ISSN 1948-9366 (online)

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2019 July 27; 11(7): 303-332

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 11 Number 7 July 27, 2019

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World Journal of Gastrointestinal Surgery

Volume 11 Number 7 July 27, 2019

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The *WJGS* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Varut Lohsiriwat, Shu-You Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
July 27, 2019

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2019 July 27; 11(7): 303-307

DOI: 10.4240/wjgs.v11.i7.303

ISSN 1948-9366 (online)

EDITORIAL

Optimizing neoadjuvant radiotherapy for resectable and borderline resectable pancreatic cancer using protons

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Author contributions: Nichols RC and Rutenberg MS equally contributed to this paper.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose. Funding: None.

Manuscript source: Invited manuscript

Received: May 16, 2019
Peer-review started: May 20, 2019
First decision: May 31, 2019
Revised: June 25, 2019
Accepted: July 25, 2019
Article in press: July 26, 2019
Published online: July 27, 2019

P-Reviewer: Aosasa S
S-Editor: Ma YJ
L-Editor: A
E-Editor: Xing YX

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Abstract

Approximately 25% of patients diagnosed with pancreatic cancer present with non-metastatic resectable or borderline resectable disease. Unfortunately, the cure rate for these "curable" patients is only in the range of 20%. Local-regional failure rates may exceed 50% after margin-negative, node-negative pancreatectomy, but up to 80% of resections are associated with regional lymph node or margin positivity. While systemic drug therapy and chemotherapy may prevent or delay the appearance of distant metastases, it is unlikely to have a significant impact on local-regional disease control. Preoperative radiotherapy would represent a rational intervention to improve local-regional control. The barrier to preoperative radiotherapy is the concern that it could potentially complicate what is already a long and complicated operation. When the radiotherapy is delivered with X-rays (photons), the entire cylinder of the abdomen is irradiated; therefore, an operating surgeon may be reluctant to accept the associated risk of increased toxicity. When preoperative radiotherapy is delivered with protons, however, significant bowel and gastric tissue-sparing is achieved and clinical outcomes indicate that proton therapy does not increase the risk of operative complications nor extend the length of the procedure.

Key words: Radiation oncology; Pancreatic cancer; Proton therapy

Core tip: Patients with resectable and borderline resectable pancreatic cancer are at a high risk of suffering postoperative local-regional failure. Preoperative radiotherapy directed to gross disease and regional lymphatic beds at high risk of harboring microscopic disease appears to be an oncologically rational intervention to reduce this risk. When proton-based radiotherapy addressing gross disease as well as high-risk regional lymphatic beds is delivered prior to surgery, it does not appear to increase the risk of

surgical complications or the duration of surgery. Because of this, we would argue that proton-based preoperative radiotherapy should be considered for patients with resectable and borderline resectable disease.

Citation: Nichols RC, Rutenberg M. Optimizing neoadjuvant radiotherapy for resectable and borderline resectable pancreatic cancer using protons. *World J Gastrointest Surg* 2019; 11(7): 303-307
URL: https://www.wjgnet.com/1948-9366/full/v11/i7/303.htm
DOI: https://dx.doi.org/10.4240/wjgs.v11.i7.303

SCOPE OF THE PROBLEM

It is an accepted oncologic principle that local disease control is a necessary condition for curing cancer. In the setting of a pancreatic malignancy, it is also generally accepted that extirpative surgery is a necessary condition for local control. For numerous reasons, however, it is arguable that surgery alone cannot reliably achieve local control in this setting. Historical data suggest that, even in the setting of negative surgical margins and negative lymph nodes, patients undergoing pancreaticoduodenectomy for localized pancreatic cancer experience a 50% to 80% risk of local-regional failure[1,2]. This local-regional failure rate is not unexpected for this procedure given that a portion of the involved organ (the pancreas) is not removed from the patient and given the close proximity of critical structures that cannot be sacrificed (*i.e.*, the superior mesenteric artery); when negative margins are in fact achieved, they often tend to be close.

Having established that local-regional failure is a significant problem for patients undergoing surgery with negative margins and negative lymph nodes, two contemporary large series from highly respected research institutions suggest that node negativity and margin negativity may be less common than generally appreciated. Investigators from Johns Hopkins University (Baltimore, MD, United States) reviewed the outcomes for 905 patients undergoing pancreaticoduodenectomy from 1995 to 2005 and reported a 79.3% incidence of lymph node positivity and a 41.1% incidence of margin positivity[3]. A similar series from investigators at Memorial Sloan Kettering Cancer Center (New York, NY, United States) reviewing 625 pancreatic resections from 2000 to 2009 reported a 16% incidence of margin positivity along with a 70% incidence of lymph node positivity[4].

ROLE FOR RADIOTHERAPY

Recognizing that local-regional failure is a common occurrence for patients undergoing margin-negative and lymph node-negative resections and simultaneously recognizing that a large share of resections are associated with margin positivity and lymph node positivity, it would appear evident that additional therapies would need to be offered to achieve a high likelihood of local-regional disease control. While systemic drug therapies may reduce the risk of hematogenous dissemination of malignancy, there are no other disease sites where such therapies have been demonstrated to improve local-regional control. Radiotherapy, however, would appear to be the most relevant intervention to address this problem.

POSTOPERATIVE RADIOTHERAPY

Postoperative radiotherapy, one of several radiotherapy options, has the potential to reduce local-regional failures to some degree. This intervention, however, has two important limitations: First, it is difficult to initiate postoperative radiotherapy before 10 to 12 wk have elapsed after major abdominal surgery. This interval allows time for microscopic foci of disease to grow unchecked in a hypoxic tumor bed. To make matters worse, many patients with indications for postoperative radiotherapy do not receive it due to postoperative complications. Secondly, the dose of radiotherapy that can safely be delivered after pancreaticoduodenectomy is generally no higher than 50 Gy with conventional fractionation.

Clinical data suggest that, even when postoperative radiotherapy is delivered,

patients experience a nontrivial incidence of local failure. Investigators from Massachusetts General Hospital (Boston, MA, United States) reviewed the medical records of 86 patients undergoing postoperative radiotherapy and demonstrated a 36% local failure rate at 3 years[5]. Data from the RTOG 97-04 trial demonstrated a 23% to 28% local-regional failure rate[6]. Given the difficulty in following these patients, it is likely that these data understate the actual local-regional failure rate. Finally, although valid criticisms of its methodology have been published, the ESPAC trials[7] suggest that postoperative X-ray-based radiotherapy may be associated with a nominal survival decrement[8,9]. In summary, it could be argued, based on radiobiologic principles as well as clinical outcome data, that postoperative radiotherapy is simply "too little and too late" to have a meaningful effect on local-regional disease control or survival.

PREOPERATIVE RADIOTHERAPY

From an oncologic perspective, preoperative radiotherapy would make a great deal of sense. In fact, preoperative radiotherapy is the standard intervention for gastrointestinal malignancies in the esophagus and rectum. Preoperative radiotherapy is also viewed as the ideal approach for the treatment of soft-tissue sarcomas. The advantage of preoperative radiotherapy is that it allows for sterilization of high-risk lymphatic sites prior to extirpative surgery. It may also increase the likelihood of a margin-negative resection because tumor shrinkage may occur away from critical structures such as the superior mesenteric artery. Finally, in regards to toxicity, while postoperative radiotherapy radiates normal tissues which will remain in the patient for the rest of his or her life, a large share of the bowel tissue that is irradiated preoperatively will be removed at the time of surgery.

While preoperative radiotherapy covering the primary tumor and at-risk lymph nodes makes sense oncologically, many surgeons are reluctant to employ this intervention given a concern that preoperative radiotherapy runs the risk of complicating what is already a complicated and time-consuming operation. Given the fact that the median operative time for a pancreaticoduodenectomy exceeds 6 ½ h[10], is understandable that a surgeon would be concerned about any intervention that could potentially lengthen the operation time.

PROTON RADIOTHERAPY

It is reasonable to be concerned that conventional X-ray based radiotherapy or intensity modulated X-ray therapy (IMRT), which involves delivering radiotherapy to the entire cylinder of the upper abdomen, might increase the risk of surgical complications. Proton radiotherapy, however, by virtue of improvements in dose distribution, would theoretically be associated with a lower risk of surgical complication while offering the oncologic benefit of neoadjuvant therapy (Figure 1).

An early study using dosimetric data comparing proton therapy and IMRT demonstrated statistically significant dose reductions to the small bowel, stomach, and right kidney[11]. Subsequent clinical data demonstrated, an absence of grade 3 toxicities for 20 patients treated with aggressive proton therapy for unresectable disease, and marginally resectable disease in the postoperative setting. Only three (15%) patients experienced grade 2 gastrointestinal toxicity in this series[12].

SURGERY AFTER PROTON THERAPY

Of particular interest from a surgical perspective, investigators at the University of Florida (Jacksonville, FL, United States) reported on a series of 5 patients who received high-dose proton radiotherapy as definitive treatment for unresectable disease who were ultimately able to undergo pancreatectomy[13]. Because these patients were felt unlikely to become surgical candidates, they all received full-dose radiotherapy to a dose of 59.4 Gy RBE over 33 fractions with concomitant capecitabine chemotherapy. The median duration of surgery for these patients was 419 minutes with a range of 290 min to 484 min. The median estimated blood loss was 850 mL. The median intensive care unit stay was 1 d. The median hospital stay was 10 d. These metrics were comparable to published data for patients undergoing pancreatectomy without prior radiotherapy[14-16]. Based on these data, we feel comfortable arguing that patients who might receive preoperative radiotherapy with protons to a lower dose (*i.e.*, 50 Gy RBE) for resectable or borderline resectable disease are not at risk of

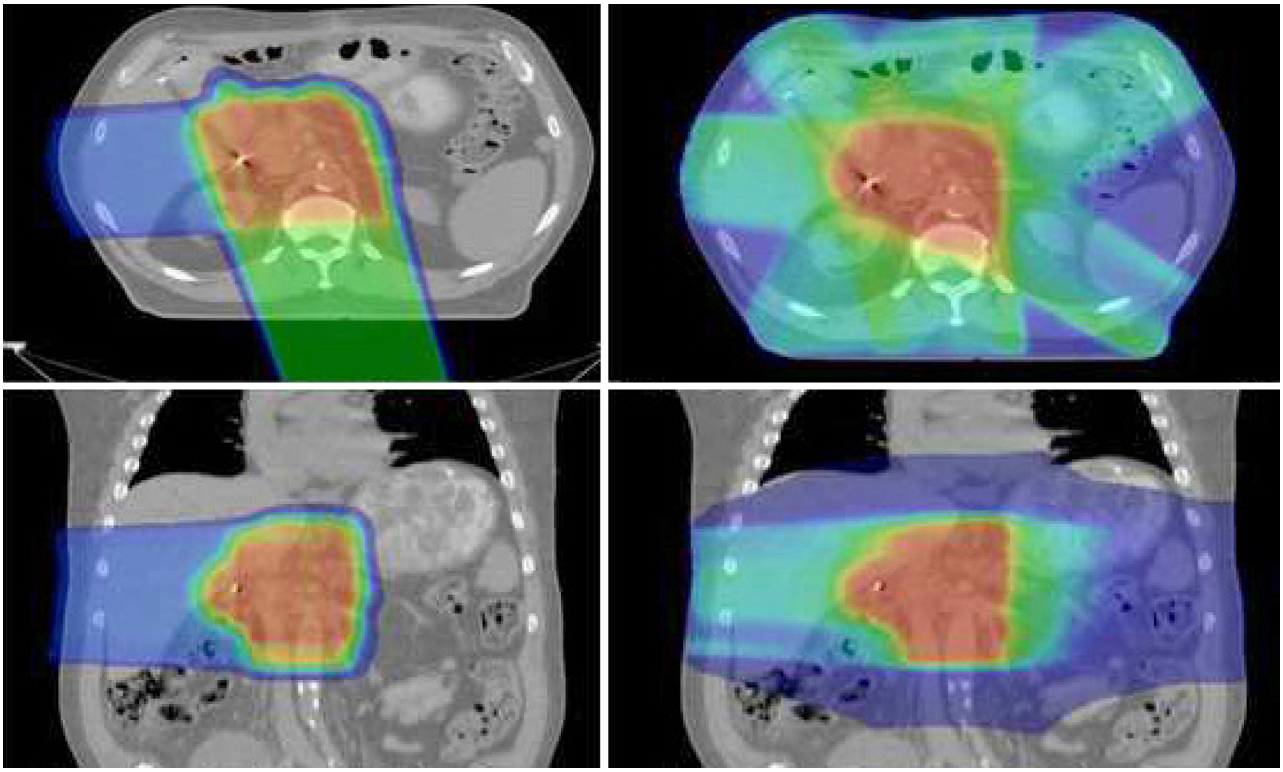

Figure 1 Images on the left side demonstrate a typical dose distribution for a patient receiving proton therapy for pancreatic cancer. Images on the right side show corresponding dose distributions for the same patient treated with intensity-modulated radiotherapy (IMRT). It is evident that protons are associated with significantly less bowel and gastric exposure compared with the IMRT plan.

unexpected surgical complications attributable to the proton radiotherapy.

LIMITATIONS OF STEREOTACTIC BODY RADIOTHERAPY

Stereotactic body radiotherapy (SBRT) has been advocated at various institutions as one form of neoadjuvant radiotherapy for patients with resectable and borderline resectable disease. This modality involves the delivery of 5 fractions of high-dose focused radiotherapy to the site of gross disease a few days prior to surgery. The putative advantage of this form of radiotherapy is that it does not delay surgery or chemotherapy. The oncologic disadvantage of this modality is that it can address only a small target containing gross disease and is unable to safely deliver meaningful dose to regional lymph nodes at high risk of harboring microscopic disease. This theoretical shortcoming of SBRT has recently been demonstrated by in the literature[17,18] where it is reported that patients undergoing pancreatectomy after SBRT demonstrate a high risk of disease recurrence in regional lymphatics that would have been irradiated by a conventionally fractionated course of preoperative radiotherapy with X-rays or protons. As such, we would argue that SBRT should not be considered an oncologically appropriate intervention in the setting of resectable or borderline resectable disease.

CONCLUSION

Patients with resectable and borderline resectable pancreatic cancer are at a high risk of suffering postoperative local-regional failure. Preoperative radiotherapy directed to gross disease and regional lymphatic beds at high risk of harboring microscopic disease appears to be an oncologically rational intervention to reduce this risk. When proton-based radiotherapy addressing gross disease as well as high-risk regional lymphatic beds is delivered prior to surgery, it does not appear to increase the risk of surgical complications or the duration of surgery. Because of this, we would argue that proton-based preoperative radiotherapy should be considered for patients with resectable and borderline resectable disease.

ACKNOWLEDGEMENTS

The authors would like to thank Jessica Kirwan, MA, and Christopher Stich for their editorial assistance and manuscript preparation.

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2019 July 27; 11(7): 308-321

DOI: 10.4240/wjgs.v11.i7.308

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Vascular calcification does not predict anastomotic leak or conduit necrosis following oesophagectomy

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Author contributions: Jefferies BJ, Forde C, Whiting JL and Griffiths EA designed the research; Jefferies BJ, Bundred J and Evans E performed the research; Jefferies BJ and Hodson J analysed the data; Jefferies BJ and Griffiths EA wrote the manuscript; all authors critically reviewed and approved the manuscript.

Institutional review board statement: The study was registered No. CARMS-15096 with University Hospitals Birmingham Clinical Audit Registration and Management System (CARMS), who granted ethical approval.

Informed consent statement: Local ethical review was obtained and confirmed that no consent was needed due to the non-interventional nature of the study.

Conflict-of-interest statement: The authors declare no conflicts of interest.

STROBE statement: The authors have read the STROBE checklist, and the manuscript was prepared and revised according to the STOBE statement checklist.

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Abstract

BACKGROUND

Anastomotic leaks (AL) and gastric conduit necrosis (CN) are serious complications following oesophagectomy. Some studies have suggested that vascular calcification may be associated with an increased AL rate, but this has not been validated in a United Kingdom population.

AIM

To investigate whether vascular calcification identified on the pre-operative computed tomography (CT) scan is predictive of AL or CN.

METHODS

Routine pre-operative CT scans of 414 patients who underwent oesophagectomy for malignancy with oesophagogastric anastomosis at the Queen Elizabeth Hospital Birmingham between 2006 and 2018 were retrospectively analysed. Calcification of the proximal aorta, distal aorta, coeliac trunk and branches of the coeliac trunk was scored by two reviewers. The relationship between these calcification scores and occurrence of AL and CN was then analysed. The

Manuscript source: Unsolicited Manuscript

Received: May 2, 2019
Peer-review started: May 9, 2019
First decision: June 12, 2019
Revised: June 17, 2019
Accepted: July 24, 2019
Article in press: June 24, 2019
Published online: July 27, 2019

P-Reviewer: Demetrashvili Z, Tao R
S-Editor: Cui LJ
L-Editor:E-Editor: Zhou BX

Esophagectomy Complications Consensus Group definition of AL and CN was used.

RESULTS

Complication data were available in n = 411 patients, of whom 16.7% developed either AL (15.8%) or CN (3.4%). Rates of AL were significantly higher in female patients, at 23.0%, compared to 13.9% in males (P = 0.047). CN was significantly more common in females, (8.0% *vs* 2.2%, P = 0.014), patients with diabetes (10.6% *vs* 2.5%, P = 0.014), a history of smoking (10.3% *vs* 2.3%, P = 0.008), and a higher American Society of Anaesthesiologists grade (P = 0.024). Out of the 14 conduit necroses, only 4 occurred without a concomitant AL. No statistically significant association was found between calcification of any of the vessels studied and either of these outcomes. Multivariable analyses were then performed to identify whether a combination of the calcification scores could be identified that would be significantly predictive of any of the outcomes. However, the stepwise approach did not select any factors for inclusion in the final models. The analysis was repeated for composite outcomes of those patients with either AL or CN (n = 69, 16.7%) and for those with both AL and CN (n = 10, 2.4%) and again, no significant associations were detected. In the subset of patients that developed these outcomes, no significant associations were detected between calcification and the severity of the complication.

CONCLUSION

Calcification scoring was not significantly associated with Anastomotic Leak or CN in our study, therefore should not be used to identify patients who are high risk for these complications.

Key words: Oesophagectomy; Anastomotic leak; Gastric conduit necrosis; Calcification; Computed tomography; Ischaemia

Core tip: Vascular calcification does not predict anastomotic leak (AL) or gastric conduit necrosis (CN) following oesophagectomy for malignancy. There is no association between vascular calcification and severity of AL or CN. AL is significantly more common in female vs male patients. Gastric CN is significantly more common in females, patients with diabetes, a history of smoking and a higher American Society of Anaesthesiologists grade. Inter-rater reliability for calcification scoring of the vessels supplying the gastric tube is excellent.

Citation: Jefferies BJ, Evans E, Bundred J, Hodson J, Whiting JL, Forde C, Griffiths EA. Vascular calcification does not predict anastomotic leak or conduit necrosis following oesophagectomy. *World J Gastrointest Surg* 2019; 11(7): 308-321
URL: https://www.wjgnet.com/1948-9366/full/v11/i7/308.htm
DOI: https://dx.doi.org/10.4240/wjgs.v11.i7.308

INTRODUCTION

Oesophagectomy is associated with relatively high incidence of complications[1]. One of the most important complications is anastomotic leak (AL), which has been shown to be associated with post-operative morbidity, subsequent anastomotic stricture and reoperation, and is associated with increased post-operative mortality, extended length of hospital stay and hospital costs[2,3]. Ischaemia of the gastric tube is a key cause of AL[4,5]. Additionally, ischaemia can progress to gastric conduit necrosis (CN), which may result in severe sepsis and death if appropriate interventions are not performed[1]. More minor forms may result in poor perfusion to the gastric tube, particularly the most cranial part, which is used to create the anastomosis[6]. It has been hypothesised that calcification of the arteries supplying the gastric tube, a surrogate marker for atherosclerosis, may contribute to tissue ischaemia and hence be linked to AL and CN.

Several studies have reported a link between vascular calcification on pre-operative

computed tomography (CT) scan and subsequent AL[7-12]. Vascular calcification burden has been shown to be strongly correlated with atherosclerotic burden. CT is the gold standard for the measurement of arterial calcification[13]. However, previous studies have been inconsistent in their findings, and there is heterogeneity between study populations.

This single centre retrospective cohort study aims to evaluate the relationship between the extent and location of calcification, as measured on the pre-operative CT scan, and subsequent AL and CN following oesophagectomy with oesophagogastric anastomosis for oesophageal cancer.

MATERIALS AND METHODS

Population

Our institution provides centralised resectional oesophageal cancer services for several hospitals in the West Midlands. The Upper gastrointestinal surgery team maintains a "Tracker" database, which records details of patient demographics, diagnosis, oncological staging, chemotherapy, surgical management, intraoperative details, post-operative outcomes and complications, survival and oncological recurrence. Data are input prospectively by consultant members of the Upper GI Team.

The study inclusion criteria were consecutive patients who had undergone oesophagectomy with oesophagogastric anastomosis for malignancy. Patients were excluded if no pre-operative CT scan was available, or they had insufficient follow up to determine whether outcomes had occurred (*i.e.*, those not discharged before 15th January 2018). Oesophagectomies for benign disease or open and close procedures due to irressectable or metastatic disease were also excluded.

Definition of outcomes

The Esophagectomy Complications Consensus Group (ECCG) consensus definitions of AL and CN were used[1]. These defined AL as a full thickness gastrointestinal surgery defect involving the oesophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification, and further classified AL as follows: Type I: Local defect requiring no change in therapy or treated medically or with dietary modification; Type II: Localized defect requiring interventional but not surgical therapy, for example, interventional radiology drain, stent or bedside opening, and packing of incision; Type III: Localized defect requiring surgical therapy.

CN was defined as ischaemia or necrosis of the gastric conduit and was classified as follows: Type I: CN focal identified endoscopically. Treatment with additional monitoring or non-surgical therapy; Type II: CN focal identified endoscopically and not associated with free anastomotic or conduit leak. Treatment with surgical therapy not involving oesophageal diversion; Type III: CN extensive. Treatment with conduit resection with diversion.

Image acquisition

Images from pre-operative CT scans of the thorax, abdomen and pelvis were analysed. CT protocols for the referring hospital were broadly similar and were typically enhanced with an iodinated contrast material administered intravenously. Chest and abdominal images were typically acquired in the arterial phase and portal venous phase, respectively. If multiple pre-operative CT scans were available, the scan closest to the date of surgery was used for analysis.

Image evaluation

Two reviewers (BJ and EE) independently evaluated all scans, and disagreements were resolved by consensus. A consultant radiologist acted as an arbitrator in the event that consensus was not reached. Reviewers were blinded to patient demographics, operative characteristics and outcomes whilst analysing the images. Inter-observer consistency was calculated between two reviewers.

The extent of calcification was reported using a visual grading system based on that used by van Rossum *et al*[7]. It uses simple definitions and can be used in standard CT diagnostic protocols. This is contrasted to other calcium scoring techniques requiring use of special-semi automatic calcium scoring software that are more difficult to integrate into routine practice[14]. The grading system classifies scans as showing no calcification, scoring 0 points, minor calcification (1 point) or major calcification (2 points). Further details of the definitions used are reported in Table 1. Calcification scores were produced for six different vessels, detailed below.

As the right gastro-epiploic artery is the principal blood supply to the gastric tube

Table 1 Details of how calcification scores were allocated to each vessel

Site	Score 1 (Minor calcification)	Score 2 (Major calcification)
Proximal aorta	Nine or fewer foci and Three or fewer foci extending over three or more sections	More than nine foci or More than three foci extending over three or more sections
Coeliac trunk	Calcifications extending over 3 or fewer sections and Maximal cross- sectional diameter of a single focus less than 10mm	Calcifications extending over three or more sections and maximal cross sectional diameter of a single focus greater than 10mm or Calcifications involving both the proximal and distal parts
Right post Coeliac arteries	One or more calcifications	NA
Left post Coeliac arteries	One or more calcifications	NA
Distal aorta	Nine or fewer foci and Three or fewer foci extending over three or more sections	More than nine foci or More than three foci extending over three or more sections or Subjectively assessed as having heavy calcifications
Aortic bifurcation	Calcifications affecting less than 40% of the circumference of the vessel	Calcifications affecting more than 40% of the circumference of the vessel

For each site, a score of zero was assigned in cases where there were no calcifications. A focus refers to a distinct area of calcification. Section refers to a single computed tomography image in the axial plane

and is supplied from the thoracic aorta via the coeliac axis, common hepatic artery and gastroduodenal artery, all of these vessels were included[15]. Although the left gastro-epiploic artery is routinely ligated during oesophagectomy, calcifications of the splenic artery, which supplies it, were still included to allow comparisons with previous studies. Branches of the coeliac axis were grouped together as the right and left post-coeliac arteries.

As there is evidence to suggest that calcification in the abdominal aorta is a general marker of arteriopathy and may be a surrogate marker for coronary artery disease[16], it was decided to include a measurement of calcification in the aorta distal to the origin of the coeliac axis, to determine whether this may also be an independent predictor of AL or CN. When the aorta was so heavily calcified that it was difficult to distinguish distinct calcification foci; a score of 2 was allocated.

As this introduced a qualitative element to the evaluation of the distal aorta, an additional quantitative measure of calcification in the aorta was also considered for comparison. The percentage of the circumference of the aorta that was calcified was measured one axial CT slice superior to the aortic bifurcation. This method has been previously used for measurement of distal aortic calcification in patients with abdominal aortic aneurysms, and was chosen for simplicity as it also used a 0-2 scoring system[17]. This is referred to as the "bifurcation" score.

The Right and Left Post-Coeliac Arteries were scored using a binary 0-1 scale, as calcifications in these smaller vessels were expected to occur relatively infrequently, thus artificially scoring more than two categories may result in imprecise estimates describing random error rather than true associations.

Surgical technique

Oesophagectomies were classified into three operative types. Open surgeries were defined as 2 or 3 stage procedures involving open abdominal incisions with open right thoracotomy. Hybrid approaches used laparoscopic abdominal gastric mobilization (5 port technique) with an open right thoracotomy (hybrid oesophagectomy) plus or minus cervical incision. Finally, minimally invasive oesophagectomies (MIOs) used 5 abdominal ports and thoracoscopic (3 thoracic ports) esophageal mobilization with either intra-thoracic or cervical anastomosis. The decision regarding operative method was at the discretion of the consultant surgeon involved. Ten consultant upper gastrointestinal surgeons were involved in oesophagogastric cancer resections throughout the study period. Before 2006 all procedures were open operations. The first laparoscopic gastric mobilization was performed in the unit in 2006 and fully minimally invasive procedures introduced in 2008.

Statistical analysis

Statistical review was performed by a biomedical statistician. Initially, the inter-rater reliability of the calcification scores were assessed using quadratic weighted Kappa

statistics. Analyses were then performed to identify any demographic factors that were associated with AL or CN. Continuous factors that were normally distributed were reported as mean ± SD, and compared between patients with and without the complication using independent samples t-tests. Continuous factors where the distribution was non-normal were reported as medians and interquartile ranges and compared between groups using non-parametric Mann-Whitney tests. Ordinal factors [*e.g.*, American Society of Anaesthesiologists grade (ASA) and T-stage] were also compared between groups using Mann-Whitney tests, whilst nominal factors (*e.g.*, gender and tumour type) were analysed using Fisher's exact tests.

The predictive accuracy of the calcification scores, with respect to AL and CN, were then assessed using ROC curves. Multivariable binary logistic regression models were then produced, in order to test whether the predictive accuracy could be improved by combining the scores together. These models used a backwards stepwise approach to variable selection, starting with all of the scores in the same model, and iteratively excluding the least predictive scores until those that were significant independent predictors of outcome remained.

Within the subgroup of patients where an outcome occurred, Spearman's correlation coefficients between the grade of the complication and the calcification scores were calculated, to assess whether there was a tendency for patients with higher score to have more severe complications[18].

Missing data were excluded from the analysis using a pairwise approach. More specifically, where a patient had missing data for one of the factors considered, they would be excluded from the analysis of that factor, but included in the analyses of the other factors for which data were available. A P-value < 0.05 was classed as statistically significant. All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY, United States). Our work has been reported in line with the STROCSS criteria[19].

RESULTS

Patient demographics

Following the exclusions shown in Figure 1, n = 413 patients were included in the final dataset. These patients had a mean age of 64.8 ± 9.5 years at the time of surgery, and the majority (78.9%) were male. More details on the demographics and comorbidities of the cohort are reported in Table 2, whilst Table 3 details disease and treatment related factors.

Data relating to complications were unavailable in n = 2 patients, hence these were excluded from the analyses of outcomes. Of the remaining n = 411, a total of 65 patients (15.8%) developed AL in the post-operative period, consisting of n = 15, n = 16 and n = 34 of grades 1, 2 and 3, respectively. CN occurred in 14 patients (3.4%), with n = 1, n = 5 and n = 8 at grades 1, 2 and 3, respectively. Of those with CN, 10/14 (71%) had an associated AL. Mortality attributed to AL was 6% (4/65) and mortality attributed to CN was 21% (3/14).

Analyses were performed to assess whether any of the factors in Tables 2 or 3 were associated with either of the complication outcomes (Supplementary Tables 1A and B and 2A and B). This found rates of AL to be significantly higher in female patients, at 23.0%, compared to 13.9% in males (P = 0.047). No other demographic or treatment related factors were found to be significantly associated with AL, including operative approach (2 *vs* 3 stage, 16.4% *vs* 9.1%, P = 0.330) or neoadjuvant chemotherapy (15.7% *vs* 16.2%, P = 1.000).

CN was significantly more common in females, (8.0% vs 2.2%, P = 0.014) patients with diabetes (10.6% *vs* 2.5%, P = 0.014), a history of smoking (10.3% *vs* 2.3%, P = 0.008), and a higher ASA grade (P = 0.024). There was no significant association with any other demographic or treatment related factor; however, it was noted that patients with CN had significantly fewer involved lymph nodes (median: 0 *vs* 1, P = 0.034).

Calcification scoring

Analysis of inter-rater reliability found that the two reviewers gave highly consistent calcification scores, with absolute agreement ranging from 95.6% to 99.0% and quadratic weighted Kappa statistics from 0.841 to 0.968 across the six vessels being analysed (Supplementary Table 3). The distribution of the cohort across the final scores is reported in Table 4. The Distal and Bifurcation scores were only recorded in n = 380 cases (92% of the cohort), as the CT scan did not show the full length of the aorta in the remainder. The same was true for n = 1 in the Proximal score.

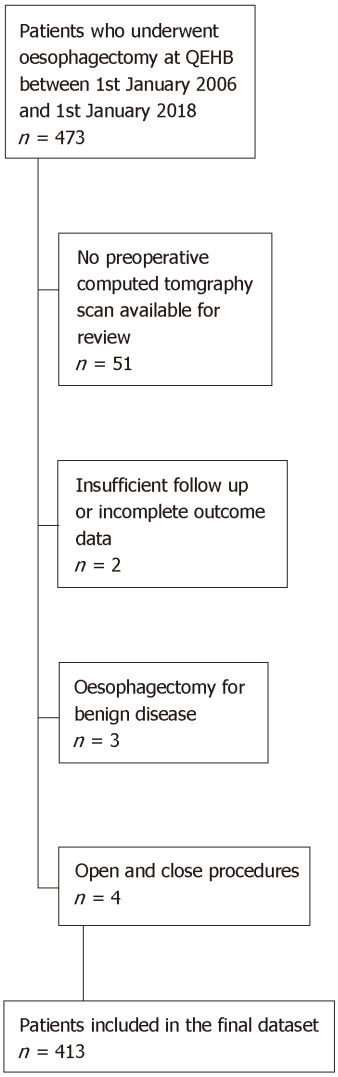

Figure 1 Flow chart showing recruitment and exclusion.

Predictive accuracy of calcification scores

As previously stated, data relating to complications were unavailable in *n* = 2 patients, hence this analysis was based on the remaining *n* = 411. None of the calcification scores were found to be significantly associated with either AL or CN (Table 4). The analysis was repeated for composite outcomes of those patients with either AL OR CN (*n* = 69, 16.7%) and for those with both AL AND CN (*n* = 10, 2.4%) and, again, no significant associations were detected (Table 5). Multivariable analyses were then performed to identify whether a combination of the calcification scores could be identified that would be significantly predictive of any of the outcomes. However, the stepwise approach did not select any factors for inclusion in the final models.

Within the subset of patients where the outcomes occurred, correlations between the calcification scores and complication grades were then assessed (Supplementary Table 4). However, no significant correlations between were detected between any of the calcification scores and the complication grades, as defined by the ECCG severity grade.

DISCUSSION

An effective method of predicting patients at high risk of AL would be clinically useful in the management of the oesophageal cancer patients, as it would facilitate better pre-operative risk counselling, closer monitoring of high risk patients and perhaps allow more timely intervention should AL occur. Our study found no statistically significant associations between scoring of calcifications of the abdominal arteries and either AL or CN. In addition, for the subgroup of patients with AL or CN,

Table 2 Patient demographics and comorbidities

	n	Statistic
Age at surgery (yr)	413	64.8 ± 9.5
Gender	413	
Female		87 (21.1)
Male		326 (78.9)
BMI (kg/m^2)	402	26.8 ± 4.9
ASA	397	
1		78 (19.6)
2		222 (55.9)
3		89 (22.4)
4		8 (2.0)
ECOG status	324	
0		146 (45.1)
1		142 (43.8)
2		36 (11.1)
Ischemic heart disease	412	
No		360 (87.4)
Yes		52 (12.6)
Renal impairment	412	
No		408 (99.0)
Yes		4 (1.0)
Diabetes	412	
No		364 (88.3)
Yes		48 (11.7)
COPD	412	
No		381 (92.5)
Yes		31 (7.5)
Previous cancer	412	
No		393 (95.4)
Yes		19 (4.6)
Significant smoking history	412	
No		354 (85.9)
Yes		58 (14.1)
Alcohol misuse/ heavy drinker	412	
No		404 (98.1)
Yes		8 (1.9)

Data are reported as *n* (%), mean ± SD, or as median (IQR), as applicable. BMI: Body mass index; ASA: American Society of Anaesthesiologists grade; ECOG: Eastern Cooperative Oncology Group Performance Status; COPD: Chronic obstructive pulmonary disease.

the grade of this complication was not found to be significantly correlated with any of the calcification scores.

Our findings are inconsistent with previous studies on the topic (Table 6). Whilst a small number of studies have found calcification to be associated with AL, the specific arteries implicated have varied between studies. Existing studies have been relatively heterogeneous in terms of operative techniques, ethnicity and other factors, which may account for the variability in results. Additionally, differences in clinical practice, such as different thresholds for investigation of leaks (such as by routine contrast swallow examination) may affect the detection rate of low grade or sub-clinical leaks, and hence be a source of heterogeneity. AL rates differed between studies, probably due to variation in a range of factors, such as cervical location of anastomosis, use of pre-operation chemoradiotherapy, and minimally invasive anastomotic techniques, which have previously been shown to be associated with increased leak rates, despite this not being the case in our cohort[2,3].

In our institution, contrast studies were only performed on suspicion of AL, as per

Table 3 Disease and treatment-related factors

	n	Statistic
Neoadjuvant chemotherapy	413	
No		69 (16.7)
Yes		344 (83.3)
Mandard score	387	
Mandard 1 (Complete)		20 (5.2)
Mandard 2		26 (6.7)
Mandard 3		69 (17.8)
Mandard 4		115 (29.7)
Mandard 5 (None)		88 (22.7)
No Chemo		69 (17.8)
Operation stages	413	
Two-stage		379 (91.8)
Three-stage		34 (8.2)
Operation type	413	
Hybrid		224 (54.2)
MIO		103 (24.9)
Open		86 (20.8)
Type of Tumour	409	
Adenocarcinoma		322 (78.7)
Adenosquamous		8 (2.0)
Squamous		65 (15.9)
Other		14 (3.4)
T-stage	410	
T0		17 (4.1)
T1		43 (10.5)
T2		51 (12.4)
T3		274 (66.8)
T4		25 (6.1)
N-stage	412	
N0		154 (37.4)
N1		171 (41.5)
N2		54 (13.1)
N3		33 (8.0)
M-stage	405	
M0		396 (97.8)
M1		9 (2.2)
R-status	407	
R0		255 (62.7)
R1		141 (34.6)
R2		11 (2.7)
Peri-neural invasion	314	
No		207 (65.9)
Yes		107 (34.1)
Lymph nodes total	412	30.3 ± 10.8
Lymph nodes involved	412	1 (0-4)

Data are reported as *n* (%), mean ± SD, or as median (IQR), as applicable. Mandard Score is a measure of tumour regression due to chemotherapy, with a score of 1 being complete regression, and 5 being no regression. MIO: Minimally invasive oesophagectomies.

previous evidence suggesting that routine testing does not improve outcome, can lead to false positive results and risks aspiration pneumonia[20,21]. Additionally, our institution previously had an aggressive policy to re-operate on AL, which probably

Table 4 Predictive accuracy of calcification scores

		Anastomotic leak			Conduit necrosis		
	Distributio nof scores	*n*/*n*(%)	AUROC (SE)	*P* Value	*n*/*n* (%)	AUROC (SE)	*P* value
Proximal	*n* = 412[1]		0.518 (0.039)	0.652		0.559 (0.067)	0.454
0	159 (38.6)	24/159 (15.1)			3/159 (1.9)		
1	199 (48.3)	31/197 (15.7)			10/197 (5.1)		
2	54 (13.1%)	10/54 (18.5)			1/54 (1.9)		
Coeliac	*n* = 413[1]		0.514 (0.039)	0.714		0.570 (0.083)	0.374
0	316 (76.5)	48/315 (15.2)			9/315 (2.9)		
1	91 (22.0)	17/90 (18.9)			4/90 (4.4)		
2	6 (1.5)	0/6 (0.0)			1/6 (16.7)		
R Post Coeliac	*n* = 413[1]		0.502 (0.039)	0.951		0.486 (0.077)	0.860
0	401 (97.1)	63/400 (15.8)			14/400 (3.5)		
1	12 (2.9)	2/11 (18.2)			0/11 (0.0)		
L Post Coeliac	*n* = 413[1]		0.492 (0.039)	0.840		0.443 (0.072)	0.465
0	337 (81.6)	54/336 (16.1)			13/336 (3.9)		
1	76 (18.4)	11/75 (14.7)			1/75 (1.3)		
Distal	*n* = 380[1]		0.499 (0.040)	0.990		0.582 (0.076)	0.297
0	50 (13.2)	6/50 (12.0)			1/50 (2.0)		
1	191 (50.3)	33/191 (17.3)			6/191 (3.1)		
2	139 (36.6)	20/137 (14.6)			7/137 (5.1)		
Bifurcation	*n* = 380[1]		0.545 (0.040)	0.275		0.492 (0.077)	0.921
0	108 (28.4)	13/108 (12.0)			4/108 (3.7)		
1	182 (47.9)	30/181 (16.6)			7/181 (3.9)		
2	90 (23.7)	16/89 (18.0)			3/89 (3.4)		

[1]The number of patients for whom the score was recorded. *P*-values are from the ROC curve analyses. AUROC: Area under the ROC curve. Analyses of outcomes exclude *n* = 2 patients for whom complication data were not available.

explains the high rate of Grade 3 leaks. Since 2012, we have favoured endoscopic methods to treat AL, which is in keeping with the current literature[22,23]. The exceptions are if the patient has a severe and life threatening leak or CN, or if endoscopic methods fail.

Although our AL rate is within previously published ranges, it is higher than the 10% audit standard set by the Association of Upper Gastrointestinal Surgeons United Kingdom[24]. This reflects the prospective nature of our complication data and the length of the data collection period, incorporating learning curves for minimal access esophagectomy[25,26] and the increase in leaks due to VEGF inhibitors used in patients during the ST03 trial which our centre recruited to[27].

Studies examining vascular calcification in colorectal anastomotic leakage have produced similarly variable results, which found no association between calcification and AL[28-31].

This is the first study to have evaluated the relationship between vascular calcification and CN in this way. Given the potentially devastating consequences for patients, research into methods of reducing morbidity from CN is highly important. One of the difficulties in investigating CN is that it remains relatively uncommon, meaning that statistical power of analyses is low. This was the case in our study, therefore although we found no statistically significant relationship between calcification and CN, this could be the result of a Type II error.

It is possible that the reason that our study found no association with AL is that examination of vascular abnormalities such as calcification is only a surrogate marker for atherosclerosis, which does not necessarily affect the actual perfusion of the gastric conduit. More complex methods of assessment of gastric conduit perfusion are available but, in general, are not readily available in clinical practice[32]. The use of Indocyanine Green to assess perfusion is a promising development to aid in a more objective assessment intra-operatively, usually after formation of the gastric conduit[33]. Our results suggest that it is micro-perfusion of the gastric conduit that may be more important in anastomotic leakage that the calcification of the main abdomino-thoracic blood vessels. As such a larger, multicentre, prospective study

Table 5 Predictive accuracy of calcification scores with respect to composite outcomes

	n	Anastomotic leak or conduit necrosis			Anastomotic leak and conduit necrosis		
		n (%)	AUROC (SE)	*P* value	*n* (%)	AUROC (SE)	*P* value
Proximal			0.518 (0.038)	0.634		0.574 (0.079)	0.426
0	159	25 (15.7)			2 (1.3)		
1	197	34 (17.3)			7 (3.6)		
2	54	10 (18.5)			1 (1.9)		
Coeliac			0.525 (0.039)	0.517		0.532 (0.094)	0.731
0	315	50 (15.9)			7 (2.2)		
1	90	18 (20.0)			3 (3.3)		
2	6	1 (16.7)			0 (0.0)		
R Post			0.501 (0.038)	0.972		0.486 (0.090)	0.882
0	400	67 (16.8)			10 (2.5)		
1	11	2 (18.2)			0 (0.0)		
L Post			0.486 (0.038)	0.716		0.458 (0.087)	0.648
0	336	58 (17.3)			9 (2.7)		
1	75	11 (14.7)			1 (1.3)		
Distal			0.501 (0.039)	0.976		0.605 (0.081)	0.259
0	50	7 (14.0)			0 (0.0)		
1	191	34 (17.8)			5 (2.6)		
2	137	22 (16.1)			5 (3.6)		
Bifurcation			0.544 (0.039)	0.272		0.481 (0.091)	0.841
0	108	14 (13.0)			3 (2.8)		
1	181	32 (17.7)			5 (2.8)		
2	89	17 (19.1)			2 (2.2)		

P values are from the ROC curve analyses. AUROC: Area under the ROC curve.

assessing both these variables by pre-operative CT assessment of calcification of the large vessels together with intra-operative micro-perfusion of the gastric conduit by indo-cyanine green perfusion is indicated to definitively answer this important question.

Another possible reason for our negative findings is that other factors could be at play, such as anastomotic tension, surgical technique and other patient factors [34]. A range of risk factors for AL have been identified[2,3,34]. To our knowledge, female gender has not previously been reported as a risk factor. Evidence relating to risk factors for CN is more sparse, although co-morbid conditions and coeliac artery stenosis have been previously implicated[35,36]. Our findings that female gender, diabetes, smoking and higher ASA grade are risk factors in our population will help us consent these patients more carefully and monitor them closely after surgery.

This study has some limitations, such as the inability to obtain all CT scans and the fact this was largely a retrospective study. However, we did utilise an accurate and prospectively maintained database with high quality outcome data.

To overcome the issues of small numbers of patients affected, further research in this area should be performed using large multi-centre datasets. Some multi-centre studies are assessing complications after oesophageal surgery, for example, Esodata (www.esodata.org)[37] and the Oesophagogastric Anastomosis Audit (OGAA; www.ogaa.org.uk) which aims to collect data of anastomotic complications after oesophagectomy, including CN, from a large group of international oesophageal units, to define the accurate incidence and outcome of this problem[38].

It is only with prospective, standardised data from these multi-centre registries that we can help address the void of high quality literature on this important topic.

In conclusion, Calcification scoring scored on pre-operative CT scans was not found to be significantly associated with AL or CN following oesophagectomy in our United Kingdom cohort and therefore cannot be used to identify or predict patients who are high risk for these complications.

Table 6 Summary of existing literature

Author (Year)	Type of Oesophagecto-my	*n1*	Anastomotic leak rate	Conduit ischaemia rate	Arterial vessels assessed	Association with anastomotic leakage or gastric conduit necrosis	Definition of anastomotic leak
van Rossum *et al*[7], 2015	3-stage	246	24%	NA	Aorta, coeliac trunk, right and left post-coeliac arteries	Aorta and right post coeliac calcification associated with leakage	Defined by either extravasation of water-soluble contrast material during a contrast material swallow study or CT scan, visualization of anastomotic dehiscence or fistulae during endoscopy, or visible loss of saliva through the cervical wound
Zhao *et al*[8], 2016	3-stage	709	17.20%	NA	Aorta, coeliac trunk, right and left post-coeliac arteries	Aorta and coeliac artery calcifications associated with leakage	Anastomotic leakage was clinically suspected, a CT scan, water-soluble contrast swallow study or endoscopy was performed
Goense *et al*[9], 2016	2-stage	167	24%	NA	Aorta, coeliac trunk, right and left post-coeliac arteries	Aortic calcification associated with leakage	Clinical signs of leakage from a thoracic drain, radiologic signs of leakage, including contrast leakage or fluid and air levels surrounding the anastomosis, or signs of anastomotic dehiscence during endoscopy or reoperation
Lainas *et al*[12], 2017	2-Stage	481	NA	2.10%	Coeliac Trunk	Extrinsic and intrinsic stenosis of the coeliac artery associated with gastric conduit necrosis	NA
Chang *et al*[10], 2018	2-stage	164	8.50%	NA	Aorta, coeliac trunk, right and left post-coeliac arteries	Calcification showed no association with leakage, coeliac trunk stenosis was associated with leakage	Anastomotic dehiscence confirmed during endoscopy or operation

Borggreve *et al*[11], 2018	3-stage	406	25.60%	NA	Coronary, supra-aortic, thoracic aorta, coeliac axis, abdominal arota, common iliac external iliac arteries; aortic valve	Calcification of coronary arteries, supra-aortic arteries, and thoracic aorta associated with leakage	Visible loss of saliva through the cervical wound, extravasation of water-soluble contrast material during a contrast swallow study or CT scan, or visualization of anastomotic dehiscence or fistulae during endoscopy or surgical re-intervention

[1]Number of patients included in the study. CT: Computed tomography; NA: Not reported.

ARTICLE HIGHLIGHTS

Research background

Anastomotic leaks (AL) are a serious complication following oesophagectomy, resulting in a reduction in both quality and quantity of life. When severe, AL can lead to conduit necrosis (CN) and complete breakdown of the anastomosis, resulting in pneumonia, sepsis and very poor patient outcomes. The formation and continued integrity of the anastomosis and gastric conduit is reliant on adequate perfusion of the gastric tube by the gastro-epiploic arcades.

Research motivation

One of the factors with the ability to affect perfusion at the anastomosis is calcification of the arteries supplying the gastric conduit and remnant oesophagus. Recent evidence has inconsistently linked calcification of these arteries with AL and CN. Arterial calcification, which can be routinely measured on pre-operative computed tomography (CT) scan, could, therefore, become an important aid in both patient selection and anastomotic risk assessment.

Research objectives

The objectives of this study were therefore to evaluate whether an association exists between calcification of arteries supplying the gastric conduit, namely the proximal aorta, distal aorta, coeliac trunk and branches of the coeliac trunk, and AL.

Research methods

Utilising routine pre-operative CT thorax, abdomen and pelvis scans, two blinded reviewers independently score vessel calcification according to the visual grading system proposed by *van Rossum et al*. Our prospectively maintained departmental database of patients undergoing oesophagectomy between 2006 and 2017 was examined to identify patients experiencing post-operative AL or CN. Inter-rater reliability of scoring of vessel calcification was statistically assessed using quadratic weighted kappa analyses. Univariable analyses was then performed to identify demographic and operative factors associated with AL. Subsequently, multivariable binary logistic regression models were produced to optimise the accuracy of AL prediction by artery calcification.

Research results

Of 411 patients with available data, 65 (15.8%) developed a AL post-operatively. Additionally, 4 patients had a CN not associated with AL. Rates of AL were higher in female patients (P = 0.047) and rates of CN were higher in female patients (P = 0.014), diabetic patients (P = 0.014), positive smoking history (P = 0.008) and higher ASA grade (P = 0.024). Inter-rater reliability scoring found excellent agreement between the two reviewers (absolute agreement 95.6%-99%). None of the calcification scores were associated with AL or CN on univariable or composite score analysis. Additionally, increasing calcification score was not associated with increasing severity of complications as defined by Esophagectomy Complications Consensus Group criteria.

Research conclusions

This study found no association between vascular calcification and AL or CN. Previous literature is highly heterogenous with regards to the location of calcification assessed, published leak definitions and AL rates. At the time of writing, this is the first study to aim to identify an association between vascular calcification in the aorta and coeliac axis branches within a United Kingdom population.

Research perspectives

This study and others will inform large prospective multi-centre studies currently being conducted, including the Oesophago-Gastric Anastomosis Audit, which aims to provide more definitive data with regards to factors associated with AL. Our results suggest that it is micro-perfusion of the gastric conduit that may be more important in anastomotic leakage that the

calcification of the main abdomino-thoracic blood vessels. As such a larger, multicentre, prospective study assessing both these variables by pre-operative CT assessment of calcification of the large vessels together with intra-operative micro-perfusion of the gastric conduit by indo-cyanine green perfusion may well be the best method to definitively answer this research question.

ACKNOWLEDGEMENTS

We would like to thank all Consultant Upper Gastrointestinal Surgeons from University Hospitals Birmingham for allowing their patients to be included in the study. Jefferies BJ received funding from the Arthur Thompson Trust in support of his intercalated BSc Clinical Anatomy studies. In addition, the Upper gastrointestinal surgery Patient Groups of UHB and Sandwell and Walsall have kindly supported the study.

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2019 July 27; 11(7): 322-332

DOI: 10.4240/wjgs.v11.i7.322

ISSN 1948-9366 (online)

META-ANALYSIS

Pancreatogastrostomy *vs* pancreatojejunostomy after pancreaticoduodenectomy: An updated meta-analysis of RCTs and our experience

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Author contributions: Li JT and Peng SY conceived and designed the study; Jin Y, Feng YY, and Hao G performed data extraction and statistical analysis; Jin Y, Feng YY, and Qi XG wrote the paper; Yu YQ, Li JT, and Peng SY reviewed and edited the manuscript; all authors read and approved the manuscript.

Supported by Training Project of Health High Level Talents in Zhejiang Province (2014).

Conflict-of-interest statement: We declare that we have no conflict of interest to this work.

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Abstract

BACKGROUND

Pancreatoduodenectomy (PD) is one of the most important operations in hepatobiliary and pancreatic surgery.

AIM

To evaluate the advantages and disadvantages of pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG).

METHODS

This meta-analysis was performed using Review Manager 5.3. All clinical randomized controlled trials, in which patients underwent PD with pancreatico-digestive tract reconstruction *via* PJ or PG, were included.

RESULTS

The search of PubMed, Wanfang Data, EMBASE, and the Cochrane Library provided 125 citations. After further analysis, 11 trials were included from nine counties. In all, 909 patients underwent PG and 856 underwent PJ. Meta-analysis showed that pancreatic fistula (PF) was a significantly lower morbidity in the PG group than in the PJ group (odds ratio [OR] = 0.67, 95% confidence interval [CI]: 0.53-0.86, P = 0.002); however, grades B and C PF was not significantly different between the two groups (OR = 0.61, 95%CI: 0.34-1.09, P = 0.09). Postoperative hemorrhage showed a significantly lower morbidity in the PJ group than in the PG group (OR = 1.47, 95%CI: 1.05-2.06, P = 0.03). Delayed gastric emptying was not significantly different between the two groups (OR = 1.09, 95%CI: 0.83-1.41, P = 0.54).

CONCLUSION

There is no difference in the incidence of grades B and C PF between the two

Manuscript source: Invited Manuscript

Received: April 16, 2019
Peer-review started: April 19, 2019
First decision: June 3, 2019
Revised: June 11, 2019
Accepted: June 20, 2019
Article in press: June 21, 2019
Published online: July 27, 2019

P-Reviewer: Aoki H, Bandyopadhyay SK, Uhlmann D
S-Editor: Cui LJ
L-Editor: Wang TQ
E-Editor: Wang J

groups. However, postoperative bleeding is significantly higher in PG than in PJ. Binding PJ or binding PG is a safe and secure technique according to our decades of experience.

Key words: Pancreaticojejunostomy; Pancreaticogastrostomy; Systematic review; Meta-analysis

Core tip: Pancreatico-digestive tract anastomosis after pancreaticoduodenectomy is still controversial. This systematic review and meta-analysis aimed to further evaluate the role and importance of pancreaticojejunostomy and pancreaticogastrostomy. We compared the complications of these two surgical procedures, including pancreatic fistula, delayed gastric emptying, and hemorrhage.

Citation: Jin Y, Feng YY, Qi XG, Hao G, Yu YQ, Li JT, Peng SY. Pancreatogastrostomy *vs* pancreatojejunostomy after pancreaticoduodenectomy: An updated meta-analysis of RCTs and our experience. *World J Gastrointest Surg* 2019; 11(7): 322-332
URL: https://www.wjgnet.com/1948-9366/full/v11/i7/322.htm
DOI: https://dx.doi.org/10.4240/wjgs.v11.i7.322

INTRODUCTION

Pancreatoduodenectomy (PD) is the main treatment procedure for benign and malignant tumors of the pancreatic head, lower common bile duct, and ampulla[1]. The incidence of complications after PD is still high, with some large pancreatic centers reporting an incidence of approximately 10-45%[2-7]. The incidence of pancreatic fistula (PF), delayed gastric emptying (DGE), and gastrointestinal or abdominal hemorrhage has been reported to be 3-45%[8], 5%-61%[9,10], and 1%-8%[11], respectively. Other complications include abdominal empyema, incision infection, and pulmonary infection[12].

Since the establishment of PD, pancreatico-digestive tract reconstruction has been a highly valued research area, which is considered to be closely related to the success /failure of the surgery[13]. In general, pancreatico-digestive tract reconstruction includes pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG). Unlike gastrointestinal anastomosis, these two types of reconstruction after pancreatic surgery are diverse, with different results and evaluations. Therefore, there is still room for improvement in PJ and PG, and these procedures are still the focus of future research in PD.

This systematic review and meta-analysis aimed to further evaluate the role and importance of pancreatico-digestive tract anastomosis. Further, the advantages and disadvantages of PJ and PG were compared to provide a valuable reference for a more reasonable and safe choice of pancreatico-digestive tract reconstruction in the future.

MATERIALS AND METHODS

Eligibility criteria

All clinical randomized controlled trials, in which patients underwent PD with pancreatico-digestive tract reconstruction *via* PJ or PG, were included.

Information sources

Studies were identified by searching electronic databases and scanning reference lists of articles. No limits were applied for languages and foreign papers were translated to English. The search was applied to Medline, Wanfang Data, EMBASE, Science Citation Index Expanded, and the Cochrane Library. The last search was run on March 15, 2019.

Search

We used the following search terms to search all trial registers and databases: Pancreatoduodenectomy or Pancreatoduodenectomies or Duodenopancreatectomy or

Duodenopancreatectomies or Pancreaticoduodenectomy or Whipple or PD or Whipple procedure or Pancreatoduodenal resection or Pancreaticoduodenal resection, Pancreaticojejunostomy or Pancreaticojejunostomies or Pancreatojejunostomy or Pancreatojejunostomies or Pancreaticoenteric anastomosis or Pancreatoenteric anastomosis or Pancreaticojejunal anastomosis or Pancreatojejunal anastomosis or PJ, or Pancreaticogastrostomy or PG.

Study selection

Eligibility assessment was performed independently in an unblinded standardized manner by two reviewers. Disagreements between reviewers were resolved by discussion.

Data collection process

One review author extracted the following data from the included studies and the second author checked the extracted data. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, a third author would take the decision.

Data items

Data were extracted from each included trial on: (1) Characteristics of trial participants including age, disease, and number of patients; (2) Intervention with PG *vs* PJ; (3) Type of outcome measures including the definition and occurrence of PF, DGE, and other postoperative complications.

Risk of bias in individual studies

To ascertain the validity of eligible randomized trials, two independent reviewers with adequate reliability determined the adequacy of randomization, concealment of allocation, blinding of patients, healthcare providers, data collectors, and outcome assessors.

Statistical analysis

The meta-analysis was performed using Review Manager 5.3. The Chi-square test was used to test heterogeneity among studies. The heterogeneity level was judged according to I^2. Relative risk (RR), weighted mean difference (WMD), standardized mean difference (SMD), and 95%CI (confidence interval) were used.

For data with clinical heterogeneity, it is not easy to merge effect quantities. First, we tested heterogeneity among studies. Then subgroup analysis or meta-regression analysis was conducted according to heterogeneity. If data were insufficient or heterogeneity cannot be found, a random-effects model was used. The homogeneity of data was tested by the χ^2 test, and the homogeneity was quantitatively analyzed by the I^2 test. If there was no statistical heterogeneity, a fixed-effects model was used. When statistical analysis showed heterogeneity, a random-effects model was used. The significance level of the hypothesis test was set at $P < 0.05$.

To assess the risk of bias across studies, we plotted the effect by the inverse of its standard error for each trial. The symmetry was assessed both visually, and formally by the Egger's test.

RESULTS

A total of 11 studies involving 11 trials were identified for inclusion in the review[14-24]. The search of PubMed, Wanfang Data, Embase, and the Cochrane Library provided 125 citations. Of the total 125 citations, 29 studies were discarded because they did not meet the inclusion criteria. Nine additional studies were discarded because full texts for these were not available. The full texts of the remaining 65 citations were examined in further detail. Following this, 51 studies were found not to meet the inclusion criteria as described, and three were repeat studies from the same institute at different time points (we chose the latest study in this case). Finally, 11 studies met the inclusion criteria and were included in the systematic review. Figure 1 shows the flow diagram of study selection (Figure 1).

From 1995 to 2016, 11 trials were included from nine counties. In all, 909 patients underwent PG and 856 underwent PJ. PF was defined and classified following the International Study Group on Pancreatic Fistula (ISGPF) consensus guidelines in seven trials[15,17-22] (Table 1). The quality of these 11 trials is presented in Figure 2.

PF data were available for all 11 trials randomizing 1765 patients and reporting data for them. In the meta-analysis, there was no significant hetero-geneity between these studies (I^2 = 20%); therefore, a fixed-effects model was applied. PF showed a significantly lower morbidity in the PG group than in the PJ group (odds ratio [OR] =

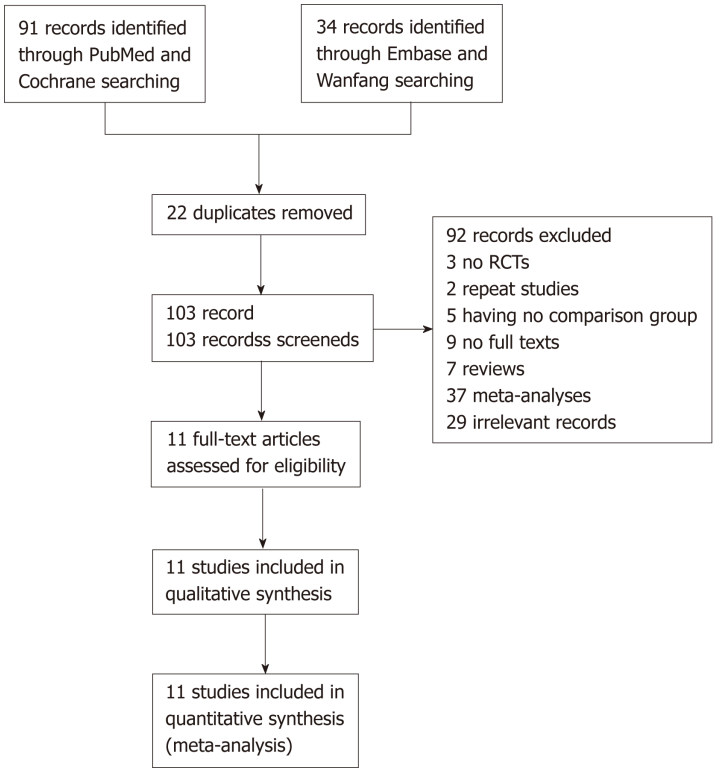


Figure 1 Study flow diagram.

0.67, 95%CI: 0.53-0.86, P = 0.002) (Figure 3). Grade A PF did not affect the disease outcome; therefore, we further analyzed the incidence of grades B and C PF. Seven trials with 603 PG and 581 PJ patients were included. In the meta-analysis, there was a significant difference in heterogeneity between these studies (I^2 = 61%); accordingly, a random-effects model was applied. Grades B and C PF was not significantly different between the two groups (OR = 0.61, 95%CI: 0.34-1.09, P = 0.09) (Figure 4).

Nine trials with 788 PG and 734 PJ patients were included for analyzing postoperative hemorrhage. In the meta-analysis, there was no significant heterogeneity between these studies (I^2 = 0%); accordingly, a fixed-effects model was applied. Postoperative hemorrhage showed a significantly lower morbidity in the PJ group than in the PG group (OR = 1.47, 95%CI: 1.05-2.06, P = 0.03) (Figure 5).

Nine trials including 780 PG and 738 PJ patients were included for the analysis of DGE. In the meta-analysis, there was no significant heterogeneity between these studies (I^2 = 47%), and therefore a fixed-effects model was applied. DGE was not significantly different between the two groups (OR = 1.09, 95%CI: 0.83-1.41, P = 0.54) (Figure 6).

DISCUSSION

PF is one of the most common complications after PD. PF not only causes serious complications such as abdominal bleeding but also increases the length of hospital stay and cost for patients. Our study showed that PG anastomosis can reduce the incidence of all grades of PF than PJ anastomosis. In 2005, the ISGPF defined PF and divided it into three levels[25]. In 2016, the group adjusted the classification of PF and defined grade A PF as a biochemical fistula[8]. Therefore, in this study, we considered the incidence of grades B/C PF in subgroup analysis. We believe that this statistical analysis has more clinical value and significance. We found no statistical difference in grades B/C PF between the two groups (PJ and PG). However, our result showed that PG anastomosis may increase the incidence of bleeding compared with PJ anastomosis.

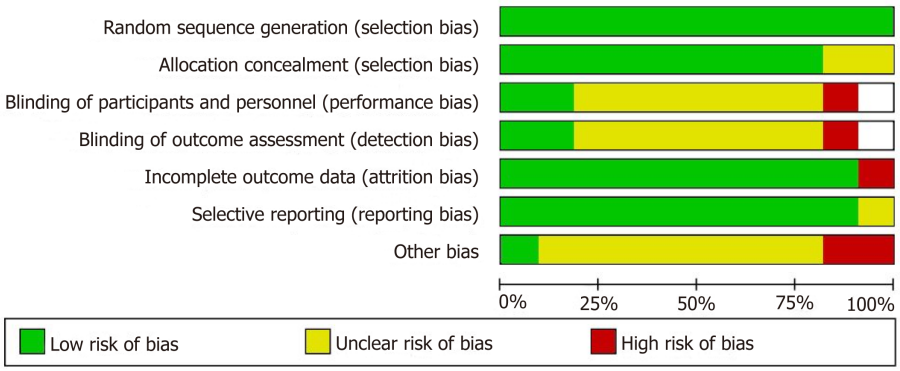
Our group has studied the anastomosis of the pancreas and digestive tract for more than 20 years, and has accumulated some experiences[7,26,27]. In 1996, we established the binding pancreaticojejunostomy (BPJ). The main feature of this surgery is that the anastomosis between the jejunum and pancreas is mainly made with a binding line. It avoids the needle hole penetrating the intestinal cavity on the surface of the

Table 1 Characteristic of included trials

Author	Year	Country	Study type	Number of PG	Number of PJ	Definition of PF
Yeo *et al*[14]	1995	United States	Single blind, controlled randomized, single center trial	73	72	PF was defined as drainage of greater than 50 mL of amylase-rid fluid on or after postoperative day 10
Duffas *et al*[23]	2005	France	Single blind, controlled randomized, multicenter trial	81	68	Fluid obtained through drains or percutaneous aspiration, containing at least 4 times normal serum values of amylase for 3 day
Bassi *et al*[25]	2005	Italy	Single blind, controlled randomized, single center trial	69	82	Any clinically significant output of fluid, rich in amylase, confirmed by fistulography
Bassi *et al*[8]	2008	Spain	Single blind, controlled randomized, single center trial	53	55	ISGPF definition
Wellner *et al*[15]	2012	Germany	Single blind, controlled randomized, single center trial	59	57	ISGPF definition
Wang *et al*[30]	2012	China	Single blind, controlled randomized, multicenter trial	83	53	ISGPF definition
El Nakeeb *et al*[20]	2013	Egypt	Single blind, controlled randomized, single center trial	45	45	ISGPF definition
Topal *et al*[18]	2013	Belgium	Single blind, controlled randomized, multicenter trial	162	167	ISGPF definition
Figueras *et al*[22]	2013	Spain	Single blind, controlled randomized, multicenter trial	65	58	ISGPF definition
Grendar *et al*[24]	2015	Canada	Single blind, controlled randomized, single center trial	48	50	Either radiologically proven anastomotic leak or continued drainage (via drain, enterocutaneous fistula, or wound) of lipaserich fluid on postoperative day 10
Keck *et al*[19]	2016	Germany	Single blind, controlled randomized, multicenter trial	171	149	ISGPF definition

PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy; PF: Postoperative pancreatic fistula.

anastomotic site, thus preventing the leakage of pancreatic juice from the pinholes, to fundamentally eliminate the possibility of PF. At present, BPJ has been applied in more than a thousand of cases, which has a significant effect on the prevention of PF after surgery[7]. In 2010, Buc, a French scholar, named BPJ procedure as Peng's PJ and reported that BPJ was a safe and secure technique[28]. In 2008, Peng created the binding pancreaticogastrostomy (BPG), which simplified the operation steps of the previous pancreas-stomach anastomosis[29]. After continuous improvement, only the bundled method was used in the posterior wall of the stomach, avoiding the suture of pancreas parenchyma and thus greatly shortening the surgical time and preventing anasto-



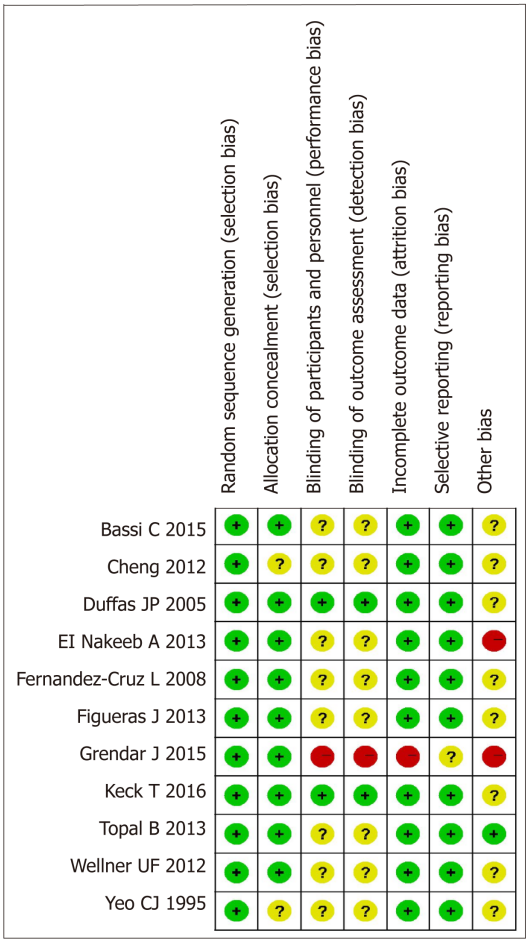


Figure 2 Quality of the included trials.

motic leakage. BPG not only solves the problem of excessive pancreatic stump but also reduces the harm of bile leakage because the biliary-enteric anastomosis is not in the same channel as PG anastomosis[27]. The mid-term results of the randomized controlled study showed that the incidence of PF in BPG and BPJ was acceptable[17].

In recent years, with the continuous development of laparoscopic technology, laparoscopic PD has gradually become an alternative method, used as a routine treatment in some pancreatic surgeries[30-32]. Thus, laparoscopic pancreatico-gastrointestinal anastomosis has become a new focus for research. Owing to the limitation of the laparoscopic visual field, pancreatic duct to mucosa anastomosis is the first choice of procedure under laparoscopy[30].

The attempt of various methods makes the technique of PJ dazzling. However, the basic content cannot be separated from pancreas-jejunum (stomach) anastomosis or pancreatic duct-jejunum (stomach) anastomosis. The objective of evaluation should be as simple as possible. Moreover, the lower the incidence of pancreatic leakage compared with classical anastomosis, the better. As long as these principles are followed, sample enlargement and randomized controlled trials should be conducted

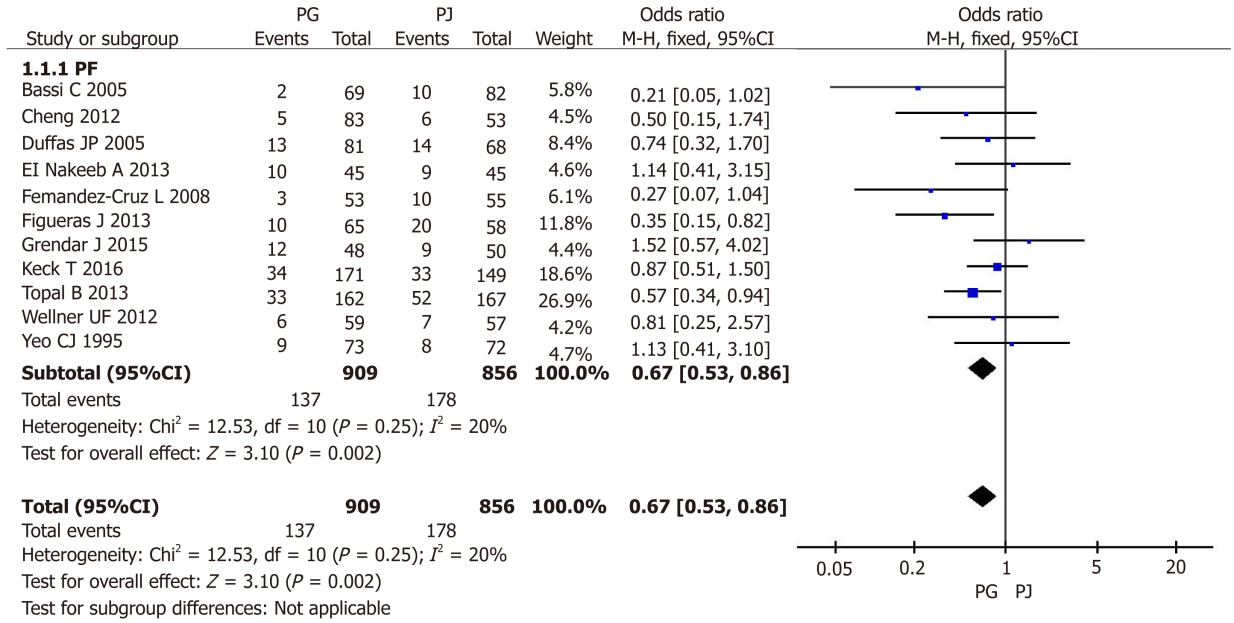


Figure 3 Forest plot of the incidence of all grades of postoperative pancreatic fistula. PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy; PF: Postoperative pancreatic fistula.

to find the best method.

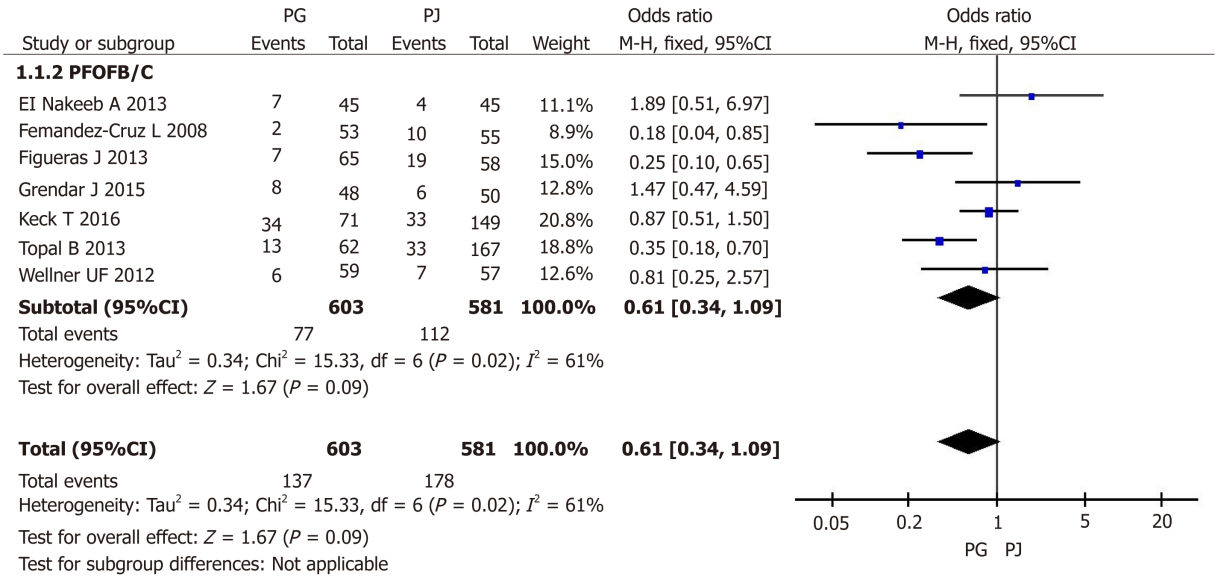


Figure 4 Forest plot of the incidence of grade B/C postoperative pancreatic fistula. PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy; PF: Postoperative pancreatic fistula.

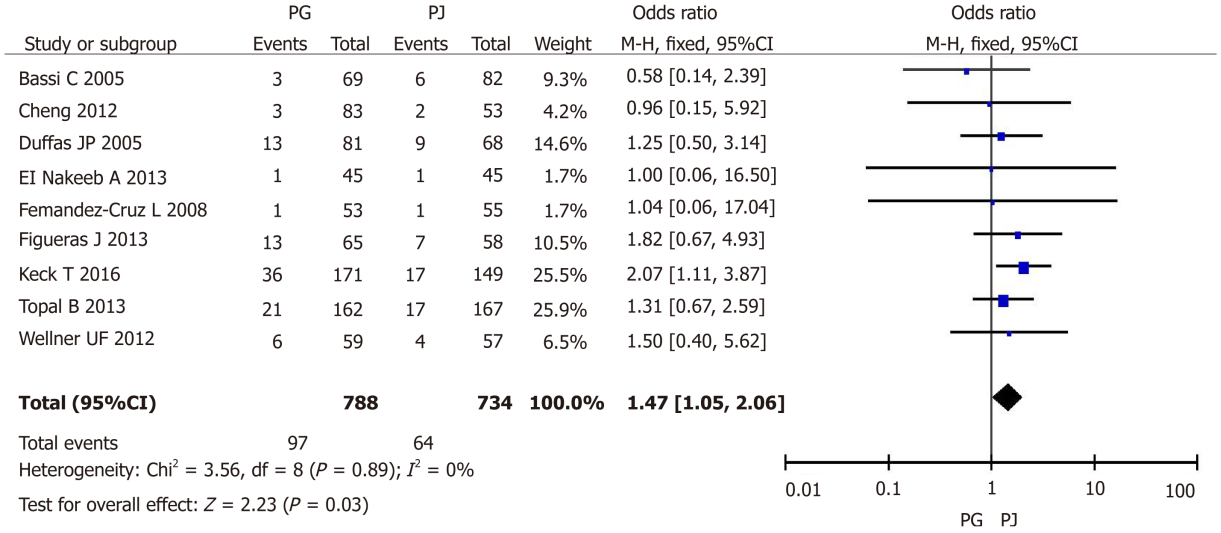


Figure 5 Forest plot of the incidence of postoperative hemorrhage. PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy.

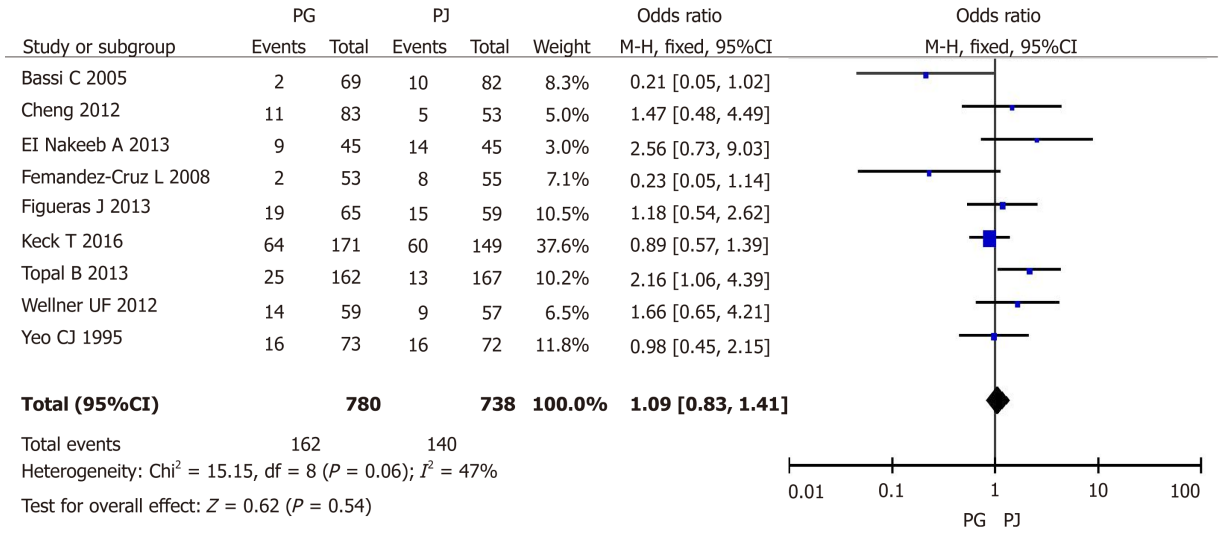


Figure 6 Forest plot of the incidence of delayed gastric emptying. PG: Pancreaticogastrostomy; PJ: Pancreaticojejunostomy; PF: Postoperative pancreatic fistula.

ARTICLE HIGHLIGHTS

Research background

Pancreatoduodenectomy (PD) is one of the most important operations in hepatobiliary and pancreatic surgery. Pancreatico-digestive tract reconstruction includes pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG). Unlike gastrointestinal anastomosis, these two types of reconstruction after pancreatic surgery are diverse, with different results and evaluations. Therefore, there is still room for improvement in PJ and PG, and these procedures are still the focus of future research in PD.

Research motivation and objectives

This systematic and meta-analysis aimed to evaluate the role and importance of pancreatico-digestive tract anastomosis. Advantages and disadvantages of PJ and PG were compared to provide a valuable reference and safe choice in the future.

Research methods

This search was applied to Medline, Wanfang Data, Embase, Science Citation Index Expanded, and the Cochrane Library. The last search was run on March 15, 2019. All clinical randomized controlled trials, in which patients underwent PD with pancreatico-digestive tract reconstruction *via* PJ or PG, were included. The Chi-square test was used to test heterogeneity among studies. The heterogeneity level was judged according to *I2*. Relative risk (RR), weighted mean difference (WMD), standardized mean difference (SMD), and 95%CI were used.

Research results

In the meta-analysis of postoperative hemorrhage, there was no significant heterogeneity between these studies (I^2 = 0%); accordingly, a fixed-effect model was applied. Postoperative hemorrhage showed a significantly lower morbidity in the PJ group than in the PG group (OR = 1.47, 95%CI: 1.05-2.06, P = 0.03). In the meta-analysis of DGE, there was no significant heterogeneity between these studies (I^2 = 47%), and therefore a fixed-effects model was applied. DGE was not significantly different between the two groups (OR = 1.09, 95%CI: 0.83-1.41, P= 0.54).

Research conclusions

Our group has studied the anastomosis of the pancreas and digestive tract for more than 20 years, and has accumulated some experiences. We established the binding pancreaticoje-junostomy (BPJ) and binding pancreaticogastrostomy (BPG). The mid-term results of the randomized controlled study showed that the incidence of PF in BPG and BPJ was acceptable.

Research perspectives

Laparoscopic pancreaticogastrointestinal anastomosis has become a new focus for research. The objective of evaluation should be as simple as possible. Moreover, the lower the incidence of pancreatic leakage compared with classical anastomosis, the better. As long as these principles are followed, sample enlargement and randomized controlled trials should be conducted to find the best method.

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