risk of postoperative bleeding.

**METHODS:** A retrospective study was conducted for patients who underwent colorectal surgery 1998-2015 at a single tertiary referral center. Various predictors were extracted from electronic medical record. The outcome of interest was the occurrence of postoperative bleeding within 7 days of surgery. Logistic regression and gradient boosting machine models were trained. Area under the receiver operating curve and area under the precision recall curve were used to evaluate the performance to different models.

**RESULTS:** Of 13,399 cases undergoing colorectal resection, 1,680 (12.5%) experienced postoperative bleeding. A total of 299 variables were evaluated. Logistic regression and gradient boosting machine models returned an area under the receiver operating curve of 0.735 and 0.822 and area under the precision recall curve of 0.287 and 0.423, respectively. In addition to well-known risk factors for postoperative bleeding, nutrition (ranked third), weakness (ranked fifth), patient mobility (ranked sixth), and activity level (ranked eighth) were found to be novel predictors in the gradient boosting machine model based on permutation importance (Table 6).

**Table 6**

Comparison of variable importance between different models that were trained using all preoperative and intraoperative variables found to be important using Boruta variable selection.

Risk factor	LR $\beta$ (P)	GBM (rank)
Anemia*	1.252 (<.001)	100 (1)
Hemophilia*	1.464 (<.001)	47.4 (2)
Nutrition	-.114 (.343)	41.7 (3)
Surgical length*	.006 (<.001)	36.3 (4)
Weakness	.776 (<.001)	30.2 (5)
Mobility	-.368 (.284)	25.6 (6)
Heart failure*	1.019 (<.001)	18.4 (7)
Activity level	-.050 (.320)	13.2 (8)
Kidney disease*	.908 (.004)	12.0 (9)
Preoperative bleeding*	2.230 (<.001)	8.1 (10)

\* Denotes known risk factors for postoperative bleeding. The  $\beta$  coefficient and P value are shown for LR. The variable importance for GBM is based on permutation importance.

**CONCLUSION:** The study identified measures of functional capacity of patient as novel predictors of postoperative bleeding. The study found that risk of postoperative bleeding can be assessed, allowing for better use of human resources in addressing this important adverse event after surgery.

## UPPER GI

### Lymfeklieren en chirurgie in de CRITICS trial

*Surgicopathological Quality Control and Protocol Adherence to Lymphadenectomy in the CRITICS Gastric Cancer Trial.* Claassen et al. *Ann Surg* 2018; 268 (6); 1008 – 1013.

Pubmed ID: 28817437

**OBJECTIVE:** The purpose of this study was to evaluate surgicopathological quality and protocol adherence for lymphadenectomy in the CRITICS trial.

**SUMMARY OF BACKGROUND DATA:** Surgical quality assurance is a key element in multimodal studies for gastric cancer. In the multicenter CRITICS trial (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach), patients with resectable gastric cancer were randomized for preoperative chemotherapy, followed by gastrectomy with a D1+ lymphadenectomy (removal of stations 1 to 9 and 11), followed by either chemotherapy or chemoradiotherapy.

**METHODS:** Surgicopathological compliance was defined as removal of  $\geq 15$  lymph nodes. Surgical compliance was defined as removal of the indicated lymph node stations. Surgical contamination was defined as removal of lymph node stations that should be left in situ. The Maruyama Index (MI, lower is better), which has proven to be an indicator of surgical quality and is strongly associated with survival, was analyzed.

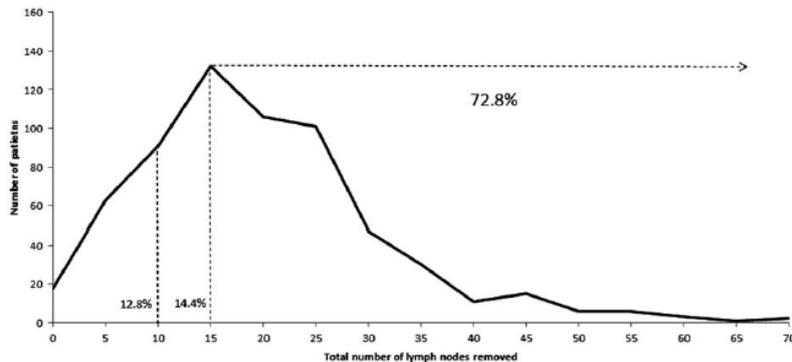


FIGURE 3. Surgicopathological compliance.

**RESULTS:** Between 2007 and 2015, 788 patients were randomized, of whom 636 patients underwent a gastrectomy with curative intent. Surgicopathological compliance occurred in 72.8% (n = 460) of the patients and improved from 55.0% (2007) to 90.0% (2015). Surgical compliance occurred in 41.1% (n = 256). Surgical contamination occurred in 59.6% (n = 371). Median MI was 1 (range 0 to 136).

**CONCLUSION:** Surgical quality in the CRITICS trial was excellent, with a MI of 1. Surgicopathological compliance improved over the years. This might be explained by the quality assurance program within the study and centralization of gastric cancer surgery in the Netherlands.

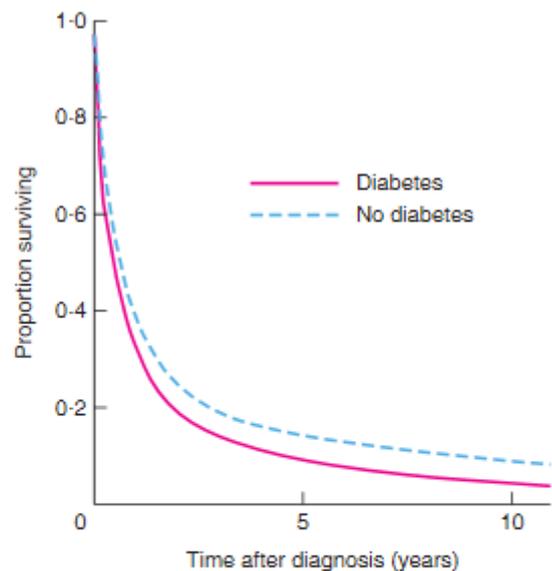
## Slechtere overleving van patiënten met adenocarcinoom van de maag en diabetes mellitus

*Population - based cohort study of diabetes mellitus and mortality in gastric adenocarcinoma. Zheng et al. BJS 2018; 105 (13); 1799 – 1806.*

Pubmed ID: 30051463

**BACKGROUND:** Gastric adenocarcinoma is a common cause of cancer death globally. It remains unclear whether coexisting diabetes mellitus influences survival in patients with this tumour. A cohort study was conducted to determine whether coexisting diabetes increases mortality in gastric adenocarcinoma.

**METHODS:** This nationwide population-based cohort study included all patients diagnosed with gastric adenocarcinoma in Sweden between 1990 and 2014. Cox proportional hazards regression and



No. at risk			
Diabetes	2173	233	119
No diabetes	21418	2424	1191

competing risks regression were used to assess the influence of coexisting diabetes on disease-specific mortality in gastric adenocarcinoma with adjustment for sex, age, calendar year and co-morbidity (Charlson Co-morbidity Index score excluding diabetes).

**RESULTS:** Among 23 591 patients with gastric adenocarcinoma, 2806 (11.9 per cent) had coexisting diabetes. Overall, patients with diabetes had a moderately increased risk of disease-specific mortality after diagnosis of gastric adenocarcinoma compared with those without diabetes, as shown by both Cox regression (hazard ratio (HR) 1.17, 95 per cent c.i. 1.11 to 1.22) and competing risks regression (sub-HR 1.08, 1.02 to 1.13). The HRs for disease-specific mortality were notably increased in diabetic patients without other co-morbidity (HR 1.23, 1.15 to 1.32) and in diabetic patients who had surgery with curative intent (HR 1.27, 1.16 to 1.38).

**CONCLUSION:** These findings indicate a worse prognosis in patients with gastric adenocarcinoma and coexisting diabetes compared with those without diabetes.

## HPB

### Gedilateerde ductus pancreaticus bij IPMN

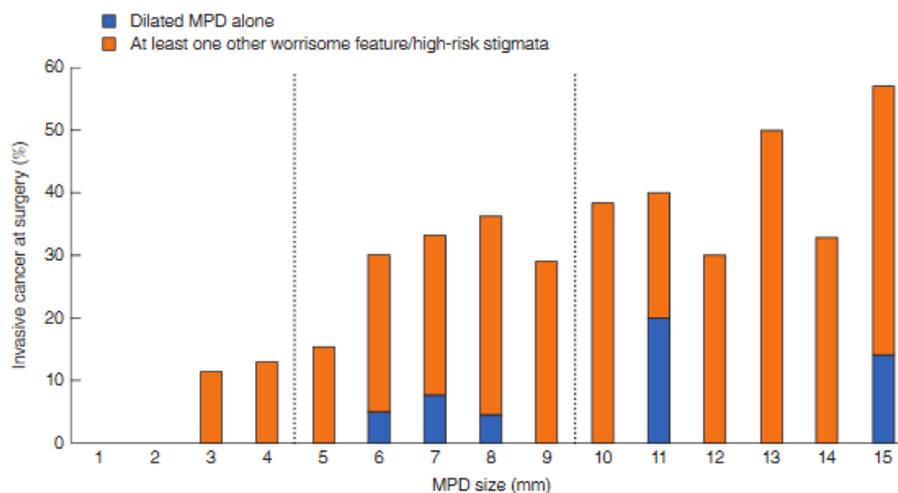
*Importance of main pancreatic duct dilatation in IPMN undergoing surveillance. Marchegiani et al; BJS 2018; 105 (13); 1825-1834.*

Pubmed ID: 30106195

**BACKGROUND:** The association between risk of pancreatic cancer and a dilated main pancreatic duct (MPD) in intraductal papillary mucinous neoplasm (IPMN) is debated. The aim of this study was to assess the role of MPD size in predicting pancreatic cancer in resected IPMNs and those kept under surveillance.

**METHOD:** All patients with IPMN referred to the Pancreas Institute, University of Verona Hospital Trust, from 2006 to 2016 were included. The primary endpoint was the occurrence of malignancy detected at surgery or during follow - up.

**RESULTS:** The final cohort consisted of 1688 patients with a median follow - up of 60 months. Main pancreatic duct dilatation was associated with other features of malignancy in both the resected and surveillance groups. In patients who underwent resection, only a MPD of at least 10 mm was an independent predictor of malignancy. In patients kept under surveillance, MPD dilatation was not associated with malignancy. Fifteen of 71 patients (21 per cent) with malignancy in the resection cohort had a dilated MPD alone, whereas only one of 30 (3 per cent) under surveillance with MPD dilatation alone developed malignancy. Patients with a dilated MPD and other worrisome features had an increased 5 - year cumulative incidence of malignancy compared with those with a non - dilated duct (11 versus 1.2 per cent;  $P < 0.001$ ); however, the risk of malignancy was not significantly increased in patients with a dilated MPD alone (4 versus 1.2 per cent;  $P = 0.448$ ).



**Fig. 2** Rate of invasive cancer after surgical resection stratified by main pancreatic duct (MPD) size in patients with a dilated MPD alone and among those presenting with at least one other worrisome feature/high-risk stigmata

**CONCLUSION:** In patients under surveillance, a dilated MPD alone was not associated with an increased incidence of malignancy in IPMN.

## R0 versus R1: alleen belangrijk bij pancreaskopresectie?

*R0 Versus R1 Resection Matters after Pancreaticoduodenectomy, and Less after Distal or Total Pancreatectomy for Pancreatic Cancer.* Demir et al; Ann Surg 2018; 268 (6); 1058-1068.

Pubmed ID: 28692477

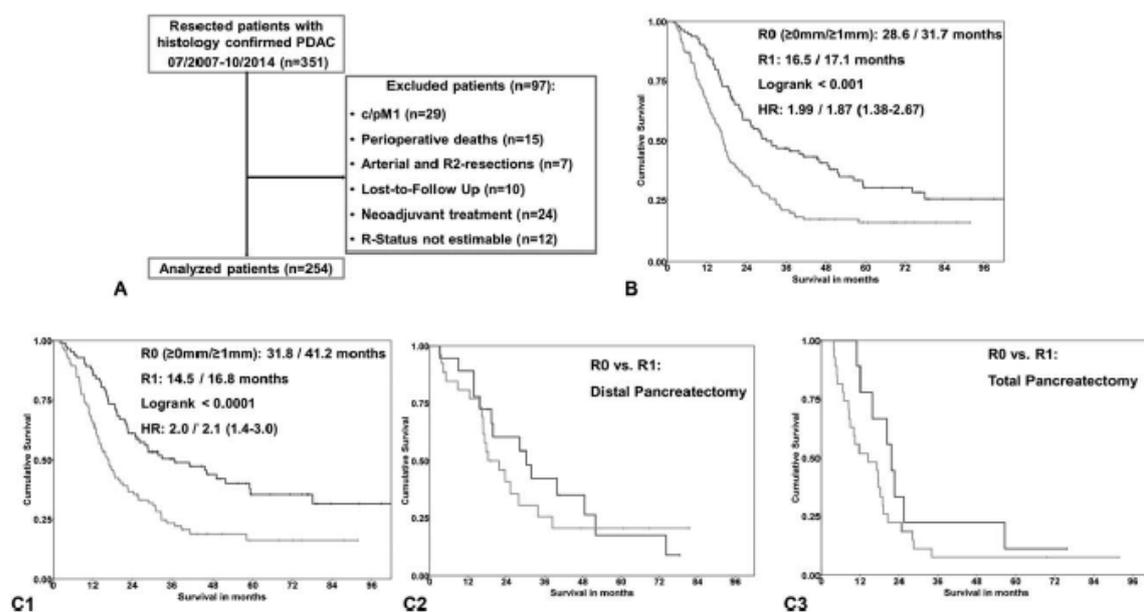
**OBJECTIVE:** The aim of this study was to decipher the true importance of R0 versus R1 resection for survival in pancreatic ductal adenocarcinoma (PDAC).

**SUMMARY OF BACKGROUND DATA:** PDAC is characterized by poor survival, even after curative resection. In many studies, R0 versus R1 does not result in different prognosis and does not affect the postoperative management.

**METHODS:** Pubmed, Embase, and Cochrane databases were screened for prognostic studies on the association between resection status and survival. Hazard ratios (HRs) were pooled in a meta-analysis. Furthermore, our prospective database was retrospectively screened for curative PDAC resections according to inclusion criteria (n = 254 patients) between July 2007 and October 2014.

**RESULTS:** In the meta-analysis, R1 was associated with a decreased overall survival [HR 1.45 (95% confidence interval, 95% CI 1.37-1.52)] and disease-free survival [HR 1.44 (1.30-1.59)] in PDAC when compared with R0. Importantly, this effect held true only for pancreatic head resection both in the meta-analysis [R0  $\geq 0$  mm: HR 1.21 (1.05-1.39) vs R0  $\geq 1$  mm: HR 1.66 (1.46-1.89)] and in our cohort (R0  $\geq 0$  mm: 31.8 vs 14.5 months, P < 0.001; R0  $\geq 1$  mm, 41.2 vs 16.8 months; P < 0.001). Moreover, R1 resections were associated with advanced tumor disease, that is, larger tumor size, lymph node metastases, and extended resections. Multivariable Cox proportional hazard model suggested G3, pN1, tumor size, and R1 (0 mm/1 mm) as independent predictors of overall survival.

**CONCLUSION:** Resection margin is not a valid prognostic marker in publications before 2010 due to heterogeneity of cohorts and lack of standardized histopathological examination. Within standardized pathology protocols, R-status' prognostic validity may be primarily confined to pancreatic head cancers.



**FIGURE 3.** R0 resection resulted in a marked survival benefit after pancreatic head resection, but not after distal or total pancreatectomy, for pancreatic cancer in the institutional cohort (Department of Surgery, Klinikum rechts der Isar, TU Munich, 2007–2015). A, The characteristics of excluded patients in the survival analyses. B, R0 was associated with a remarkably improved overall survival (R0  $> 0$  mm: 28.6 mo, R0  $\geq 1$  mm: 31.7 mo) when compared with R1 resection (R0  $> 0$  mm: 16.5 mo, R0  $\geq 1$  mm: 17.1 mo). Depicted is the graph for R0  $\geq 1$  mm. C, Importantly, the survival benefit for R0 was present only after pancreaticoduodenectomy, but not after distal or total pancreatectomy. Depicted is the graph for R0  $\geq 1$  mm. mo indicates months.

## LEVERCHIRURGIE

# Laparoscopisch *versus* open chirurgie voor colorectale levermetastasen

*Laparoscopic vs Open Surgery for Colorectal Liver Metastases.* Ratti et al; JAMA Surg 2018; 153 (11); 1028-1035.

Pubmed ID: 30027220

**IMPORTANCE:** Surgery represents the mainstay treatment of colorectal liver metastases. Indications for the laparoscopic approach in this setting have been widened and there is a need to confirm the benefits of minimally invasive liver surgery (MILS) in patients with complex disease states.

**OBJECTIVES:** To compare outcomes of laparoscopic surgery with those of open surgery for liver metastases from colorectal cancer, focusing on the characteristics of modern MILS and therefore overcoming possible selection bias related to different policies for patients' eligibility for MILS over time.

**DESIGN, SETTING, AND PARTICIPANTS:** A cohort study of 885 resections performed for liver metastases from colorectal cancer between January 1, 2004, and June 30, 2017, at the Hepatobiliary Surgery Unit of San Raffaele Hospital, Milano, Italy, comprising 187 laparoscopic and 698 open resections. Procedures performed using the MILS approach with a ratio of MILS to total resections per year of more than 30% were considered and were matched by propensity scores (ratio of 1:4) to procedures performed using the open approach with a ratio of MILS to total resections per year of less than 30%.

**MAIN OUTCOMES AND MEASURES:** The primary end point was short-term outcomes, including morbidity, mortality, functional recovery, and interval between surgery and adjuvant treatments; the secondary end point was long-term outcomes.

### RESULTS

Among this cohort (104 patients in the MILS group; 46 women and 58 men; median age, 62 years [range, 35-81 years]; and 412 patients in the open group; 181 women and 231 men; median age, 60 years [range, 37-80 years]), primary end-point data showed a significantly higher incidence of postoperative morbidity in patients who underwent open resections compared with those who underwent MILS (94 [22.8%] vs 21 [20.2%];  $P = .04$ ). Patients in the MILS group had fewer major complications (Dindo-Clavien grades III-V) compared with patients in the open group (Dindo-Clavien grades III-V; 7 [6.7%] vs 35 [8.5%];  $P = .03$ ) as well as shorter lengths of stay (median [range] duration, 3 [2-35] vs 5 [4-37] days;  $P = .02$ ). Oncologic results were not compromised by the laparoscopic approach (Figure 2A-B).

**CONCLUSIONS AND RELEVANCE:** In this study, the results of the propensity score matching analysis between modern laparoscopic surgery and previous open surgery appear to confer more comparable cohorts for complexity, further supporting the advantages of laparoscopy in the surgical treatment of liver metastases from colorectal cancer. The increase in use that laparoscopy has experienced appears to be based on increased feasibility, widening of eligibility criteria for patients, enhanced clinical effectiveness, and oncologic outcomes. All these elements together suggest that up to 70% of patients appear to be candidates for this minimally invasive surgical approach in high-volume centers.

# Uitkomsten van laparoscopische leverresectie geconverteerd naar open procedure

*Conversion for Unfavorable Intraoperative Events Results in Significantly Worse Outcomes During Laparoscopic Liver Resection: Lessons Learned From a Multicenter Review of 2861 Cases.* Halls et al.; Ann Surg 2018; 268 (6); 1051-1057.

Pubmed ID: 28582270

**OBJECTIVE:** To investigate the risk factors for conversion during laparoscopic liver resection and its effect on patient outcome in a large cohort of patients. Additional analysis of outcomes in patients who required conversion for unfavorable intraoperative findings and conversion for unfavorable intraoperative events will be performed to establish if the cause of conversion affects outcome.

**SUMMARY BACKGROUND DATA:** Multiple previous studies demonstrate that laparoscopic liver surgery reduces intraoperative blood loss, hospital stay, and morbidity while maintaining comparable oncological and survival outcomes when compared with open liver resections. However, limited information is available regarding the possible sequelae of conversion to open surgery, especially with regards to cause of conversion.

**METHODS:** A retrospective analysis of 2861 cases from prospectively maintained databases of 7 tertiary liver centers across Europe was performed.

**RESULTS:** Neo-adjuvant chemotherapy, previous liver resection(s), resections for malignant lesions, postero-superior location, and the extent of the resection are associated with an increased risk of conversion. Patients who require conversion have longer operations with higher blood loss; a longer HDU and total hospital stay, increased frequency and severity of complications and higher 30- and 90-day mortality. Patients who had an elective conversion for an unfavorable intraoperative finding had better outcomes than patients who had an emergency conversion secondary to an unfavorable intraoperative event in terms of HDU and total hospital stay, severity of complication, and 90-day mortality.

**CONCLUSIONS:** Our study highlights the risk factors for conversion and suggests that conversion for unfavorable intraoperative events is associated with worse outcomes.

## BARIATRISCHE CHIRURGIE

### Roux-en-Y Gastric Bypass: 10-jaars resultaten

*Roux-en-Y Gastric Bypass: Ten-year Results in a Cohort of 658 Patients.* Duvoisin et al.; Ann Surg 2018; 268 (6); 1019-1029.

Pubmed ID: 29194086

**OBJECTIVE:** The aim of this paper is to report, with a high follow-up rate, 10-year results in a large cohort of patients after Roux-en-Y gastric bypass (RYGBP) done essentially by laparoscopy.

**BACKGROUND:** RYGBP has been performed for 50 years, including 20 years by laparoscopy, yet very few long-term results have been reported, mostly after open surgery.

**METHODS:** Prospective bariatric database established since the introduction of bariatric surgery. Retrospective data analysis on weight loss, long-term complications, quality of life, and comorbidities.

**RESULTS:** In all, 658 consecutive patients (515 women/143 men) were included: 554 with primary RYGBP, 104 with reoperative RYGBP. There was 1 (0.15%) postoperative death. Thirty-two (5%) patients died during follow-up from causes unrelated to surgery. Ten years after primary RYGBP, patients lost  $28.6 \pm 10.5\%$  of their initial weight, corresponding to a mean of 13.2 body mass index (BMI) units. Among them, 72.8% achieved a BMI <35. Weight loss  $\geq 20\%$  was seen in 80.3% and <10% in 3.9% of patients. Results were similar in patients undergoing primary or reoperative RYGBP, but were better in patients who were initially less obese (BMI <50 kg/m) than in superobese patients.

Quality of life and comorbidities significantly improved with 80% resolution or improvement of metabolic comorbidities. All patients required supplementations, and 14.6% required long-term reoperation.

**CONCLUSIONS:** RYGBP provides long-term satisfactory weight loss up to 10 years, and significantly improves quality of life and comorbidities. Long-term complications requiring reoperation can develop. Mineral and vitamin supplementation are universally necessary. Other more effective surgical options should be discussed in patients with very severe obesity.

## Effectiviteit van bariatrische procedures

*Comparative Effectiveness and Safety of Bariatric Procedures in Medicare-Eligible Patients: A Systematic Review.* Panagiotou et al.; JAMA Surg 2018; 153 (11);e183326.

Pubmed ID: 30193303

**IMPORTANCE:** The prevalence of obesity in patients older than 65 years is increasing. A substantial number of beneficiaries covered by Medicare meet eligibility criteria for bariatric procedures.

**OBJECTIVE:** To assess the comparative effectiveness and safety of bariatric procedures in the Medicare-eligible population.

**EVIDENCE REVIEW:** This systematic review was conducted according to the PRISMA guidelines. Articles were identified through searches of PubMed, Embase, CINAHL, PsycINFO, Cochrane Central Trials Registry, Cochrane Database of Systematic Reviews, and scientific information packages from manufacturers, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and US Food and Drug Administration drugs and devices portals from January 1, 2000, to June 31, 2017. Randomized and nonrandomized comparative studies that evaluated bariatric procedures in the Medicare-eligible population were eligible. Six researchers extracted data on design, interventions, outcomes, and study quality. Findings were synthesized qualitatively; a planned meta-analysis was not undertaken owing to clinical heterogeneity.

**FINDINGS:** A total of 11 455 citations were screened for eligibility. Of those, 16 met the eligibility criteria. Compared with no surgery or conventional weight-loss treatment, bariatric surgery results in greater weight loss. Overall mortality after 30 days is lower among bariatric patients (hazard ratio, HR, 0.50; 95% CI, 0.31-0.79, in the study with the longest follow-up of 5.9 years), although, based on 1 study, mortality within 30 days of surgery was higher than in nonsurgically treated controls (1.55% vs 0.53%;  $P < .001$ ). Bariatric surgery is associated with lower risk of cardiovascular disease (HR, 0.59; 95% CI, 0.44-0.79 in the largest study comparison) and with improvements in respiratory, musculoskeletal, metabolic, and renal outcomes (increase in estimated glomerular filtration rate, 9.84; 95% CI, 8.05-11.62 mL/min/1.73m<sup>2</sup>). Compared with sleeve gastrectomy (SG) and adjustable gastric banding (AGB), Roux-en-Y gastric bypass (RYGB) appears to be associated with greater weight loss (percent excess weight loss, 23.8% [95% CI, 16.2%-31.4%] at the longest follow-up of 4 years) but the 3 procedures have similar associations with most non-weight loss outcomes. Overall postoperative complications are not statistically significantly different between RYGB and SG, although major and/or serious complications are more common after RYGB. However, these associations are susceptible to at least moderate risk of confounding, selection, or measurement biases.

**CONCLUSIONS AND RELEVANCE:** In the Medicare population, there is low to moderate strength of evidence that bariatric surgery as a weight loss treatment improves non-weight loss outcomes. Well-designed comparative studies are needed to credibly determine the treatment effects for bariatric procedures in this patient population.