NUTRITION & PANCREATIC SURGERY

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NUTRITION & PANCREATIC SURGERY

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General introduction and thesis outline

PANCREATIC SURGERY

The pancreas

The pancreas is a flat gland, about 15 cm in length, which lies in the upper abdomen, behind the stomach in the retroperitoneal space. The pancreas is divided into a head, body and tail (Figure 1). The pancreatic head rests in the duodenal curve, the body lies behind the base of the stomach, and the tail ends at the spleen. The neck of the pancreas lies between the body and head in front of the superior mesenteric artery and vein, whereas the lower part of the head (uncinate process) hooks around both vessels.

The pancreas is a secretory organ with an endocrine (internal hormonal) and exocrine (external digestive) function. External digestive pancreatic enzymes are secreted by the acinar cells, via the side branches into the main pancreatic duct, through the ampulla of Vater into the duodenum. The distal part of the common bile duct passes through the pancreatic head and also enters the duodenum through the ampulla of Vater.

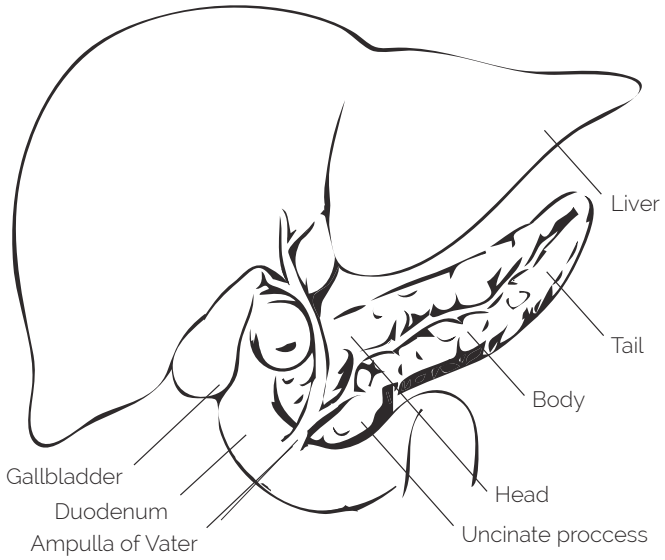

Figure 1 The pancreas and its surrounding organs

Pancreatic diseases

The most common diseases of the pancreas are inflammation (pancreatitis) and cancer.

Pancreatitis can be divided in acute pancreatitis, characterized by acute onset pain in the upper abdomen, nausea and vomiting, and chronic pancreatitis, which is associated with chronic pain and/or endocrine and exocrine insufficiency.

Pancreatic cancer may not be the most common type of cancer, it does account for one of the most frequent causes of cancer-related deaths worldwide.[1,2] There are several

types of pancreatic cancer, involving both the endocrine and exocrine tissue, but more than 85% of pancreatic tumors are invasive ductal adenocarcinoma.[3] Patients diagnosed with pancreatic cancer are usually between 60 and 80 years old and typically present with non-specific symptoms, such as abdominal pain and weight loss. Also obstructive jaundice, caused by obstruction of the distal bile duct, is a common symptom of pancreatic cancer.[4] Pancreatic cancer is associated with rapid growth and early systemic dissemination. Due to this combination of (usually late) general symptoms and aggressive tumor nature, patients are often diagnosed at an advanced stage. At the time of diagnosis, approximately 50% of patients present with locally unresectable disease and about 35% of patients have distant metastases.[5] These patients are not eligible for surgery and palliative chemotherapy is the only option to improve life expectancy. Altogether, pancreatic cancer is associated with a poor prognosis with an overall 5-year survival rate of only 6%.[1]

Pancreatoduodenectomy

For the small minority of patients with resectable pancreatic cancer, surgery is the only curative treatment option.[6] Also in case of several benign or premalignant lesions of the pancreas, surgery is indicated to treat symptoms (e.g. pain due to chronic pancreatitis or large cystic lesions) or prevent malignant transformation (e.g. in case of main duct intraductal papillary mucinous neoplasms or ampullary adenoma).[7,8] If the disease is located in the pancreatic head or periampullary region, pancreatoduodenectomy is the procedure of first choice.

Pancreatoduodenectomy consists of an en bloc resection of the pancreatic head, the duodenum and the adjacent lymph nodes, with or without preservation of the distal part of the stomach (pylorus), with a cholecystectomy. Reconstruction consists of a pancreatic, hepatic and enteric anastomosis (Figure 2).

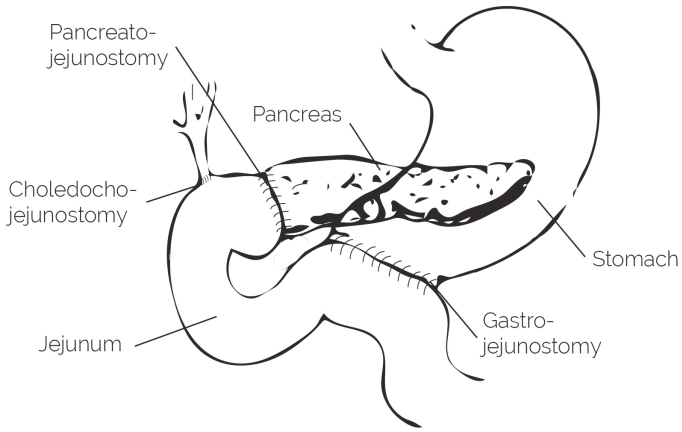

Figure 2 Anastomosis after pancreatoduodenectomy with resection of the pylorus

The first pancreatoduodenectomy was performed in 1912 by Kausch,[9] but Whipple was the one who popularized this operation in 1935.[10] Pylorus-preserving pancreatoduodenectomy (PPPD) was introduced by Watson in 1944[11] and then reintroduced by Traverso and Longmire in 1978.[12] It was thought that preservation of the pylorus is more physiologic and may improve postoperative gastrointestinal function. PPPD has been considered the standard procedure for several decades, since preservation of the pylorus had no negative impact on postoperative gastric emptying[13] and no benefit was seen of hemigastrectomy.[14] However, currently there is an on-going trend towards subtotal stomach-preserving (or pylorus-resecting) pancreatoduodenectomy, with the objective to reduce the incidence of delayed gastric emptying.[15]

Postoperative complications

As of its introduction, the number of pancreatoduodenectomies has increased considerably. Not only because the indication for this procedure has expanded to a broad spectrum of periampullary diseases, but also patient eligibility for surgery extended significantly, e.g. because vascular resections are performed increasingly.[7,16] In the past decade, there has been a strong trend towards centralization of pancreatic surgery, resulting in a decrease in mortality to about 2-5% in high-volume centers.[7,17–19] Morbidity after pancreatoduodenectomy has also declined gradually over the past few decades due to advances in surgical and perioperative care,[20,21] but it continues to be a significant problem with current rates varying between 18-54%, even in high-volume centers.[22] The main complications after pancreatoduodenectomy are pancreatic fistula (i.e. healing/sealing failure of the pancreatic anastomosis or a parenchymal leak not directly related to the anastomosis), haemorrhage and delayed gastric emptying (DGE).[4,14]

DGE, also known as gastroparesis, represents the inability to return to a standard diet by the end of the first postoperative week and includes prolonged nasogastric intubation of the patient. Three different grades (A, B, and C) are defined by the International Study Group on Pancreatic Surgery (ISGPS) based on the impact on the clinical course and postoperative management (Table 1).[23]

Table 1 Definition of DGE according to the International Study Group on Pancreatic Surgery (ISGPS)

DGE grade	NGT required	Unable to tolerate solid oral intake by POD	Vomiting/ gastric distension	Use of prokinetics
A	4–7 days or reinsertion > POD 3	7	±	±
B	8–14 days or reinsertion > POD 7	14	+	+
C	14 days or reinsertion > POD 14	21	+	+

DGE, Delayed gastric emptying; POD, Postoperative day; NGT, Nasogastric tube.

DGE occurs in 33-45% of patients after pancreatoduodenectomy[24–26] and up until today, its aetiology is not well known. One of the hypotheses is that a decrease in plasma levels of motilin (a hormone controlling the interdigestive migrating contractions) due to resection of the duodenum may result in DGE, as the use of intravenous erythromycin, a motilin receptor agonist, may reduce DGE by up to 37%.[27,28] Others have advocated various technical methods to decrease the incidence of DGE after pancreatoduodenectomy (e.g. pyloric dilatation,[29] preservation of the left gastric vein,[30] or antecolic versus retrocolic reconstruction of gastric drainage[31,32]), but none have shown significant efficacy in large randomized controlled trials. Other causes of DGE are extended radical surgery and complications after pancreatoduodenectomy, such as pancreatic fistula.[22,33] The main consequence of DGE is that it interferes with the resumption of a normal oral food intake and that it thereby results in a prolonged hospital stay.[34] Therefore, nutritional support is frequently indicated to prevent malnutrition and enhance postoperative recovery after pancreatoduodenectomy.

NUTRITION

Nutritional support of surgical patients has undergone significant advances since a direct relationship between malnutrition and postoperative outcomes was demonstrated for the first time in the 1930's and further established in the following decades.[35–38] Currently, there are several options for nutritional support. Oral nutritional supplements (i.e. multi-nutrient liquid, semi-solid or powder products) are the least invasive option, but inefficient in patients not tolerating oral intake, such as in case of DGE.

Parenteral nutrition

Parental nutrition was invented in the late 1960's by Dudrick to provide nutritional support when patients were unable to absorb nutrients via the gastrointestinal tract. Parenteral nutrition is a nutritional formula, containing proteins, carbohydrates, lipids, vitamins and minerals, that is delivered directly into the bloodstream via a central venous catheter. Although parenteral nutrition is usually successful in providing adequate nutrition, it is associated with several complications such as hyperglycaemia, volume overload and an increased risk of infection.[39,40]

Enteral nutrition

Enteral nutrition, also referred to as 'tube feeding', refers to the delivery of a nutritionally complete formula directly into the stomach, duodenum or jejunum. In contrast to parenteral nutrition, enteral nutrition has the ability to stimulate gut contractility, prevent mucosal atrophy, maintain gut integrity and prevent bacterial translocation.[41–44] Enteral nutrition can be delivered via various routes.

Nasogastric feeding may be appropriate in many patients, but in cases of increased risk of aspiration (e.g., in patients with DGE, severe gastroesophageal reflux, gastroduodenal dissociation, or gastric outlet obstruction), gastroduodenal inflammation, or proximal enteric fistula, nasoenteral feeding is indicated.[45–47] Post-pyloric enteral access can be obtained through a nasoenteral feeding tube or through more permanent percutaneous options such as a surgical feeding jejunostomy or percutaneous endoscopic gastrostomy with jejunal extension (Figure 3).

Guidelines

There is a discrepancy in nutritional guidelines on the optimal feeding strategy after pancreatoduodenectomy. The current guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN) recommend routine use of early enteral nutrition in patients undergoing major gastrointestinal surgery for cancer.[43] Parenteral nutrition is only recommended in patients in whom enteral nutrition is not feasible or not tolerated.[48]

In contrast, the current American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend postoperative nutritional support only in patients who are unlikely to meet their nutrient needs orally for a period of 7–10 days, which does not apply to most patients after pancreatoduodenectomy.[49] As in the ESPEN guidelines, parenteral nutrition is recommended not to be routinely given in the postoperative period. However, both guidelines focus on major gastrointestinal surgery for cancer in general and not specifically on post-pancreatoduodenectomy patients. The enhanced recovery after surgery (ERAS) guidelines for perioperative care for pancreatoduodenectomy recommend that patients should be allowed a normal diet as soon as possible after surgery without restrictions and that enteral nutrition should only be given on specific indications.[50] However, these recommendations are based on one single study in patients undergoing major upper gastrointestinal- or hepato-pancreato-biliary surgery and not solely on patients who underwent pancreatoduodenectomy.[51]

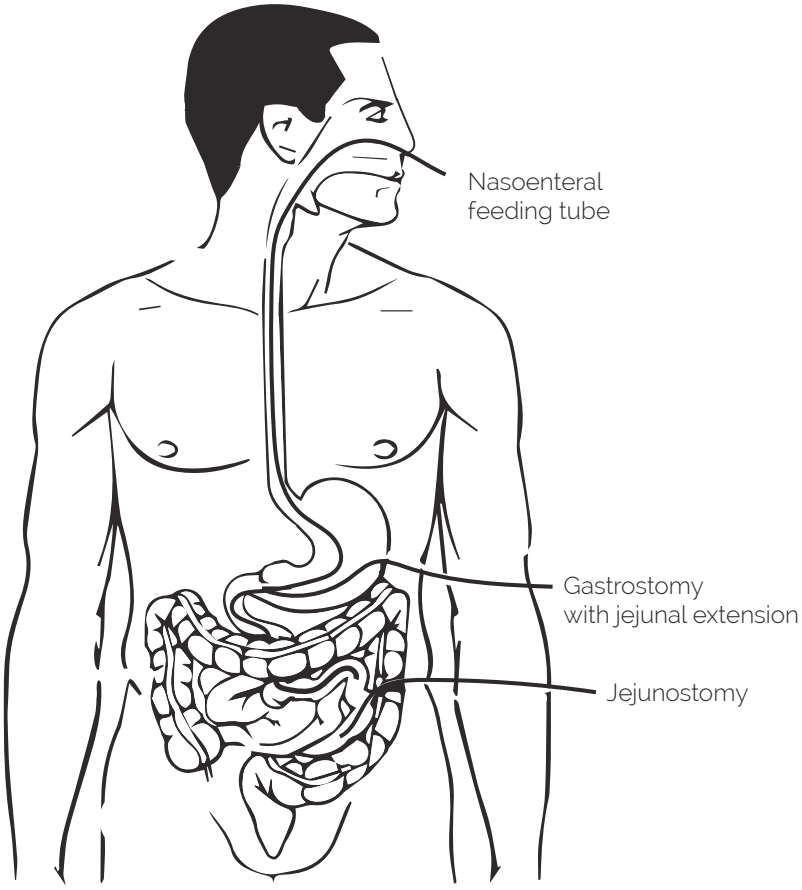

Figure 3 Enteral feeding routes

THESIS OUTLINE

The discrepancy in nutritional guidelines and lack of specific evidence concerning the optimal feeding strategy after pancreatoduodenectomy led to the clinical research presented in this thesis. **Chapter 2** systematically reviews the available literature regarding the different feeding options after pancreatoduodenectomy. Postoperative outcomes are compared between an oral diet, three different enteral feeding routes, and parenteral nutrition, focusing on both efficacy and safety. **Chapter 3** retrospectively assesses the efficacy and feeding-related complications of the various feeding strategies after pancreatoduodenectomy in a single tertiary referral center where the routine postoperative feeding strategy changed twice during the 10-year study period. Based on the findings in the literature review and the complications associated with tube feeding, this center changed its feeding protocol again from routine nasoenteral tube feeding to an early oral feeding strategy with on-demand tube feeding. **Chapter 4** evaluates whether this change in the routine postoperative feeding strategy improved outcomes in a prospective observational cohort study with historical controls. Altogether, it seems that there is no evidence to support routine nutritional support after pancreatic surgery and that early oral feeding may be considered the preferred feeding strategy after pancreatoduodenectomy. Nevertheless, it is suggested that some subgroups of patients, for example those with preoperative symptoms of gastric outlet obstruction, have such a high risk of developing DGE that routine intraoperative nasoenteral feeding tube placement may still be indicated. **Chapter 5** determines whether clinical outcomes after pancreatoduodenectomy in these patients differ between early oral feeding and routine postoperative tube feeding in a multicenter retrospective cohort study. Within an early oral feeding strategy, there are still patients who require tube feeding because they do not tolerate an oral diet. Since this need for nutritional support is usually temporary, these patients generally receive a nasoenteral feeding tube. Blind placement of nasoenteral feeding tubes is usually unsuccessful and may lead to complications due to inadvertent placement in the respiratory tract.[52,53] Therefore, nasoenteral tubes are usually placed by endoscopy or in some centers, mainly in the United States, by fluoroscopy. A new technique (electromagnetic (EM) guided bedside placement; which can be performed by trained nurses) was introduced in 2006 and may offer several benefits regarding logistics, patient discomfort and costs. **Chapter 6** systematically reviews the literature regarding EM-guided, endoscopic, and fluoroscopic nasoenteral feeding tube placement. **Chapter 7** retrospectively compares the success rate of EM-guided and endoscopic placement of nasoenteral feeding tubes in surgical patients in a tertiary referral center which has gained several years of experience with EM-guided tube placement. So far, an altered anatomy of the upper gastrointestinal tract, such as after pancreatoduodenectomy, had been considered a relative contraindication for EM-guided tube placement, due to

the altered route of the feeding tube and the dreaded increased risk of complications. **Chapter 8** is a prospective single center pilot study that determines the success rate of bedside EM-guided tube placement compared with endoscopic placement in patients after pancreatoduodenectomy. Based on the findings of this pilot, patients after pancreatoduodenectomy were included in **Chapter 9**, a multicenter randomized controlled trial determining the effectiveness of EM-guided placement compared with endoscopic placement of nasoenteral feeding tubes in surgical patients requiring nasoenteral feeding. Some patients require prolonged enteral access due to complications (e.g. biliary leaks) and suffer from the consequences of the need for several repeated tube placement procedures due to tube related complications such as dislodgement and blockage. **Chapter 10** is a retrospective single center study that presents the technique and feasibility of percutaneous transhepatic feeding tube placement in 40 patients requiring both prolonged biliary drainage and enteral access as a potentially suitable alternative to the conventional routes.

Table 2 Summary of research questions addressed in this thesis

Chapter	
2	What is the optimal feeding route after pancreatoduodenectomy regarding efficacy and safety according to the available literature?
3	What is the difference in efficacy and feeding-related complications between nasoenteral, jejunostomy and parenteral feeding after pancreatoduodenectomy?
4	Does a change in the routine feeding strategy from nasoenteral tube feeding to early oral feeding improve clinical outcomes after pancreatoduodenectomy?
5	In patients with preoperative symptoms of gastric outlet obstruction, what is the difference in clinical outcomes after pancreatoduodenectomy between postoperative early oral feeding and routine tube feeding?
6	What is the efficacy and safety of bedside electromagnetic guided, endoscopic, and fluoroscopic placement of nasoenteral feeding tubes in adults according to the available literature?
7	What is the difference in success rates of electromagnetic guided and endoscopic placement of nasoenteral feeding tubes in surgical patients?
8	In patients after pancreatoduodenectomy, how does the feasibility and safety of bedside electromagnetic guided placement of nasoenteral feeding tubes relate to endoscopic placement?
9	Is electromagnetic guided placement of nasoenteral feeding tubes by nurses at least as effective as endoscopic placement by gastroenterologists in surgical patients requiring nasoenteral feeding?
10	Is percutaneous transhepatic feeding tube placement feasible in patients requiring both prolonged percutaneous transhepatic biliary drainage and enteral access?

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2

Systematic review of five feeding routes after pancreatoduodenectomy

Br J Surg. 2013 Apr;100(5):589-98

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ABSTRACT

Background

Current European guidelines recommend routine enteral feeding after pancreatoduodenectomy (PD), whereas American guidelines do not. The aim of this study was to determine the optimal feeding route after PD.

Methods

A systematic search was performed in PubMed, Embase and the Cochrane Library. Included were studies on feeding routes after PD that reported length of hospital stay (primary outcome).

Results

Of 442 articles screened, 15 studies with 3474 patients were included. Data on five feeding routes were extracted: oral diet (2210 patients), enteral nutrition via either a nasojejunal tube (NJT, 165), gastrojejunostomy tube (GJT, 52) or jejunostomy tube (JT, 623), and total parenteral nutrition (TPN, 424). Mean (s.d.) length of hospital stay was shortest in the oral diet and GJT groups (15(14) and 15(11) days respectively), followed by 19(12) days in the JT, 20(15) days in the TPN and 25(11) days in the NJT group. Normal oral intake was established most quickly in the oral diet group (mean 6(5) days), followed by 8(9) days in the NJT group. The incidence of delayed gastric emptying varied from 6 per cent (3 of 52 patients) in the GJT group to 23.2 per cent (43 of 185) in the JT group, but definitions varied widely. The overall morbidity rate ranged from 43.8 per cent (81 of 185) in the JT group to 75 per cent (24 of 32) in the GJT group. The overall mortality rate ranged from 1.8 per cent (3 of 165) in the NJT group to 5.4 per cent (23 of 424) in the TPN group.

Conclusion

There is no evidence to support routine enteral or parenteral feeding after PD. An oral diet may be considered as the preferred routine feeding strategy after PD.

INTRODUCTION

Pancreatoduodenectomy (PD) is the treatment of choice for resectable (pre)malignant neoplasms of the pancreatic head, ampulla, distal bile duct and duodenum.[1] PD is associated with a relatively high morbidity rate, including a high incidence of delayed gastric emptying that may interfere with the resumption of a normal diet.[2–4] Several enteral and parenteral feeding strategies have been investigated to cope with this problem. It has been suggested that routine early enteral tube feeding is not indicated after surgery for upper gastrointestinal malignancies.[5,6] In contrast, several studies have advocated the routine use of tube feeding in these patients as it might reduce infection rates and length of hospital stay.[7–11] This difference of opinion is also evident in current nutritional guidelines. The current guidelines of the European Society for Parenteral and Enteral Nutrition recommend routine use of early enteral nutrition in patients undergoing major gastrointestinal surgery for cancer, including PD.[12] In contrast, the current American Society for Parenteral and Enteral Nutrition guidelines recommend postoperative nutritional support only in patients who are unlikely to meet their nutrient needs orally for a period of 7–10 days, which is not necessarily the case after PD.[13] Both of these guidelines are, however, based on limited studies in patients with gastrointestinal cancer, mainly colorectal and gastric, which might hamper the compliance of clinicians with these recommendations. There is a lack of specific evidence concerning the optimal feeding strategy after PD. One systematic review previously addressed the role of routine enteral and parenteral nutrition after PD.[14] This 5-year-old review did not differentiate between the various enteral feeding routes, assess their associated complications or examine the methodological quality of the included studies. Moreover, several new studies have been published since then, that have investigated the role of fast-track (enhanced recovery after surgery) oral diet strategies. The present systematic review of the literature compared outcomes of feeding an oral diet and enteral and parenteral feeding routes after PD, focusing on both efficacy and safety.

METHODS

Study selection

A systematic literature search was performed in PubMed, Embase and the Cochrane Library for studies published to 26 April 2011. This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] Search terms used were 'PPPD or pancreaticoduodenectomy or pancreatoduodenectomy or pancreatic resection or pancreatectomy or Whipple' and 'nutrition or feeding or nasogastric or nasojejunal or jejunostomy', restricted to title, abstract and keywords. Titles and abstracts,

and subsequently full-text articles, were screened independently by two authors based on inclusion and exclusion criteria. Disagreement on eligibility was addressed by discussion and consensus. Reference lists of all included papers and PubMed 'related articles' were searched manually to identify initially missed but relevant studies.

Eligibility criteria

Included were studies concerning feeding after PD (both pylorus-preserving PD and classical Whipple), reporting on length of hospital stay (primary outcome), with the full text available in English. Excluded were: review articles, opinion papers, case reports, animal studies and studies not reporting results of different routes separately. For some studies, certain investigated groups were excluded: those with combined feeding routes, unclear definitions of feeding protocols or any supplements in addition to the standard formula. If multiple series with overlapping cohorts were available from one center, only the most recent study was included. Results of two variations within one feeding route (for example cyclic versus continuous jejunostomy feeding) were combined.

Assessment of methodological quality

The methodological quality of the studies was assessed independently by two authors. All studies were graded according to the Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence.[16] Because both randomized and cohort studies were included, it was not possible to apply a classical bias risk assessment method for the included articles. The risk of bias was therefore assessed using a standardized list of ten potential risks of bias, based on the Oxford CEBM Critical Appraisal Skills Programme appraisal sheets for randomized controlled trials and cohort studies.[17–19]

Data extraction

Study characteristics, including sample size, study design, study interval, study population, and type and route of nutritional support, were obtained from the included studies. Where available, the following data were extracted from the included studies: length of hospital stay, time to resumption of normal diet, duration of (par)enteral nutrition, overall morbidity, incidence of delayed gastric emptying (International Study Group of Pancreatic Surgery (ISGPS) grade B/C[20] or similar) and postoperative pancreatic fistula (International Study Group on Pancreatic Fistula (ISGPF) grade B/C[21] or similar), tube-related complications and mortality. First authors of included papers were contacted if data were missing.

Statistical analysis

Mean (s.d.) or median (range) values were extracted from articles or obtained from the study authors if necessary. Weighted mean (s.d.) values were calculated using the mean (s.d.)

values reported in the individual studies, or those derived from median (range) values using the methods described by Hozo and colleagues.[22] Total overall morbidity and mortality rates, and incidence of delayed gastric emptying and postoperative pancreatic fistula, were calculated. A sensitivity analysis was performed to assess the impact of methodological quality on the primary outcome (length of hospital stay). Analysis for the primary endpoint was repeated using data only from studies of the highest quality, defined as both a level of evidence of 1, 2 or 3 and a maximum of one item (of 10) suggestive of risk of bias. A sensitivity analysis was also carried out to assess the impact of a fast-track strategy on the outcome of oral diet after PD. This involved analysis of the primary endpoint only in studies (or groups within studies) that did not use a fast-track strategy.

RESULTS

The literature search and selection of articles for review is summarized in Fig. 1. Characteristics of the 15 included studies (7 randomized trials, 7 cohort studies and 1 case–control study) are shown in Table 1.[23–37] Formal meta-analysis was not performed because of the obvious heterogeneity between studies. Eventually, data on five feeding routes were extracted: oral diet (2210 patients), enteral nutrition via either nasojejunal tube (NJT, 165), gastrojejunostomy tube (GJT, 52) or jejunostomy tube (JT, 623), and total parenteral nutrition (TPN, 424).

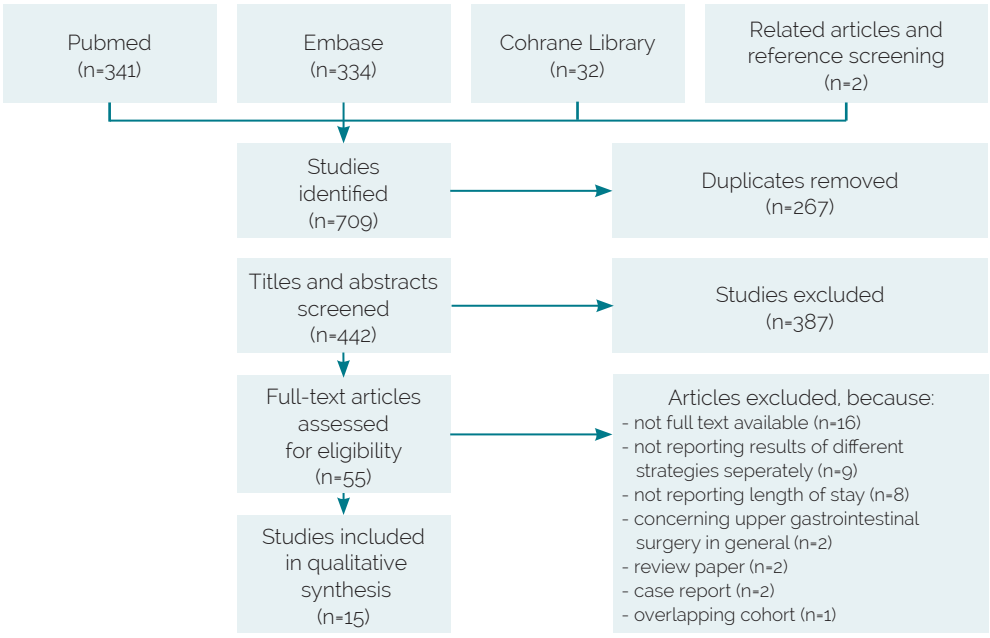

Figure 1 Selection of articles for review

Table 1 Study characteristics

Reference	Year	Country	Study design	Sample size	Study interval (years)	Study population	Investigated groups
Brennan[23]	1994	USA	RCT	117	5.5	Major pancreatic resection (including 97% PD)	TPN No nutritional support
Van Berge Hene-gouwen[24]	1997	Nether-lands	RCT	57	1.3	Pylorus-preserving PD	Jejunostomy tube cyclic‡ Jejunostomy tube continuous‡
Gianotti[25]	2000	Italy	RCT	212	NR	PD for lesion of either pancreatic head or periampullary region	TPN Jejunostomy tube with standard formula Jejunostomy tube with immunonutrition*
Martignoni[26]	2000	Switzer-land	Retrosp cohort	62	2.5	PD	Jejunostomy tube No enteral feeding
Baradi[27]	2004	USA	Retrosp cohort	180	7	PD	Enteral feeding (jejunostomy or gastrojejunostomy tube)* No enteral feeding
Mack[28]	2004	USA	RCT	36	2.8	PD for periampullary tumour	Gastrojejunostomy tube Surgeon's routine
Jo[29]	2006	South Korea	RCT	60	1	PD for periampullary tumour	TPN TPN with glutamine*
Berberat[30]	2007	Germany	Retrosp cohort	255	1	Pancreatic resection in general (including 61% PD)	Fast-track oral diet
Kennedy[31]	2007	USA	Retrosp cohort	135	2.8	PD	Prepathway oral diet* Critical pathway oral diet
Rayes[32]	2007	Germany	RCT	80	NR	Pylorus-preserving PD	Nasojejunal tube with standard formula Nasojejunal tube with standard formula and synbiotics*
Balzano[33]	2008	Italy	Retrosp cohort	504	8	PD	Traditional oral routine‡ Fast-track oral diet‡

*Excluded from the analysis; ‡results combined for analysis. RCT, randomized clinical trial; PD, pancreatoduodenectomy; TPN, total parenteral nutrition; NR, not reported.

Reference	Year	Country	Study design	Sample size	Study interval (years)	Study population	Investigated groups
Hallay[34]	2008	Hungary	RCT	22	3.5	Resection of head of pancreas because of cancer	TPN TPN and nasojejunal tube*
Akizuki[35]	2009	Japan	Case–control	82	5	PD	Nasojejunal tube
Yermilov[36]	2009	USA	Retrosp cohort	1873	10	PD for adeno-carcinoma of pancreas	No nutritional support TPN Jejunostomy tube
Abu Hilal[37]	2010	UK	Retrosp cohort	100	1.5	Pancreatic resection in general (including 93% PD)	Jejunostomy tube Gastrojejunostomy tube Nasojejunal tube

*Excluded from the analysis; ǂresults combined for analysis. RCT, randomized clinical trial; PD, pancreatoduodenectomy; TPN, total parenteral nutrition; NR, not reported.

Five of the seven randomized clinical trials were designed to investigate the additional value of an adaptation to one of the feeding strategies, such as addition of a supplement (for example glutamine, synbiotics) to the standard formula or cyclic versus continuous enteral feeding.[24,25,29,32,34] Only two studies randomized between two different feeding routes; Mack and co-workers[28] randomized patients at the time of PD to GJT feeding or to an oral diet, whereas Brennan and colleagues[23] randomized between TPN and no TPN. Of the eight studies that included an oral diet group, three were designed to investigate the role of a fast-track protocol (generally fluids on day 1 after surgery and solid foods from day 2);[30,31,33] in the other five, oral diet served as a control.[23,26–28,36]

Methodological quality

Details of the methodological quality of the included studies are shown in Table 2. None of the randomized clinical trials, except those investigating a supplement to the standard formula, blinded participants or study personnel, because it was considered practically impossible. Confounding by indication was a common risk of bias in most cohort studies because the chosen feeding strategy was determined by surgeon's preference, which had not been accounted for in further analysis.

Primary outcome

Mean length of hospital stay was shortest in the oral diet and GJT groups, at 15(14) and 15(11) days respectively, followed by 19(12) days in the JT, 20(15) days in the TPN and 25(11) days in the NJT group (Table 3).

Table 2 Assessment of methodological quality

Reference	Level of evidence	Random allocation	Blinding	Intention-to-treat analysis	Same treatment, follow-up and data collection	Similar groups	Follow-up	Recruiting/ selection bias	Classification bias	Measurement bias	Confounding by indication
Brennan[23]	2	○	◎	●	●	●	●	–	–	–	–
Van Berge [24]	3	○	◎	●	●	●	●	–	–	–	–
Gianotti[25]	3	●	◎	○	●	●	●	–	–	–	–
Martignoni[26]	3	–	–	–	–	●	●	●	●	●	◎
Baradi[27]	3	–	–	–	–	◎	●	●	●	●	◎
Mack[28]	2	●	◎	●	●	●	●	–	–	–	–
Jo[29]	3	●	●	○	●	●	●	–	–	–	–
Berberat[30]	4	–	–	–	–	–	●	–	–	–	–
Kennedy[31]	3	–	–	–	–	●	●	◎	●	◎	●
Rayes[32]	3	●	●	●	●	●	●	–	–	–	–
Balzano[33]	3	–	–	–	–	●	●	◎	●	●	●
Hallay[34]	3	◎	◎	○	●	○	●	–	–	–	–
Akizuki[35]	4	–	–	–	–	–	●	–	–	–	–
Yermilov[36]	3	–	–	–	–	◎	◎	●	◎	●	●
Abu Hilal[37]	3	–	–	–	–	●	●	●	●	●	◎

●, Consistent with criteria, low risk of bias; ◎, partly consistent with criteria/unknown risk of bias; ○, not consistent with criteria, high risk of bias; –, not applicable

Secondary outcomes

Resumption of normal diet was reported in seven studies (Table 4). It was established most quickly in the oral diet group, after a mean duration of 6(5) days, followed by 8(9) days in the NJT, 11(5) days in the TPN, 12(11) days in the JT and 14(8) days in the GJT group. Duration of artificial feeding was reported in seven studies. The mean duration of enteral nutrition was 9(8) days in the NJT, 12(7) in the JT and 10(8) days in the GJT group. Mean duration of parenteral nutrition was 13(6) days in the TPN group. Some 29.4 per cent of patients (55 of 187) in the oral diet group received parenteral nutrition at some point during their hospital stay, for a mean duration of 7(11) days, owing to complications such as delayed gastric emptying. One study reported that TPN was started immediately after surgery because of preoperative weight loss or malnutrition in six of 16 patients.[28] As the basic feeding strategy in this group was an oral diet, these patients were included in the oral diet group according to the intention-to-treat principle. Overall morbidity was lowest in the JT group with a mean rate of 43.8 per cent (81 of 185 patients), followed by 49.4 per cent (310 of 627) in the oral diet, 50 per cent (48 of 96 patients) in the TPN, 56 per cent (24 of 43) in the NJT and 75 per cent (24 of 32) in the GJT group.

Table 3 Length of hospital stay (days)

	Oral diet	Nasojejunal tube	Gastro-jejunostomy tube	Jejunostomy tube	TPN	P
Brennan[23]	14 (6–88)*	–	–	–	16 (7–72)*	NR
Van Berge [24]	–	–	–	16 (9–73)*	–	
Gianotti[25]	–	–	–	17.0(6.1)	18.8(6.4)	NR
Martignoni[26]	15 (9–56)*	–	–	23 (13–74)*	–	< 0.01
Baradi[27]	14.8(8.8)	–	–	–	–	
Mack[28]	15.8(7.8)	–	11.5(2.9)	–	–	0.01
Jo[29]	–	–	–	–	14.5 (9–41)*	
Berberat[30]	10 (4–115)*	–	–	–	–	
Kennedy[31]	7(NR)*	–	–	–	–	
Rayes[32]	–	22(16)	–	–	–	
Balzano[33]	14 (7–110)*	–	–	–	–	
Hallay[34]	–	–	–	–	17 (9–24)*	
Akizuki[35]	–	32 (19–93)*	–	–	–	
Yermilov[36]	16.4(10.8)*	–	–	18.7(12.5)*	22.5(16.6)	NR
Abu Hilal[37]	–	15 (8–60)*	17 (8–64)*	16 (10–55)*	–	0.353
Overall	15(14)	25(11)	15(11)	19(12)	20(15)	

Values are mean (s.d.) unless indicated otherwise; *values are median (range). TPN, total parenteral nutrition; NR, not reported.

Table 4 Time to resumption of normal diet

	Definition	Oral diet	Naso-jejunal tube	Gastro-jejunostomy tube	Jejunostomy tube	TPN	P
Van Berge [24]	First day of normal diet	–	–	–	10 (5–68)*	–	
Gianotti[25]	First day of solid diet	–	–	–	9.8 (3.8)	10.4 (3.7)	NR
Baradi[27]	Time when regular diet was started	10.5(7.7)	–	–	–	–	
Jo[29]	Time to soft diet	–	–	–	–	11.5(7.4)	
Berberat[30]	Return to normal food	5 (1–24)*	–	–	–	–	
Akizuki[35]	Start of solid diet	–	7 (4–39)*	–	–	–	
Abu Hilal[37]	Resumption of normal diet	–	10 (5–39)*	14 (7–37)*	14 (6–53)	–	0.018
Overall		6(5)	8(9)	14(8)	12(11)	**11(5)**	

Values are mean (s.d.) unless indicated otherwise; *values are median (range). TPN, total parenteral nutrition; NR, not reported.

Table 5 Delayed gastric emptying

	Definition	Oral diet	Naso-jejunal tube	Gastro-jejuno-stomy tube	Jejuno-stomy tube	TPN	P
Brennan[23]	Nasogastric tube drainage of > 500 ml on POD 6	1 of 57	–	–	–	2 of 60	0.38
Van Berge [24]	Gastric stasis, requiring nasogastric intubation for ≥ 10 days, or inability to tolerate a regular diet on or after POD 14	–		–	14 of 57	–	
Gianotti[25]	NR	–	–	–	9 of 73	10 of 68	
Martignoni[26]	Nasogastric tube for > 10 days postop., vomiting > 3 consecutive days after POD 5 and if X-ray with water-soluble contrast medium revealed hold-up of contrast medium in stomach	5 of 32	–	–	17 of 30	–	0.01
Mack[28]	Inability to tolerate oral intake on or after POD 14	4 of 16	–	0 of 20	–	–	0.03
Jo[29]	Inability to tolerate a regular or normal diet by POD 14, or gastric stasis that required nasogastric decompression for ≥ 7 days at any time	–	–	–	–	4 of 28	
Berberat[30]	Need to leave in nasogastric tube in place for > 10 days or reinsertion after POD 10	20 of 255	–	–	–	–	
Kennedy[31]	Persistent vomiting or inability to tolerate diet requiring replacement of nasogastric tube	8 of 91	–	–	–	–	
Rayes[32]	NR	–	4 of 40	–	–	–	
Balzano[33]	Need for nasogastric decompression or vomiting occurring after POD 10	97 of 504	–	–	–	–	
Akizuki[35]	Grade B or C according to ISGPS,	–	19 of 82	–	–	–	
Abu Hilal[37]	NR	–	5 of 43	3 of 32	3 of 25	–	0.937
Overall		135 of 955 (14.1)	28 of 165 (17.0)	3 of 52 (6)	43 of 185 (23.2)	16 of 156 (10.3)	

Values in parentheses are percentages. TPN, total parenteral nutrition; POD, postoperative day; NR, not reported. ISGPS, International Study Group of Pancreatic Surgery.

Table 6 Postoperative pancreatic fistula

	Definition	Oral diet	Naso-jejunal tube	Gastro-jejuno-stomy tube	Jejuno-stomy tube	TPN	P
Brennan[23]	NR	5 of 57	–	–	–	8 of 60	0.62
Van Berge [24]	NR	–	–	–	4 of 57	–	
Gianotti[25]	Sterile pancreatic fistula	–	–	–	9 of 73	8 of 68	NR
Baradi[27]	Late pancreatic fistula (after POD 30)	0 of 82	–	–	–	–	
Mack[28]	Radiographically detected leak, or drainage > 50 ml on or after POD 10	1 of 16	–	1 of 20	–	–	NR
Jo[29]	Amylase and lipase in drain fluid ≥ 3 times normal upper limits of serum level, or drainage sustained after POD 7, and drainage fluid ≥ 10 ml/day	–	–	–	–	0 of 28	
Berberat[30]	Persisting secretions of > 30 ml/day amylase-rich fluid (> 5000 units/ml) for > 10 days postop or recurrence of amylase-rich fluid in an intra-abdominal abscess	4 of 255	–	–	–	–	
Kennedy[31]	Output of > 30 ml/day amylase-rich fluid (> 3 times serum value) for > 10 days postop.	2 of 91	–	–	–	–	
Rayes[32]	NR	–	4 of 40	–	–	–	
Balzano[33]	Grade B or C according to ISGPS	65 of 504	–	–	–	–	
Akizuki[35]	NR	–	13 of 82	–	–	–	
Abu Hilal[37]	NR	–	0 of 43	1 of 32	1 of 25	–	0.451
Overall		77 of 1005 (7.7)	17 of 165 (10.3)	2 of 52 (4)	14 of 155 (9.0)	16 of 156 (10.3)	

Values in parentheses are percentages. TPN, total parenteral nutrition; NR, not reported; POD, postoperative day; ISGPS, International Study Group of Pancreatic Surgery.

Most studies distinguished between early versus late, minor versus major or infectious versus non-infectious complications, without reporting overall numbers. The mean incidence of delayed gastric emptying varied from 6 per cent (3 of 52 patients) in the GJT group to 23.2 per cent (43 of 185) in the JT group (Table 5). The incidence in the oral diet group was 14.1 per cent (135 of 955). Definitions varied widely, with only one study[35] using

the ISGPS definition. The same applied to postoperative pancreatic fistula.[33] The mean incidence of pancreatic fistula varied from 4 per cent (2 of 52 patients) in the GJT group, to 10.3 per cent in the NJT and TPN groups (17 of 165 and 16 of 156 patients respectively) (Table 6). Mortality rates ranged from 1.8 per cent (3 of 165 patients) in the NJT group to 2 per cent (1 of 52) in the GJT, 4.4 per cent (96 of 2178) in the oral diet, 4.7 per cent (28 of 593) in the JT and 5.4 per cent (23 of 424) in the TPN group.

Safety

Tube-related complications were addressed in only two studies, including a total of 241 patients.[25,37] The incidence varied from 12 per cent (5 of 43 patients) in the NJT group, caused mainly by blockage and dislodgement, to 14 per cent (14 of 98) in the JT group, mainly due to blockage, and 34 per cent (11 of 32) in the GJT group, owing to blockage and peritonitis after removal. Increased infection rates in the TPN group were reported by both studies that compared complication rates between TPN and oral diet or enteral nutrition groups.[23,25] One study also reported specific TPN-related metabolic complications, which were present in two of 60 patients.[23] No complications specifically related to an oral diet were reported in the included studies. One study reported a higher incidence of vomiting in the oral diet group than with enteral tube feeding: 29 per cent (24 of 82) versus 10 per cent (10 of 98).[27] In one study that reported on weight loss during the hospital stay, there was no difference between the oral diet and enteral nutrition groups (mean 3.8 versus 4.4 kg).[26]

Sensitivity analysis

No major changes in length of hospital stay were found when the analysis was restricted to studies of higher quality (those with the lowest risk of bias).[23–26,28,29,32,33,37] In the oral diet group, length of hospital stay decreased from 15 to 14 days; hospital stay was also reduced in the NJT and TPN groups (to 18 and 17 days respectively). Sensitivity analysis demonstrated that a fast-track strategy had no major impact on the primary endpoint.[23,26–28,33,36] The length of hospital stay in the oral diet group increased from 15 to 16 days when the analysis was restricted to studies (or groups within studies) that did not use a fast-track strategy.

DISCUSSION

This systematic review has compared the outcomes of the five most frequently used feeding routes after PD, and analysed methodological quality and feeding-related complications. No major differences in outcomes were detected between an oral diet, enteral nutrition via either a NJT, JGT or DT, and TPN after PD. As several relevant outcomes (length of hospital stay, time to resumption of normal diet) appeared to be most favourable (or at least not inferior) in the oral diet group, oral feeding may be considered as the preferred strategy

after PD. Although few studies reported on feeding-related complications after PD, these complications have been described in the general feeding literature. NJTs dislodge in up to 36 per cent patients within the first week.[38–42] Percutaneous JTs can cause potentially life-threatening torsion and bowel necrosis in 0.4 per cent of patients.[43] TPN is associated with a well-documented increased risk of infection.[44] Although data are scarce, an oral diet strategy does not seem to be associated with such risks, as confirmed in the present study. It should be noted that the oral feeding protocols of the studies in this review varied considerably. Several studies included a fast-track (enhanced recovery) programme,[30,31,33] whereas others described the oral diet strategy as 'no nutritional support/enteral feeding', without providing clear specifications.[23,26–28,36]The fast-track regimens consisted of an early start (within 24 h) and stepwise increase in oral intake, but also a pain management protocol, early mobilization and routine pharmacological support for early gastrointestinal function. In two studies that compared such fast-track regimens with more traditional protocols, it was concluded that fast-track protocols resulted in a reduced incidence of delayed gastric emptying and shorter hospital stay, without increasing readmission rates, thereby decreasing costs and improving patient comfort.[31,33] The present analysis demonstrated that a fast-track strategy had only a minor (1 day) impact on hospital stay in the oral diet group. Nonetheless, an average of 29.4 per cent of patients fed orally required nutritional support, mainly because oral intake was insufficient or owing to complications such as pancreatic fistula. Characteristics of these patients were not specified separately. In the present studies only sparse details on preoperative nutritional status were reported, making it difficult to evaluate its impact on decision-making and outcomes. Future prospective studies should aim at preoperative identification of those who are at high risk of requiring postoperative nutritional support. These patients could then receive preoperative nutritional support, as recommended by the current nutritional guidelines,[12,13] and/or a NJT during surgery, thereby minimizing both malnutrition and patient discomfort. The potential effect of preoperative nutritional support is of course dependent on severity of jaundice and biliary drainage. The present analysis differs considerably from the previous review on this topic[14] as the latter included only four of the 15 studies reviewed here. There are some limitations that must be taken into account. First, the quality of the included studies is moderate. Sensitivity analysis, however, revealed no impact of methodological quality on the primary outcome of this study. Second, of the seven randomized clinical trials, only two directly compared outcomes of two different feeding routes.[23,28] In addition, another three (of 8) non-randomized studies directly compared outcomes of two or three different feeding routes.[26,36,37] One could argue that the primary outcome measure of this study (length of hospital stay) is subject to the influence of several factors other than nutrition, such as differences in discharge policies between Western and Eastern countries, or the gradual reduction in length of stay associated with enhanced recovery programmes over the past few decades. For the latter,

no such trend could be observed when comparing the oldest studies (length of stay 14–16 days)[23,24] with the most recent ones (15–32 days).[35,37] In addition, length of stay was the most commonly reported outcome in the literature on this topic. Outcome measures that are more specifically related to feeding (such as time to resumption of normal oral diet, serum albumin levels or weight loss during hospital stay) were rarely reported. Another limitation is that definitions of various endpoints varied widely among the studies. For example, only two studies[33,35] used the ISGPS or ISGPF definition of delayed gastric emptying or postoperative pancreatic fistula, known to result in a relatively high incidence of complications.[3] The definition of oral diet and regular standards of care also varied between studies. Finally, a subgroup analysis of the primary outcome in patients with delayed gastric emptying could not be performed, as the included studies did not report outcomes for the subgroups of patients with and without delayed gastric emptying. These shortcomings should be borne in mind when interpreting the results of this systematic review. This review summarized the available evidence on feeding routes after PD, including assessment of methodological quality, without an attempt at meta-analysis, as this would have been inappropriate given the heterogeneity in study designs and protocols.

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3

Efficacy and complications of nasojejunal, jejunostomy and parenteral feeding after pancreatoduodenectomy

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ABSTRACT

Background

European nutritional guidelines recommend routine use of enteral feeding after pancreatoduodenectomy (PD) whereas American guidelines do not. Data on the efficacy and, especially, complications of the various feeding strategies after PD are scarce.

Methods

Retrospective monocenter cohort study in 144 consecutive patients who underwent PD during a period wherein the routine post-PD feeding strategy changed twice. Patients not receiving nutritional support (n=15) were excluded. Complications were graded according to the Clavien-Dindo classification and the International Study Group of Pancreatic Surgery (ISGPS) definitions. Analysis was by intention-to-treat. Primary endpoint was the time to resumption of normal oral intake.

Results

129 patients undergoing PD (111 pylorus preserving) were included. 44 patients (34%) received enteral nutrition via nasojejunal tube (NJT), 48 patients (37%) via jejunostomy tube (JT) and 37 patients (29%) received total parenteral nutrition (TPN). Groups were comparable with respect to baseline characteristics, Clavien ≥II complications (P=0.99), in-hospital stay (P=0.83) and mortality (P=0.21). There were no differences in time to resumption of normal oral intake (primary endpoint; NJT/JT/TPN: median 13, 16 and 14 days, P=0.15) and incidence of delayed gastric emptying (P=0.30). Duration of enteral nutrition was shorter in the NJT- compared to the JT-group (median 8 vs. 12 days, P=0.02). Tube related complications occurred mainly in the NJT-group (34% dislodgement). In the JT-group, relaparotomy was performed in three patients (6%) because of JT-leakage or strangulation leading to death in one patient (2%). Wound infections were most common in the TPN group (NJT/JT/TPN: 16%, 6% and 30%, P=0.02).

Conclusion

None of the analysed feeding strategies was found superior with respect to time to resumption of normal oral intake, morbidity and mortality. Each strategy was associated with specific complications. Nasojejunal tubes dislodged in a third of patients, jejunostomy tubes caused few but potentially life-threatening bowel strangulation and TPN doubled the risk of infections.

INTRODUCTION

Pylorus-preserving pancreatoduodenectomy (PD) is the treatment of choice for (pre-) malignant neoplasms of the pancreatic head, ampulla, distal bile duct and duodenum.[1] PD is associated with a relatively high morbidity rate, including a high incidence of delayed gastric emptying.[2–4] The current guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN) recommend routine use of early enteral nutrition in case of patients undergoing major gastrointestinal surgery for cancer, including PD.[5] In contrast, the current American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines recommend postoperative nutritional support only in patients whom it is anticipated will be unable to meet their nutrient needs orally for a period of 7 to 10 days, which is not necessarily the case after PD.[6] Specific evidence concerning the optimal feeding strategy after PD is scarce and hence the choice of feeding strategy depends mainly on individual preference. Although enteral and parenteral feeding after PD may be associated with complications, there are surprisingly little data available on this subject.

In our department, the preferred routine post-PD feeding strategy changed twice in the past 10 years; from jejunostomy tube feeding (JT) to total parenteral nutrition (TPN) to nasojejunal tube feeding (NJT). These changes were initiated by a perceived high rate of feeding-related complications associated with the JT and TPN feeding strategies as well as a lack of clear evidence in favour of any feeding technique. The aim of this study was to assess the efficacy and feeding-related complications of the various feeding strategies after PD in a single tertiary referral center.

METHODS

Patients

A retrospective monocenter cohort study was performed in all 144 consecutive patients who underwent (pylorus preserving) PD at the University Medical Center Utrecht, between January 1st 2001 and December 30th 2010. Patients were categorised according to the feeding strategy decided upon prior to or during surgery: enteral feeding via NJT or JT, or TPN. Patients who could not be classified in these three groups or had no follow-up were excluded (n=15). See the ' Results' section for details.

Surgical Approach

PD was performed by a team specialised in hepatobiliary and pancreatic surgery. Reconstruction was typically performed with end-to-side duct-to-mucosa pancreatojejunostomy (ISGPS type IAS0),[7] end-to-side hepaticojejunostomy and (antecolic) duodeno(gastro)jejunostomy.

Routes of Nutrition

Enteral nutrition was delivered via either nasojejunal tube or jejunostomy tube. In the period January 2001–May 2010, Nutrison Standard was used and since May 2010 Nutrison Protein Plus (both from Nutricia, The Netherlands). In the NJT group, a nasojejunal tube (Freka Trelumina Tube, Fresenius Kabi Ltd, UK) was advanced for at least 30 cm through the duodenojejunostomy after the creation of the dorsal part of this anastomosis. In the JT group, a jejunostomy tube (Freka FCJ Set FR 9, Fresenius Kabi Ltd, UK) was advanced through the abdominal wall and into the bowel after the reconstruction phase of the pancreatoduodenectomy. The tube was advanced for at least 30 cm and fixated to the bowel and the abdominal wall. In both the NJT and JT groups, enteral nutrition was started the first morning postoperatively at a rate of 25 ml/h and increased with 25 ml per day (2001–2009) or per 6 h (since May 2010) to the required amount as advised by the consulting dietitian.

TPN (NuTRIflex Lipid Special, B. Braun, Germany) was delivered via a central venous line. TPN was started the morning after surgery at a rate of 42 ml/h and increased with 500 ml per day to the required amount, according to dietitians' advice.

In the NJT and JT groups, TPN was only given when enteral feeding was unsuccessful, but according to the intention-to-treat principle these patients remained in their assigned groups.

Oral intake was started on patient's request and modulated depending on digestive symptoms. When oral intake exceeded 50% of the daily required caloric intake, enteral or parenteral nutritional support was ceased. In the NJT group, the feeding tube was removed at this stage. In the JT group, the tube was only removed in the outpatient department 6 weeks postoperatively. Patients in the JT and TPN group received a nasogastric tube for gastric decompression only if necessary.

Definitions

Postoperative pancreatic fistula, delayed gastric emptying and post-pancreatectomy haemorrhage were defined according to the International Study Group of Pancreatic Surgery (ISGPS) definitions.[8–10] All complications were graded according to the Clavien–Dindo classification.[11] The postoperative course was defined to be complicated if a complication occurred that required medical therapy or any form of intervention (Clavien–Dindo grade II or higher). Chyle leakage requiring very low fat elemental enteral nutrition was graded as Clavien–Dindo grade II, if there was no other indication for enteral nutrition (anymore). Infectious complications had to be confirmed by a positive culture result. Severe preoperative weight loss was defined as weight loss of 10% or more within 6 months or 5% or more within 1 month prior to surgery.

Data Collection

Data were retrospectively collected from computerised clinical records. Baseline characteristics collected were patient demographics, body mass index (BMI), severe preoperative weight loss, indication for surgery, diagnosis, surgeon, type of surgery, operative time and blood loss.

Primary outcome was the time to resumption of normal oral intake, defined as the postoperative day on which intake was reported to be adequate by the treating physician or dietitian.

Secondary outcomes were time to start of oral and solid food intake, duration of (par) enteral nutrition, use of prokinetic agents, postoperative surgical, general and tube-related complications (in-hospital and during readmission), incidence of postoperative pancreatic fistula, delayed gastric emptying, post-pancreatectomy haemorrhage and chyle leakage, length of hospital stay, readmission within 30 days after discharge, relaparotomy and in-hospital mortality.

Statistical Analysis

Analysis was by intention-to-treat. Values are expressed as median and interquartile range, unless specified otherwise. Data were analysed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous non-normally distributed variables were compared using the Kruskal– Wallis or Mann–Whitney U test, and categorical variables were compared by chi-square or Fisher's exact test as appropriate. For multivariable analysis, the binary logistic regression model was used. Statistical dependence between two non-parametric variables was assessed by Spearman correlation. A P value <0.05 was considered significant.

RESULTS

Patients

Of the 144 patients who had undergone a (pylorus preserving) PD in the study period, 15 patients were excluded because they had no nutritional support (n=9), received enteral nutrition via nasogastric tube (n=4), underwent a modified surgical intervention (status after previous total gastrectomy, n=1) or were transferred to another hospital (n=1) leaving 129 patients eligible for further analysis.

Of these 129 patients, 44 (34%) received enteral nutrition via NJT, 48 patients (37%) via JT and 37 patients (29%) received TPN. Baseline characteristics, including age, gender, BMI, severe preoperative weight loss, indication for surgery, diagnosis, procedure and blood loss did not differ between the groups (see Table 1). The three groups only differed in terms of the surgeon performing the procedure and the operative time.

Table 1 Baseline characteristics

	Nasojejunal tube (n=44)	Jejunostomy tube (n=48)	Total parenteral nutrition (n=37)	P
Male	59%	69%	57%	0.47
Age	63 (61-67)	65 (57-72)	66 (60-72)	0.34
BMI	24.2 (22.0-26.7)	24.3 (22.8-25.9)	23.8 (22.0-26.9)	0.96
Severe preoperative weight loss*	15 (34%)	14 (41%)	10 (34%)	0.79
Indication				0.62
suspected malignancy	21 (48%)	33 (69%)	23 (62%)	
proven malignancy	14 (32%)	11 (23%)	10 (27%)	0.29
other	9 (20%)	4 (8%)	4 (11%)	
Diagnosis				0.28
pancreatic adenocarcinoma	19 (43%)	23 (48%)	11 (30%)	
ampullary adenocarcinoma	4 (9%)	11 (23%)	8 (22%)	
cholangiocarcinoma	6 (14%)	3 (6%)	7 (19%)	
benign	7 (16%)	3 (6%)	4 (11%)	
other	8 (18%)	8 (17%)	7 (19%)	
Procedure				0.13
pylorus preserving PD	34 (77%)	44 (92%)	29 (78%)	
extended PD**	10 (23%)	4 (8%)	8 (22%)	
Intraoperative parameters				
operative time (min)	370 (318-438)	291 (265-361)	367 (312-412)	0.001
blood loss (cc)	800 (500-1350)	1000 (550-1500)	800 (575-1500)	0.43
RBC transfusion (units)	0 (0-0)	0 (0-2)	0 (0-1)	0.20
FFP transfusion (units)	0 (0-0)	0 (0-0)	0 (0-0)	0.72

BMI=body mass index, PD=pancreatoduodenectomy, RBC=red blood cells, FFP=fresh frozen plasma
* 17% missing data
** Whipple's PD (n=5), PD+hemicolectomy (n=3), PD+hemicolectomy+nefrectomy (n=3), PD+hemicolectomy+portal vein (n=2), PD+portal vein (n=5), PD+partial corpus/cauda resection (n=2), total pancreatectomy (n=1), total pancreatectomy+portal vein (n=1)

Efficacy

Time to resumption of normal oral intake (primary endpoint) did not differ between the three groups, with a median duration of 13 (10–19), 16 (13–24) and 14 (10–22) days in the NJT, JT and TPN group, respectively (P=0.15). Duration of enteral nutrition was significantly shorter in the NJT group compared to the JT group [median 8 (6–12) vs. 12 (8–18) days, P=0.02]. Time to start of oral intake was significantly shorter in the TPN-group, with a median duration of 5 (3–7), 5 (4–11) and 4 (2–5) days in the NJT, JT and TPN group, respectively (P=0.02). All outcomes of nutritional and hospitalisation parameters are shown in Table 2.

Table 2 Nutritional and hospitalization parameters

	Nasojejunal tube (n=44)	Jejunostomy tube (n=48)	Total parenteral nutrition (n=37)	P	P enteral only*
Primary endpoint					
Time to resumption of normal oral intake (days)	13 (10-19)	16 (13-24)	14 (10-22)	0.15	0.09
Secondary endpoints					
Duration of enteral nutrition (days)	8 (6-12)	12 (8-18)	0 (0-0)		0.02
Duration of parenteral nutrition (days)	0 (0-6)	0 (0-0)	9 (7-14)		0.06
Time to start oral intake (days)	5 (3-7)	5 (4-11)	4 (2-5)	0.02	0.11
Time to start solid food intake (days)	9 (6-12)	12 (9-17)	9 (7-13)	0.10	0.06
Use of prokinetics (n)	12 (27%)	23 (48%)	14 (38%)	0.15	0.05
Length of hospital stay (days)	17 (12-23)	19 (14-24)	16 (13-27)	0.83	0. 58
Readmission within 30 days (n)	2 (4.5%)	3 (6.3%)	6 (16.2%)	0.19	1.00

* Nasojejunal vs jejunostomy tube

Table 3 Postoperative complications

	Nasojejunal tube (n=44)	Jejunostomy tube (n=48)	Total parenteral nutrition (n=37)	P	P enteral only*
Overall morbidity					0.26
Clavien-Dindo grade I-V	37 (84%)	44 (92%)	34 (92%)	0.49	0.91
Clavien-Dindo grade ≥ II	27 (61%)	30 (63%)	23 (62%)	0.99	0.29
Surgical morbidity**	36 (82%)	43 (90%)	33 (89%)	0.52	0.40
General morbidity***	20 (45%)	26 (54%)	17 (39%)	0.55	0.06
Tube related morbidity	18 (41%)	11 (23%)	6 (16%)	0.03	0.92
Relaparotomy	7 (16%)	8 (17%)	7 (19%)	0.93	
number of procedures	19	15	13		
of which tube related	0	4	0		0.27
Mortality	2 (4.5%)	6 (12.5%)	1 (2.7%)	0.21	
of which tube related	0	1	0		

* Nasojejunal vs jejunostomy tube
** Including pancreatic fistula, delayed gastric emptying, postoperative haemorrhage , ileus, anastomic bowel leak, chyle leak, biliary leak, fascial dehiscence, bowel ischemia, enterocutaneous fistula, cholangitis, wound infection and Intra-abdominal abscess.
*** Including line infection, urinary tract infection, pneumonia, deep venous thrombosis and pulmonary embolis

General Complications

Morbidity and mortality rates are shown in Table 3. Overall morbidity requiring therapy or intervention (Clavien–Dindo grade II or higher) and mortality did not differ between the

Table 4 General and surgical morbidity

	Nasojejunal tube (n=44)	Jejunostomy tube (n=48)	Total parenteral nutrition (n=37)	P	P enteral only*
Pancreatic fistula (grade B/C)	5 (11%)	6 (13%)	4 (11%)	1.00	
Delayed gastric emptying (grade B/C)	15 (34%)	24 (50%)	15 (40%)	0.30	
Postoperative haemorrhage (grade B/C)	6 (14%)	4 (8%)	3 (8%)	0.67	
Ileus	2 (5%)	5 (10%)	0 (0%)	0.13	
Anastomic bowel leak	1 (2%)	0 (0%)	0 (0%)	0.63	
Chyle leak	9 (20%)	11 (23%)	2 (5%)	0.08	
Biliary leak	5 (11%)	4 (8%)	3 (8%)	0.86	
Fascial dehiscence	2 (5%)	0 (0%)	3 (8%)	0.13	
Bowel ischemia	1 (2%)	1 (2%)	0 (0%)	1.00	
Enterocutaneous fistula	1 (2%)	0 (0%)	1 (3%)	0.53	
Other surgical complications	3 (7%)	2 (4%)	2 (5%)	0.89	
Infections					
Cholangitis	3 (7%)	0 (0%)	2 (5%)	0.22	
Wound infection	7 (16%)	3 (6%)	11 (30%)	0.02	0.19
Intra-abdominal abscess	3 (7%)	1 (2%)	2 (5%)	0.58	
Line infection	8 (18%)	7 (15%)	3 (8%)	0.42	
Urinary tract infection	6 (14%)	6 (13%)	3 (8%)	0.79	
Pneumonia	9 (20%)	8 (17%)	4 (11%)	0.50	
Deep venous thrombosis	1 (2%)	1 (2%)	0 (0%)	1.00	
Pulmonary embolism	3 (7%)	1 (2%)	2 (5%)	0.58	
Other general complications	10 (23%)	12 (25%)	14 (32%)	0.27	

* nasojejunal vs jejunostomy tube, only reported when overall P value <0.05

groups. Surgical and general complication rates are listed in Table 4. The rates of clinically relevant postoperative pancreatic fistula (grade B/C, ISGPF), delayed gastric emptying (grade B/C, ISPGS) and postoperative haemorrhage (grade B/C, ISGPS) did not differ between the groups (overall rates 12%, 42% and 10%, respectively).

Feeding-Related Complications

Tube-related complications were more common in the NJT group as compared to the JT group (41% vs. 23%, P=0.06). This difference was mainly caused by a 34% (n=15) dislodgement rate of the intraoperatively placed nasojejunal tubes (Table 5). These dislodgements occurred after a median of 7 (5–12) days. Tubes were replaced in eight of the 15 patients. The complications in the JT group tended to be more severe, including leakage and torsion

Table 5 Tube related morbidity

	Nasojejunal tube (n=44)	Jejunostomy tube (n=48)	Total parenteral nutrition (n=37)	P	P enteral only*
Dislodgement of primary placed tube	15 (34%)	4 (8%)	3 (8%)	0.001	0.002
Disabling blockage	4 (9%)	5 (10%)	0 (0%)	0.11	1.00
Infection of feeding tube/central venous line**	0 (0%)	1 (2%)	3 (8%)	0.10	1.00
Haemorrhage (not requiring transfusion)	0 (0%)	2 (4%)	0 (0%)	0.33	0.50
Other***	0 (0%)	5 (10%)	0 (0%)	0.01	0.06
Tube related relaparotomy	0 (0%)	3 (6%)	0 (0%)	0.11	0.24
Tube related mortality	0 (0%)	1 (2.3%)	0 (0%)	1.00	1.00

* nasojejunal vs jejunostomy tube
* see table 4 for all infectious complications
*** 2 small bowel leakage, 2 bowel torsion, 1 subcutaneous emphysema and fluid collection around insertion site

of the small bowel around the tube, requiring four relaparotomies in three patients (6 %) and eventually leading to death in one patient (2 %), due to multiorgan failure caused by small bowel ischaemia. The rate of wound infections was significantly higher in the TPN group (NJT/JT/TPN=16%, 6% and 30%, P=0.02).

Multivariable Analysis

The patient volume increased during the 10-year study period. Average annual volume in the first 3 years was 5 versus 25 in the last 3 years (P=0.001). Therefore, year of procedure was entered as a variable in a multivariable logistic regression analysis that also adjusted for differences in age, gender, BMI and surgeon. After adjustment, there still was no difference between the three feeding strategies in the rate of morbidity or mortality.

Age and gender were found to be an independent factor influencing morbidity (Clavien–Dindo grade II or higher). A 1-year increase in age had an OR of 1.05 in developing a complication (P=0.02). The male gender had an OR of 2.48 in developing a complication compared to the female gender (P=0.02). No independent factors for mortality were found.

DISCUSSION

This is the largest comparative study to date on efficacy and complications of jejunostomy, nasojejunal and total parenteral feeding after PD. None of the feeding strategies was found superior with respect to time to resumption of normal oral intake, morbidity and mortality. Each strategy was associated with specific complications. Nasojejunal tubes dislodged

in a third of patients, jejunostomy tubes caused few but potentially lifethreatening bowel strangulation and TPN doubled the risk of wound infections. Although these complications varied widely in both incidence and severity, it seems that if feeding is desired a nasojejunal tube is the feeding strategy of choice, as replacement of a nasojejunal tube (although frequently required) is to be preferred over infections and bowel strangulation.

Only one study previously compared the efficacy and safety of different routes of enteral nutritional support after PD.[12] This monocenter cohort study analysed 100 patients receiving enteral nutrition via either percutaneous transperitoneal jejunostomy, gastrojejunostomy or nasojejunal tube. This study did not use ISGPS definitions or multivariable analysis to account for confounders such as surgeon's preference. As in our study, no significant differences were observed between the groups in time to resumption of normal oral intake, as well as in hospital stay, while duration of feeding was significantly shorter in NJT patients. Tube related complications, however, were observed less frequently than in our study. Dislodgement of the NJT was seen in only 5% of patients, as compared to 34% in our study. The authors stated this relatively low dislodgement rate to be caused by the use of a tube with a wider diameter (10/8 French), enabling more secure fixation at the nostrils. The tubes used in our study, however, have an even larger diameter (16/9 French) due to the three lumina. In the general feeding literature, a dislodgement rate of NJTs of 16–36% has been reported.[13–17] Several techniques have been described to prevent inadvertent NJT dislodgement. One of the most successful ones is nasal bridling.[18] In a randomized controlled trial (n=80), comparing the nasal bridle technique with an adhesive tape device, dislodgement rate was reduced from 63% in the unbridled to 18% in the bridled group, with only few and minor adverse events.[19] Another technique is the clipping of the tip of the nasojejunal tube to the bowel mucosa,[20] but this is impractical during laparotomy.

Although rare, bowel strangulation and leakage are well-known, potentially lethal complications of percutaneous jejunostomy tubes. In a series of 2,022 patients undergoing laparotomy for mostly complex upper-abdominal operations, jejunostomy resulted in 34 tube-related complications in 29 patients (1.5%).[21] The most common complication was occlusion or dislodgement in 15 patients (0.7%), and the most serious complication was bowel necrosis in three patients (0.2%), leading to death in two patients. Intestinal occlusion and volvulus was described in three patients (0.2%), leading to death in one and intra-abdominal infections in three other (0.2%). A literature review in 1,788 patients with jejunostomy tubes found a strangulation rate of 0.3% and an intra-abdominal infection rate of 0.8%.[21]

Increased risk of infections with the use of parenteral nutrition is also well known. A meta-analysis by Braunschweig et al., combining 27 randomized controlled trials (n=1,827), found

a significantly increased risk of infections with parenteral compared to enteral nutrition (RR 0.64),[22] corresponding with the results of a previous study in patients after PD.[23]

Duration of enteral nutrition was found to be significantly shorter in the NJT group compared to the JT group (median 8 vs. 12 days). This can be explained by the fact that enteral feeding in the NJT group was often interrupted due to tube dislodgement, and attempts to stop enteral nutrition were undertaken earlier to stimulate oral intake and relief patients of their tube before discharge.

The strength of the current study lies in the use of the generally accepted ISGPS definitions and the Clavien–Dindo classification for postoperative complications, making comparison of data more reliable. It is known that the use of the ISGPS definitions results in a relatively high incidence of complications.[3] The main limitation of this study is its retrospective design and therefore nonrandom (but rather chronological) allocation of patients into the different feeding strategies. Furthermore, during the study period the annual volume of PD increased. However, as there was no relation between the studies primary endpoint (time to resumption of normal oral intake) and surgeon (P=0.50) or year of surgery (P=0.21), we feel the impact of these confounders is small. The group of patients with an oral diet after PD was too small and heterogeneous for reliable conclusions and hence not included in the analysis.

Interestingly, several large studies found good results with a normal oral diet (without routine nutritional support) after PD. Yermilov et al. reviewed the California Cancer Registry (1994–2003) for outcomes of 1,873 patients who underwent PD for adenocarcinoma receiving either parenteral feeding (14%), jejunostomy tube feeding (23%) or an oral diet without supplemental nutritional support (63%).[24] This study did not include data on nasojejunal feeding. They showed a significantly shorter length of hospital stay in the normal diet cohort. Martignoni et al. prospectively studied a cohort of 64 patients and reported, besides an increase in length of stay, a significantly higher prevalence of delayed gastric emptying in patients with enteral nutrition, compared to patients with an oral diet.[25] In contrast to these studies, two other studies suggest that routine enteral nutrition is better than 'standard care'. In a randomized controlled trial (n=36) by Mack et al., length of hospital stay was reduced by routine gastrojejunostomy tube feeding as compared to 'standard care' after PD.[26] This study did not define 'standard care'. Baradi et al. retrospectively studied patients with postoperative nasojejunal or gastrojejunal tube feeding or an oral diet after PD (n=180).[27] Enteral feeding was associated with significantly less use of TPN and lower rates of readmission and complications. Length of stay did not differ between the two groups.
If an oral postoperative diet is used, what strategy should be followed? A recent review

suggested that implementation of a fast-track perioperative pathway [or enhanced recovery after surgery (ERAS) program] in pancreatic surgery could lead to reduced hospital stay and reduced costs without an increase in morbidity, mortality or readmission rates.[28]

The discrepancy between current European 'routine' and American 'on-demand' guidelines and the feeding related complications described in this study support use of the American 'on-demand' nutrition guidelines. One could argue that patients should be started on a regular oral diet as soon as possible after PD as is current practice after most other major surgeries. Only in case of severe preoperative weight loss or a complicated postoperative course (such as pancreatic fistula),[29] enteral nutrition should be started. This 'on-demand' strategy would prevent many patients from the discomfort of a feeding tube/line and would save the additional costs of enteral feeding. Future randomized studies should test this hypothesis by comparing outcomes of a routine oral diet (with on-demand nasojejunal feeding) with routine nasojejunal feeding after PD.

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Early oral feeding after pancreatoduodenectomy enhances recovery without increasing morbidity

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ABSTRACT

Objective

The aim of this study was to evaluate whether a change in the routine feeding strategy applied after pancreatoduodenectomy (PD) from nasojejunal tube (NJT) feeding to early oral feeding improved clinical outcomes.

Methods

An observational cohort study was performed in 102 consecutive patients undergoing PD. In period 1 (n=51, historical controls), the routine postoperative feeding strategy was NJT feeding. This was changed to a protocol of early oral feeding with on-demand NJT feeding in period 2 (n=51, consecutive prospective cohort). The primary outcome was time to resumption of adequate oral intake.

Results

The baseline characteristics of study subjects in both periods were comparable. In period 1, 98% (n=50) of patients received NJT feeding, whereas in period 2, 53% (n=27) of patients did so [for delayed gastric empting (DGE) (n=20) or preoperative malnutrition (n=7)]. The time to resumption of adequate oral intake significantly decreased from 12 days in period 1 to 9 days in period 2 (P=0.015), and the length of hospital stay shortened from 18 days in period 1 to 13 days in period 2 (P=0.015). Overall, there were no differences in the incidences of complications of Clavien–Dindo Grade III or higher, DGE, pancreatic fistula, postoperative haemorrhage and mortality between the two periods.

Conclusions

The introduction of an early oral feeding strategy after PD reduced the time to resumption of adequate oral intake and length of hospital stay without negatively impacting postoperative morbidity.

INTRODUCTION

Pancreatoduodenectomy (PD) is the treatment of choice for resectable (pre-)malignant neoplasms in the pancreatic head or periampullary region.[1] Although postoperative mortality rates have decreased over recent decades,[2] PD is still associated with significant morbidity, including a 33–45% incidence of delayed gastric emptying (DGE),[3–5] which interferes with the resumption of a normal diet after surgery and frequently results in the need for nutritional support and a prolonged hospital stay.[6]

Some studies have suggested that enteral nutrition after PD reduces hospital length of stay (LoS), readmission rates and complication rates.[7–9] The guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN) recommend the routine use of early enteral nutrition in all patients undergoing major gastrointestinal resections for cancer.[10] By contrast, the current American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines recommend the use of on-demand postoperative nutritional support.[11] In addition, a recent systematic review suggested that oral feeding, with on-demand nasojejunal tube (NJT) feeding, is the most appropriate routine feeding strategy after PD because it is at least non-inferior to enteral and parenteral nutrition in terms of hospital LoS and risk for complications.[12] Furthermore, nasoenteral and parenteral feeding strategies are associated with specific complications, including the dislodgement of NJTs in a third of patients, bowel strangulation and perforation following percutaneous jejunostomy (albeit rarely) and, in cases of parenteral nutrition, an up to twice as high risk for infectious complications.[13–17] However, studies directly comparing early oral feeding with routine NJT feeding after PD are lacking.

The discrepancy in views on the optimal routine feeding strategy after PD (routine versus on-demand nasoenteral feeding) and the lack of evidence to support routine (par)enteral nutrition after PD led the study institution to change its feeding protocol from routine NJT feeding to an early oral feeding strategy with on-demand NJT feeding. The aim of this study was to evaluate whether this change in the routine postoperative feeding strategy improved outcomes.

METHODS

Patients

An observational, non-randomized, prospective cohort study with historical controls was performed in 111 consecutive patients undergoing PD at the University Medical Center Utrecht from June 2010 to December 2012. A subset of these patients (n=20) has been described in a previous study.[13] Included were adult patients undergoing any of classic Whipple PD, pylorus-preserving PD or total pancreatectomy for any indication. Excluded

were all patients who underwent PD in the transition period (October–December 2011), during which the new early oral feeding strategy was introduced on the ward (n=9). In this transition period, all nurses and treating physicians attended a training session conducted by the study coordinator and the department's dietician to explain the standardized early oral feeding protocol. To further improve adherence, the protocol was made available to all nurses and physicians on a plastic card on the ward. No other changes in surgical or medical treatment strategy (e.g. surgical technique, erythromycin use) that might influence outcomes were introduced during the entire study period. Patients were categorized into two groups based on the period in which they underwent surgery and thereby the routine feeding protocol to which they were subjected.

Period 1: Routine NJT feeding

In period 1 (June 2010 to September 2011), the routine postoperative feeding strategy was NJT feeding. Enteral nutrition was delivered via a NJT (Freka Trelumina tube; Fresenius Kabi Ltd, Runcorn, UK), which was placed in the jejunum during PD. The tube was introduced by the anaesthesiologist through the nose, into the stomach and advanced for ≥30 cm through the duodeno- or gastrojejunostomy into the efferent limb after the creation of the dorsal part of this anastomosis. The tube was secured to the nostrils with tape. The patency of the tube was tested before the abdomen was closed. Enteral nutrition (NV Nutricia, Zoetermeer, the Netherlands) was started on the first postoperative morning at a rate of 25 ml/h and increased by 25 ml per 6 h to the amount advised by the consulting dietician according to national guidelines.[18] In the event of dislodgement of the NJT, the tube was replaced only when oral intake in the following days was expected to be inadequate.
Oral intake was started depending on digestive symptoms. When oral intake was adequate, enteral nutrition was discontinued. The NJT was removed at this stage.

Period 2: Early oral feeding strategy

The early oral feeding strategy implemented in period 2 (January–December 2012) involved the resumption of oral intake as per the feeding protocol. Patients were started on oral feeding immediately after surgery and were given liquid drinks from day 0 (day of surgery), solid food from day 2 and a regular diet from day 3. Oral nutritional supplements given twice per day (200 ml Nutridrink Protein; NV Nutricia) were initiated on day 2 and discontinued at discharge.
Oral intake was recorded daily and evaluated on days 4 and 7 by the consulting dietician. When oral intake was insufficient on postoperative day 7 (<50% of the required daily calorie/protein intake as calculated by the dietician), a NJT was endoscopically placed (on-demand) and enteral nutrition was administered until oral intake was adequate.
In patients who were found to suffer from malnutrition at preoperative screening, a NJT

was placed during PD to enable the provision of postoperative enteral nutrition according to the protocol followed in period 1. According to the intention-to-treat principle, these patients were included in the early oral feeding strategy group (period 2). Oral feeding was initiated simultaneously according to the early oral feeding protocol, but no oral nutritional supplements were given.

Preoperative management

In both periods, all patients were preoperatively screened for malnutrition in the outpatient department by trained nurses using the Malnutrition Universal Screening Tool (MUST)[19] and were informed about the postoperative feeding strategy. In the event of malnutrition [idefined by a MUST score of ≥2, a body mass index (BMI) of <18.5 kg/m^2 and/or severe preoperative weight loss], patients were referred to a dietician and started on preoperative nutritional support, including oral nutritional supplements or enteral nutrition, if possible, at least 14 days before surgery.

Surgical approach

The surgical approach was identical in both periods. Pancreaticoduodenectomy was performed by a team specializing in hepatobiliary and pancreatic surgery. Reconstruction was performed with an end-to-side, duct-to-mucosa pancreatojejunostomy [International Study Group of Pancreatic Surgery (ISGPS) type IAS0[20]] over a 6-cm, 6-Fr stent, end-to-side hepaticojejunostomy and antecolic end-to-side duodenojejunostomy (pylorus-preserving PD) or antecolic gastrojejunostomy combined with a Roux-en-Y reconstruction (Whipple procedure).

Postoperative management

Postoperative management was similar in both periods. Early postoperative analgesia was achieved epidurally or, when contraindicated or when epidural placement was not successful, by i.v. patient-controlled analgesia. Nasogastric tubes were removed on day 1 unless the drainage amount per 24 h was >300 ml. In such cases, the tube was removed when the drainage amount per 24 h dropped to <300 ml. Patients were mobilized out of bed from day 1 under the guidance of a physiotherapist or nurse. Peripancreatic drains were removed when the drainage amount per 24 h was <50 ml and amylase content was less than three times the upper normal serum value (measured on days 1, 3 and 5). Total parenteral nutrition (TPN) was started only when enteral feeding was unsuccessful or contraindicated. Patients were discharged when they were fully mobile (i.e. they had achieved autonomous activity or returned to their preoperative level of activity), oral intake was adequate and there was no evidence of local or systemic complications.

Definitions

All postoperative complications were graded according to the Clavien–Dindo system of classification.[21] The postoperative course was defined as complicated if a complication occurred that required any form of intervention (Clavien–Dindo Grade III or higher). Both postoperative NJT placement and NJT replacement after dislodgement were graded as representing a Clavien–Dindo Grade III incident. Postoperative pancreatic fistula, DGE and post-pancreatectomy haemorrhage were defined according to ISGPS definitions.[22–24] Cancer stage was defined according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system.[25] Severe preoperative weight loss was defined as unintentional weight loss of ≥10% of body weight within 6 months or ≥5% of body weight within 1 month prior to presentation at the outpatient department. Oral intake was defined as adequate when it exceeded 50% of the daily required caloric intake with an upward trend, or when it was reported as adequate by the treating physician or dietician. Tube dislodgement was defined as the displacement of the tip of the feeding tube into D2 or more proximally in the gastrointestinal tract, making the continuation of tube feeding unsafe or impossible.

Data collection

From 1 January 2012 (period 2), data were prospectively collected and entered into an electronic database. Prior to this date (period 1), data were retrospectively collected from computerized clinical records and daily notes. Baseline characteristics collected were patient age, sex, American Society of Anaesthesiologists (ASA) physical status, BMI, MUST score, severe preoperative weight loss, preoperative dietary intervention, histopathological diagnosis, cancer stage and type of procedure.

Outcomes

The primary outcome was time to resumption of adequate oral intake. Secondary outcomes were time to start of oral and solid food intake, TPN use, duration of (par)enteral nutrition, use of prokinetic agents, weight loss during admission, postoperative surgical, general and tube-related complications (in-hospital and during readmission), incidence of postoperative pancreatic fistula, DGE, post-pancreatectomy haemorrhage, length of hospital and intensive care unit (ICU) stays, readmission within 30 days after discharge and in-hospital mortality.

Statistical analysis

Sample size was based on the number of eligible patients treated according to the early oral feeding strategy in a 1-year period (2012, period 2). These patients were compared with a control group, which included an equal number of eligible patients who were treated before the implementation of the new feeding strategy (period 1).

Analyses were performed according to intention to treat, meaning that there were no

Table 1 Baseline characteristics

	Period 1 Routine NJT feeding (n=51)	Period 2 Early oral feeding with on-demand NJT feeding (n=51)	P
Male, n (%)	36 (71)	29 (57)	0.149
Age, years, median (IQR)	65 (58–74)	67 (63–74)	0.223
Body mass index, kg/m², median (IQR)	24.7 (21.9–26.9)	25.8 (23.3–28.4)	0.061
MUST score ≥2, n (%)	7 (17)	12 (26)	0.308
Severe weight loss, n (%)	21 (41)	18 (36)	0.539
Preoperative dietary intervention, n (%)	17 (33)	25 (49)	0.108
Preoperative enteral nutrition, n (%)	6 (12)	5 (10)	0.750
ASA class, n (%)			0.103
1	12 (24)	16 (31)	
2	34 (67)	24 (47)	
3	5 (10)	11 (22)	
AJCC cancer stage ≥IIa, n (%)	38 (75)	43 (84)	0.221
Histopathological diagnosis, n (%)			0.844
Pancreatic adenocarcinoma	20 (39)	25 (49)	
Ampullary adenocarcinoma	9 (18)	9 (18)	
Cholangiocarcinoma	8 (16)	5 (10)	
Duodenal adenocarcinoma	1 (2)	2 (4)	
Neuroendocrine tumour	4 (8)	4 (8)	
Pancreatitis	5 (10)	2 (4)	
Other	4 (8)	4 (8)	
Procedure, n (%)			0.621
Pylorus-preserving PD	37 (73)	33 (65)	
Whipple PD	2 (4)	5 (10)	
Total pancreatectomy	1 (2)	2 (4)	
PD with additional resection	11 (22)	11 (32)	

NJT, nasojejunal tube; IQR, interquartile range; MUST, Malnutrition Universal Screening Tool; ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on Cancer; PD, pancreatoduodenectomy.

crossovers between groups. Values are expressed as the median and interquartile range (IQR), unless specified otherwise. Data were analysed using IBM SPSS Statistics for Windows Version 20 (IBM Corp., Armonk, NY, USA). Continuous non-normally distributed variables were compared using the Mann–Whitney U-test. Categorical variables were compared using the chi-squared test or Fisher's exact test as appropriate. For multivariable analysis, a binary logistic regression model was used. A two-tailed P-value of <0.05 was considered to indicate statistical significance. To assess the presence of any potential negative effects of early oral feeding in patients with a complicated postoperative course, subgroup analyses

Table 2 Nutritional and hospitalization parameters

	Period 1 Routine NJT feeding (n=51)	Period 2 Early oral feeding with on-demand NJT feeding (n=51)	P
Postoperative nutritional parameters			
Time to adequate oral intake, days, median (IQR)	12 (10–18)	9 (6–20)	0.013
Enteral nutrition use, n (%)	50 (98)	27 (53)	<0.001
Duration of enteral nutrition, days, median (IQR)	8 (6–13)	10 (5–20)	0.638
Parenteral nutrition use, n (%)	21 (41)	13 (26)	0.093
Duration of parenteral nutrition, days, median (IQR)	13 (7–23)	16 (7–25)	0.972
Use of prokinetics, n (%)	22 (43)	27 (53)	0.322
Postoperative weight/preoperative weight, %, median (IQR)	103 (97–106)	98 (96–103)	0.092
Hospitalization parameters			
Length of stay, days, median (IQR)	18 (12–28)	13 (9–24)	0.015
Intensive and medium care unit stay, days, median (IQR)	1 (1–4)	1 (1–3)	0.574
Readmission within 30 days, n (%)	4 (8)	7 (14)	0.338

NJT, nasojejunal tube; IQR, interquartile range.

for the main nutritional and hospitalization parameters were performed in patients with (and without) a complicated postoperative course, DGE and pancreatic fistulae. An additional subgroup analysis was performed in period 2 based on the placement of a NJT in order to assess whether patients who eventually required NJT feeding in period 2 were disadvantaged by the early oral feeding strategy.

RESULTS

Patients

Between January and December 2012 (period 2), 51 patients underwent PD with routine postoperative early oral feeding including on-demand NJT feeding. Another 51 consecutive patients who underwent PD with routine postoperative NJT feeding between June 2010 and September 2011 (period 1) served as historical controls. Baseline characteristics of patients did not differ between the periods (Table 1).

Efficacy

In period 2, postoperative time to the resumption of adequate oral intake decreased by 3 days and hospital LoS decreased by 5 days (Table 2).

Reasons for NJT feeding in period 2 (n=27) were DGE in 20 patients and preoperative

Table 3 Morbidity and mortality

	Period 1 Routine NJT feeding (n=51)	Period 2 Early oral feeding with on-demand NJT feeding (n=51)	P
Overall morbidity, n (%)			
Clavien–Dindo Grades I–V	46 (90)	35 (69)	0.007
Clavien–Dindo Grade III or higher	24 (47)	23 (45)	0.843
Surgical morbidity, n (%)	45 (88)	32 (63)	0.003
Delayed gastric emptying (grade B/C)	16 (31)	18 (35)	0.674
Pancreatic fistula (grade B/C)	6 (12)	6 (12)	0.999
Postoperative haemorrhage (grade B/C)	6 (12)	5 (10)	0.750
Surgical site infection	21 (41)	12 (24)	0.090
Intra-abdominal abscess	4 (8)	6 (12)	0.505
Anastomotic bowel leak	4 (8)	5 (10)	0.999
Chyle leak	8 (16)	5 (10)	0.539
Fascial dehiscence	6 (12)	6 (12)	0.999
Other surgical complications	7 (14)	4 (8)	0.338
General morbidity, n (%)	22 (43)	22 (43)	0.999
Infections			
Cholangitis	4 (8)	0	0.118
Line infection	3 (6)	3 (6)	0.999
Urinary tract infection	6 (12)	1 (2)	0.112
Pneumonia	10 (20)	6 (12)	0.276
Other general complications	13 (26)	17 (33)	0.385
Tube-related morbidity	24 (47)	13 (26)	0.023
Dislodgement of primary placed tube, n (%)	22 (43)	10 (20)	0.010
Day of dislodgement, median (IQR)	8 (5–12)	6 (3–7)	0.077
Requiring replacement, n (%)	8 (16)	7 (14)	0.780
Disabling blockage, n (%)	3 (6)	4 (8)	0.999
Other tube-related complications[a], n (%)	0	1 (2)	0.999
Mortality, n (%)	3 (6)	1 (2)	0.617

[a]Nasal pressure ulcer. NJT, nasojejunal tube; IQR, interquartile range.

malnutrition in seven patients. In patients with DGE, NJT feeding was initiated after a median of 7 days (IQR: 4–8 days). Seven patients in whom additional postoperative nutrition was indicated by signs of preoperative malnutrition (see definition in Materials and methods) did not receive a NJT during PD for logistical reasons (e.g. the correct feeding tube was not available). Three of these patients received NJT feeding secondarily after 1, 2 and 5 days,

Table 4 Subgroup analysis: nutritional and hospitalization parameters in patients with and without complications, DGE or pancreatic fistula

	Complication not present			Complication present		
	Period 1 Routine NJT feeding	Period 2 Early oral feeding with on-demand NJT feeding	P	Period 1 Routine NJT feeding	Period 2 Early oral feeding with on-demand NJT feeding	P
Overall morbidity (Clavien–Dindo Grades III and higher)	(n=27)	(n=28)		(n=24)	(n=23)	
Time to adequate oral intake, days, median (IQR)	11 (9–14)	6 (4–8)	<0.001	14 (11–37)	21 (14–33)	0.412
Length of stay, days, median (IQR)	15 (11–20)	9 (8–13)	<0.001	22 (17–48)	26 (14–46)	0.774
Delayed gastric emptying (grade B/C)	(n=35)	(n=33)		(n=16)	(n=18)	
Time to adequate oral intake, days, median (IQR)	11 (9–14)	7 (5–9)	<0.001	19 (14–53)	25 (14–44)	0.798
Length of stay, days, median (IQR)	17 (11–26)	9 (8–14)	<0.001	24 (16–53)	30 (22–54)	0.721
Pancreatic fistula (grade B/C)	(n=45)	(n=45)		(n=6)	(n=6)	
Time to adequate oral intake, days, median (IQR)	12 (10–16)	8 (6–14)	0.002	32 (13–70)	37 (19–81)	0.699
Length of stay, days, median (IQR)	18 (11–26)	11 (9–18)	0.007	50 (24–70)	49 (22–85)	0.999

NJT, nasojejunal tube; IQR, interquartile range.

respectively, and were discharged after a median of 15 days (IQR: 11–31 days). The other four patients were discharged without ever having received enteral nutrition after a median of 8 days (IQR: 6–11 days).

Complications

Morbidity and mortality rates are shown in Table 3. Overall morbidity requiring intervention (Clavien–Dindo Grade III or higher) and mortality did not differ between the periods.

The incidence of dislodgement of a primarily placed NJT significantly decreased from 43% of patients in period 1 to 20% in period 2. As only 27 patients in period 2 received a NJT, the rates of dislodgement of primarily placed tubes were similar in both periods [22 of 50 tubes (44%) in period 1 and 10 of 27 tubes (37%) in period 2; P=0.554].

Subgroup analyses

Results of subgroup analyses in patients with and without an uncomplicated postoperative course, DGE and pancreatic fistulae are shown in Table 4.

Table 5 Subgroup analysis: nutritional and hospitalization parameters based on timing of NJT placement

	Period 1	Period 2			
	Routine intra-operative NJT (n=51)	Intra-operative NJT (n=7)	Post-operative NJT (n=20)	No NJT (n=24)	P
Time to adequate oral intake, days, median (IQR)	12 (10–18)	17 (10–30)	18 (12–30)	6 (4–8)	<0.001
Length of stay, days, median (IQR)	18 (12–28)	24 (17–35)	22 (14–42)	9 (7–11)	<0.001

IQR, interquartile range.

Results of subgroup analyses regarding NJT feeding are shown in Table 5. There was no significant difference in hospital LoS between patients in period 1 [median LoS: 18 days (IQR: 12–30 days)] and the 20 patients (39%) in period 2 who eventually required NJT feeding [median LoS: 22 days (IQR: 14–42 days)] (P=0.303). In patients who did not require NJT feeding in period 2, hospital LoS was significantly reduced by 9 days [median LoS: 9 days (IQR: 7–11 days)] in comparison with patients in period 1 [median LoS: 18 days (IQR: 12–30 days)] (P≤0.001).

Multivariable analysis

A multivariable logistic regression analysis that adjusted for differences in age, gender, BMI, MUST score of ≥2, ASA class of ≥3 and cancer stage of ≥II found no difference between the two periods in rates of morbidity [Clavien–Dindo Grade III or higher: odds ratio (OR) 0.96, 95% confidence interval (CI) 0.38–2.44] or mortality (OR 0.13, 95% CI 0.00–9.44). Male patients had a greater risk for developing morbidity than female patients (OR: 2.81, 95% CI 1.04–7.59; P=0.041). No independent factors for mortality were found.

DISCUSSION

In the present study, the introduction of an early oral feeding strategy after PD was found to have significantly reduced the time to resumption of adequate oral intake and hospital LoS, without increasing morbidity or readmission rates. Early oral feeding was not associated with noticeable downturns in patients who eventually required NJT feeding or in patients with a complicated postoperative course (e.g. DGE).

This study focused on the impact of introducing a single facet of a fast-track or enhanced recovery after surgery (ERAS) protocol after PD, namely, early oral feeding. Although previous studies have supported early oral feeding after PD, these studies assessed the impact of introducing a wide range of new measures in ERAS programmes, rather than just the impact of early oral feeding and thus do not make clear the actual impact of early

Table 6 Oral feeding protocols in studies on early oral feeding after pancreatoduodenectomy

	Current study (2013)	Abu Hilal (2013)[26]	Nikfarjam (2013)[28]	Balzano (2008)[27]	Kennedy (2007)[29]
Day 0	Liquid diet	Sips of water			
Day 1	Liquid diet	60-100 mL/h to include energy drinks			Start sips of water and ice chips ≤ 30 mL/hr
Day 2	Solid food and oral nutritional supplements	Clear fluids	Liquid diet		Clear liquid diet
Day 3	Regular diet as tolerated and oral nutritional supplements	Soup and jelly/ soft diet	Progression to a soft diet as tolerated in the next few days	Clear fluid intake (free amount)	Regular diet
Day 4		Diet as tolerated		Solid food intake	
Day 5				Diet increase on daily basis (given as 5-6 small meals) until reaching a calorie intake of 1000 kcal on day 8	
Nasogastric tube removal	Day 1 or when drainage amount is less than 300mL/24hr	Day 4 unless high output	Day 1 or when drainage amount is less than 300mL/6hr	Day 1 if drainage amount <300 mL	Day 1

oral feeding.[26–29] Table 6 shows the postoperative oral feeding protocol applied in the present study in comparison with the protocols applied in previous studies. All previous studies reported a reduction in LoS without an increase in complications. The traditional feeding protocols used in the control groups in these previous studies were, however, either ill-defined or included both oral and enteral feeding.[27–29] Only one of these studies, an observational single-surgeon study, compared the clinical outcomes of patients in whom an enhanced recovery programme including early oral feeding after PD was implemented (n=20) with outcomes in a control group subjected to routine NJT feeding (n=24).[26] The enhanced recovery programme was associated with an earlier return to a liquid and solid diet, reduced hospital LoS and a decreased readmission rate, without any increase in the incidence of morbidity in comparison with the control group. When these results are compared with those of the present study, it seems that early oral feeding is especially responsible for these improvements.

Notably, one retrospective cohort study, which compared 152 patients who received routine

NJT feeding with 123 controls who received non-protocolized oral feeding between 2000 and 2009, suggested that routine NJT feeding is superior in terms of time to resumption of oral intake, and incidences of DGE and postoperative haemorrhage, but not in terms of LoS.[9] However, in this study, the routine feeding strategy changed from one of oral feeding to one of routine enteral nutrition, which represents an opposite change to that implemented in the present study. Moreover, oral feeding was non-protocolized and thus is likely to have carried a risk for suboptimal and uncoordinated treatment, whereas the feeding strategy in the present study was protocolized and was supervised by dieticians in both periods.
The overall hospital LoS in the present study was relatively long in comparison with the 10–13 days generally reported.[30–33]This may be explained by the fact that the present study group had not yet implemented a formal ERAS strategy in this study population because the protocol involved a change in the feeding strategy specifically, rather than a change in the entire postoperative management strategy.

The conventional reluctance to initiate early oral feeding probably arises from the fear of an increased risk for postoperative complications; for example, the stimulation of pancreatic secretion may increase the risk for pancreatic fistula and gastric stasis due to DGE leading to aspiration. However, these concerns are not substantiated by the findings of the present study, nor of those of a recent systematic review of five feeding strategies after PD, which found no relevant differences in the incidence of pancreatic fistula between oral and (par) enteral feeding groups.[12] By contrast, complications related to (par)enteral nutrition, such as the frequent dislodgement of NJTs, are well known.[13–17] In the present study, 44% of NJTs placed during PD (period 1) became dislodged after a median of only 8 days. The fact that only a third of dislodged tubes required replacement can be seen to represent a further argument in favour of the 'on-demand' strategy for NJT feeding after PD. An early oral feeding strategy might therefore prevent unnecessary tube placement. This study also demonstrated that an early oral feeding strategy does not lead to unfavourable outcomes in patients who eventually do require NJT feeding. The present authors found no significant difference in hospital LoS between patients who received routine NJT feeding in period 1 and the 39% of patients in period 2 who eventually required the insertion of a NJT (18 days versus 22 days).

In patients who received routine early oral feeding, there was a trend towards less TPN use, which is favourable as TPN is associated with an increased risk for infection.[34] By contrast, other studies comparing enteral nutrition [via a (gastro)jejunostomy tube] with oral feeding after PD have reported an increase in TPN in the latter group.[7,8] In these patients, however, TPN was started directly if oral intake was insufficient without using enteral nutrition first.

The main limitation of the present study concerns the comparison of retrospective and prospective data. Selection bias may not have played a relevant role as patients in both periods represent consecutive cohorts. This assumption is supported by the absence of differences in baseline patient characteristics such as age, ASA physical status and cancer stage. There is, however, a clear risk for information bias in period 1 (with retrospective data collection), but such a bias would normally lead to the under-reporting of complications and thus a better outcome in period 1. Interestingly, as the rate of complications is actually slightly lower in period 2, information bias is unlikely to have had a relevant impact on the outcomes of this study. In addition, discharge criteria were not changed during the study period. Whether or not the study carries a high risk for performance bias is arguable because postoperative instructions to patients, regarding the resumption of oral intake, differed between the two periods. These instructions (e.g. encouraging the early introduction and increase of oral intake in period 2) are, however, an important element of the intervention under investigation and thus one of the positive aspects of the early oral feeding strategy. In addition, although its cohort was larger than that in the only previous study to have compared early oral feeding with routine NJT feeding,[26] this study included a relatively small sample and therefore lacks the necessary power to prove true superiority of early oral feeding. Future research should ideally include a high-quality, randomized controlled trial to confirm the positive impact of an early oral feeding strategy, with on-demand NJT feeding, on outcomes after PD in comparison with routine NJT feeding.

In conclusion, this observational cohort study demonstrated that the introduction of an early oral feeding strategy, with on-demand NJT feeding, reduced the time to resumption of adequate oral intake and hospital LoS after PD, without having a negative impact on postoperative morbidity.

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5

Feeding patients with preoperative symptoms of gastric outlet obstruction after pancreatoduodenectomy: early oral or routine nasojejunal tube feeding?

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ABSTRACT

Background

Early oral feeding is currently considered the optimal routine feeding strategy after pancreatoduodenectomy (PD). Some have suggested that patients with preoperative symptoms of gastric outlet obstruction (GOO) who undergo PD have such a high risk of developing delayed gastric emptying that these patients should rather receive routine postoperative tube feeding. The aim of this study was to determine whether clinical outcomes after PD in these patients differ between postoperative early oral feeding and routine tube feeding.

Methods

We analyzed a consecutive multicenter cohort of patients with preoperative symptoms of GOO undergoing PD (2010-2013). Patients were categorized into two groups based on the applied postoperative feeding strategy (dependent on their center's routine strategy): early oral feeding or routine nasojejunal tube feeding.

Results

Of 497 patients undergoing PD, 83 (17%) suffered from preoperative symptoms of GOO. 49 patients received early oral feeding and 29 patients received routine tube feeding. Time to resumption of adequate oral intake (primary outcome; 14 vs. 12 days, p=0.61) did not differ between these two feeding strategies. Furthermore, overall complications and length of stay were similar in both groups. Of the patients receiving early oral feeding, 24 (49%) ultimately required postoperative tube feeding. In patients with an uncomplicated postoperative course, early oral feeding was associated with shorter time to adequate oral intake (8 vs. 12 days, p=0.008) and shorter hospital stay (9 vs. 13 days, p<0.001).

Conclusion

Also in patients with preoperative symptoms of GOO, early oral feeding can be considered the routine feeding strategy after PD.

INTRODUCTION

Early oral feeding is currently considered the optimal routine feeding strategy after pancreatoduodenectomy (PD), in line with the enhanced recovery after surgery (ERAS) guidelines.[1–6] However, approximately 30-50% of these patients require nutritional support in the postoperative period, mainly due to delayed gastric emptying (DGE).[6,7] Intraoperative placement of a nasojejunal feeding tube may therefore be beneficial for these patients to prevent malnutrition in the first postoperative week, which is known to be associated with increased morbidity, mortality, length of hospital stay and costs.[8–10] It also avoids the burden of postoperative feeding tube placement.

Routine intraoperative feeding tube placement in all patients undergoing PD is, however, associated with a prolonged length of hospital stay as compared to early oral feeding and has no impact on complication rates.[4,6] Furthermore, up to 36% of these tubes dislodge within the first postoperative week and need to be replaced during the course of DGE.[11,12] Nonetheless, some subgroups of patients have such a high risk of developing DGE that routine intraoperative nasojejunal feeding tube placement in these subgroups may still be indicated.[7,13,14] For example, gastric outlet obstruction (GOO) occurs in up to 5 to 25% of patients with pancreatic or periampullary cancer,[7,15–19] and has been previously associated with a threefold increased risk of DGE after PD.[7] Since symptoms of GOO lead to inadequate oral intake, preoperative nutritional interventions are usually undertaken to improve the nutritional status and reduce the negative impact on morbidity and mortality.[20–23] It is, however, unclear whether patients with preoperative symptoms of GOO can be managed according to the current standard (early oral feeding) or should receive routine nasojejunal tube feeding.

The aim of this study was therefore to determine whether clinical outcomes after PD in these patients differ between early oral feeding and routine postoperative tube feeding.

METHODS

Patients

We analyzed a consecutive cohort of 497 patients undergoing PD between January 2010 and December 2013, who were identified from the prospectively maintained databases of three tertiary referral centers; the Academic Medical Center Amsterdam, VU University Medical Center Amsterdam and University Medical Center Utrecht. Included were all patients with preoperative symptoms of GOO. A subset of these patients (n=24) has been described in a previous study.[6] Patients receiving a feeding jejunostomy were excluded, because they represent a highly selected malnourished subgroup of patients. Patients were categorized into two groups based on the applied postoperative feeding strategy:

Table 1

Definition of gastric outlet obstruction[7]	
Two or more of the following preoperative symptoms:	Vomiting
	Dysphagia
	Nausea
	Loss of appetite
	Postprandial complaints (abdominal pain, early satiation or bloating)
Present at the time of diagnosis or during the work-up to surgery	
Not relieved by preoperative biliary drainage (i.e. related to obstructive jaundice)	

early oral feeding (with on-demand tube feeding) or routine nasojejunal tube feeding. The choice of feeding strategy depended on the center's routine strategy at that time (early oral feeding in one center and routine tube feeding in one other, whereas the third center changed strategies from tube feeding to early oral feeding halfway the study period).

Gastric outlet obstruction

GOO was defined according to a previously validated definition (Table 1).[7] Standardized outpatient clinic letters and discharge letters were screened for the presence of these symptoms. If neither the presence nor the absence of the symptoms was specifically mentioned, they were scored as being absent.

Early oral feeding

Patients receiving early oral feeding were started on a liquid diet on day 0 (day of surgery), and advanced to solid food from day 2 and a regular diet from day 3 if tolerated. The consulting dietitian evaluated oral intake. If indicated, oral nutritional supplements (Nutridrink Protein; NV Nutricia, the Netherlands) were initiated on day 2, and continued after discharge. If oral intake was considered to be inadequate (<50% of the daily-required caloric intake) on postoperative day 7, a nasojejunal feeding tube was placed endoscopically.

Routine postoperative tube feeding

Enteral nutrition was delivered via a nasojejunal feeding tube, which was placed intraoperatively in the efferent jejunal limb. Enteral nutrition was started in the morning on postoperative day 1 and increased to the amount advised by the consulting dietitian over the following hours to days as tolerated. In case of dislodgement of the tube, replacement was only performed when oral intake was expected to remain inadequate during the following days. Oral intake was started and advanced as tolerated. Enteral nutrition was discontinued and the feeding tube was removed when oral intake was adequate according to the dietitian or treating physician (>50% of the daily-required caloric intake with an upward trend).

Perioperative management

Patients who suffered from preoperative malnutrition were referred to a dietitian and started on preoperative nutritional support (i.e. oral nutritional supplements or (par)enteral nutrition depending on digestive symptoms and severity of malnutrition). Preoperative malnutrition was defined as a body mass index (BMI) of <18.5 kg/m^2 and/or severe preoperative weight loss (i.e. unintentional weight loss of ≥10% of body weight within 6 months or ≥5% of body weight within 1 month prior to presentation at the outpatient clinic).

PD was performed either pylorus preserving or as classic Whipple by teams specialized in hepato-pancreato-biliary surgery. Reconstruction consisted of a jejunal loop with an end-to-side pancreaticojejunostomy, hepaticojejunostomy, and ante- or retrocolic duodenojejunostomy (pylorus-preserving PD) or gastrojejunostomy (Whipple procedure).

Postoperative parenteral nutrition was only indicated when enteral feeding was unsuccessful or contraindicated. Patients were discharged when they had achieved autonomous activity or returned to their preoperative level of activity, oral intake was adequate (or home enteral nutrition was arranged) and there were no signs of local or systemic complications.

Outcomes

Primary outcome was the time to resumption of adequate oral intake. Oral intake was defined to be adequate when it exceeded 50% of the daily-required caloric intake with an upward trend, or when reported as adequate by the treating physician or dietitian. Secondary outcomes were time to solid intake, (par)enteral nutrition use, duration of (par)enteral nutrition, pancreatic fistula, DGE, post-pancreatectomy hemorrhage, other complications (surgical, general or feeding related), length of hospital stay, readmission within 30 days after discharge and in-hospital mortality. Postoperative pancreatic fistula, DGE and post-pancreatectomy hemorrhage were defined according to International Study Group of Pancreatic Surgery definitions.[24–26] Chyle leaks were defined as chylous drainage output requiring a high-protein, low-fat, medium-chain triglyceride (MCT) oral diet, enteral or parenteral nutrition. All postoperative complications were graded according to the Clavien–Dindo system.[27] Complications requiring postoperative feeding tube placement or replacement (e.g. after dislodgement or blockage) were graded as Clavien–Dindo grade 3 since they required endoscopic intervention.

Data collection

Baseline characteristics and postoperative outcomes were collected from prospectively recorded databases. Preoperative symptoms of GOO and additional nutrition related data (i.e. preoperative severe weight loss, preoperative dietary intervention, postoperative duration of (par)enteral nutrition use and feeding related complications), were retrospectively collected from patient files and computerized clinical records.

Table 2 Baseline characteristics of study cohort

	Early oral feeding (n=49)	Routine tube feeding (n=29)	P
Male	13 (27%)	16 (55%)	0.01
Age* (years)	61 (±11)	66 (±7)	0.01
BMI* (kg/m²)	23.8 (±3.9)	23.6 (±3.8)	0.85
Severe weight loss	24 (49%)	17 (61%)	0.32
ASA physical status			0.29
I	14 (29%)	4 (14%)	
II	28 (57%)	19 (66%)	
III/IV	7 (14%)	6 (21%)	
Histopathologic diagnosis			
Pancreatic adenocarcinoma	25 (51%)	19 (66%)	
Periampullary adenocarcinoma	3 (6%)	3 (10%)	
Cholangiocarcinoma	3 (6%)	1 (3%)	
Duodenal adenocarcinoma	7 (14%)	3 (10%)	
Neuroendocrine tumor	1 (2%)	1 (3%)	
Pancreatitis	4 (8%)	1 (3%)	
Other	6 (12%)	1 (3%)	
AJCC cancer stage≥2	42 (88%)	26 (90%)	>0.99
Preoperative biliary drainage	19 (39%)	12 (41%)	0.82
Preoperative dietary intervention			0.24
None	20 (41%)	7 (24%)	
Oral nutritional supplements	16 (33%)	8 (28%)	
Enteral nutrition	8 (16%)	8 (28%)	
Parenteral nutrition	5 (10%)	6 (21%)	

BMI, Body Mass Index; ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on Cancer.
*Data are mean (± SD)

Statistical analysis

Patients were analyzed in the feeding group they were initially assigned to (i.e. intention-to-treat principle). Data were analyzed using IBM SPSS statistics for Windows Version 21 (SPSS Inc, Chicago, Illinois). Continuous non-normally distributed variables were compared using the Mann-Whitney U-test and expressed as median (interquartile range), unless specified otherwise. Categorical variables were compared using chi-squared or Fisher's exact test as appropriate. A two-tailed p-value of <0.05 was considered to indicate statistical significance. A subgroup analysis was performed in patients with and without postoperative complications (Clavien-Dindo grade ≥3) to assess whether there was an advantage of one of the feeding strategies in these subgroups.

Table 3 Postoperative nutritional and hospitalization parameters

	Early oral feeding (n=49)	Routine tube feeding (n=29)	P
Time to adequate oral intake (days)	14 (7-19)	12 (10-22)	0.61
Time to start solid food (days)	4 (2-9)	8 (6-11)	0.002
Enteral nutrition use	24 (49%)	29 (100%)	<0.001
Duration of enteral nutrition (days)	10 (5-21)	9 (5-14)	0.32
Parenteral nutrition use	9 (18%)	11 (38%)	0.05
Duration of parenteral nutrition (days)	11 (8-25)	10 (3-14)	0.92
Length of stay (days)	13 (8-18)	13 (12-21)	0.15
Readmission within 30 days	3 (6%)	5 (17%)	0.14
related to feeding	2 (4%)	2 (7%)	0.62

RESULTS

Patients

Preoperative symptoms of GOO were present in 83 of 497 (17%) patients undergoing PD in this multicenter study. Five patients who received a feeding jejunostomy were excluded, leaving 78 patients for analysis. Of these patients, 49 (63%) received early oral feeding and 29 (37%) routine postoperative tube feeding. Baseline characteristics are shown in Table 2. Patients receiving routine tube feeding were older and more often female.

Nutrition and hospitalization parameters

The time to resumption of adequate oral intake did not differ between both groups (Table 3). Of the patients receiving early oral feeding, 24 (49%) ultimately required postoperative tube feeding, because of DGE (n=21), inadequate oral intake for other reasons (n=2) or chyle leak (n=1). Tube feeding in these patients was initiated after a median of 7 (6-8) days after PD. Nine (18%) patients in the early oral feeding group and 11 (38%) patients in the routine tube feeding group required parenteral nutrition (p=0.05), because of recurrent feeding tube related complications (n=6), intolerance of enteral nutrition (n=4), chyle leak (n=3), ileus (n=2), or other reasons (n=6). Length of hospital stay was similar in both groups (Table 3).

Complications

Complication rates are shown in Table 4. Overall complication rates (Clavien-Dindo grade ≥3) were similar in both groups (55% vs. 38%, p=0.14). In the early oral feeding group, these included DGE requiring endoscopic tube placement (n=21), tube dislodgement or blockage requiring endoscopic replacement (n=10), post-pancreatectomy hemorrhage (n=3) and pancreatic fistula (n=5) and other (n=3). In the routine tube feeding group, complications

Table 4 Postoperative complications

	Early oral feeding (n=49)	Routine tube feeding (n=29)	P
Surgical complications			
Delayed gastric emptying (grade B/C)	20 (41%)	11 (38%)	0.80
Pancreatic fistula (grade B/C)	5 (10%)	2 (7%)	>0.99
Postoperative hemorrhage (grade B/C)	3 (6%)	2 (7%)	>0.99
Wound infection	4 (8%)	9 (31%)	0.01
Intra-abdominal abscess	4 (8%)	1 (3%)	0.64
Chyle leak	3 (6%)	7 (24%)	0.03
Biliary leak	1 (2%)	2 (7%)	0.55
Other surgical complications	4 (8%)	6 (21%)	0.16
General complications			
Cholangitis	0	1 (3%)	0.37
Line infection	1 (2%)	1 (3%)	>0.99
Urinary tract infection	3 (6%)	3 (10%)	0.66
Pneumonia	3 (6%)	3 (10%)	0.66
Other general complications	5 (10%)	7 (24%)	0.11
Feeding related complications			
Dislodgement	14 (29%)	14 (48%)	0.08
requiring replacement	9	5	
Disabling blockage	2 (4%)	8 (28%)	0.004
requiring replacement	1	0	
Mortality	2 (4%)	1 (3%)	>0.99

graded as Clavien-Dindo Grade ≥3 included tube dislodgement or blockage requiring endoscopic replacement (n=5), post-pancreatectomy hemorrhage (n=2), pancreatic fistula (n=2) and other (n=6).

Wound infections (8% vs 31%, p=0.01) and chyle leaks (6% vs 24%, p=0.03) were more frequent in the routine tube feeding groups, as well as feeding tube related complications (31% vs 62%, p=0.007) (see Table 4). There were no differences in mortality between the two groups.

Subgroup analysis

Subgroup analysis in patients with an uncomplicated postoperative course showed that both time to resumption of adequate oral intake (8 vs. 12 days, p=0.008) and length of hospital stay (9 vs. 13 days, p<0.001) were significantly shorter in the early oral feeding group, whereas there were no differences between the two groups in patients with complications (Table 5).

Table 5 Subgroup analysis in patients with and without postoperative complications

	Early oral feeding	Routine tube feeding	P
Patients without postoperative complications	(n=22)	(n=18)	
Time to adequate oral intake (days)	8 (7-12)	12 (9-16)	0.008
Length of stay (days)	9 (8-10)	13 (11-17)	<0.001
Patients with postoperative complications	(n=27)	(n=11)	
Time to adequate oral intake (days)	18 (14-38)	16 (11-43)	0.61
Length of stay (days)	16 (14-28)	17 (12-28)	0.97

DISCUSSION

In this multicenter cohort study in patients with preoperative symptoms of GOO, overall clinical outcomes after PD did not differ between postoperative early oral feeding and routine tube feeding. There were no differences between the two groups in time to adequate oral intake, postoperative complications and length of hospital stay. Half of patients with preoperative symptoms of GOO tolerated early oral feeding after PD and even in patients with a complicated postoperative course there were no differences in time to adequate intake and hospital stay between routine or delayed (on-demand) tube feeding. In patients with an uncomplicated postoperative course on the other hand, both these outcomes were significantly shorter with early oral feeding. Therefore, early oral feeding seems to be the feeding strategy of choice after PD, also in patients with preoperative symptoms of GOO.

To our knowledge, this is the first study to compare clinical outcomes after PD with two feeding strategies in patients with preoperative symptoms of GOO. We focused on this subgroup since it was previously suggested that these patients have a threefold greater risk of developing DGE,[7] which triggered some surgeons to administer routine postoperative tube feeding in these patients. In the present study, the incidence of preoperative symptoms of GOO in the entire series was 17%, which is comparable to the 5-25% reported in literature.[7,15–19] The incidence of DGE in these patients was, however, only slightly increased compared to the cohort of patients without preoperative symptoms of GOO in our study period (40% vs 31%) or the overall incidence of DGE.[28,29]

Several other subgroups of patients who might benefit from intraoperative feeding tube placement have been suggested.[13,14,30] For example, patients with pre- or intraoperative risk factors such as age over 80 years, higher ASA physical status, BMI >25, low serum albumin, pathology of pancreatic origin, soft pancreatic texture, small pancreatic duct diameter, emergency surgery, and operative blood loss ≥700mL, were found to be more likely to

develop postoperative (major) complications.[13,14,30] However, only 35% of these patients at high risk of postoperative morbidity actually required enteral nutrition as compared to 22% in low-risk patients.[13] Similarly, in the entire cohort of patients receiving early oral feeding in our study period, only 49% of patients with GOO ultimately required postoperative feeding tube placement as compared to 37% in the non-GOO population. Altogether, relevant pre- or intraoperative predictive factors for the need for nutritional support after PD seem difficult to identify. Moreover, the potential harms of insufficient nutrition in the first postoperative week and the benefits of early postoperative tube feeding may be overestimated, although an impact of the applied feeding strategy on the incidence of DGE cannot be excluded.[31,32] Our subgroup analysis showed that even in patients with a complicated postoperative course, who are unlikely to tolerate an oral diet in the first postoperative week, the administration of routine tube feeding had no benefit over early oral feeding with on-demand (delayed) tube feeding. Patients with an uncomplicated postoperative course on the other hand, had a significantly reduced time to resumption of adequate oral intake (8 vs. 12 days) and hospital stay (9 vs. 13 days) with early oral feeding compared with patients receiving routine tube feeding. Furthermore, the incidence of chyle leaks was significantly higher in the routine tube feeding group. Although this difference between routine tube feeding and early oral feeding was not shown in our previous study in patients after PD,[6] it may be caused by the administration of enteral nutrition, which is known to increase the risk of chyle leaks becoming clinically obvious.[33–35] In addition, the use of parenteral nutrition tended to be higher in the group receiving routine tube feeding, mainly due to tube related complications.

The majority of postoperative complications in patients receiving early oral feeding can be attributed to DGE requiring an endoscopic intervention, i.e. nasojejunal feeding tube placement. Although endoscopic placement of a feeding tube causes discomfort to the patient, it is less severe than other Clavien-Dindo grade 3 complications such as pancreatic fistula or post-pancreatectomy hemorrhage requiring intervention. Furthermore, the use of a bedside method of feeding tube placement under electromagnetic guidance may reduce patient discomfort, since the procedure is less invasive and does not require conscious sedation, prolonged fasting or transportation between wards.[36]

The main limitation of this study is the risk of information bias through the retrospective data collection of preoperative symptoms of GOO. Moreover, about one third of jaundiced patients did not undergo preoperative biliary drainage due to early surgery, which makes it difficult to exclude obstructive jaundice as cause of their preoperative symptoms. These two factors may lead to an under- or overestimation of the number of patients with GOO. However, since no comparison was made between patients with and without GOO, this bias is unlikely to have a relevant impact on the results. Some selection bias may have

been introduced by the non-randomized categorization of patients. The choice of feeding strategy, however, depended on the center's routine strategy at that time, rather than patient characteristics. Only five patients, who suffered from severe preoperative malnutrition, consequently received an intraoperative feeding tube whilst their center's routine strategy was early oral feeding at that time, and were therefore analyzed in the routine postoperative tube feeding group. This is, however, not reflected in the baseline characteristics since BMI and severe weight loss were similar in both groups. Only age and male:female ratio were slightly different between the two groups, but are unlikely to have a major impact on our primary outcome. Despite these limitations, the limited sample size and lack of postoperative nutritional parameters, the results of this study suggest that also in patients with preoperative symptoms of GOO, early oral feeding can be considered the routine feeding strategy after PD. Future studies should ideally include a randomized controlled trial comparing outcomes after PD with early oral and routine nasojejunal tube feeding in patients with and without preoperative symptoms of gastric outlet obstruction.

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6

Systematic review on bedside electromagnetic guided, endoscopic and fluoroscopic placement of nasoenteral feeding tubes

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ABSTRACT

Background

Nasoenteral tube feeding is frequently required in hospitalized patients to either prevent or treat malnutrition, but data on the optimal strategy of tube placement are lacking.

Objective

To compare the efficacy and safety of bedside electromagnetic (EM)-guided, endoscopic, and fluoroscopic placement of nasoenteral feeding tubes in adults.

Design

Systematic review of the literature.

Patients

Adult hospitalized patients requiring nasoenteral feeding.

Interventions

EM-guided, endoscopic and/or fluoroscopic nasoenteral feeding tube placement.

Main Outcome Measurements

Success rate of tube placement and procedure- or tube-related adverse events.

Results

Of 354 screened articles, 28 studies were included. Data on 4056 patients undergoing EM-guided (n=2921), endoscopic (n=730), and/or fluoroscopic (n=405) nasoenteral feeding tube placement were extracted. Tube placement was successful in 3202 of 3789 (85%) EM-guided procedures compared with 706 of 793 (89%) endoscopic and 413 of 446 (93%) fluoroscopic procedures. Reinsertion rates were similar for EM-guidance (270 of 1279 [21%] patients) and endoscopy (64 of 394 [16%] patients) or fluoroscopy (10 of 38 [26%] patients). The mean (standard deviation) procedure time was shortest with EM-guided placement (13.4 [12.9] minutes), followed by endoscopy and fluoroscopy (14.9 [8.7] and 16.2 [23.6] minutes, respectively). Procedure-related adverse events were infrequent (0.4%, 4%, and 3%, respectively) and included mainly epistaxis. The tube-related adverse event rate was lowest in the EM-guided group (36 of 242 [15%] patients), followed by fluoroscopy (40 of 191 [21%] patients) and endoscopy (115 of 384 [30%] patients) and included mainly dislodgment and blockage of the tube.

Limitations

Heterogeneity and limited methodological quality of the included studies.

Conclusion

Bedside EM-guided placement of nasoenteral feeding tubes appears to be as safe and effective as fluoroscopic or endoscopic placement. EM-guided tube placement by nurses may be preferred over more costly procedures performed by endoscopists or radiologists, but randomized studies are lacking.

INTRODUCTION

Hospitalized patients are frequently unable to maintain sufficient oral intake because of the disease itself or as a consequence of treatment. In these patients, nutritional support is indicated because a significantly reduced or absent caloric intake leads to malnutrition, which is known to be associated with increased morbidity, mortality, length of hospital stay, and costs.[1,2]

In patients with a functioning intestinal tract, enteral feeding is preferred over parenteral nutrition, as the latter is associated with significantly increased morbidity and costs.[3–5] Nasogastric feeding may be appropriate in many patients, but in cases of increased risk of aspiration (eg, in patients with severe GERD, gastroduodenal dissociation, gastroparesis, or gastric outlet obstruction), gastroduodenal inflammation, or proximal enteric fistula, nasoenteral feeding is indicated.[6,7] Postpyloric tube placement can be challenging, especially in patients with gastroparesis. Blind placement is usually unsuccessful and may lead to serious adverse events such as pneumothorax and pneumonia due to inadvertent lung placement in more than 2% of placement attempts.[8] The conventional alternative methods, endoscopy and fluoroscopy, are more successful and much safer, but also relatively bothersome and expensive due to the need for a medical specialist to perform the procedure and patient transportation between the clinical ward and the endoscopy or radiology department. In addition, endoscopic or fluoroscopic placement is frequently delayed due to limited hospital resources, leading to a delay in the start of nasoenteral feeding.

In 2006, a bedside electromagnetic (EM)-guided placement method for nasoenteral feeding tubes was introduced. With the aid of an EM-transmitting stylet at the tip of the feeding tube and a receiver placed in the epigastric region, the path of the tube can be tracked in real-time on a monitor until it has reached its desired position, and the stylet can be withdrawn (Fig. 1). This method may be more patient-friendly and cost-effective compared with endoscopy or fluoroscopy because it can be performed on the ward at the patient's bedside by a specialized nurse. Confirmation of the tube's position on abdominal radiograph is unnecessary because the system was shown to correlate with radiographs in 99.5% of cases and is cleared by the U.S. Food and Drug Administration for placement confirmation.[9] Moreover, repositioning of a tube that has dislodged in the stomach can be done by reinserting the stylet through the tube without the need for a fully repeated procedure.[9–12] However, comparative evidence regarding the various methods of nasoenteral feeding tube placement is lacking.

The aim of this systematic review of the literature is to compare the outcomes of EM-guided, endoscopic, and fluoroscopic nasoenteral feeding tube placement in adults, focusing on efficacy and safety.

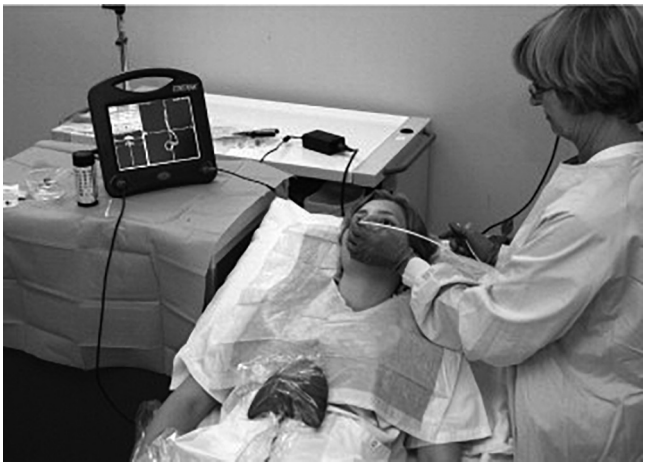

Figure 1 Nasoenteral feeding tube placement under electromagnetic guidance. The electromagnetic signal from the stylet is tracked by the receiver at the patient's epigastric region and reflected as a yellow line on the monitor. Reprinted from Mathus-Vliegen et al.[25]

METHODS

Study selection

A systematic literature search was performed in PubMed, Embase and the Cochrane Library for studies published between January 1 2006, and January 3 2014. This review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[13] Search terms used were electromagnetic, endoscopic or fluoroscopic and nasoenteral or post-pyloric and tube(s), feeding or nutrition and synonyms, restricted to title, abstract and keywords (see Supplemental Table 1 for the full electronic search strategy). Titles and abstracts and subsequently full-text articles were screened independently by 3 authors (A.G., M.J.P. and T.R.) based on inclusion and exclusion criteria. Disagreement on eligibility was addressed by discussion and consensus. Reference lists of all included papers and PubMed related articles were screened manually to identify initially missed but relevant studies.

Eligibility criteria

Included were studies concerning EM-guided, endoscopic, and/or fluoroscopic nasoenteral feeding tube placement reporting on the success rate of tube placement (primary outcome) that were available as full- text available articles in English. Only studies published after the introduction of EM-guided tube placement (2006) were included to increase homogeneity between the study populations, as indications for post-pyloricpostpyloric tube placement have changed over time.

Excluded were review articles, editorials, case reports or cohort studies including fewer than 20 patients, animal studies, and studies in children. For some studies, some investigated groups were excluded: those on other than the 3 investigated methods (eg, blind placement, self-advancing tubes, or the use of prokinetics) or on nasogastric tube placement. Results of 2 variations within 1 placement method (eg, transnasal vs transoral endoscopic tube placement) were combined.

Assessment of methodological quality

The methodological quality of all included studies was assessed independently by 3 authors (A.G., M.J.P., and T.R.). Studies were graded according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence.[14] The risk of bias was assessed by using the Cochrane Collaboration's tool and the Newcastle–Ottawa Quality Assessment Scale for randomized, controlled trials (RCTs) and cohort studies, respectively.[15,16]

Data extraction

Study characteristics, including country of origin, study design, study population, sample size, placement methods and type of tubes, were obtained from the included studies. Where available, the following data were extracted from the included studies: success rate of feeding tube placement, reinsertion rate, procedure time, time to initiation of feeding, procedure- and tube-related adverse events, mortality, and patient-reported outcomes. A placement procedure was defined as successful when the tip of the tube was in a postpyloric position. Tube reinsertion was defined as any repeat procedure after either failed primary placement or after blockage or dislodgment of the tube. Dislodgment of the tube included both inadvertent removal by the patient or medical personnel and spontaneous migration of the tube. Blockage of the tube included both kinking and clogging.

Statistical analysis

For dichotomous data, weighted overall rates were calculated. For continuous data, mean (standard deviation [SD]) values were extracted. If mean (SD) and ranges could not be retrieved from the study authors, median values and ranges were reported. Mean (SD) values for combined groups within individual studies and overall weighted mean (SD) values were calculated by using the mean (SD) values reported in the individual studies or those derived from median (range) values, by using the methods described by Hozo et al.[17]

RESULTS

The literature search and selection of articles for review are summarized in Figure 2. A total of 354 unique articles were identified. After screening titles and abstracts, 47 articles

remained. After assessing the full text of these papers, 19 further papers were excluded. Reasons for exclusion were as follows: not in English (n=4), full text not available (n=3), no report on success rate (n=3), sample size fewer than 20 patients (n=3), study in children (n=3), review paper (n=1), editorial (n=1), and conference proceedings (n=1). One study was included despite a minor subset (9%) of pediatric patients because the impact on the overall results was thought to be negligible.[9] Reference lists and PubMed related-articles screening yielded no additional articles. Characteristics of the 28 included studies (4 RCTs and 24 cohort studies) are summarized in Table 1 and Table 2.[6,9–12,18–40] Formal meta-analysis was not performed because of the obvious heterogeneity between studies.

The studies included a total of 4056 patients undergoing 1 or more EM-guided (n=2921), endoscopic (n=730), and/or fluoroscopic (n=405) nasoenteral feeding tube placements. Most studies were performed in critically ill/intensive care patients. Only 2 studies performed a head-to-head comparison between 2 of the investigated placement methods. Qin et al[34] retrospectively compared fluoroscopy with a range of endoscopic techniques (which were combined for the purpose of this review), whereas Holzinger et al[31] randomized between EM-guided and endoscopic placement. The other 3 comparative studies (all RCTs) were designed to investigate an alteration to the conventional endoscopic technique[19,33] or compared endoscopy with a blind self-advancing method.[24]

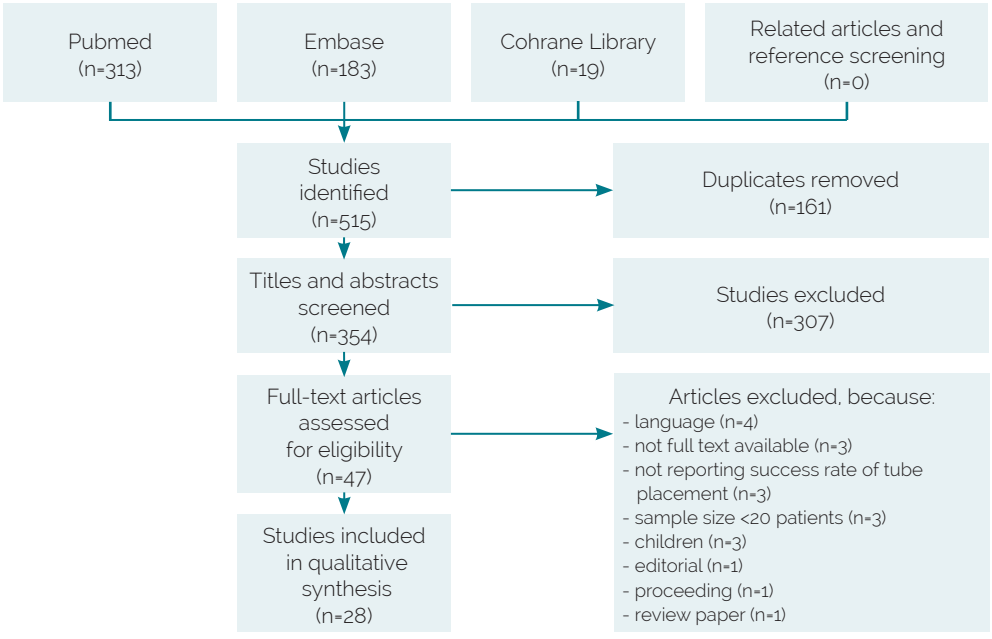

Figure 2 Systematic search and selection strategy according to the PRISMA statement

Table 1 Study characteristics of randomized, controlled trials

Reference (year)	Country	Study population	Sample size	Investigated tube placement methods	Type of tube
Wildi[19] (2007)	Switzerland	ICU patients	78	Transnasal endoscopy, over the guidewire, 92-cm long endoscope	Triple lumen, 16F, 150 cm
			79	Transnasal endoscopy, over the guidewire, 133-cm long endoscope	Triple lumen, 16F, 150 cm
Holzinger[24] (2009)	Austria	ICU patients	21	Self-advancing‡	NA
			21	Transnasal endoscopy, pull	Triple lumen, 16F, 150 cm
Holzinger[31] (2011)	Austria	ICU patients	44	EM-guided	Single lumen, 10F, 140 cm
			22	Transnasal endoscopy, pull	Double lumen, 9F + 16F, 150 cm
Hirdes[33] (2012)	Nether-lands	Overall hospital population	72	Transnasal endoscopy, over the guidewire, unclipped*	Triple lumen, 16F, 150 cm or single lumen
			71	Transoral endoscopy, pull, clipped*	Triple lumen, 16F, 150 cm or single lumen

ICU, Intensive care unit; NA, not applicable; EM, electromagnetic.
*Results combined for the analysis.‡Excluded from the analysis.

Table 2 Study characteristics of cohort studies

Reference (year)	Country	Study design	Study population	Sample size	Investigated tube placement methods	Type of tube
Wiggins[18] (2006)	U.S.	Retrosp cohort	Overall hospital population	42	Transoral endoscopy, push	Single lumen, 12F
Gray[10] (2007)	U.S.	Prosp cohort	ICU patients	81	EM-guided	Single lumen, 10F, 140 cm
				20	Blind*	NA
De Aguilar-Nasci-mento[20] (2007)	U.S.	Retrosp cohort	Overall hospital population	575	Blind nasogastric*	NA
				183	Fluoroscopy	Single lumen, 8F
				932	Blind*	NA
Bouman[6] (2008)	Nether-lands	Prosp cohort	Overall hospital population	131	Transoral endoscopy, push (through the scope)	Single lumen, 10F, 125 cm
Mahadeva[21] (2008)	Malaysia	Prosp cohort	Noncritically ill patients	22	Transnasal endoscopy, over the guidewire	Single lumen, 10F, 114 cm

ICU, Intensive care unit; EM, electromagnetic; NA, not applicable.
*Excluded from the analysis. ‡Results combined for the analysis.

Reference (year)	Country	Study design	Study population	Sample size	Investigated tube placement methods	Type of tube
Thurley[22] (2008)	U.K.	Retrosp cohort	Overall hospital population	159	Fluoroscopy	Single lumen, 145 cm (occasionally triple lumen, 16F, 150 cm)
Chen[23] (2009)	China	Cohort study	ICU patients	49	Transnasal endoscopy, over the guidewire	Single lumen, 10F, 130 cm
Mathus-Vliegen[25] (2010)	Nether-lands	Prosp cohort	Overall hospital population	50	EM-guided, period 1‡	Single lumen, 10F, 140 cm
				160	EM-guided, period 2‡	Single lumen, 10F, 140 cm
			ICU patients	50	EM-guided, period 3‡	Single lumen, 10F, 140 cm
Taylor[29] (2010)	U.K.	Retrosp cohort	ICU patients	62	EM-guided	Single lumen
				58	Blind nasogastric, after erythromycin administration*	NA
				38	Blind nasogastric, after metoclopramide administration*	NA
Windle[26] (2010)	U.K.	Retrosp cohort	Overall hospital population	29	EM-guided, postpyloric	Single lumen, 8F, 140 cm
				7	EM-guided, nasogastric*	NA
Black[28] (2010)	U.S.	Cohort study	Overall hospital population	50	Transnasal endoscopy, Davis tube	Single lumen, 12F, 105 cm
Welpe[27] (2010)	Switzer-land	Prosp cohort	ICU patients	38	Fluoroscopy	Triple lumen, 16F, 150 cm
Hemington-Gorse[11] (2011)	U.K.	Retrosp cohort	ICU burn patients	21	EM-guided	Single lumen
Koop-mann[32] (2011)	U.S.	Retrosp cohort	Overall high-risk hospital population	715	Tube team period, EM-guided	Single lumen
				102	Tube team period, blind*	NA
				729	Blind*	NA
Powers[9] (2011)	U.S.	Prosp cohort	Overall hospital population	194	EM-guided	Single lumen
Rivera[12] (2011)	U.S.	Prosp cohort	ICU patients	616	EM-guided	Single lumen, 10F, 109 or 140 cm

ICU, Intensive care unit; EM, electromagnetic; NA, not applicable.
*Excluded from the analysis. ‡Results combined for the analysis.

Reference (year)	Country	Study design	Study population	Sample size	Investigated tube placement methods	Type of tube
Zick[30] (2011)	Germany	Prosp cohort	ICU patients	27	Transnasal endoscopy, push (through the endoscope) by ICU physicians	Single lumen, 8F, 400 cm
Qin[34] (2012)	China	Retrosp cohort	Overall hospital population	25	Fluoroscopy	Single lumen, 10F, 130 cm
				27	Transoral endoscopy, pull‡	Single lumen, 10F, 130 cm
				23	Transnasal endoscopy, over the guidewire‡	Single lumen, 10F, 130 cm
				6	Transoral endoscopy, over the guidewire‡	Single lumen, 10F, 130 cm
Zhang[35] (2012)	China	Cohort study	Overall hospital population	51	Transnasal endoscopy, over the guidewire	Single lumen or triple lumen, 16F, 150 cm
Hashi-moto[36] (2012)	Japan	Retrosp cohort	ICU patients	28	Transnasal endoscopy, over the guidewire, single check‡	Single lumen
				14	Transnasal endoscopy, over the guidewire, double check‡	Single lumen
Kaffarnik[40] (2013)	Germany	Prosp cohort	Surgical ICU patients	51	EM-guided	Single lumen
Wang[38] (2013)	China	Retrosp cohort	ICU patients	142	EM-guided	Single lumen, 10F, 140 cm
Powers[39] (2013)	U.S.	Prosp cohort	Overall hospital population	632	EM-guided	Single lumen
Boyer[37] (2013)	U.S.	Retrosp cohort	ICU patients	74	EM-guided	Single lumen
				71	Self-advancing*	NA

ICU, Intensive care unit; EM, electromagnetic; NA, not applicable.
*Excluded from the analysis. ‡Results combined for the analysis.

Methodological quality

Details of the methodological quality of the included studies are shown in Table 3 and Table 4. The quality of the included studies was moderate. None of the RCTs blinded participants or study personnel, because it was considered practically impossible. About half of the cohort studies included very select populations (eg. critically ill/intensive care patients) not representative of the general hospitalized patients requiring nasoenteral feeding. In comparative cohort studies, groups were frequently not or poorly comparable. In addition, primary endpoints of the studies (eg. successful tube placement) were not defined in 8 of 24 cohort studies, making the evaluation of outcome assessment impossible.

Table 3 Assessment of methodological quality of randomized controlled trials according to the Cochrane Collaboration's tool

Reference	Level of evidence	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Wildi[19]	3	●	○	○	○	○	○
Holzinger[24]	3	○	○	○	○	○	○
Holzinger[31]	2	○	○	○	○	●	○
Hirdes[33]	3	●	●	○	○	●	○

●, Consistent with criteria, low risk of bias; ○, partly consistent with criteria/unknown risk of bias; ○, not consistent with criteria, high risk of bias.

Efficacy

Overall, successful placement was achieved in 3202 of 3789 (85%) of EM-guided, 706 of 793 (89%) endoscopic, and 413 of 446 (93%) fluoroscopic procedures (Table 5). Reinsertion rates were also similar among EM-guidance (270 of 1279 [21%] patients), endoscopy (64 of 394 [16%] patients), and fluoroscopy (10 of 38 [26%] patients), but were reported differently in the 16 studies that reported on reinsertion (Table 6).

The mean (SD) procedure time was shortest with EM-guided placement (13.4 [12.9] minutes), followed by endoscopy and fluoroscopy (14.9 [8.7] and 16.2 [23.6] minutes, respectively) (Table 7). The time between the physician's order and feeding initiation was reported in 4 studies on EM-guided placement and ranged from 7.4 to 15 hours, but in none of the studies on endoscopy and only 1 study on fluoroscopy (median, 2.4 hours).

Safety

Procedure-related adverse events were infrequent because they occurred in 10 of 2849 (0.4%) EM-guided, 29 of 744 (4%) endoscopic, and 7 of 263 (3%) fluoroscopic placement procedures. The most frequent adverse events were epistaxis (n=29), intractable retching (n=5), and sinusitis (n=4). Two studies reported on a case of upper GI bleeding related to the endoscopic procedure: 1 originated from a gastric ulcer and led to abortion of the procedure and the other occurred during removal of the clip-assisted tube and required endoscopic intervention.[30,33]

Only 12 studies reported on tube-related adverse event rates, which were lowest in the EM-guided group (36 of 242 [15%] patients), followed by fluoroscopy (40 of 191 [21%] patients) and endoscopy (115 of 384 [30%] patients). The most common tube-related adverse events

Table 4 Assessment of methodological quality of cohort studies according to the Newcastle-Ottawa quality assessment Scale

Reference	Level of evidence	Selection bias				Measurement bias		
		Represen-tative recruitment	Selection of controls	Ascertain-ment of exposure	Comparable groups	Outcome assessment	Follow-up duration	Follow-up complete
Wiggins[18]	4	●	-	●	-	◎	●	○
Gray[10]	3	○	●	●	◎	●	●	●
De Aguilar[20]	3	●	●	●	◎	●	●	●
Bouman[6]	4	●	-	●	-	●	●	●
Mahadeva[21]	4	○	-	●	-	◎	●	●
Thurley[22]	4	●	-	●	-	◎	●	○
Chen[23]	4	○	-	●	-	●	◎	●
Mathus-Vliegen[25]	4	-	●	-	●	-	●	●
Taylor[29]	4	●	●	●	○	◎	●	●
Windle[26]	4	●	-	●	-	◎	●	●
Black[28]	4	◎	-	●	-	◎	◎	●
Welpe[27]	4	○	-	●	-	●	◎	◎
Hemington-Gorse[11]	4	-	○	-	●	-	◎	●
Koopmann[32]	3	●	○	●	●	●	●	◎
Powers[9]	4	●	-	●	-	●	●	●
Rivera[12]	4	○	-	●	-	●	●	●
Zick[30]	4	○	-	●	-	◎	◎	◎
Qin[34]	3	●	●	●	○	◎	◎	●
Zhang[35]	4	●	-	●	-	◎	◎	●
Hashimoto[36]	4	○	●	●	◎	●	◎	●
Kaffarnik[40]	4	●	-	●	-	◎	●	●
Wang[38]	4	○	-	●	-	●	●	●
Powers[39]	4	○	-	●	-	●	●	●
Boyer[37]	3	○	●	●	●	●	●	●

●, Consistent with criteria, low risk of bias; ◎, partly consistent with criteria/unknown risk of bias; ○, not consistent with criteria, high risk of bias; -, not applicable.

were dislodgment (n=149) and blockage (n=34) of the tube. Three cases of GI bleeding due to ulcers or mucosal defects requiring diagnostic endoscopy were reported after endoscopic tube placement.[30] No tube-related mortality was described.

Table 5 Success rate of nasoenteral feeding tube placement

	Initial placement method			P
	Electromagnetic guided	Endoscopic	Fluoroscopic	
Randomized controlled trials				
Wildi[19]		132/157 (84%)		
Holzinger[24]		21/21 (100%)		
Holzinger[31]	39/44 (89%)†	8/22 (36%)†		0.009
Hirdes[33]		124/143 (87%)†		
Cohort studies				
Wiggins[18]		41/42 (98%)		
Gray[10]	63/81 (78%)			
De Aguilar[20]			175/183 (96%)	
Bouman[6]		103/104 (99%)‡		
Mahadeva[21]		19/22 (86%)		
Thurley[22]			183/200 (92%)*	
Chen[23]		47/49 (96%)		
Mathus-Vliegen[25]	217/260 (83%)			
Taylor[29]	60/69 (87%)*‡			
Windle[26]	20/29 (69%)‡			
Black[28]		48/50 (96%)		
Welpe[27]			32/38 (84%)	
Hemington-Gorse[11]	37/44 (84%)*			
Koopmann[32]	951/1134 (84%)*			
Powers[9]	191/194 (98%)			
Rivera[12]	583/805 (72%)*			
Zick[30]		28/34 (82%)*		
Qin[34]		55/56 (98%)	23/25 (92%)	NR
Zhang[35]		43/51(84%)†‡		
Hashimoto[36]		37/42 (88%)		
Kaffarnik[40]	55/70 (79%)†‡			
Wang[38]	135/142 (95%)			
Powers[39]	819/843 (97%)*‡			
Boyer[37]	32/74 (43%)			
Total	3202/3789 (85%)	706/793 (89%)	413/446 (93%)	

NR, not reported;* Multiple tubes per patient; † after first attempt.‡ not routinely confirmed by radiography

Table 6 Tube reinsertions

	Initial placement method			P
	Electromagnetic guided	Endoscopic	Fluoroscopic	
Randomized controlled trials				
Holzinger[31]	5/44 (11%)*	14/22 (64%)*		NR
Hirdes[33]		23/143 (16%)		
Cohort studies				
Wiggins[18]		4/38 (11%)		
Gray[10]	9/81 (11%)*			
Mahadeva[21]		2/22 (9%)		
Chen[23]		2/49 (4%)*		
Mathus-Vliegen[25]	37/260 (14%)*			
Windle[26]	3/29 (10%)†			
Welpe[27]			10/38 (26%)*†	
Hemington-Gorse[11]	10/21 (48%)†			
Zick[30]		7/27 (26%)*†		
Zhang[35]		7/51 (14%)*		
Hashimoto[36]		5/42 (12%)*		
Kaffarnik[40]	15/70 (21%)*			
Wang[38]	7/142 (5%)†			
Powers[39]	184/632 (29%)			
Total	270/1279 (21%)	64/394 (16%)	10/38 (26%)	

NR, not reported; * after failed initial placement; † after dislodgement/blockage

Patient-reported outcomes

Patient-reported outcomes (eg, pain, discomfort) were poorly addressed in the included studies. Only 1 study reported on procedure- or tube-related complaints for EM-guided tube placement.[25] In this study, about one third of patients reported transient symptoms of pain or discomfort in the nose, throat, or abdomen during placement. Patient-reported outcome data on endoscopic or fluoroscopic nasoenteral feeding tube placement were lacking.

DISCUSSION

This is the first systematic review to compare the efficacy and safety of EM-guided, endoscopic and fluoroscopic nasoenteral feeding tube placement in adults. Success and

Table 7 Procedure time in minutes

	Initial placement method			P
	Electromagnetic guided	Endoscopic	Fluoroscopic	
Randomized controlled trials				
Wildi[19]		8.1 (4.7)		
Holzinger[24]		20 (12)		
Hirdes[33]		13.5 (8.1)		
Cohort studies				
Wiggins[18]		11.5 (5-26)†		
Mahadeva[21]		18 (12-45)*		
Chen[23]		6.6 (5.5)		
Mathus-Vliegen[25]	17.3 (15.2)			
Taylor[29]	17 (2-110)†			
Windle[26]	6.2 (1.4-12.8)†			
Black[28]		23 (9)		
Welpe[27]			17 (5-125)*	
Powers[9]	12 (1-52)*			
Zick[30]		28 (12)		
Qin[34]		13.3 (3.7)	14.9 (5.8)	NR
Zhang[35]		20.4 (10-35)*		
Hashimoto[36]		12.6 (2.5)		
Kaffarnik[40]	7.6 (4.7)			
Wang[38]	20.12 (3.71)			
Total	13.4 (12.9)	14.9 (8.7)	16.2 (23.6)	

NR, not reported;
Values are mean (SD) unless indicated otherwise; *, values are median (range);†, values are mean (range).

reinsertion rates of EM-guided placement were similar to the conventional placement techniques. Minor adverse events consisted of epistaxis and dislodgement or blockage of the tube and were equally present in all three techniques. Decision on the preferred technique can therefore be made on logistics, costs and patient's or health care provider's preference. EM-guided tube placement by trained nurses may be considered as a suitable alternative for nasoenteral feeding tube placement in adults, especially given the potential benefits regarding patient comfort, use of hospital resources and costs.

Data on patient reported outcomes are scarce, but promising results have been reported

for EM-guided tube placement.[25] In addition, procedure times, although reported in only a few studies, may be shorter for EM-guidance compared with endoscopy and fluoroscopy (Table 7), especially when the time required for patient transportation and radiographic conformation is also taken into account, which was not the case in the included studies. Because of this reduction in procedure time and the decreased dependence on available hospital resources (eg, medical staff, endoscopy/fluoroscopy facilities, and patient transportation), the time between physician's order and initiation of tube feeding may be reduced, although this was not demonstrated as such in the included studies.

The reduction in the use of hospital resources (eg, personnel, patient transportation, radiography) compared with endoscopy or fluoroscopy also makes EM-guided tube placement a more cost-effective method. True cost-effectiveness analyses of these methods have never been performed, but cost savings have been described for EM-guided tube placement. The absence of the need for radiographic confirmation can lead to a reduction in costs per feeding tube placement.[10,11,26,29,39,41] Because of an additional reduction in personnel and patient transportation, EM-guided placement can lead to a significant cost reduction, which is suggested to be as high as $1000 per attempt compared with endoscopy,[26] despite higher tube purchase costs ($135 for a tube with an EM-transmitting stylet vs $35 for a regular tube;[11] prices are converted from British pounds to U.S. dollars based on the 2013 Organisation for Economic Cooperation purchasing power parity exchange rates[42]). The costs of implementing the new process include the training of nurses and $7925 per Cortrak Enteral Access System unit (to our knowledge the only available EM-guided system).[11,26] In addition, in some patients, EM-guided placement will be unsuccessful and the aid of direct visualization with endoscopy, with associated costs, remains required to correctly place the tube.

This analysis is unique in its systematic comparison of different nasoenteral feeding tube placement modalities. There are, however, some limitations that must be taken into consideration when interpreting the results of this systematic review.

The methodological quality of the included studies is moderate, and the results are biased by nonrepresentative or noncomparable populations and nonindependent outcome assessment. In addition, all but 2 cohort studies[9,26] were single-center studies. More importantly, there is a considerable lack of studies comparing different placement modalities. Only 2 studies comparing 2 of the 3 investigated methods could be included. Holzinger et al[31] randomized critically ill patients to either EM-guided or endoscopic nasoenteral feeding tube placement and concluded that EM-guided placement was as fast, safe, and successful as the endoscopic method. The success rate of the first endoscopic attempt in this study was, however, remarkably low (36%) compared with the other studies

and their initial success rate of EM-guidance in the same patient category (89%). The success rate after 2 attempts increased to 95% for endoscopy and 91% for EM-guidance. An explanation for this difference was not provided. Because of the small sample size of this study, the negative influence on the overall success rate of endoscopy, as presented in this review, is negligible. Qin et al[34] retrospectively compared fluoroscopy with 3 different endoscopic techniques, with special interest in the guidewire-assisted technique with ultraslim gastroscopy, and concluded that the latter represents a safe, quick, and effective method for providing enteral nutrition.

Importantly, it must be noted that 2 studies (1 RCT and 1 retrospective cohort study) comparing endoscopy and fluoroscopy were not included in our review because they were published before 2006.[43,44] To increase homogeneity between the study populations, studies before the introduction of the EM-guided method were excluded. However, inclusion of these 2 studies would not have altered the results or conclusions of this review because their results were comparable with the included studies (success rates of 90%-96% for endoscopy and 93%-94% for fluoroscopy).

As is apparent from the aforementioned studies, the majority of studies on nasoenteral feeding tube placements are performed in critically ill patients. Although these patients are an important subset, they are not the only hospitalized patients requiring nasoenteral feeding. Common indications for nasoenteral (ie, postpyloric) feeding are severe gastroesophageal reflux or high gastric residuals (eg, caused by gastroparesis), leading to an increased risk of aspiration and failure to reach the nutritional goals.[6,7,45] Also in patients with gastroduodenal inflammation or duodenal fistula, nasoenteral feeding may be preferred over nasogastric feeding.[6,46] It is well-known that patients after abdominal surgery frequently have gastroparesis.[47,48] In specific situations, eg, after pancreatoduodenectomy, the incidence of gastroparesis and the need for postoperative nutritional support can be as high as 53%.[49–51] Unfortunately, the evidence of the feasibility of the EM-guided method in these patients, especially those with an altered upper GI anatomy after surgery, is scarce. Only 1 of the included studies reported EM-guided placement to be successful in 3 patients after upper GI surgery,[40] but no conclusions can be drawn based on this small number of patients, and further research should be performed in this subset of patients. Because the path of the tube, which is important for the determination of the tube's position, is changed because of the altered anatomy, EM-guided placement is presumably less successful and cannot fully replace endoscopy in this subset of patients.

Another limitation of this review is the heterogeneity of the included studies. Not only are the populations diverse, but the definitions and means of reporting success and reinsertion

rates also differ from study to study. Some studies, for example, included repeat attempts in their success rate, whereas others reported the success rate of the initial attempt only, and sometimes no definitions were given at all. The same applies to reinsertions because some studies only reported on second attempts after initial failure and others only on replacements after dislodgment or blockage of the tube, which probably leads to an underestimation of the true number of reinsertions. Therefore, it is difficult to compare the results of these outcomes between the individual studies. In addition, the endoscopic techniques were significantly different between or even within studies. No major differences in success rates of the different endoscopic techniques have been reported so far.[25,34]Also, in this systematic review, no major differences between the transoral (pull, 96%; push, 98%-99%; over the guidewire, 100%) and transnasal (pull, 36%-100%; push, 82%; over the guidewire, 78%-100%) techniques were seen (Supplemental Table 2). For the purposes of this review, all endoscopic techniques were therefore clustered into 1 group to allow comparison with the other 2 modalities.

Because of the heterogeneity in study populations, designs and protocols and lack of comparative (randomized, controlled) studies, a formal meta-analysis could not be performed. This review therefore merely summarizes the available evidence on EM-guided, endoscopic, and fluoroscopic nasoenteral feeding tube placement, including assessment of methodological quality.

In conclusion, based on the currently available literature, EM-guided nasoenteral feeding tube placement in adult patients appears to be as safe and effective as fluoroscopic or endoscopic placement while offering some distinct advantages. However, the moderate quality of the available evidence, selection of populations, limited comparison with conventional placement methods, and a lack of data on patient-related outcomes and cost-effectiveness endorse the importance of an RCT with an adequate sample size to assess the true effectiveness and benefits, such as patient-reported outcomes and costs, of EM-guided nasoenteral feeding tube placement. Currently, such a multicenter trial is under way in the Netherlands (CORE trial, NTR4420; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4420).

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Supplemental table 1

Full electronic search strategy for PubMed
(electromagn*[Title/Abstract] OR cortrak[Title/Abstract]) OR
((endoscop*[Title/Abstract] OR fluoroscop*[Title/Abstract] OR radiolog*[Title/Abstract]) AND
(nasoenteral[Title/Abstract] OR nasojejunal[Title/Abstract] OR nasoduodenal[Title/Abstract] OR postpyloric[Title/Abstract] OR post-pyloric[Title/Abstract] OR nasointestinal[Title/Abstract] OR nasoenteric[Title/Abstract] OR jejunal[Title/Abstract])) AND
(tube[Title/Abstract] OR tubes[Title/Abstract] OR feeding[Title/Abstract] OR nutrition[Title/Abstract]) NOT
(Animals[Mesh:noexp] NOT humans [mesh]) AND
("2006/01/01"[Date - Publication] : "2014/01/03"[Date - Publication])

Supplemental table 2

Success rates of different endoscopic techniques	
Transoral endoscopy	
Pull	
Hirdes[33]	69/71 (96%)*
Qin[34]	26/27 (96%)
Push	
Wiggins[18]	41/42 (98%)
Bouman[6]	103/104 (99%)
Over the guidewire	
Qin[34]	6/6 (100%)
Transnasal endoscopy	
Pull	
Holzinger[24]	21/21 (100%)
Holzinger[31]	8/22 (36%)
Black[28]	48/50 (96%)ǂ
Push	
Zick[30]	28/34 (82%)
Over the guidewire	
Wildi[19]	132/157 (84%)
Hirdes[33]	56/72 (78%)
Mahadeva[21]	19/22 (86%)
Chen[23]	47/49 (96%)
Qin[34]	55/56 (98%)
Zhang[35]	43/51(84%)
Hashimoto[36]	37/42 (88%)
* clip assisted tube; ǂ Davis tube	

7

Endoscopic versus bedside electromagnetic-guided placement of nasoenteral feeding tubes in surgical patients

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ABSTRACT

Background

Nasoenteral tube feeding is often required in surgical patients, mainly because of delayed gastric emptying. Bedside electromagnetic (EM) guided tube placement by specialized nurses might offer several advantages (e.g. reduced patient discomfort and costs) over conventional endoscopic placement. The aim of this study was to compare the success rate of EM-guided to endoscopic placement of nasoenteral feeding tubes in surgical patients.

Materials and Methods

A retrospective cohort study was performed in 267 adult patients admitted to two gastrointestinal surgical wards who received a nasoenteral feeding tube by EM-guidance or endoscopy. Eighteen patients were excluded because of insufficient data. Patients were categorized according to the primary tube placement method. Subgroup analysis was performed in patients with altered upper gastrointestinal anatomy. Primary endpoint was successful tube placement at or beyond the duodenojejunal flexure.

Results

A total of 249 patients were included, of which 90 patients underwent EM-guided and 159 patients underwent endoscopic tube placement. Both groups were comparable for baseline characteristics. Primary tube placement was successful in 74/90 patients (82%) in the EM-guided group versus 140/159 patients (88%) in the endoscopic group (P=0.20). In patients with altered upper gastrointestinal anatomy success rates were significantly lower in the EM-guided group (58 vs. 86%, P=0.004). There were no significant differences in tube related complications such as dislodgement or tube blockage.

Conclusions

Bedside EM-guided placement of nasoenteral feeding tubes by specialized nurses did not differ from endoscopic placement by gastroenterologists regarding feasibility and safety in surgical patients with unaltered upper gastrointestinal anatomy.

INTRODUCTION

Delayed gastric emptying occurs in approximately 2% of surgical patients and may lead to weeks of prolonged hospitalization.[1,2] In specific situations, e.g. after pancreato-duodenectomy, the incidence of delayed gastric emptying can be even up to 45%.[3,4] Delayed gastric emptying, or gastroparesis, can be caused by the disease itself, surgery, postoperative complications such as intra-abdominal infections, or concomitant underlying diseases such as diabetes. Delayed gastric emptying leads to large gastric residuals, nausea and vomiting, and makes normal oral feeding or nasogastric tube feeding impossible. Along with other reasons for insufficient intake, such as obstruction of the esophagus or dysphagia, it makes post-pyloric feeding a frequent need on surgical wards.[1,5–7]

Commonly, when patients are not able to achieve at least 50 per cent of their daily required caloric intake for several consecutive days, a nasoenteral feeding tube is placed fluoroscopically or, as in our center, by endoscopy and enteral nutrition is started. After endoscopic placement of the tube an abdominal x-ray (AXR) is required to determine whether the tube is in the correct position. This process is relatively labor-intensive, as it involves gastroenterologists, nurses and radiologists, and requires patient transportation between different departments. Nasoenteral feeding tubes dislodge in 5-38% of patients and frequently require replacement.[8–14] Replacement again causes patient discomfort and increased workload for medical staff and therefore additional costs.

In 2006, a non-endoscopic bed-side electromagnetic (EM) guided placement technique of nasoenteral feeding tubes by specialized nurses, using the Cortrak® Enteral Access System (Figure 1), was introduced.[15] This method is more patient friendly as it is less invasive, does not require conscious sedation or prolonged fasting and can be performed on the ward at the patients' bedside. The real-time tracking of the tube's position on a monitor enables precise placement of the tube and makes the AXR confirmation unnecessary.[16–19] Moreover, repositioning of a tube that has dislodged into the stomach can be done with the Cortrak® guide wire whereas with endoscopy this would require a repeat procedure.[16] In addition to the reduction in patient discomfort, these benefits may also lead to a reduction in the use of hospital resources and costs. Several studies have previously reported promising results on the feasibility of EM-guided nasoenteral tube placement.[16–26] These studies were, however, either performed on the intensive care unit (ICU) in critically ill patients, lacked sufficient follow up to identify long term complications such as dislodgement or did not compare outcomes to endoscopic nasoenteral feeding tube placement. Studies in surgical patients are lacking because of the perceived difficulty of EM-guided placement of nasoenteral feeding tubes in this subset of patients, especially those with altered upper gastrointestinal (GI) anatomy. The aim of this study was to compare the success rate of EM-guided to endoscopic placement of nasoenteral feeding tubes in surgical patients.

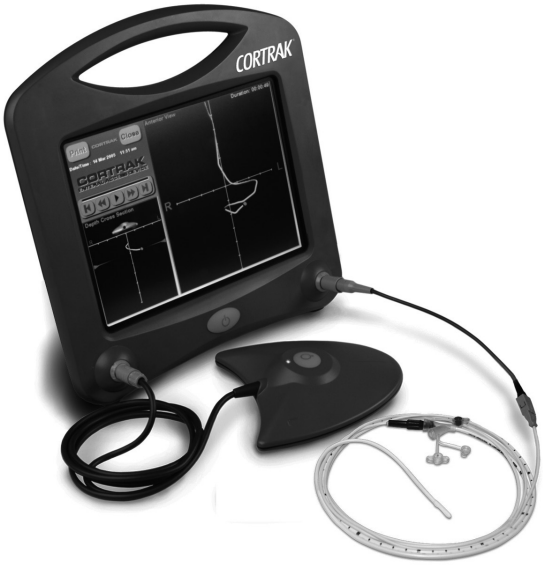


Figure 1 The Cortrak® Enteral Access System (electromagnetic transmitting stylet, smart receiver unit and enteral feeding tube). Image reproduced with permission of CORPAK MedSystems.

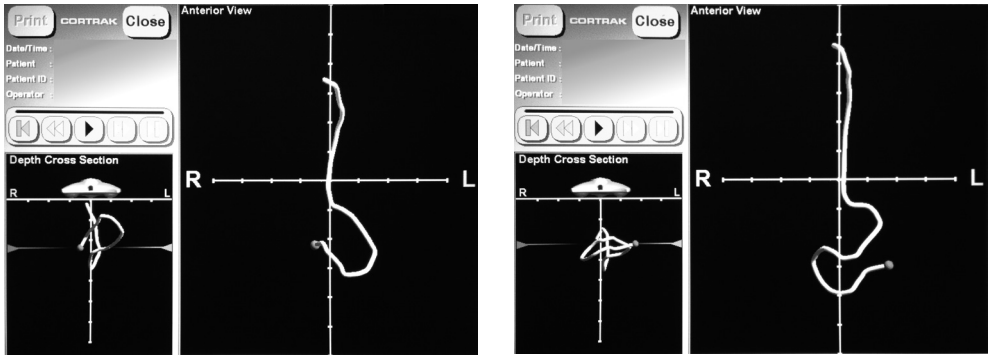
METHODS

Patients

A retrospective single-center cohort study was performed in patients admitted to the two gastrointestinal surgical wards of the Academic Medical Center in Amsterdam between January 1st 2010 and July 1st 2012. All consecutive adult patients receiving a nasoenteral feeding tube during their stay on the surgical ward for any indication (e.g. tube feeding, bile restitution and enteroclysis) were identified by screening all nasoenteral tube placement procedure records within the study period. Excluded were patients of whom no data on tube placement were available. Categorization of patients was done according to the applied method at initial tube placement: either EM-guided or endoscopic. Fluoroscopic placement is not performed in our center and only rarely in the Netherlands. The choice of either EM-guided or endoscopic placement was at random and partly dependent on whether the treating physician was aware of the new technique and the available resources. During the study period, EM-guided tube placement was gradually introduced on the surgical wards. Contraindications for EM-guided tube placement were a history of esophageal varices, stenosis or obstruction in the upper digestive tract or an esophageal resection within the past 30 days. Although initially an altered upper GI anatomy was considered to be a relative contraindication, over time, with getting more experience, also patients with altered upper GI anatomy received EM-guided tubes.

Electromagnetic guided placement

EM-guided nasoenteral feeding tube placement was performed with the Cortrak® Enteral Access System (CORPAK MedSystems, Buffalo Grove, IL, USA) at the patients' bedside, with the patient lying in supine position. The procedures were performed by two dedicated endoscopy nurses with broad experience in patients admitted to other clinical wards (e.g. internal medicine. neurology) and the ICU. They received a full day training session followed by 25 supervised placements, prior to starting independent placement on the wards. A feeding tube (Corflo® Nasojejunal feeding tube, 10 Fr, CORPAK MedSystems, Buffalo Grove IL, USA) containing an EM transmitting stylet at the tip was introduced through the nasal cavity and advanced into the duodenum up to or beyond the duodenojejunal flexure. The signal transmitted by the stylet was tracked by a smart receiver unit (Cortrak® Smart Receiver Unit™, CORPAK MedSystems, Buffalo Grove, IL, USA), placed near the patient's xyphoid process. A monitor displayed the signal as a real-time image of the stylet's location and was used to track the feeding tube until it reached the preferred placement position (Figure 2). Finally, the stylet was removed from the tube and the feeding tube was secured to the nostrils with tape. The stylet was kept at the patient's bedside in case of need for repositioning of the feeding tube. Confirmation of the tubes' position on AXR was not required as we previously demonstrated an accurate position on the Cortrak screen in 98% of 260 patients as compared to AXR.[23] Moreover, the Cortrak® system is cleared by the Food and Drug Administration (FDA) for placement confirmation.[16,18] When the procedure was unsuccessful the tube was placed by endoscopy.



A B

Figure 2 The path of the tip of the feeding tube as displayed on the monitor. The tip is visible as a dot and the path is reflected by a yellow line. The tube follows (A) a straight line down the esophagus, along the greater curvature of the stomach, through the pylorus into the duodenal bulb and subsequently (B) down the duodenum into the jejunum.

Endoscopic placement

Endoscopic nasoenteral feeding tube placement was performed by a trained gastroenterologist, or by a supervised gastroenterologist registrar, assisted by two endoscopy nurses in the endoscopy unit. An endoscope (Transnasal gastroscope, Olympus America Inc., Center Valley, Pennsylvania, USA) was inserted through the nasal cavity and advanced into the duodenum to its desired position. Conscious sedation was used if indicated. A guide wire (MC-260-035, FMH medical B.V., Veenendaal, the Netherlands) was inserted in the working channel of the endoscope and advanced into the duodenum while the endoscope was pulled back carefully. Subsequently, the feeding tube (Flocare pur tube, 10 Fr, Nutricia, the Netherlands) was advanced over the guidewire. Finally, the guide wire was removed and the tube was secured to the nostrils with tape. An AXR was performed within 3 hours after placement and reviewed by a radiologist to confirm the feeding tube's position. In case of inaccurate tube position the entire endoscopic procedure was repeated.

Definitions

Tube placement was considered successful when the tube was at or preferably beyond the duodenojejunal flexure on the display screen (EM-guided placement) or AXR (endoscopic placement) and when tube feeding could be started successfully without signs of feeds entering the stomach. Tube dislodgement was defined as displacement of the feeding tube making continuation of tube feeding unsafe or impossible. Length of primary tube stay was defined as the number of days that the feeding tube was in its correct position. Altered upper GI anatomy was defined as any alteration in the anatomy of the part of the GI tract the feeding tube passes on its way to Treitz' ligament due to surgery (such as esophageal/ gastric surgery, fundoplication and pancreatoduodenectomy).

Data collection

Data were retrospectively collected from electronic patient records and patient charts with daily notes. Baseline characteristics collected were age, sex, body mass index (BMI), indication for hospitalization, initial indication for tube feeding and presence of altered upper GI anatomy. Primary outcome was the success rate of initial nasoenteral feeding tube placement. Secondary outcomes were reinsertion rate, exposure to AXR, length of primary tube stay, duration of tube feeding, use of prokinetics, use of total parenteral nutrition (TPN), length of hospital stay, mortality and tube related complications, including dislodgement, blockage, tube related discomfort and pain.

Statistical analysis

Sample size was based on the total number of eligible patients receiving a nasoenteral feeding tube in the study period. Analysis was by intention to treat, meaning there were

no crossovers between the groups. Data were analyzed using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA). The distribution of variables was determined using the Kolmogorov-Smirrnov test. For comparison of normally distributed continuous variables, the independent-samples t test was used and values were expressed as mean (±SD). Continuous non-normally distributed variables were compared using the Mann-Whitney U test and values were expressed as median (interquartile range). Categorical variables were compared by Chi-square or Fisher's exact test as appropriate. Patients with missing data were excluded from analysis and the percentage of missing data was reported for each outcome. A two-tailed P value <0.05 was considered statistically significant.
In order to evaluate the influence of altered upper GI tract anatomy on success and dislodgement rates, a subgroup analysis was performed in patients with and without altered upper GI tract anatomy.

RESULTS

Patients

After screening 267 patients, 18 were excluded because no data on tube placement was available, leaving 249 patients eligible for the final analysis. Most frequent reasons for hospitalization were hepatopancreatobiliary or colorectal surgery (50% of all patients). Initial tube placement was under EM-guidance in 90 (36%) patients and by endoscopy in 159 (64%) patients. Baseline characteristics, including age, sex, BMI, indication for hospitalization and indication for enteral feeding were similar for both groups. Altered upper GI anatomy after previous (mainly HPB) surgery was less frequently present in the EM-guided group as compared to the endoscopic group (16% vs. 55%, P<0.001), reflecting the relative contraindication for EM-guided tube placement. Details are shown in Table 1.

Feasibility

Success rate of initial tube placement did not differ between both groups, with 74 of 90 (82%) successful initial placements in the EM-guided group as compared to 140 of 159 (88%) in the endoscopic group (P=0.20) (Table 2). There was no difference in the need for replacement (31% in the EM-guided group vs. 41% in the endoscopic group, P=0.12), nor in the number of replacements after primary placement [median number of replacements [1 (1-2) vs. 1 (1-3) respectively, P=0.63]. Indications for replacement were mainly unsuccessful prior tube placement, tube dislodgement and blockage (see tube related complications). Replacement was performed by endoscopy in 83% of replacements in the EM-guided group and in 86% of replacements in the endoscopic group (P=0.97). There were less AXRs performed in the EM-guided group; each patient received a mean (SD) of 0.62 (0.96) AXRs in the EM-guided group compared to 1.02 (0.90) AXRs in the endoscopic group

Table 1 Baseline characteristics

	EM-guidance (n=90)	Endoscopy (n=159)	P
Age, mean (± SD), years	59 (15)	62 (13)	0.07
Male, n (%)	53 (59)	91 (57)	0.79
BMI[a], median (IQR), kg/m^2	25 (22-28)	24 (22-28)	0.32
Indication for hospitalization, n (%)			0.81
Elective surgery	53 (59)	96 (60)	
Esophageal/gastric	1 (2)	7 (7)	
Colorectal	28 (53)	17 (18)	
HPB	18 (34)	62 (65)	
Other[b]	6 (11)	10 (10)	
No elective surgery	37 (41)	63 (40)	
Pancreatitis	2 (5)	4 (6)	
Ileus	1 (3)	4 (6)	
Malnutrition	1 (3)	5 (8)	
Complications previous surgery[c]	20 (54)	25 (40)	
Malignancy	5 (14)	15 (24)	
Other[d]	8 (22)	10 (16)	
Indication for nasoenteral feeding, n (%)			0.72
Delayed gastric emptying	81 (90)	147 (92)	
Malnutrition	3 (3)	3 (2)	
Other[e]	6 (7)	9 (6)	
Recent surgery prior to tube placement, n (%)	74 (82)	122 (77)	0.30
Interval between surgery and tube placement, median (IQR), days	8 (6-14)	8 (7-14)	0.94
Altered upper gastrointestinal anatomy, n (%)	19 (21)	88 (55)	<0.001

EM, electromagnetic; BMI, body mass index; IQR, interquartile range; HPB, hepatopancreatobiliary
[a.] 4% missing data
[b.] Including kidney, small intestinal, thyroid, ENT and splenic surgery
[c.] Including malaise, anastomotic leakage, wound infection, abscess, ileus, fistula and bile leakage
[d.] Including inflammatory bowel disease, intestinal bleeding, peritonitis, sepsis, shock, abscess and esophageal achalasia
[e.] Including bile restitution, enteroclysis, esophageal perforation, dysphagia, obstruction ileus and aspiration pneumonia

(P=0.002). AXRs in the EM-guided group were performed to assure the tube's position after either endoscopic replacement (50%), EM-guided initial placement (45%) or EM-guided replacement (5%).

Nutrition and hospitalization parameters

The median duration of tube feeding was 7 days in both groups [7 (3-11) vs. 7 (3-13) days in the EM-guided group and the endoscopic group respectively, P=0.49]. Additional TPN was

Table 2 Feasibility and complications

	EM-guidance (n=90)	Endoscopy (n=159)	P
Primary endpoint			
Success rate of primary tube placement, n (%)	74 (82)	140 (88)	0.20
Secondary endpoints			
Reinsertion, n (%)	28 (31)	65 (41)	0.12
Total number of reinsertions	52	134	
by endoscopy, n (%)	43 (83)	115 (86)	0.59
by EM-guidance, n (%)	9 (17)	19 (14)	0.59
Number of AXRs, n (%)	56/142 (39)	162/293 (55)	0.002
Length of primary tube stay, median (IQR), days	4 (1-8)	4 (1-8)	0.43
Overall duration of tube feeding, median (IQR), days	7 (3-11)	7 (3-13)	0.49
Prokinetics use[a], n (%)	67 (74)	109 (69)	0.32
Parenteral nutrition use[a], n (%)	26 (32)	56 (35)	0.30
Length of hospital stay, median (range), days	21 (15-32)	20 (14-33)	0.83
Tube related complications			
Dislodgement, n (%)	20 (22)	54 (34)	0.05
Number of dislodgements, median (IQR)	1 (1-2)	1 (1-2)	0.85
Blockage, n (%)	4 (4)	5 (3)	0.59
Number of blockages, mean (± SD)	0.06 (0.23)	0.06 (0.24)	0.81
Duration until blockage, mean (± SD), days	9 (5.9)	8 (6.8)	0.74
Tube related discomfort, n (%)	21 (23)	37 (23)	0.99
Tube related pain, n (%)	9 (10)	12 (8)	0.50
Mortality, n (%)	3 (3)	7 (4)	0.68

EM, electromagnetic; AXR, abdominal x-ray; IQR, interquartile range
[a] After nasoenteral feeding tube placement

required in 26 of 90 (32%) patients in the EM-guided group and in 56 of 159 (35%) patients in the endoscopic group (P=0.30). There was no difference in length of hospital stay between both groups [21 (15-32) vs. 20 (14-33) days respectively, P=0.83]. Other postoperative parameters are shown in Table 2.

Tube related complications

Tube related complications are shown in Table 2. Dislodgement of the primary tube occurred in 20 of 90 (22%) patients in the EM-guided group as compared to 54 of 159 (34%) patients in the endoscopic group (P=0.05). Length of primary tube stay was 4 (1-8) days in both groups (P=0.43). Tube blockage, tube related discomfort and tube related pain rates were similar in both groups.

Table 3 Subgroup analysis

	EM-guidance	Endoscopy	P
Altered upper-GI anatomy	n=19	n=88	
Success rate primary tube placement, n (%)	11 (58)	76 (86)	0.004
Dislodgement rate, n (%)	4 (21)	28 (32)	0.35
Normal upper-GI anatomy	n=71	n=71	
Success rate primary tube placement, n (%)	63 (89)	64 (90)	0.78
Dislodgement rate, n (%)	16 (23)	26 (37)	0.06

EM, electromagnetic; GI, gastrointestinal

Subgroup analysis

Results of subgroup analysis in patients with and without altered upper GI anatomy are shown in Table 3. In patients with altered upper GI anatomy, primary tube placement was less successful in the EM-guided group, with 11 of 19 (58%) successful initial placements as compared to 76 of 88 (86%) successful initial placements in the endoscopic group (P=0.004). Dislodgement rates were comparable between both placement methods (21% vs. 32%, P=0.35). There were no significant differences between both methods in patients with a normal upper GI anatomy.

DISCUSSION

In this single-center retrospective cohort study, bedside EM-guided placement of nasoenteral feeding tubes was equally successful (~90%) as endoscopic placement in surgical patients with unaltered upper GI anatomy. The success rate of EM-guided placement was lower (58%) in patients with altered upper GI anatomy. There were no significant differences in tube related complication rates between both groups. The number of AXRs used to determine correct positioning of the tubes was significantly lower in the EM-guided group. Given the potential benefits of EM-guided nasoenteral feeding tube placement regarding patient comfort, use of hospital resources and costs, EM-guided placement may be considered the method of choice in surgical patients with normal upper GI anatomy.

This is the largest comparative study to date on the feasibility of EM-guided versus endoscopic nasoenteral feeding tube placement in surgical patients. Only one previous study compared EM-guided to endoscopic placement of nasoenteral feeding tubes.[20] This randomized controlled trial in mechanically ventilated (non-surgical) critically ill patients is, however, relatively small (n=66) and mainly focused on successful placement. As in our study, there was no significant difference in success rates between the two placement

methods, with success rates of 91% in the EM-guided and 95% in the endoscopic group (P=0.57). These higher success rates as compared to our study can be explained by the fact that these rates included all patients who had a feeding tube placed whether it was the initial or a repeat procedure, whereas in our study only the success rate of the first attempt was reported. Success rates in other large studies on the feasibility of EM-guided tube placement were comparable to our study with rates ranging between 72% and 98%.[18,19,22,23] In all these studies, however, patients with previous upper GI tract surgery were excluded. In contrast, in our study 107 of 249 patients (43%) had an altered upper GI anatomy, resulting in a more challenging patient population. Only one cohort study previously reported successful EM-guided nasoenteral tube placement in three patients after upper GI surgery.[21] However, no firm conclusions can be drawn based on this small number of patients and it was not documented whether any similar procedures had failed.

The number of AXRs used to determine correct positioning of the feeding tubes was significantly lower in the EM-guided group. This was also demonstrated in previous studies and can be explained by the fact that tube placement confirmation on AXR is not necessary in EM-guided tube placement.[16–19] The omission of AXRs is one of the major advantages of EM-guided tube placement as it reduces both patient discomfort, logistics of transportation and costs.

Both EM-guided and endoscopic placement were found to be relatively safe methods. The most common tube related complication was tube dislodgement. Endoscopically placed nasoenteral feeding tubes are known to dislodge in up to 40% of patients within the first week.[8,12,13,27] Complications of EM-guided placed feeding tubes are less well known. Tube related pain and discomfort were never analyzed before in studies on EM-guided tube placement, but in our study no differences were found as compared to endoscopic placement. There was, however, a trend towards a slightly lower dislodgement rate in the EM-guided group. This may be due to the initial placement position (i.e. often less advanced placement with endoscopy due to the limited length of the endoscope and possibility of displacement during withdrawal of the guidewire) or the use of more rigid tubes in EM-guided placement.

Due to the retrospective design, procedure times, time between physician order and successful placement, time to feeding initiation and costs could not be reported in this study. The previous study comparing EM-guided and endoscopic placement reported comparable implementation times for both techniques (median 11 and 15 minutes respectively).[20] Unfortunately, they did not take into account the duration of the entire process, including transportation between wards and AXR confirmation, which is likely to

Table 4 Estimated costs of EM-guided and endoscopic nasoenteral feeding tube placement

	EM-guidance	Endoscopy
Feeding tube	$139	$18
Guide wire		$44
Nurse	$39	$79
Specialist		$73
Patient transportation between wards		$15
AXR		$82
Replacement procedures	$167[a]	$260[b]
Total	$345	$570

EM, electromagnetic; AXR, abdominal X-ray
[a.] based on a mean of 0.58 replacement procedures (of which 83% endoscopic and 17% EM-guided procedures);
[b.] based on a mean of 0.84 replacement procedures
Costs based on the results of this study, following the Dutch manual for cost research.[28] Conversion from euros to dollars was based on 2013 OECD purchasing power parity exchange rates[29]

be reduced with EM-guided placement. Also costs can be significantly reduced with this technique. Due to a reduction in AXR costs, personnel and patient transportation, EM-guided placement can lead to an estimated cost reduction of $225 per patient, despite higher tube purchase costs (calculation based on the results of this study, following the Dutch manual for cost research[28], see Table 4). The costs of implementing the new process (e.g. training of nurses and purchase of the Cortrak® Enteral Access System unit of $ 7925[17,26]) can be easily recovered within the first year of use due to the previously mentioned savings or may be waived according to the hospital's feeding tube contract and annual usage.

The main limitation of this study is its retrospective design, introducing a clear risk of information bias due to the retrospective data collection from patient records. Patient reported outcomes such as discomfort and pain, especially during the placement procedure, may have been underreported or are not reported at all. Additionally, there is a risk of selection bias due to the non-random allocation of patients into the different placement methods. The traditional reluctance in the use of EM-guided tube placement method in patients with an altered upper GI-tract, led to an uneven distribution of these patients over the two groups. A subgroup analysis, however, confirmed that both methods were equally successful in patients without an alteration in the upper-GI tract. On the other hand, it also showed that more experience should be gained with the application of the EM-guided method in patients after upper-GI surgery.

CONCLUSION

Bedside EM-guided placement of nasoenteral feeding tubes by specialized nurses did

not differ from endoscopic placement by gastroenterologists regarding feasibility and safety in surgical patients with a normal upper gastrointestinal anatomy in this retrospective study with risk of selection bias. Future research should ideally include a large, preferably multicenter, randomized controlled trial comparing EM-guided to endoscopic nasoenteral feeding tube placement, in both patients with and without altered upper GI anatomy. This trial (CORE trial; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4420) is currently underway in the Netherlands and pays specific attention to patient comfort, use of hospital resources and cost effectiveness, including a health economic assessment, to determine the magnitude of the potential benefits of EM-guided tube placement.

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8

Electromagnetic guided versus endoscopic placement of nasojejunal feeding tubes after pancreatoduodenectomy: a prospective pilot study

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ABSTRACT

Objective

An altered anatomy such as after pancreatoduodenectomy is currently seen as relative contraindication for bedside electromagnetic (EM)-guided nasojejunal feeding tube placement. The aim of this study was to determine the feasibility and safety of bedside EM-guided placement of nasojejunal feeding tubes as compared with endoscopy in patients after pancreatoduodenectomy.

Methods

We performed a prospective monocenter pilot study in patients requiring enteral feeding after pancreatoduodenectomy (July 2012– March 2014). Primary end point was the success rate of primary tube placement confirmed on plain abdominal x-ray followed by successful enteral feeding.

Results

Overall, 53 (42%) of 126 patients who underwent pancreatoduodenectomy required a nasojejunal feeding tube, of which 36 were placed under EM-guidance and, in 17, it was placed by endoscopy. Initial tube placement was successful in 21 (58%) of 36 patients with EM-guidance and 9 (53%) of 17 patients with endoscopy (P=0.71). No complications occurred during the placement procedures. Dislodgement and/or blockage of the tube occurred in 14 (39%) of 36 patients in the EM-guided group and 8 (47%) of 17 patients in the endoscopic group (P=0.57).

Conclusions

Bedside EM-guided placement of nasojejunal feeding tubes by nurses was equally successful as endoscopic placement in patients after pancreatoduodenectomy.

INTRODUCTION

Early oral feeding is currently considered as the routine feeding strategy after pancreatoduodenectomy.[1,2] Routine placement of a jejunostomy or nasoenteral feeding tube during surgery is therefore not warranted, also because it is associated with specific tube related complications.[3,4] However, since delayed gastric emptying (DGE) is a frequent complication after pancreatoduodenectomy,[5–8] around 30-50% of patients after pancreatoduodenectomy will ultimately require postoperative enteral feeding.[9,10] These patients will have to undergo postoperative placement of a nasojejunal feeding tube and up to 27% of these patients will require a second or third procedure due to dislodgement or blockage of the tube.[3,4,9]

There are various techniques for nasojejunal feeding tube placement, but they all have their specific disadvantages. Blind placement of feeding tubes beyond the pylorus is frequently unsuccessful and may lead to complications such as pneumothorax and pneumonia due to inadvertent placement in the bronchus.[11] Therefore, nasojejunal feeding tubes are usually placed by endoscopy or under fluoroscopy. These techniques are relatively labour-intensive and costly as it involves consulting other medical specialists and transportation of postoperative patients to endoscopy or radiology suites. Furthermore, repositioning of a dislodged tube frequently requires a fully repeated procedure.

Bedside electromagnetic (EM) guided placement by specialized nurses has been found to be a simple and safe alternative in several patient categories.[12–20] Success rates of tube placement are similar to conventional techniques and repositioning of a dislodged tube can be done with the EM-guided stylet without the need for a fully repeated procedure.[12–14,18] In addition, EM-guided placement may offer several advantages for both patients and hospitals. No fasting is required and discomfort during placement is reduced. Moreover, potentially hazardous, unsupervised transportation is prevented and costs are lower, because only nurses are involved. The extent of these benefits have, however, yet to be determined in a randomized controlled trial.

An altered anatomy of the upper gastrointestinal tract (eg, after pancreatoduodenectomy, oesophageal/gastric surgery) has been considered a relative contraindication for EM-guided tube placement, due to the altered route of the feeding tube, which may hamper the placement process, and the dreaded increased risk of complications.[12,15,19,20] In small subsets of cohort studies, success rates of EM-guided nasojejunal tube placement in patients with an altered anatomy (eg, after esophageal/gastric surgery) were found to be significantly lower compared to patients with normal anatomy.[17,18] However, specific data on the feasibility of this technique in the presence of a gastro/duodenojejunostomy after pancreatoduodenectomy are not available, neither for conventional placement techniques.[21]

The aim of this prospective study was to determine the success rate of bedside EM-guided

placement of nasojejunal feeding tubes as compared to endoscopic placement in patients after pancreatoduodenectomy.

MATERIALS AND METHODS

Patients

We performed a prospective monocenter pilot study in patients undergoing pancreatoduodenectomy in the Academic Medical Center in Amsterdam between July 2012 and March 2014. The study protocol was approved by the local ethics committee (METC AMC W12_132 #12.17.0264). All consecutive adult patients requiring enteral feeding were screened for eligibility. Patients with the following contraindications for EM-guided placement were excluded: upper gastrointestinal stenosis or obstruction, oesophageal varices, or the presence of an implanted medical device that may be affected by electromagnetic field of the EM-guided system or vice versa (except for pacemakers and defibrillators). Patients requiring tube placement when EM-guided placement was not possible for logistic reasons (ie, in weekends or in case of unavailability of specialized personnel) were included as controls and underwent endoscopic placement.

Surgical approach

Pancreatoduodenectomy was performed by a team specialized in hepatobiliary and pancreatic surgery. Reconstruction was performed using an end-to-side, invagination pancreatojejunostomy [International Study Group of Pancreatic Surgery (ISGPS) type IBSO],[22] end-to-side hepaticojejunostomy, and ante- or retrocolic end-to-side duodenojejunostomy (pylorus-preserving pancreatoduodenectomy) or gastrojejunostomy (classic Whipple's resection). Intraoperative placement of feeding tubes was not performed.

Electromagnetic guided placement

EM-guided nasoenteral feeding tube placement was performed with the Cortrak® Enteral Access System (CORPAK MedSystems, Buffalo Grove, IL, USA; see Figure 1) at the patient's bedside, with the patient lying in supine position. During this pilot phase, the procedures were performed by two dedicated endoscopy nurses (AD and MR) with over 5 years' experience with the technique. If a nasogastric decompression tube was in place, it was advised, but not mandatory, to empty the stomach and remove the nasogastric tube before proceeding (and reinsert it again after the procedure). Pre-procedural fasting was not required. A receiver unit was placed near the patient's xyphoid process. A single-lumen feeding tube (Corflo® Nasojejunal feeding tube, 10 Fr, CORPAK MedSystems, Buffalo Grove IL,USA) containing an EM-transmitting stylet at the tip was then introduced through the nasal cavity and advanced into the efferent jejunal limb. Both the stylet and the receiver

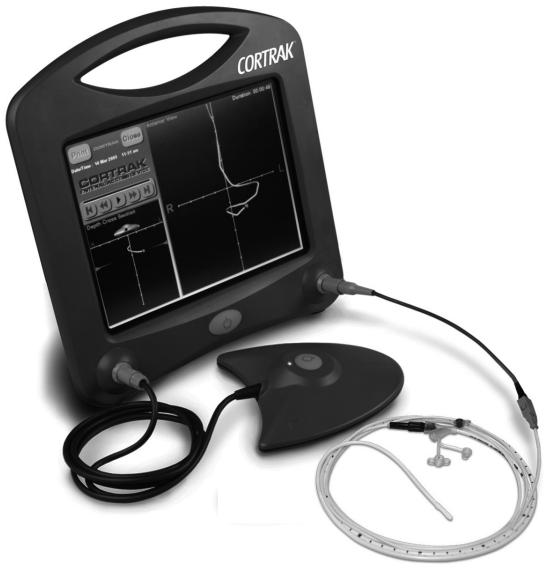
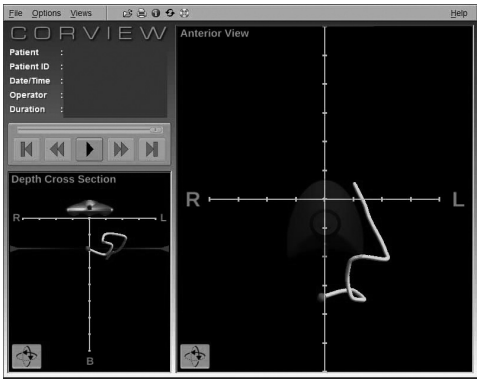


Figure 1 The Cortrak® Enteral Access System (electromagnetic transmitting stylet, receiver unit and enteral feeding tube). The tip of the tube is displayed on the monitor as a dot and the path of the tube is reflected by a yellow line. Image reproduced with permission of CORPAK MedSystems

unit were connected to the monitor unit that provides a graphic display of the location of the tip of the feeding tube and the followed track (see Figure 2A). Adequate positioning was assessed by the path of the tube on the monitor. Once the tube was in its desired position (efferent limb), the stylet was removed from the tube and the feeding tube was secured to the nostrils with tape. The stylet was kept at the patient's bedside in case of need for repositioning of the feeding tube. A plain abdominal x-ray (AXR) was performed within 3 hours after placement and reviewed by a radiologist to confirm the feeding tube's position (see Figure 2B). In case of an unsuccessful tube position on AXR, whereas it was considered successful on the monitor by the nurse, repositioning with the EM-guided stylet was attempted. In the other cases of failure, the tube was placed by endoscopy.
In patients in whom EM-guided placement was successful, dislodgement (eg, into the stomach) or blockage (eg, due to kinking) of the tube was preferably resolved with the EM-guided stylet. Otherwise, a fully repeated procedure, with reinsertion of the tube through the nose and oesophagus, was performed, provided that there was an ongoing indication for enteral feeding (as advised by the consulting dietitian).

Endoscopic placement

Endoscopic nasoenteral feeding tube placement was performed by a trained gastroenterologist, or by a supervised gastroenterologist registrar, assisted by two



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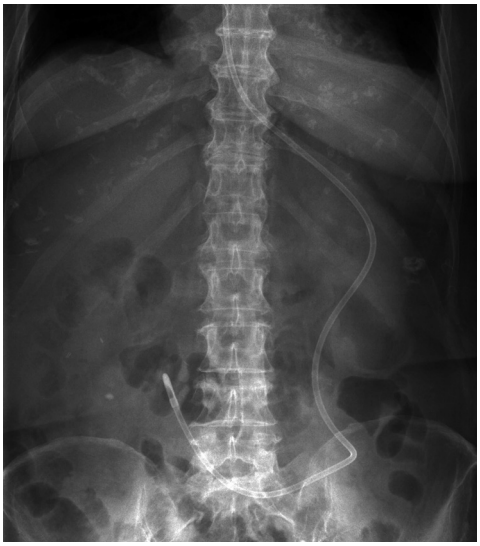

B

Figure 2 The path of the tip of the feeding tube as displayed on the monitor (A) and the tube on plain abdominal x-ray (B).

endoscopy nurses in the endoscopy unit. Patients fasted from midnight but clear fluids were allowed up to 3 hours before the procedure. Conscious sedation was used if indicated (eg, requested by the patient). An endoscope (Transnasal gastroscope, Olympus America Inc., Center Valley, Pennsylvania, USA) was inserted through the nasal cavity and advanced into the efferent jejunal limb. A guidewire (MC-260-035, FMH medical B.V.,Veenendaal, the Netherlands) was inserted in the working channel of the endoscope and advanced into the efferent limb while the endoscope was pulled back carefully. Subsequently, the feeding tube (Flocare pur tube, 10 Fr, Nutricia, the Netherlands) was advanced over the guidewire. Finally, the guidewire was removed and the tube was secured to the nostrils with tape. An AXR was performed within 3 hours after placement and reviewed by a radiologist to confirm the feeding tube's position. In case of inaccurate tube position, the entire endoscopic procedure was repeated.

Definitions

Tube placement was considered successful when the tube was in the efferent jejunal limb on AXR according to the radiologist and treating physician, followed by successful enteral feeding, without signs of feeding entering the stomach. Tube dislodgement was defined as displacement of the feeding tube making continuation of tube feeding unsafe (eg, because it is delivered into the stomach in the presence of gastroparesis) or impossible (eg, when the tube had been removed from the patient).

Data Collection

Data regarding EM-guided feeding tube placement were prospectively collected in an

electronic database. Data regarding endoscopy were collected from the electronic patient files. Baseline characteristics collected were age, sex, American Society of Anesthesiologists (ASA) physical status, body mass index (BMI), diagnosis, type of pancreatoduodenectomy, initial indication for tube feeding, and the interval between surgery and tube placement. Primary endpoint was the success rate of primary tube placement. Secondary outcomes were procedure or tube related complications [ie, inadvertent lung placement, aspiration, epistaxis, dislodgement (spontaneous or due to inadvertent removal), blockage (due to clogging or kinking) or other], use and duration of enteral and parenteral nutrition, need for tube replacement, type, indication and success rate of replacement procedures and length of hospital stay. Procedure time was only recorded for EM-guided feeding tube placement.

Statistical Analysis

Sample size was based on the total number of eligible patients receiving a nasoenteral feeding tube in the study period (July 2012-March 2014). Data were analyzed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). The distribution of variables was determined using the Kolmogorov–Smirnov test. Normally distributed continuous variables were expressed as mean (±SD) and compared with the independent-samples t-test. Continuous non-normally distributed variables were expressed as median (interquartile range) and compared using the Mann–Whitney U test. Categorical variables were expressed as absolute number (percentage) and compared by Chi-square or Fisher's exact test as appropriate. To determine the learning curve effect on success rates and procedure times of EM-guided feeding tube placement, we compared outcomes of the first 10 to the subsequent 26 procedures. In order to evaluate the influence of resection of the pylorus on success rates of both techniques and procedure times of EM-guided placement, a subgroup analysis was performed in patients who underwent a classic Whipple procedure and patients who underwent a pylorus preserving pancreatoduodenectomy.

RESULTS

Patients

In the study period, 126 patients underwent pancreatoduodenectomy of whom 53 (42%) required nasojejunal tube feeding. In 17 patients EM-guided placement was not possible because of unavailability of the two specialized nurses. These patients received a feeding tube by endoscopy. The remaining 36 patients underwent EM-guided nasojejunal feeding tube placement. There were no differences in baseline characteristics between the two groups (see Table 1). Overall, the tubes were placed at a median of 8 (6-11) days after pancreatoduodenectomy. The most common indication for tube placement was DGE in 48 of 53 (91%) patients.

Table 1 Baseline characteristics

	EM-guidance (n=36)	Endoscopy (n=17)	P
Age (years)	67 (±7)	69 (±10)	0.49
Male	19 (53%)	10 (59%)	0.68
ASA			0.15
I	2 (6%)	3 (18%)	
II	28 (78%)	9 (53%)	
III	6 (17%)	5 (30%)	
BMI (kg/m²)	25.4 (±4.0)	23.4 (±3.5)	0.78
Diagnosis			0.17
Pancreatic adenocarcinoma	8 (22%)	5 (29%)	
Cholangiocarcinoma	12 (33%)	2 (12%)	
Duodenal carcinoma	1 (3%)	4 (24%)	
Ampullary adenocarcinoma	2 (6%)	1 (6%)	
IPMN	4 (11%)	2 (12%)	
Other*	7 (19%)	2 (12%)	
Type of pancreatoduodenectomy			0.10
Pylorus preserving	29 (81%)	10 (59%)	
Classic Whipple	7 (19%)	7 (41%)	
Indication for tube placement			>0.99
Delayed gastric emptying	32 (89%)	16 (94%)	
Chyle leak	3 (8%)	1 (6%)	
Gastric outlet obstruction	1 (3%)	0	
Interval surgery - tube placement (days)	8 (6-11)	7 (7-14)	0.87

ASA, American Society of Anesthesiologists; BMI, Body mass index; IPMN, Intraductal papillary mucinous neoplasm
* Including: ampullary adenoma, pancreatitis, Gastrointestinal stromal tumour, carcinoma derived from IPMN, neuroendocrine tumour, acinar cell carcinoma, and metastasis of hemangiopericytoma.

Feasibility

Success rates of initial placement procedures did not differ between EM-guidance [21 of 36 (58%; 95% CI 41-75%)] and endoscopy [9 of 17 (53%; 95% CI 26-79%)] (P=0.71).

Initial EM-guided tube placement was deemed to be successful on the monitor in 25 of 36 (69%) patients. Median procedure time was 25 (15-35) minutes. Reasons for failure included inability to pass the stomach (n=1) or pylorus/anastomosis (n=9) or recurrent kinking of the tube near the anastomosis (n=1). In 10 of these 11 patients a feeding tube was placed successfully in a mean of 1.4 (±1.7) endoscopic procedures. In the other patient, parenteral nutrition was started after 4 attempts had failed.

Four (11%) tubes that were deemed to be successfully placed on the EM-guided monitor, were found to be located in the stomach (n=3) or afferent limb (n=1) on AXR. In 3 of these

Table 2 Feasibility and complications

	EM-guidance (n=36)	Endoscopy (n=17)	P
Successful primary tube placement	21 (58%)	9 (53%)	0.71
Enteral nutrition use	34 (94%)	14 (82%)	0.31
Duration of enteral nutrition (days)	12 (5-29)	9 (7-13)	0.06
Parenteral nutrition use	9 (25%)	6 (35%)	0.52
Duration of parenteral nutrition (days)	8 (7-40)	8 (4-17)	0.19
Hospital stay (days)	20 (13-35)	22 (17-28)	0.67
Procedure or tube related complications			
Dislodgement	11 (31%)	8 (47%)	0.24
Blockage	5 (14%)	0	0.16
Number of replacement procedures per patient			0.08
0	13 (36%)	12 (71%)	
1	9 (25%)	1 (6%)	
2	5 (14%)	4(24%)	
≥ 3	9 (25%)	0	

4 patients a second attempt resulted in successful placement. The other patient had resumed an adequate oral intake by the time a third attempt could take place.

Initial endoscopic placement was deemed to be successful by the gastroenterologist in 16 of 17 (94%) patients. Failure was caused by excessive gastric stasis leading to abortion of the procedure because of the risk of aspiration. Seven (44%) of these tubes were found to be located in the stomach (n=6) or afferent limb (n=1) on AXR. In 5 of 8 patients in whom the initial endoscopic placement had failed, a tube was placed successfully in a subsequent endoscopic procedure. In the remaining three, parenteral nutrition was initiated.

Enteral nutrition was started in 34 of 36 (94%) patients in the EM-guided group and 14 of 17 (82%) patients in the endoscopic group (P=0.31). Parenteral nutrition was administered to 8 of 36 (22%) patients after EM-guided versus 6 of 17 (35%) patients after endoscopic placement (P=0.52), because tube placement was unsuccessful (n=4) or nutrition goals could not be reached by means of enteral nutrition (n=10).

Complications and replacements

No complications occurred during the placement procedures. Tube related complications occurred in 14 of 36 (39%) patients in the EM-guided group and 8 of 17 (47%) patients in the endoscopic group (P=0.57) (see Table 2). These complications together with failed placement attempts led to one or more replacement procedures in 23 of 36 (64%) versus 7 of 17 (41%) patients (P=0.11). A total of 69 replacement procedures were required of which 20 (29%) were performed under EM-guidance and 49 (71%) by endoscopy. Endoscopic

Table 3 Replacement procedures

	EM-guidance (n=20)	Endoscopy (n=49)	P
Type of procedure			<0.001
Repositioning with EM-guided stylet	6 (30%)	-	
Fully repeated procedure	14 (70%)	49 (100%)	
Indication			0.004
Failed primary placement	4 (20%)	17 (35%)	
Failed replacement	2 (10%)	14 (29%)	
Dislodgement	8 (40%)	17 (35%)	
Blockage	6 (30%)	1 (2%)	
Successful procedure	13 (65%)	33 (67%)	0.85

procedures were generally performed because of previously failed placement attempts, whereas EM-guided replacements were mostly undertaken because of dislodgement or blockage of the tube (see Table 3). Success rates of replacement procedures were comparable for both techniques.

Subgroup analyses

Success rates of primary EM-guided tube placement were comparable between the first 10 and subsequent 26 patients (60% vs. 58%, P>0.99). Procedure time decreased from 34 (±21) to 25 (±11) minutes (P=0.11).

No differences in success rate were found between patients after classic Whipple's resection and patients after pylorus preserving pancreatoduodenectomy for EM-guidance (57% vs. 59%, P>0.99) or endoscopy (71% vs. 40%, P=0.33). Procedure times of EM-guided procedures were 37 (±25) minutes after a classic Whipple procedure as compared to 25 (±11) minutes in patients after a pylorus preserving procedure (P=0.05).

DISCUSSION

Bedside EM-guided placement of nasojejunal tubes after pancreatoduodenectomy was equally successful as endoscopy in patients after pancreatoduodenectomy. Tube related complications such as dislodgement and blockage were comparable between both techniques . Taking into account the potential benefits for both patients and hospital resources, EM-guided nasojejunal feeding tube placement may therefore offer a reasonable first option as alternative for endoscopy, although future, randomized studies are needed to confirm these preliminary findings.

This is the first study to specifically assess the feasibility of EM-guided nasojejunal feeding tube placement as compared to endoscopy in patients after pancreatoduodenectomy, so we can only compare our outcomes with other patient categories. The success rate of primary tube placement in this study seems rather low compared to the previously reported 69-98% for EM-guided and 82-100% for endoscopic tube placement.[12,15,19–21] However, in our previous retrospective cohort study in surgical patients, we already showed that tube placement may be less successful in patients with an altered upper gastrointestinal (GI) anatomy.[18] In that study, EM-guided placement was found to be successful in 58% of patients with an altered upper GI anatomy, as compared to 89% of patients with normal anatomy. In the present study, we prospectively studied EM-guided placement in patients after pancreatoduodenectomy, as this placement technique was not yet applied in this specific group of patients, and found similar success rates. Interestingly, success rates of endoscopy were also low in the present study, resulting in similar success rates of both initial and replacement procedures for EM-guidance and endoscopy. Although these results may be biased by selection because of the way the placement technique was determined (ie, not randomized), this effect is probably minimal because both groups were comparable regarding baseline characteristic and the decision was based on logistics rather than patient characteristics. Patients after pancreatoduodenectomy are therefore presumably a challenging subset of patients, especially since a total of five (9%) patients were eventually started on parenteral nutrition because tube placement was repeatedly unsuccessful.

In total, more than half of patients in this study required replacement of the feeding tube. This is partly due to the relatively low success rate of both primary placement and replacement procedures. It is also the consequence of the high dislodgement rate of nasojejunal feeding tubes in general. In the present study, dislodgement occurred in 36% of patients, which is comparable to previous studies in patients after pancreatoduodenectomy receiving tube feeding via an endoscopically placed tube.[3,4,9] A potential benefit of the EM-guided technique is that incorrectly placed or dislodged tubes, which are not completely removed, can be repositioned with the EM-guided stylet. This prevents discomfort since the tube does not have to pass the nose and oropharynx again, and is less costly since the original tube and stylet can be used. In the present study, about one third of the EM-guided replacement procedures could be performed with the original stylet.

Because the EM-guided system was shown to correlate with AXR in 99.5% of cases and is cleared by the Food and Drug Administration (FDA) for placement but also for confirmation of the position of the tube, radiographic confirmation of the correct position is actually not mandatory.[15,23] However, because we were unfamiliar with the technique in this patient

category thus far, we did perform an AXR after each placement procedure that was deemed successful on the EM-guided monitor. There was a discrepancy between the position on the EM-guided monitor and AXR in 4 (11%) patients. This may be explained by inexperience of the nurses with the altered anatomy (and thereby path of the tube) in patients after pancreatoduodenectomy (Figure 2), which is one of the most important lessons that can be drawn from this study. In contrast to patients with normal upper GI anatomy where the tube follows the esophagus, greater curvature and duodenum into the jejunum, in patients after pancreatoduodenectomy the tube goes straight down through the stomach into the efferent jejunal limb. However, with respect to the success rate, no learning curve was seen. Procedure times on the other hand decreased over time (34 for the first 10 procedures vs. 25 minutes for the subsequent 26 procedures).

Because the inability to pass the pylorus was the most frequent cause of failure of EM-guidance, one might expect success rates to be higher and procedure times to be shorter after resection of the pylorus. Success rates were, however, similar and procedure times were paradoxically longer after a classic Whipple's resection compared with pylorus preserving pancreatoduodenectomy (25 vs. 37 minutes, respectively). However, 4 of 7 procedures in patients after a classic Whipple procedure were performed in the first part of the study. It is therefore difficult to determine whether the differences in procedure times between the two resection types were due to the learning curve effect or the resection of the pylorus.
Also for endoscopy there was a discrepancy between the tube's position according to the gastroenterologist and AXR in a substantial number (44%) of patients, which was most presumably caused by coiling of the tube in the stomach during retraction of the scope or guidewire. Radiographic confirmation of the tube's positions after endoscopic placement is therefore essential before tube feeding is initiated.

In one third of patients requiring nasojejunal feeding in our study period, the tube could not be placed with EM-guidance, because neither of the two nurses was available for tube placement. Currently, in our center a team of five nurses has been trained and is available on all working days to place EM-guided tubes in patients with an altered upper GI anatomy. Besides this risk of selection bias, the major limitations of this pilot study are its relatively small sample size and focus on feasibility and complications rather than the potential benefits (reduction in patient discomfort and costs) of EM-guided placement. We have previously estimated a cost reduction of $225 per patient, based on our retrospective results in surgical patients.[18] A randomized controlled trial with adequate sample size is however needed to assess the true effectiveness and benefits of EM-guided placement. Based on the findings of the present study we are currently performing such a randomized controlled

multicenter trial, including patients after pancreatoduodenectomy (CORE trial, NTR4420, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4420). Special attention is given to the magnitude of potential benefits of EM-guided placement, such as reduced patient discomfort and costs as compared to endoscopic placement.

In conclusion, this prospective monocenter pilot study shows that bedside EM-guided placement of nasojejunal tubes in patients after pancreatoduodenectomy may be considered as an alternative for more costly and demanding conventional techniques, but the magnitude of the potential benefits for patients as well as hospital resources have yet to be determined.

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9

Electromagnetic guided bedside placement of nasoenteral feeding tubes by nurses versus endoscopic placement by gastroenterologists (CORE): a multicenter, randomized, non-inferiority trial

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ABSTRACT

Background

Electromagnetic (EM) guided bedside placement of nasoenteral feeding tubes by nurses may improve efficiency and reduce patient discomfort and costs compared with endoscopic placement by gastroenterologists. However, evidence supporting this task shift from gastroenterologists to nurses is limited. We aimed to compare the effectiveness of EM-guided and endoscopic nasoenteral feeding tube placement.

Methods

In this multicenter, randomized, non-inferiority trial, adult patients admitted to gastrointestinal surgical wards in five Dutch hospitals requiring nasoenteral feeding were randomly assigned (1:1) to undergo EM-guided or endoscopic nasoenteral feeding tube placement. The primary endpoint was the need for reinsertion of the feeding tube (e.g., after failed initial placement or due to tube related complications). The trial was designed to assess non-inferiority of EM-guided placement with a pre-specified non-inferiority margin of 10%. Primary analyses were by intention-to-treat. The trial is registered in the Dutch Trial Register, number NTR4420.

Findings

Between March 13, 2014 and March 25, 2015, we enrolled 154 patients, of whom 136 (88%) had undergone gastrointestinal surgery. Reinsertion was required in 29 (36%) of 80 patients in the EM-guided group and 31 (42%) of 74 patients in the endoscopic group (absolute risk difference -6%, upper limit of one-sided 95% CI 7%; p for non-inferiority=0·022). No significant differences were seen in placement related complications (2 [2·6%] vs. 5 [6·8%], relative risk [RR] 0·38, 95% CI 0·08-1·87; p=0·26) or tube related complications, such as dislodgement and blockage (43 [54%] vs. 36 [49%], RR 1·11, 95% CI 0·81-1·51; p=0·52).

Interpretation

Electromagnetic guided bedside placement of nasoenteral feeding tubes by nurses was non-inferior to endoscopic placement by gastroenterologists in surgical patients and may be considered the preferred technique for nasoenteral feeding tube placement.

INTRODUCTION

Gastroparesis, or delayed gastric emptying, occurs in 10-40% of patients after major gastrointestinal surgery.[1–5] Postoperatively, early oral feeding has become routine practice as advised by the enhanced recovery after surgery (ERAS) guidelines.[6–8] Some patients, however, will not tolerate early oral feeding due to gastroparesis and may eventually become malnourished, which negatively affects clinical outcomes.[9–11] Therefore, it is common practice to place a nasoenteral feeding tube for enteral nutrition in patients who do not achieve at least half of their daily required caloric intake for several days.[12]

Placement of a nasoenteral feeding tube can be challenging, especially in patients with gastroparesis or an altered gastrointestinal anatomy after surgery. Blind placement is usually unsuccessful and may lead to complications, such as aspiration and pneumonia due to inadvertent airway placement.[13,14] Nasoenteral feeding tubes are therefore typically placed endoscopically by gastroenterologists. Endoscopic feeding tube placement, however, requires pre-procedural fasting, patient transportation between wards, and radiological confirmation of the tube's position. Additionally, the demand for endoscopic procedures in general has increased considerably over the past decades, e.g. due to the introduction of colorectal screening programs.[15] Several studies have shown that some tasks in healthcare, including endoscopies and colonoscopies, can successfully be shifted from physicians to nurses.[16–19]

Electromagnetic (EM) guided tube placement is a technique which allows for bedside placement of nasoenteral feeding tubes by trained nurses.[20] The redundancy of a gastroenterologist, patient transportation, and radiological confirmation have been suggested to be beneficial to the patient and lead to a significant cost reduction.[20–23] Furthermore, tubes that have dislodged into the stomach can be repositioned with the EM-guided stylet, without the need for a fully repeated procedure. Previously, non-comparative studies have suggested that success rates and complications of the EM-guided technique are similar to those of endoscopic tube placement,[24] but these studies lack data on patient-reported outcomes and costs. Moreover, studies in surgical patients, especially those with an altered upper gastrointestinal anatomy after surgery, are scarce. Most studies, including the only randomized trial,[25] were performed in a single-center intensive care setting.

Accordingly, we designed this multicenter, randomized, non-inferiority trial to determine the effectiveness of EM-guided bedside nasoenteral feeding tube placement by nurses compared with endoscopic placement by gastroenterologists in surgical patients requiring nasoenteral feeding.

METHODS

Study design and patients

We performed an investigator-initiated, multicenter, randomized, non-inferiority trial in two university and three teaching hospitals in the Netherlands. The design and rationale of the CORE trial were published previously.[26] Adult patients admitted to gastrointestinal surgical wards with an indication for enteral nutrition via a nasoenteral feeding tube, as indicated by the treating physician and/or consulting dietitian, were eligible for inclusion. We excluded patients with a contraindication for enteral feeding or EM-guided placement, patients requiring tube placement during weekends or national holidays, and patients unable or unwilling to provide informed consent. The study complied with the declaration of Helsinki and the study protocol was approved by the institutional review board of the Academic Medical Center (Amsterdam, the Netherlands) and subsequently by all participating centers individually. All participating patients provided written informed consent prior to randomisation.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to undergo either EM-guided or endoscopic placement of a nasoenteral feeding tube. Permuted-block randomisation, with concealed varying block sizes of two, four, or six, was performed centrally via an online module using a computer-generated randomisation sequence. Randomisation was stratified by center and the presence of an altered upper gastrointestinal (oesophageal, gastric, or duodenal) anatomy after previous surgery. Blinding of patients and care providers was considered impossible given the obvious differences between the two tube placement methods.

Procedures

EM-guided nasoenteral feeding tube placement was performed at the patient's bedside on the gastrointestinal surgical ward by a trained nurse. Prior to participation in the trial, all nurses completed the structured EM-guided training programme. This programme involves a full-day training session in the Academic Medical Center (Amsterdam, the Netherlands) followed by at least 25 placement procedures, according to the previously established learning curve.[23] Preprocedural fasting was not required. Using an EM transmitting stylet, a receiver unit, which was placed at the patient's epigastric region, and a monitor (Cortrak® Enteral Access System, Corpak Medsystems, Wheeling, Ill, US), the nurse followed the path of the feeding tube (CORFLO® Ultra-Lite Feeding Tube, 10 Fr, 140 cm, CORPAK MedSystems, Buffalo Grove, IL, USA) on the monitor, while advancing the tube to a post-pyloric position (preferably near or beyond the duodenojejunal flexure). Adequate positioning was assessed by the nurse using the tube's path on the monitor.

Abdominal radiography was not required, as the EM-guided system was shown to correlate with abdominal radiography in 99.5% of cases and has Food and Drug Administration (FDA) clearance to confirm the tube's position.[20,27] When the tip of the tube had not passed the pylorus 30 minutes after insertion of the tube, the procedure was aborted and endoscopic tube placement was attempted.

Endoscopic nasoenteral feeding tube placement was performed at the endoscopy department by a trained gastroenterologist (or supervised gastroenterologist in training), assisted by one or two endoscopy nurses. Patients fasted from midnight, but clear fluids were allowed up to three hours before the procedure. Conscious sedation was used if indicated (e.g. requested by the patient). A nasal or oral endoscope was introduced into the duodenum or jejunum. According to the gastroenterologist's preference, the single lumen feeding tube was either advanced through the endoscope or advanced over a guide wire (see Appendix 1 for an overview of techniques and materials) and placed as far as possible in the duodenum or jejunum (preferably near or beyond the duodenojejunal flexure). Within three hours after tube placement, an abdominal radiograph was performed and reviewed by an independent radiologist, who was not involved in the study. In case of incorrect feeding tube placement, repeat endoscopic tube placement was performed.

After confirmation of the correct position of the feeding tube, enteral nutrition was initiated and increased to the required amount as advised by the treating physician, whenever possible after consulting a dietitian. When enteral nutrition was no longer indicated (i.e. oral intake exceeded 50% of the patient's daily required caloric intake with an upward trend), it was ceased and the feeding tube was removed. In case of confirmed dislodgement or irreversible blockage of the tube, replacement (or, if possible, repositioning) was performed using the allocated technique, except after failed initial EM-guided placement.

Clinical data with regard to baseline characteristics and outcomes were collected during hospital admission using written standardised case report forms (CRFs) by the local treating physician or the study coordinators. The CRFs were crosschecked with source data by the study coordinators. After each (re)placement procedure, patients were asked to complete a short questionnaire consisting of a visual analogue scale (VAS) scoring sheet for five dimensions (i.e. discomfort, pain, social embarrassment, anxiety, and total burden, similar to a previous study[28]) and the question whether they would recommend the procedure to a friend or colleague in the same situation.

Patients were followed for as long as they were hospitalised and, in case of discharge with a nasoenteral feeding tube in situ, during outpatient clinic- or day-care visits until removal of the feeding tube.

Outcomes

The primary endpoint was the need for reinsertion of the feeding tube, defined as the

insertion of an endoscope or tube in the oesophagus for (re)placement of the feeding tube after the primary placement procedure. Tubes were reinserted if there was an ongoing indication for enteral feeding (as advised by the consulting dietitian) after for example an unsuccessful primary placement procedure or dislodgement/blockage of the tube. Endoscopic placement after a failed initial EM-guided attempt was also considered a reinsertion, whereas repositioning via the EM transmitting stylet alone was not, since reinsertion in the oesophagus was not required in these instances.

Predefined secondary endpoints included success rate of primary tube placement; duration of the tube placement procedure; interval between physician order, tube placement, start of feeding, and reaching the feeding goal; duration of tube feeding; duration of primary tube stay; need for feeding related interventions (including EM-guided repositioning without reinsertion of the tube); tube (placement) related complications; use of parenteral nutrition; length of hospital stay; in-hospital mortality; patient-reported outcomes; and healthcare costs. Successful tube placement was defined as the tip of the feeding tube positioned beyond the descending part of the duodenum or in the efferent jejunal limb (in the presence of a gastro- or duodenojejunostomy) on the EM monitor or abdominal radiograph (depending on the placement method) followed by successful enteral feeding without signs of feeding entering the stomach. Dislodgement was defined as any displacement of the feeding tube, confirmed on the EM monitor or abdominal radiograph, making continuation of tube feeding unsafe or impossible. Blockage was defined as the inability to pass feeding through the tube (i.e. due to clogging or kinking) requiring replacement or removal of the tube. Healthcare costs included the costs of the EM-guided or endoscopic nasoenteral feeding tube placement procedure as well as the costs of feeding related diagnostic and therapeutic interventions including reinsertions. Real unit costs rather than charges were based on the 2013 hospital ledger. Overhead costs were considered alike for both tube placement procedures.

Statistical analyses

The trial was designed to assess non-inferiority of EM-guided placement in terms of reinsertions with a pre-specified non-inferiority margin of 10% as upper limit. Based on previous studies and experiences from our pilot study,[24,29] we assumed a 22% reinsertion rate in the EM-guided group versus 30% in the endoscopic group. Enrolment of 154 patients was calculated to provide 80% power to detect non-inferiority at a one-sided alpha of 0.05, assuming a 5% loss to follow-up. A chi-square non-inferiority test was used to determine non-inferiority.[30] A multivariable logistic regression model for the primary endpoint was used to further underpin non-inferiority of EM-guided placement in the presence of potentially prognostic variables such as treatment center and the presence of an altered upper gastrointestinal anatomy.

Primary and secondary endpoints were analysed using SPSS Statistics Version 21 (IBM Corp., Armonk, NY, USA). Analyses were performed according to intention-to-treat principles. Exploratory, per-protocol and as-treated analyses were performed for the primary endpoint. Except for the primary analysis for non-inferiority, a difference with a two-tailed p-value of less than 0.05 was considered statistically significant. A predefined subgroup analysis was performed in patients with an altered upper gastrointestinal anatomy after previous surgery. Healthcare costs were compared according to as-treated principles after non-parametric bootstrapping drawing 1,000 samples of the same size as the original samples and with replacement. The mean difference is reported with its 95% for bias corrected and accelerated confidence interval (95% BcaCI).
The CORE trial is registered in the Dutch Trial Register, number NTR4420.

Role of the funding source

The trial was an investigator-initiated study supported by unrestricted grants from Agis Healthcare Innovation Fund (Amersfoort, the Netherlands), Zilveren Kruis Healthcare Insurance Foundation (Leiden, the Netherlands) and CORPAK MedSystems UK (Gatwick, United Kingdom). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The senior and corresponding author (MB) and study coordinators (AG, TR) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between March 13, 2014 and March 25, 2015, we randomly assigned 154 of 206 eligible patients to undergo EM-guided (80 patients) or endoscopic (74 patients) nasoenteral feeding tube placement (Figure 1), who were all included in the intention-to-treat analysis. One patient assigned to the EM-guided group did not receive a feeding tube since he resumed adequate oral intake before tube placement. For the same reason, two patients did not undergo a replacement procedure after the EM-guided placement had failed, but were considered as having undergone a reinsertion for the analyses. Five patients assigned to the endoscopic group underwent EM-guided placement due to logistic reasons (unavailability of a gastroenterologist). Two patients died (one in each group), due to anastomotic dehiscence or complicated diverticulitis leading to sepsis and multi organ failure, with a nasoenteral feeding tube in situ without having reached the primary endpoint. Baseline characteristics, as presented in Table 1, were equally distributed between the two groups. Gastrointestinal surgery was performed a median of 6 (5-8) days prior to tube placement in 136 (88%) patients. The remaining 18 (12%) patients had varying surgical conditions that did not require surgery.

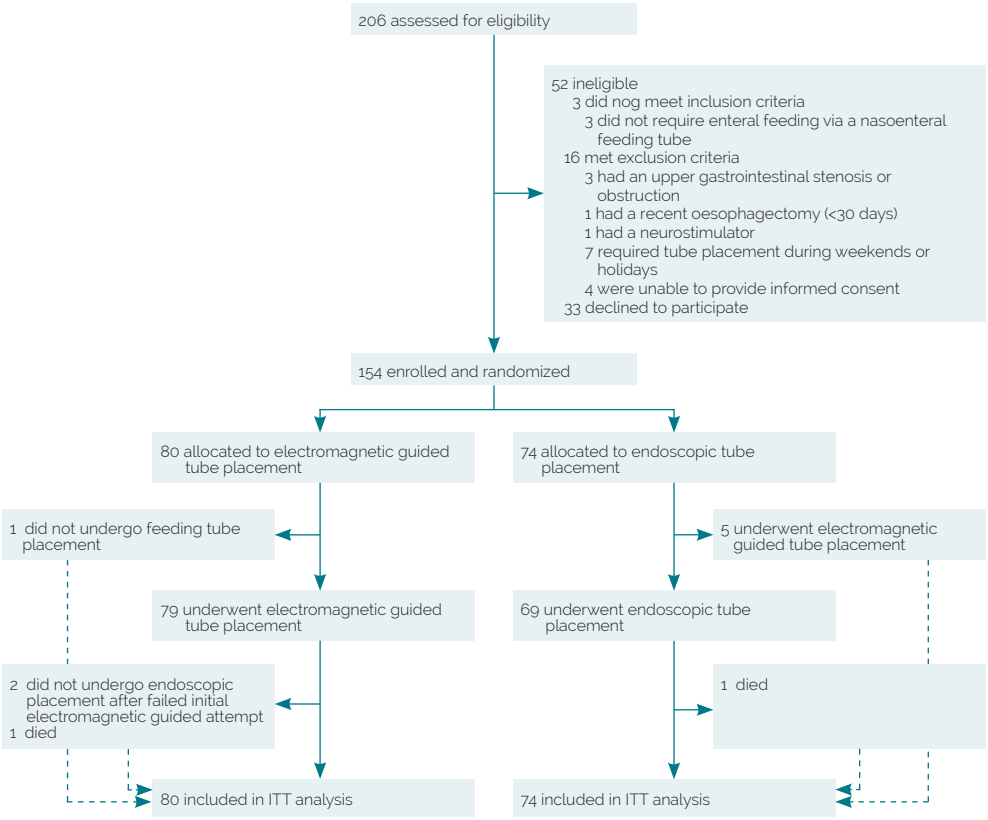

Figure 1 Flow chart of participants in the CORE trial according to CONSORT

Reinsertion of the tube occurred in 29 (36%) patients in the EM-guided group and 31 (42%) patients in the endoscopic group (absolute risk difference -6%, upper limit of one-sided 95% CI 7%, p for non-inferiority=0.022). Per-protocol and as-treated analyses supported non-inferiority of EM-guidance for reinsertions (risk difference [upper limit 95% CI] -7% [7%], p=0.018 and -8% [5%], p=0.012, respectively). If, in a hypothetical worst-case scenario, all patients in the EM-guided group who did not receive a feeding tube or died with the feeding tube in situ, had had a reinsertion, EM-guided placement would still be non-inferior (risk difference [upper limit 95% CI] -3%[10%], p=0.047). A multivariable logistic regression model, including placement method, center and presence of an altered upper gastrointestinal anatomy, showed a one-sided upper limit of the odds ratio for reinsertion of 1.26 for EM-guided versus endoscopic placement, which is below the critical limit for non-inferiority of 1.50, based on the observed 42% replacement rate in the endoscopic group plus the non-inferiority margin of 10%.

Table 1 Baseline characteristics of study participants

	EM-guided tube placement (n=80)	Endoscopic tube placement (n=74)
Age (years)	63.2 (14.4)	64.6 (13.1)
Men	41 (51.3)	42 (56.8)
Body-mass index (kg/m^2)	25.6 (22.4-27.7)	24.7 (22.4-26.9)
ASA physical status		
I	10 (12.5)	8 (10.8)
II	49 (61.3)	41 (55.4)
III	21 (26.3)	24 (32.4)
IV	0	1 (1.4)
Indication for hospital admission		
Elective surgery	60 (75.0)	53 (71.6)
Surgical complications	5 (6.3)	12 (16.2)
Pancreatitis	6 (7.5)	1 (1.4)
Ileus	4 (5.0)	1 (1.4)
Other	5 (6.3)	7 (9.5)
Indication for enteral nutrition		
Postoperative gastroparesis	54 (67.5)	54 (73.0)
Malnutrition	14 (17.5)	14 (18.9)
Pancreatitis	6 (7.5)	2 (2.7)
Ileus	4 (5.0)	2 (2.7)
Other	2 (2.5)	2 (2.7)
Use of prokinetic agents	49 (61.3)	46 (62.2)
Surgery prior to tube placement	69 (86.3)	67 (90.5)
Colorectal surgery	35	38
Hepato-pancreato-biliary surgery	21	18
Other gastrointestinal surgery	13	11
Interval between surgery and randomisation (days)	6 (5-8)	6 (5-9)
Altered upper gastrointestinal anatomy	14 (17.5)	14 (18.9)
Pylorus preserving pancreatoduodenectomy	6	8
Classic Whipple	4	3
Gastroenterostomy	2	2
Other	2	1

Data are mean (SD), number (%) or median (IQR). ASA, American Society of Anesthesiologists

No significant differences were noted in the intention-to-treat analysis of the success rates of primary tube placement (56 [71%] vs. 52 [70%], RR 1.01 (95% CI 0.82-1.24), p=0.93). Conscious sedation was used in none (0%) of the patients in the EM-guided group compared with 61 (82%) patients in the endoscopic group.

Table 2 Primary and secondary endpoints

	EM-guided tube placement (n=80)	Endoscopic tube placement (n=74)	Relative Risk [EM-guided/ Endoscopic] (95% CI)	P
Success of primary placement	56 (70.9)*	52 (70.3)	1.01 (0.82-1.24)	0.93
Position of primary placed tube on imaging				0.08
Unsuccessful procedure	12 (15.2)	7 (9.5)		
Gastric	0 (0.0)	5 (6.8)		
Duodenal bulb	1 (1.3)	4 (5.4)		
Duodenum, descending part	8 (10.1)	6 (8.1)		
Duodenum, horizontal part	15 (19.0)	8 (10.8)		
Duodenum, ascending part	20 (25.3)**	18 (24.3)		
Jejunum	20 (25.3)	18 (24.3)		
Jejunal limb of anastomosis	3 (3.8)	8 (10.8)		
Duration of total placement procedure (incl. preparation/recovery) (minutes)	31 (25-45)	60 (40-85)		<0.001
Duration intervention (minutes)	15 (10-27)	11 (8-18)		0.004
Interval physician order - tube placement (minutes)	195 (104-302)	228 (165-367)		0.029
Interval physician order - start of feeding (minutes)	424 (255-1158)	535 (401-1558)		0.001
Reaching feeding goal	65 (81.3)	61 (82.4)	0.99 (0.85-1.14)	0.85
Interval physician order - reaching feeding goal (hours)	61 (31-114)	56 (44-95)		0.70
Duration of primary tube stay (days)	7 (3-13)	6 (4-10)		0.87
Duration of tube feeding (days)	10 (5-24)	7 (4-17)		0.18
Use of parenteral nutrition	31 (38.8)	25 (33.8)	1.15 (0.75-1.75)	0.52
Duration of parenteral nutrition (days)	8 (5-18)	15 (5-30)		0.25
Placement related complications	2 (2.6)	5 (6.8)	0.38 (0.08-1.87)	0.26
Epistaxis	0	4		
Other***	2	1		
Tube related complications	43 (53.8)	36 (48.6)	1.11 (0.81-1.51)	0.53
Dislodgement	36 (45.0)	32 (43.2)	1.04 (0.73-0.28)	0.83
Spontaneous	16	12		
By patient or personnel	20	20		
Blockage	11 (13.8)	4 (5.4)	2.54 (0.85-7.64)	0.08
Aspiration	0	1 (1.4)	-	0.48
Other****	2 (2.5)	3 (4.1)	0.62 (0.11-3.59)	0.67

* Not including one patient who did not undergo feeding tube placement; ** Including two patients with a gastroenterostomy, resulting in unsuccessful feeding; *** Failure of EM-guided tracking system, Hyperventilation, and respiratory distress requiring ICU admission; **** Leakage of tube (n=2), anastomotic ulcer, upper gastrointestinal bleeding (n=2). Data are number (%) or median (IQR).

	EM-guided tube placement (n=80)	Endoscopic tube placement (n=74)	Relative Risk [EM-guided/ Endoscopic] (95% CI)	P
Need for reinsertion*****	29 (36.2)	31 (41.9)	0.87 (0.58-1.29)	0.47
Need for feeding related intervention (incl. repositioning)	40 (50.0)	31 (41.9)	1.19 (0.84-1.69)	0.31
Length of hospital stay (days)	12 (7-22)	10 (7-18)		0.22
In-hospital mortality	2 (2.5)	5 (6.8)	0.38 (0.08-1.87)	0.26

***** Primary endpoint. Data are number (%) or median (IQR).

There were no significant differences in placement or tube related complications (Table 2). Two patients in the endoscopic group developed a serious adverse event requiring intervention. One patient became hypoxic during the endoscopic procedure and was admitted to the intensive care unit for one day. The other patient required therapeutic endoscopy for bleeding from a duodenal ulcer. There was no tube related mortality.

Patient-reported outcomes are presented in Figure 2. There were no significant differences in pain, social embarrassment, anxiety, and total burden. The level of discomfort was significantly higher in the EM-guided group (median [IQR] 3.9 [2.0-6.7] vs. 2.0 [0.2-5.6], p=0.009), but EM-guided placement received higher recommendation scores (median [IQR] 8.2 [4.8-9.9] vs. 5.5 [2.3-7.8], p=0.008). There were no significant differences in patient-reported outcomes between the EM-guided and endoscopic replacement procedures (data not shown).

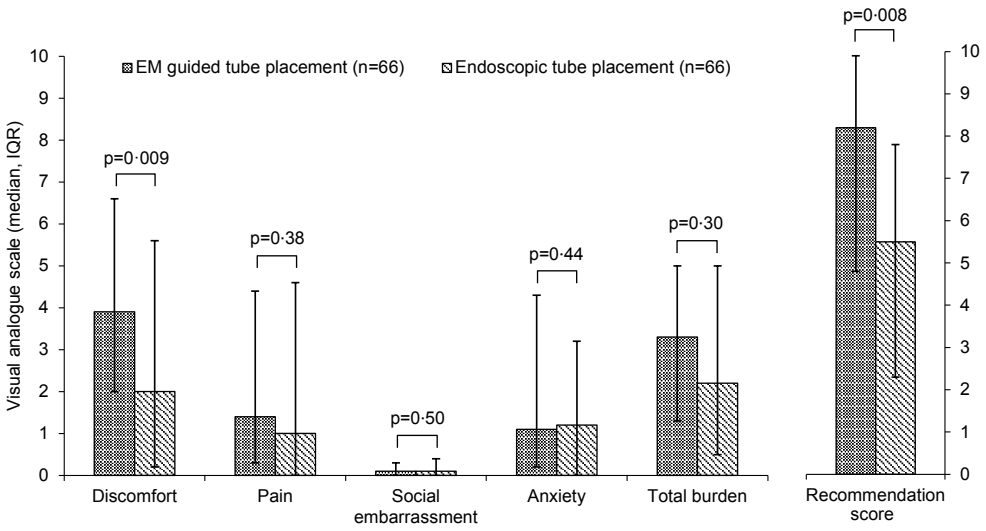

Figure 2 Patient-reported outcomes using the Visual Analogue Scale (VAS), with the five dimensions ranging from 0 (no complaints) to 10 (maximum complaints) and recommendation scores ranging from 0 (not recommended) to 10 (highly recommended).

The mean sum of healthcare costs was € 304 per initial EM-guided placement procedure and € 320 per initial endoscopic procedure (see Appendix 2). Taking into account the diagnostic investigations and tube related complications and interventions, EM-guided placement led to a non-significant mean healthcare cost reduction of € 116 (95% BCaCI -288-34) per patient (€ 584 [95% BCaCI 504-669] in the EM-guided group vs. € 700 [95% BCaCI 585-835] in the endoscopic group, p=0.15).
In the predefined subgroup of patients with an altered upper gastrointestinal anatomy, non-inferiority in terms of reinsertions could not be claimed for EM-guided placement (9 [64%] vs.10 [71%], risk difference [upper limit 95% CI] -7% [24%], p=0.29). The success rate of primary tube placement was non-significantly lower in the EM-guided group (5 of 14 [36%] procedures vs. 9 of 14 [64%] procedures, RR 0.55 (95% CI 0.25-1.24), p=0.13). In patients with an unaltered upper gastrointestinal anatomy, EM-guided placement was non-inferior in terms of reinsertions (20 [30%] vs. 21 [35%], risk difference [upper limit 95% CI] -5% [9%], p=0.037) and the success rate was similar between the two groups (51 of 65 [79%] procedures vs. 43 of 60 [72%] procedures, RR 1.10 (95% CI 0.89-1.34), p=0.38).

DISCUSSION

This trial in surgical patients showed that EM-guided bedside placement of nasoenteral feeding tubes by trained nurses was non-inferior in terms of reinsertions compared with endoscopic placement by gastroenterologists. No significant differences were found in success and complication rates of both techniques. Although patients experienced more discomfort, overall recommendation scores were higher for EM-guided placement. Furthermore, EM-guided placement had logistical advantages and overall healthcare costs were slightly lower.

Our event rates for the primary endpoint (reinsertions in 34% vs. 42% of patients) are higher than reported in previous studies on nasoenteral feeding tube placement (21% vs. 16%).[24] Whereas previous studies reported only the repeat procedures after failed initial placement or only the replacements after dislodgement or blockage of the tube, we included both. Moreover, the vast majority of previous studies had a single-center, retrospective, non-comparative design. Only one single-center study randomized patients to either EM-guided or endoscopic nasoenteral feeding tube placement.[25] This study had a small sample size (66 patients) with a rather low success rate of the first endoscopic procedure (36%), whereas reinsertions after tube related complications or failed replacements were not reported. Furthermore, this study only included critically ill patients admitted to the intensive care, most of whom already receive some form of conscious sedation. In contrast, our trial included patients admitted to gastrointestinal surgical wards, where patients are

not sedated and the prevalence of gastroparesis, which may hamper post-pyloric tube placement due to gastric stasis, and the presence of an altered upper gastrointestinal anatomy are high. Since even in this challenging population the outcomes of EM-guided placement were non-inferior to endoscopy, the results of our trial are probably generalizable to the overall hospital population.

The reinsertion rate in the EM-guided group in our study was slightly lower compared with endoscopy, because tubes that had dislodged into the stomach could frequently be repositioned with the stylet without removal of the tube. This is one of the advantages of EM-guided over endoscopic feeding tube placement, because patients consider passage of the tube through the nose and oropharynx to be the most burdensome part of tube placement.[23]

We found no significant differences in the most common indications for reinsertion (i.e. failed initial placement or tube related complications) between the two techniques. Success rates in our trial (71% vs. 70%) are somewhat lower compared to the 85% and 89% reported in literature for EM-guidance and endoscopy, respectively.[24] This is explained by the rather strict definition of success in our study, i.e. the tube had to be positioned beyond the descending part of the duodenum in order to prevent spontaneous retrograde tube migration or reflux of enteral nutrition. If any post-pyloric position had been accepted, as in previous studies, success rates in our study would have been 85% for EM-guidance and 84% for endoscopy. Another factor that may have influenced success rates is the inclusion of patients with an altered upper gastrointestinal anatomy. We have previously demonstrated that in patients after pancreatoduodenectomy, accounting for 21 of 28 patients with an altered anatomy included in our study, EM-guided but also endoscopic tube placement is more challenging and consequently less successful,[29] as was confirmed by our subgroup analysis.

Tube related complications in our study were somewhat higher compared to previous reports.[24] This trial, however, is the first study to make a prospective head-to-head comparison in tube related complications between the two techniques and it is well known that in retrospective studies, complications, especially when they do not require intervention, are easily missed. There was a trend towards more blockages in the EM-guided group (14% vs. 5%). A possible explanation may be slight differences in the material or internal lumen of the tubes used in both placement procedures.[31–33]

Besides our primary endpoint and the associated secondary endpoints, this trial also aimed to objectify other suggested advantages of EM-guided placement. The reduction in the

total procedure time, the time between physician order and tube placement, and the time to start of feeding reflect the logistical advantages of EM-guided placement, since there is no time lost in recovering from sedation, patient transportation or waiting for radiographic confirmation of the tube's position.

Another major advantage of EM-guided tube placement is that only one nurse is required to perform the bedside procedure, as compared to a gastroenterologist assisted by one or two endoscopy nurses in a specialized department for endoscopic placement. Besides facilitating gastroenterologists to fulfil the increasing demand for other endoscopic procedures such as colorectal screening programs, in our study this also resulted in a cost reduction of €116 per patient. Costs analyses were according to as-treated principles, based on the assumption that placement with the non-assigned technique was based on logistics rather than patient characteristics. Also in an intention-to-treat analysis, however, a cost reduction of €97 per patient was seen. A substantial proportion of the costs lies in abdominal radiographs to confirm the tube's position. Although radiographic confirmation is recommended, there are no guidelines dictating its use and some centers choose to follow clinical symptoms of malposition instead. Interestingly, in our study, a significant proportion (15 of 67) of 'successfully positioned' tubes according to the gastroenterologist, were found to be located in the stomach (7%), duodenal bulb (6%) or descending duodenum (9%), potentially leading to an increased risk of aspiration, which justifies the use of radiography. Nonetheless, even when the costs for radiography were excluded, EM-guided placement still was associated with lower costs (data not shown).

Patient-reported outcomes on nasoenteral feeding tube placement have not been investigated before, except for a small subgroup in a previous study from one of our own centers.[23] We systematically asked patients for their experience of the placement procedure using a standardised questionnaire. Contrary to our hypothesis, patients did not report differences in pain, anxiety, social embarrassment, or total burden between the two techniques, but did report more discomfort during EM-guided placement than during endoscopy. This finding is probably related to the large differences in the use of conscious sedation (82% in the endoscopic group vs. 0% in the EM-guided group). The use of sedation is considered a major advantage of endoscopy by patients and was therefore also one of the most frequently reported reasons for patients to decline participation in the trial. Conscious sedation is however associated with a small risk of cardiopulmonary complications such as hypoxia,[34,35] which occurred in one patient in our trial, who was consequently admitted to the intensive care unit. On the other hand, recommendation scores were significantly higher in the EM-guided group, which supports the overall hypothesis that EM-guided placement is a more patient-friendly approach. It should be noted though that these differences in

patient-reported outcomes were only seen for the primary placement procedures, not for the replacement or repositioning procedures.

Our findings should be interpreted in view of several potential limitations. Seven of 206 eligible patients (3%) had to be excluded because tube placement was warranted while no nurse was available to perform EM-guided placement. On the other hand, five patients assigned to endoscopic placement underwent EM-guided placement because there was no gastroenterologist available to perform the procedure. Per-protocol and as-treated analyses, however, both supported non-inferiority of EM-guided placement.
Due to the pragmatic design of our trial, the choice of endoscopic technique for nasoenteral feeding tube placement was left to the gastroenterologist's discretion, resulting in the use of several techniques in the trial. However, no major differences in success rates of the different endoscopic techniques have been reported so far.[24]
Based on the results of our trial, it is difficult to draw any definitive conclusions on the application of EM-guided placement in the subset of patients with an altered upper gastrointestinal anatomy given the relatively small and single center subgroup included in this trial. In our previous prospective pilot study, EM-guided placement was equally successful as endoscopic placement in patients after pancreatoduodenectomy.[29] In this trial, however, the success rate was lower in the EM-guided group compared to endoscopy, but also compared to the 58% success rate previously reported. Future prospective studies should investigate whether an EM-guided first approach is not disadvantageous for patients with an altered upper gastrointestinal anatomy.
EM-guided placement is currently not embedded in standard care facilities of most hospitals, and therefore requires an implementation process. This process includes structured training of nurses. Our training program includes a full-day training session, followed by 25 (supervised) placement procedures to complete the learning curve.[23] Ideally, a sufficient number of nurses are trained to facilitate tube placement on working days, as well as weekends or holidays, but also to ensure at least one placement procedure per nurse per week to maintain skills. If volume permits, it may also be beneficial to train (surgical) ward nurses to perform the EM-guided placements, as was recently initiated in one of our centers. This process, which will obviously have to be assessed and evaluated, could potentially further improve logistics and reduce costs.

In conclusion, EM-guided bedside placement of nasoenteral feeding tubes by nurses was non-inferior to endoscopic placement by gastroenterologists in terms of effectiveness in surgical patients, while offering advantages in logistics and costs, and may therefore be considered the preferred technique for nasoenteral feeding tube placement.

ACKNOWLEDGEMENTS

We sincerely thank all patients for their participation in the study. We thank all involved nutritionists, research nurses, and medical and nursing staff at the participating centers for their efforts in the enrolment and care of patients involved in this study.
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RESEARCH IN CONTEXT

Evidence before this study

Prior to the start of the trial we performed a systematic review of the literature in PubMed, Embase, and the Cochrane Library for studies concerning EM-guided and/or endoscopic nasoenteral feeding tube placement published between January 1, 2006, and January 3, 2014.[24] The search terms used were electromagnetic or endoscopic, and nasoenteral or post-pyloric and tube(s), feeding, or nutrition and synonyms. Because of the heterogeneity in study populations, designs and protocols in the available (non-comparative) studies, a formal meta-analysis could not be performed. Moreover, the definitions and means of reporting success and reinsertion rates (primary endpoint of our trial) differed from study to study. One previous single-center study randomized patients to either EM-guided or endoscopic nasoenteral feeding tube placement and concluded that EM-guided placement was as fast, safe, and successful as the endoscopic method.[25] This study was, however, performed in critically ill patients and had a small sample size (66 patients). Moreover, the success rate of the first endoscopy was remarkably low (36%) and reinsertion rates were not reported.
We updated our systematic review by a literature search performed on September 6, 2015, which yielded no relevant new articles except our own retrospective study.[36] In this study we also found no differences between EM-guided and endoscopic placement regarding feasibility and safety in surgical patients with unaltered upper gastrointestinal anatomy.

Added value of this study

Our multicenter, randomized, non-inferiority trial was performed in surgical patients, including those with an altered upper gastrointestinal anatomy, and adds data on the perceived advantages of EM-guided nasoenteral feeding tube placement, such as logistics, patient-reported outcomes and costs.

Implications of all the available evidence

EM-guided bedside placement of nasoenteral feeding tubes by nurses is non-inferior to endoscopic placement by gastroenterologists in terms of reinsertions, while offering some distinct advantages, and may therefore be considered the preferred technique for nasoenteral feeding tube placement.

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Appendix 1 Endoscopic techniques and materials

Center	Technique	Endoscope	Guidewire	Feeding tube
1	Transnasal over the guidewire	Transnasal gastroscope XP160, Olympus, Center Valley, PA, USA	Amplatz, 260 cm, Boston Scientific Corporate, Marlborough, MA, USA	Flocare PUR, 10 Fr, 130 cm, Nutricia, the Netherlands
2	Transnasal over the guidewire	Transnasal gastroscope XP160, Olympus, Center Valley, PA, USA	Jagwire, 260 cm, Boston Scientific Corporate, Marlborough, MA, USA	NJP10/130, 10 Fr, 130 cm, Medicina Ltd, Bolton, UK
3	Transnasal over the guidewire	Transnasal gastroscope XP180, Olympus, Center Valley, PA, USA	Jagwire, 450 cm, Boston Scientific Corporate, Marlborough, MA, USA	Nutrisafe 2, 10 Fr, 125 cm, Vygon, Ecouen, France
4	Transoral through the scope	Fujinon gastroscope, FUJIFILM Europe GmbH, Düsseldorf, Germany	NA	Cobra, 10 Fr, 300 cm, Cobra Medical BV, Groningen, the Netherlands
5	Transoral through the scope	Gastroscope GF 180, Olympus, Center Valley, PA, USA	NA	Nutrisafe 2, 10 Fr, 125 cm, Vygon, Ecouen, France

NA, not applicable

Appendix 2 Costs

	Costs	Mean costs per patient	
		EM-guided tube placement (n=84)	Endoscopic tube placement (n=69)
Primary procedure			
EM-guided	€ 304	€ 304	-
Endoscopic	€ 320	-	€ 320
Additional costs			
X-rays	€ 46	€ 41	€ 93
Complications			
Therapeutic endoscopy	€ 310	-	€ 4
Additional ICU admission	€ 1186	-	€ 17
Reinsertions			
EM-guided			
Replacement	€ 304	€ 51	€ 22
Repositioning	€ 53	€ 15	-
Endoscopic	€ 320	€ 172	€ 241
Fluoroscopic	€ 126	€ 2	€ 2
	Total (95% BCaCI)	€ 584 (504-669)	€ 700 (585-835)

ICU, Intensive care unit; BCaCI, Bias corrected and accelerated confidence interval

10

Percutaneous transhepatic feeding tube placement: a single-center experience in 40 consecutive patients

Submitted

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ABSTRACT

Objective

Our aim was to determine the application and feasibility of percutaneous transhepatic feeding tube placement.

Summary Background Data

Enteral access can be obtained via various routes (e.g. nasoenteral or jejunostomy feeding tubes), but all routes have their specific drawbacks. In a select subset of patients, who also require prolonged percutaneous transhepatic biliary drainage (PTBD), transhepatic feeding tube placement may offer a suitable alternative, but data regarding this technique are lacking.

Methods

We performed a retrospective monocenter cohort study in patients with PTBD undergoing percutaneous transhepatic feeding tube placement between April 2003 and February 2015. The feeding tube was placed by an interventional radiologist alongside a pre-existent PTBD catheter.

Results

Overall, 43 patients underwent transhepatic feeding tube placement, of whom 3 were excluded because data were lacking. Patients had a PTBD catheter for the management of surgical complications (e.g. bile leak or duodenal perforation, n=28), palliative drainage (n=5), perioperative biliary decompression (n=3) or other indications (n=4). Indications for tube placement were bile restitution (n=8) or the need for enteral feeding (n=32) due to severe gastroparesis, insufficient intake, duodenal perforation, enterocutaneous fistula, or gastric outlet obstruction. 38 of 40 (95%) initial tube placements were successful. Tube related complications included dislodgement (n=8), blockage (n=3), bile leakage (n=4), cholangitis (n=1) and bleeding (n=1) and led to the need for replacement in 9 (23%) patients and removal of the tube in only 1 (3%) patient.

Conclusions

Transhepatic feeding tube placement alongside a pre-existent PTBD catheter was safe and successful in this series and may be considered in patients requiring both prolonged PTBD and enteral access.

INTRODUCTION

Despite the widespread implementation of enhanced recovery after surgery (ERAS) programs,[1–4] enteral nutrition is still frequently required in surgical care.[5] Especially in conditions or complications prohibiting oral intake, such as duodenal perforation or postoperative delayed gastric emptying, enteral nutrition is essential to facilitate the recovery process. In contrast to parenteral nutrition, which is associated with an increased risk of infections and metabolic side effects, enteral nutrition has the ability to maintain gut integrity and stimulate gut contractility.[5–8] Enteral access can be obtained via various routes, but all routes have their specific downsides.[9] Nasoenteral feeding tubes are discomforting to patients and tend to dislodge (into the stomach), which leads to discontinuation of feeding, risk of aspiration and the need for replacement.[10–13] Therefore, in patients requiring prolonged enteral access, a feeding jejunostomy or percutaneous endoscopic gastrostomy (with jejunal extension) is usually recommended, although these are associated with, albeit rare, severe complications, such as bleeding, peritonitis (i.e. due to leakage) and bowel strangulation.[13–16]

In patients requiring prolonged percutaneous transhepatic biliary drainage (PTBD), for instance because of duodenal perforation, perioperative biliary decompression or surgical complications, transhepatic feeding tube placement may offer a suitable alternative for prolonged enteral access. The transhepatic feeding tube allows enteral access through a percutaneous route, which is already necessary for biliary drainage (see Figure 1). Several case reports have reported on transhepatic feeding tubes,[17–20] but to date evidence about the feasibility and long term application in a larger population is lacking. The aim of this study was to determine the application and feasibility of percutaneous transhepatic feeding tube placement .

METHODS

Patients

We performed a retrospective monocenter cohort study in all consecutive patients undergoing percutaneous transhepatic feeding tube placement between April 2003 and February 2015 in the Academic Medical Center in Amsterdam, which is a national referral center for PTBD and bile duct injuries. Patients were considered for transhepatic feeding tube placement when they had a PTBD catheter and required prolonged enteral access for either enteral nutrition or bile restitution. Patients were identified by a search in a prospectively maintained database of all interventional radiological procedures performed within the study period. Patients of whom no details regarding the transhepatic feeding tube placement procedure were available were excluded.

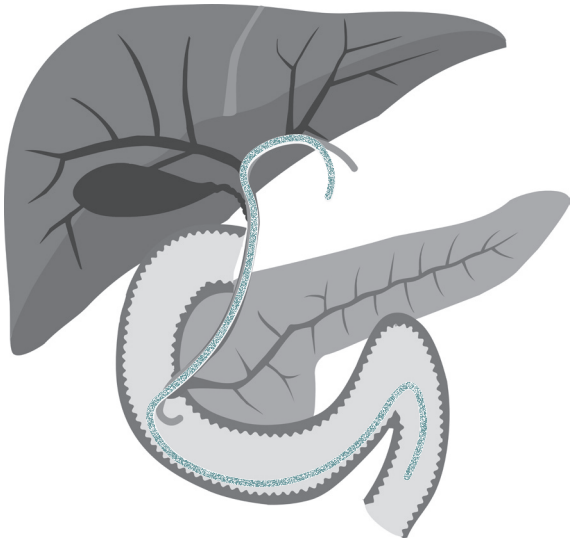

Figure 1 Percutaneous transhepatic feeding tube (blue) alongside a percutaneous transhepatic biliary drainage catheter.

Feeding tube placement

Percutaneous transhepatic feeding tube placement was performed by one of three interventional radiologists with extensive experience with PTBD procedures. Analgesia was achieved by local subcutaneous lidocaine injection and/or intravenous fentanyl, combined with midazolam for sedation. An extra stiff guide wire (Amplatz, Cook Medical, Bloomington, USA) was advanced through the pre-existing biliary drainage catheter, after which the catheter was exchanged for a sheath (8-10 Fr, Super Arrow-Flex Sheath Introducer, Arrow International, Reading, USA) over the guide wire. A cobra catheter and an angled wire (Terumo, Somerset, USA) were then inserted through the sheath and advanced into the duodenum or jejunum (preferably past the duodenojejunal flexure) or into the efferent jejunal limb if appropriate, following the pre-existing transhepatic route. After removal of the sheath and cobra catheter, the canal was optionally expanded with the use of a 20 Fr coons dilatator (Cook medical, Bloomington, USA). The angled wire was then exchanged for a second extra stiff wire. Subsequently, both the biliary drainage catheter (10 Fr, Cook Medical, Bloomington, USA) and the feeding tube (8 Fr, Corpak MedSystems UK, Gatwick, UK) were advanced over the guide wires. The position of the biliary drain and the feeding tube was confirmed using fluoroscopy (Figure 2). Finally, the guide wires were removed and the catheters were sutured to the skin. When the feeding tube required replacement (e.g. after dislodgement or blockage) the entire procedure was repeated starting at the insertion of the guide wires.

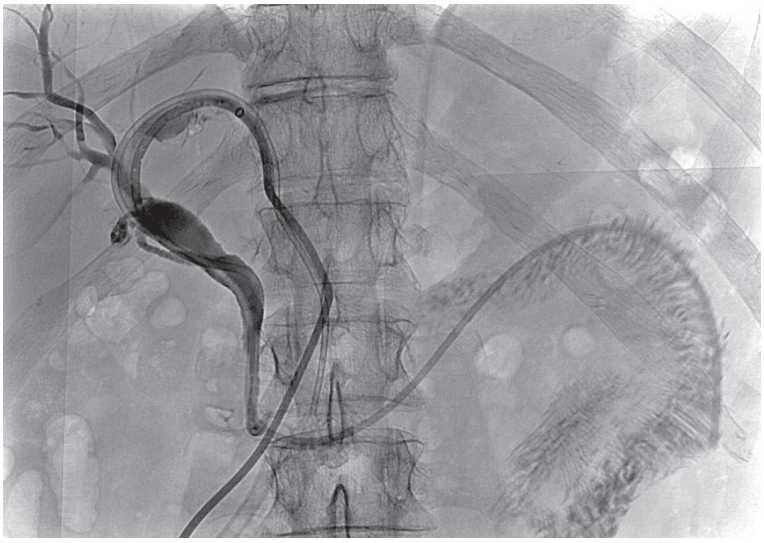

Figure 2 Fluoroscopy after percutaneous transhepatic feeding tube placement.

Data Collection

Data were retrospectively collected from electronic patient records and patient charts with daily notes. Baseline characteristics collected were age, sex, body mass index (BMI), diagnosis, indication for PTBD, feeding route prior to transhepatic feeding tube placement and indication for transhepatic feeding tube placement. Primary endpoint was the success rate of primary tube placement, defined as a correct position (in the duodenum or jejunum) followed by successful administration of nutrition or bile via the tube. Secondary outcomes were tube position, procedure time, length of hospital stay, readmission, length of primary tube stay, duration of feeding/bile restitution, procedure or tube related complications [i.e dislodgement, blockage (due to clogging or kinking) or infections], replacements, length of hospital stay, readmission, and mortality. Complications were recorded during (re)admission or during outpatient clinic visits. Patients who were discharged with the transhepatic feeding tube in situ, were regularly followed up by the consulting dietitian to monitor any problems with the tube.

Statistical Analysis

Data were analyzed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean (±SD) or median (interquartile range) as appropriate. Categorical variables were expressed as absolute number (percentage).

RESULTS

Table 1 Baseline characteristics of patients receiving a percutaneous transhepatic feeding tube

	n=40
Age (years)	61 (± 14)
Male	25 (63%)
BMI (kg/m²)	24.2 (± 4.5)
Diagnosis	
Malignant	25 (63%)
Pancreatic carcinoma	9
Cholangiocarcinoma	8
Colorectal carcinoma (liver metastasis)	3
Duodenal carcinoma	2
Other*	3
Benign	15 (38%)
Cholelithiasis	7
Other**	8
Indication for percutaneous biliary drainage	
Management of complications	28 (70%)
Palliative drainage	5 (13%)
Perioperative decompression	3 (8%)
Other***	4 (10%)
Feeding route prior to transhepatic feeding tube placement	
Oral	11 (28%)
Enteral	7 (23%)
Parenteral	20 (50%)
Indication for transhepatic feeding tube placement	
Bile restitution	8 (20%)
Enteral nutrition	32 (80%)
Gastroparesis	13
Insufficient intake due to other reasons	11
Duodenal perforation	5
Enterocutaneous fistula	2
Gastric outlet obstruction	1

* Gallbladder carcinoma, pancreatic neuroendocrine tumor, urothelial carcinoma.
** Traumatic liver laceration, traumatic pancreas laceration, pancreatitis, cholangitis, appendicitis, abdominal aortic aneurysm, duodenal perforation e.c.i., ampullary adenoma.
*** Cholangitis, drainage of central liver abscess, pancreatitis induced bile duct perforation, bile duct compression due to hematoma.

Patients

In our study period, 43 patients underwent transhepatic feeding tube placement. Three patients were excluded because data on the placement procedure were lacking, leaving 40 patients eligible for analysis. Baseline characteristics are shown in Table 1. All patients

Table 2 Feasibility and complications

	n=40
Successful primary tube placement	38 (95%)
Tube position	
Duodenum	5 (13%)
Jejunum	20 (50%)
Efferent jejunal limb	13 (33%)
Procedure time (minutes)	33 (29-43)
Primary tube in place (days)*	29 (15-50)
Total duration of transhepatic feeding/bile restitution (days)**	42 (19-76)
Tube related complications	
Dislodgement	8(20%)
Blockage	3 (8%)
Cholangitis	1 (3%)
Bleeding	2 (5%)
Bile leakage alongside biliary drain/ feeding tube	4 (10%)
Patient-reported outcomes	
Pain	5 (13%)
Discomfort	4 (10%)

* 15% missing data due to loss to follow-up
** 28% missing data due to loss to follow-up

had a PTBD catheter in situ for a median of 22 (9-38) days prior to the feeding tube placement procedure. The most common indication for PTBD was the management of surgical complications, including anastomotic leak after hepaticojejunostomy (n=10), bile duct injury (n=9), duodenal perforation (n=7) or enterocutaneous fistula (n=2). Nearly half of patients (45%) received parenteral nutrition prior to the transhepatic feeding tube placement. The transhepatic feeding tubes were placed for bile restitution (n=8) or enteral nutrition (n=32).

Feasibility

Initial tube placement was successful in 38 of 40 (95%) patients. Median procedure time was 33 (29-43) minutes. Reasons for failure included recurrent dislodgement of the tube during the procedure (n=1) and the inability to visualize the efferent jejunal limb (n=1). In the first patient a second attempt was successful. The second patient received a nasoenteral feeding tube by endoscopy.

Median length of hospital stay after tube placement was 12 (5-34) days. 29 of 40 patients (73%) were discharged with the transhepatic feeding tube in situ. Follow-up data were available for 19 of these patients. Three (8%) patients were readmitted after a median of 12 (11-20) days for tube related complications.

Overall, the primary placed tube remained in the correct position for a median of 29 (15-50) days. Patients received enteral nutrition and/or bile for a mean of 42 (19-76) days.

Complications

No severe complications occurred during the placement procedures. One patient experienced severe pain during the procedure. Overall, tube related complications occurred in 23 (58%) patients (see Table 2). Complications included dislodgement (n=8), blockage (n=3), bile leakage (n=4), and cholangitis (n=1) and required replacement in 9 (23%) patients. In one patient (3%) the feeding tube and PTBD catheter had to be removed because of bleeding from the PTBD catheter, resulting in a decrease in hemoglobin concentration and the need for blood transfusion. There was no tube related mortality.

DISCUSSION

Transhepatic feeding tube placement alongside a pre-existent PTBD catheter was relatively safe and successful in this series and may therefore be considered as alternative in patients requiring both prolonged PTBD and enteral access.

This is the largest series to date on transhepatic feeding tube placement. Four case reports have previously described the application of a similar technique in a total of 9 patients.[17–20] All of these patients were diagnosed with an unresectable malignant gastrointestinal tumor and received a PTBD catheter for palliative drainage. The transhepatic feeding tube was placed because of mechanical obstruction in the gastoduodenal region prohibiting oral intake. Our study included 5 patients in a palliative setting, but the majority of PTBD catheters were placed for the management of complications, such as bile leakage or duodenal perforation. This illustrates that the technique can be applied more widely than solely in the palliative setting.

The primary procedure was successful in 95%. Only one patient eventually required an alternative enteral access route. In the previously published case reports the success rate was 100%, but this may be subject to publication bias. Nevertheless, the high success rate reflects that the technique of transhepatic feeding tube placement is relatively simple in patients who already have a PTBD catheter, when performed by an experienced interventional radiologist.
In our series, the primary placed tube remained in the correct position for a median of 29 days and the transhepatic route was used for the administration of enteral nutrition or bile for a median of 42 days. In the before mentioned case reports on transhepatic feeding tube placement, long term follow-up was lacking, except for one patient in whom the use of the

tube extended to 3.5 months.[17–20]

Although 23 (58%) patients developed a complication, only 10 (25%) patients required replacement or removal of the tube due to complications during the entire follow-up period. Complaints of discomfort or pain and leakage of bile alongside the PTBD catheter were transient and are well known complaints associated with PTBD catheters.[21,22] Also cholangitis and bleeding, which both led to the need for replacement or removal of the PTBD catheter and feeding tube, are known complications of PTBD,[21,23,24] and are not necessarily the consequence of the presence of a feeding tube in the biliary tract. Dislodgement occurred in 8 (20%) patients and required replacement in most cases. The only previous study on transhepatic feeding tubes describing complications, reported dislodgement in 2 of 4 (50%) patients.[19] Dislocation of feeding tubes is common, especially for nasoenteral feeding tubes with dislodgement rates up to 36%.[10,11] However, also more invasive alternatives such a feeding jejunostomies or percutaneous endoscopic gastrostomy (with jejunal extension) dislocate in 1-8%.[13,15,16] Moreover, these routes are also associated with more severe complications such as upper gastrointestinal bleeding, leakage leading to peritonitis and even bowel strangulation.[13–16] Transhepatic feeding tube placement is not without complications, but may save patients from repeated endoscopic replacement procedures or discomfort in the nose as compared to nasoenteral feeding tubes, and an additional percutaneous access point, with the previously mentioned risks, compared with gastroenterostomies or jejunostomies.

The retrospective nature of this study may have led an underreporting of complications and patient-reported outcomes (information bias) since these were extracted from patient files with daily notes from the treating care providers. In addition there was some loss-to-follow up, since the majority of patients was discharged with the feeding tube still in situ. Patients were, however, regularly followed-up by the consulting dietitian (unless transferred to another care facility). For complications leading to the impossibility to use the tube, patients were readmitted or attended the outpatient clinic in our center, which was recorded in their patient file. Another limitation is the selection of patients, since the procedure was only performed in a very select subset of patients requiring prolonged enteral access. However, this is the natural consequence of the fact that transhepatic feeding tube placement is only suitable for patients who required prolonged PTBD and should be performed by an interventional radiologist with experience with PTBD procedures.

Taking these considerations into account, this study shows that transhepatic feeding tube placement can be successfully and safely applied in patients requiring both prolonged PTBD and enteral access.

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11

Summary and future perspectives

SUMMARY

The research presented in this thesis has answered several questions regarding nutrition after (pancreatic) surgery and has already changed or provides a basis for changes is the postoperative management of these patients.

Feeding strategies after pancreatoduodenectomy

First, we aimed to determine the optimal feeding strategy after pancreatoduodenectomy and compared postoperative outcomes with the use of various feeding routes. The available nutritional guidelines give conflicting recommendations and are all based on studies after major gastrointestinal surgery for cancer in general and not specifically on post-pancreatoduodenectomy patients.[1–3] In **Chapter 2** we systematically reviewed the available literature regarding the different feeding strategies after pancreatoduodenectomy. A total of 15 studies on feeding in 3474 patients after pancreatoduodenectomy were included and data on five feeding routes were extracted: oral diet, enteral nutrition via either a nasoenteral-, gastrojejunostomy or jejunostomy tube and total parenteral nutrition. Length of hospital stay was shortest in the oral diet and gastrojejunostomy groups. Resumption of normal oral intake, which is a more specifically feeding-related outcome measure and less dependent on other postoperative parameters compared with length of hospital stay, was also established most quickly with a oral feeding strategy. There seemed to be no evidence to support routine nutritional support with enteral or parenteral nutrition after pancreatoduodenectomy.

In addition, **Chapter 3** presents a retrospective cohort study in 129 patients and demonstrated that each feeding strategy after pancreatoduodenectomy is associated with specific complications. Nasoenteral feeding tubes dislodged in a third of patients, jejunostomy tubes caused few but potentially life-threatening bowel strangulation and parenteral nutrition doubled the risk of infections. There were no differences in time to resumption of normal oral intake, morbidity or length of hospital stay between the three groups.

Based on the findings in Chapter 2 and 3, we concluded that early oral feeding may be the preferred routine feeding strategy after pancreatoduodenectomy and therefore we designed an observational cohort study, presented in **Chapter 4**, to evaluate whether a change in the routine feeding strategy from nasoenteral tube feeding to early oral feeding improved clinical outcomes. In a comparison between 51 historical controls receiving nasoenteral tube feeding and a consecutive prospective cohort of 51 patients receiving early oral feeding, time to resumption of adequate oral intake and length of hospital stay significantly decreased with early oral feeding. No negative impact of early oral feeding on postoperative morbidity was seen, which led us to conclude that early oral feeding with on-demand tube feeding, is the feeding strategy of choice after pancreatoduodenectomy.

Half of patients in the early oral feeding group received nasoenteral feeding on-demand, because they developed delayed gastric empting in the postoperative course or because of severe preoperative malnutrition.

The hypothesis that some subgroups of patients, who are at high risk of severe preoperative malnutrition and/or postoperative delayed gastric emptying, may benefit from routine tube feeding in the postoperative period, was further investigated in **Chapter 5**. Preoperative symptoms of gastric outlet obstruction (i.e. vomiting, dysphagia, nausea, loss of appetite and postprandial complaints) have been previously associated with a threefold increased risk of delayed gastric emptying after pancreatoduodenectomy.[4–9] We analyzed a consecutive multicenter cohort of 78 patients with preoperative symptoms of gastric outlet obstruction to determine whether clinical outcomes after pancreatoduodenectomy in these patients differed between postoperative early oral feeding and routine tube feeding. The applied postoperative feeding strategy in this study was dependent on the centers' routine strategy at that time, rather than on patient characteristics. The time to resumption of adequate oral intake, overall complications and length of hospital stay did not differ between these two feeding strategies. In patients with an uncomplicated postoperative course, however, early oral feeding was associated with shorter time to adequate oral intake and shorter length of hospital stay, which led to the conclusion that also in patients with preoperative symptoms of gastric outlet obstruction, early oral feeding can be considered the routine feeding strategy after pancreatoduodenectomy.

Nasoenteral feeding tube placement

Up to 50% of patients presented in Chapters 4 and 5 ultimately required postoperative tube feeding on-demand, because they did not tolerate early oral feeding. Although routine intraoperative tube placement has been abandoned within the early oral feeding strategy, many patients still have to undergo postoperative feeding tube placement, which is typically done endoscopically by gastroenterologists. Blind placement is usually unsuccessful, especially in patients with delayed gastric emptying, and may lead to complications due to inadvertent placement in the respiratory tract.[10,11] Fluoroscopic tube placement by radiologists is feasible but rarely used in the Netherlands. Endoscopic feeding tube placement is however bothersome for both patients and caregivers due to the need for preprocedural fasting, patient transportation and radiological confirmation. Furthermore, the demand for endoscopic procedures in general has increased significantly over the past decades reducing its availability.[12] Therefore, we aimed to investigate whether the task of nasoenteral feeding tube placement can be shifted from gastroenterologists at endoscopy departments to nurses at the patient's bedside through the use of an electromagnetic guided tube placement system. In **Chapter 6** we systematically reviewed the literature regarding electromagnetic guided, endoscopic and fluoroscopic nasoenteral feeding tube

placement. A total of 28 studies were included and data on 4056 patients undergoing nasoenteral feeding tube placement were extracted. Success rates were comparable for the three different tube placement techniques. Also the reinsertion rate, which is a more representative outcome measure for the (long-term) efficacy of the technique, was similar for the three techniques. The sixteen studies reporting this outcome, however, used various definitions. Procedure-related complications were infrequent for all three techniques. Tube-related complications included mainly the well-known complications associated with nasoenteral feeding tubes, namely tube dislodgement and blockage. Altogether, bedside electromagnetic guided placement appeared to be as safe and effective as fluoroscopic or endoscopic placement, but there was a large heterogeneity between studies. Moreover, most studies were performed in critically ill patients at the intensive care unit and only one study made a head-to-head comparison between electromagnetic guided and endoscopic tube placement.

In **Chapter 7** we retrospectively compared electromagnetic guided to endoscopic placement of nasoenteral feeding tubes in 249 adult patients admitted to two gastrointestinal surgical wards. Overall, success rates of primary tube placement were comparable for both techniques, except for the small subgroup of patients with an altered upper gastrointestinal anatomy, wherein success rates were significantly lower in the electromagnetic guided group. There were no significant differences in tube related complications such as dislodgement or blockage. We concluded that bedside electromagnetic guided placement did not differ from endoscopic placement regarding feasibility and safety in surgical patients with an unaltered upper gastrointestinal anatomy. Additional research in patients with an altered anatomy was warranted, because the presence of an altered anatomy of the upper gastrointestinal tract, such as after pancreatoduodenectomy, had thus far been considered a relative contraindication for electromagnetic guided tube placement.

To investigate the presumed increased risk of technical failure and complications in these patients, we designed the prospective pilot study in 53 patients after pancreatoduodenectomy, presented in **Chapter 8**. Initial tube placement was successful in 58% of patients who underwent electromagnetic guided placement, but also endoscopic placement was only successful in 53% of patients. No complications occurred during the placement procedures and tube-related complications were similar to those of patients with an unaltered anatomy.

All previous studies, including our own, focused mainly on the technical success of the placement procedures and lacked data on the perceived advantages of electromagnetic guided nasoenteral feeding tube placement, such as logistics, patient-reported outcomes and costs. **Chapter 9** describes the CORE trial, a multicenter randomized controlled trial that aimed to determine non-inferiority of electromagnetic guided placement in terms of efficacy and to objectify the suggested advantages compared with endoscopic placement

of nasoenteral feeding tubes in surgical patients. The need for reinsertion of a feeding tube (e.g. after failed initial placement or dislodgement/blockage of the tube) occurred in 36% of patients in the electromagnetic guided group and 42% of patients in the endoscopic group, which established non-inferiority of electromagnetic guided placement. No significant differences were found in success and complication rates of both techniques and, although patients experienced more discomfort during electromagnetic guided placement, overall patient recommendation scores were higher. Furthermore, electromagnetic guided placement had logistical advantages and overall healthcare costs were lower, which led us to conclude that electromagnetic guided placement may be considered the preferred technique for nasoenteral feeding tube placement.

Although electromagnetic guidance makes nasoenteral feeding tube placement less bothersome, there is a subgroup of patients who require prolonged enteral nutrition and consequently suffer from several repeated tube placement procedures (e.g. after dislodgement or blockage) and discomfort in the nose due to the long-term presence of the tube. Therefore, in patients requiring prolonged enteral access, a feeding jejunostomy or gastrojejunostomy is usually recommended, but these are associated with severe complications,[13–16] as was also shown in Chapter 2 and 3. In **Chapter 10** we present an alternative technique for prolonged enteral access alongside a pre-existent percutaneous transhepatic biliary drainage catheter. This technique was successful in 95% of the initial tube placement procedures and only led to known complications of feeding tubes (e.g. dislodgement and blockage) and percutaneous transhepatic biliary drainage catheters (e.g. cholangitis, bile leak and bleeding). Transhepatic feeding tube placement may therefore offer a suitable alternative in a select group of patients who require both prolonged enteral access and biliary drainage (e.g. because of duodenal perforation, perioperative biliary decompression or surgical complications).

Table 1 Summary of research questions and main finding presented in this thesis

Chapter	
2	*What is the optimal routine feeding route after pancreatoduodenectomy regarding efficacy and safety according to the available literature?*
	There is no evidence to support routine enteral or parenteral feeding after pancreatoduodenectomy. An oral diet may be considered the preferred routine feeding strategy after pancreatoduodenectomy.
3	*What is the difference in efficacy and feeding-related complications between nasoenteral, jejunostomy and parenteral feeding after pancreatoduodenectomy?*
	None of the analyzed feeding strategies was found superior with respect to time to resumption of normal oral intake, morbidity and mortality. Each strategy was associated with specific complications. Nasoenteral tubes dislodged in a third of patients, jejunostomy tubes caused few but potentially life-threatening bowel strangulation and parenteral nutrition doubled the risk of infections.

Chapter	
4	*Does a change in the routine feeding strategy from nasoenteral tube feeding to early oral feeding improve clinical outcomes after pancreatoduodenectomy?*
	The introduction of an early oral feeding strategy after pancreatoduodenectomy reduced the time to resumption of adequate oral intake and length of hospital stay without negatively influencing postoperative morbidity.
5	*In patients with preoperative symptoms of gastric outlet obstruction, what is the difference in clinical outcomes after pancreatoduodenectomy between postoperative early oral feeding and routine tube feeding?*
	Overall clinical outcomes did not differ between postoperative early oral feeding and routine tube feeding. Also in patients with preoperative symptoms of gastric outlet obstruction, early oral feeding can be considered the routine feeding strategy after pancreatoduodenectomy.
6	*What is the efficacy and safety of bedside electromagnetic guided, endoscopic and fluoroscopic placement of nasoenteral feeding tubes in adults according to the available literature?*
	Bedside electromagnetic guided placement of nasoenteral feeding tubes appears to be as safe and effective as fluoroscopic or endoscopic placement. Electromagnetic guided tube placement by nurses may be preferred over more costly procedures performed by gastroenterologists or radiologists, but randomized studies were lacking.
7	*What is the difference in success rates of electromagnetic guided and endoscopic placement of nasoenteral feeding tubes in surgical patients?*
	Bedside electromagnetic guided placement of nasoenteral feeding tubes by specialized nurses did not differ from endoscopic placement by gastroenterologists regarding feasibility and safety in surgical patients with normal upper gastrointestinal anatomy.
8	*In patients after pancreatoduodenectomy, how does the feasibility and safety of bedside electromagnetic guided placement of nasoenteral feeding tubes relate to endoscopic placement?*
	Bedside electromagnetic guided placement of nasoenteral feeding tubes by nurses was equally successful as endoscopic placement in patients after pancreatoduodenectomy.
9	*Is electromagnetic guided placement of nasoenteral feeding tubes by nurses at least as effective as endoscopic placement by gastroenterologists in surgical patients requiring nasoenteral feeding?*
	Electromagnetic guided bedside placement of nasoenteral feeding tubes by trained nurses was non-inferior in terms of reinsertions compared with endoscopic placement by gastroenterologists. Since electromagnetic guided placement had logistical advantages and overall healthcare costs were slightly lower, it may be considered the preferred technique for nasoenteral feeding tube placement.
10	*Is percutaneous transhepatic feeding tube placement feasible in patients requiring both prolonged percutaneous transhepatic biliary drainage and enteral access?*
	Transhepatic feeding tube placement alongside a pre-existent percutaneous transhepatic biliary drainage catheter was safe and successful and may be considered in highly selected patients requiring both prolonged percutaneous transhepatic biliary drainage and enteral access.

FUTURE PERSPECTIVES

Although the research presented in this thesis has answered several questions regarding the perioperative management of patients undergoing (pancreatic) surgery, many questions still remain.

Early oral feeding after pancreatoduodenectomy

The research presented in Chapter 2-5 has repeatedly shown that early oral feeding can be considered the optimal feeding strategy after pancreatoduodenectomy. Many centers have by now adopted this strategy and several studies have demonstrated the benefits of early oral feeding within ERAS or fast-track recovery programs.[17–23] Nevertheless, the debate about whether patients after pancreatoduodenectomy should receive postoperative nutritional support is still ongoing.[24–26] Future research should therefore ideally include a high-quality, randomized controlled trial to confirm the positive impact of an early oral feeding strategy on outcomes after pancreatoduodenectomy compared with routine nasoenteral tube feeding. Such a trial was registered in the Clinical Trials registry in 2012,[27] but has not started recruiting participants yet.

Other aspects of enhanced recovery in pancreatic surgery

The introduction of an early oral feeding strategy has relieved most patients after pancreatoduodenectomy from the discomfort of a nasoenteral feeding tube. However, patients still receive a nasogastric tube during surgery for gastric decompression, which is frequently only removed one or two days after surgery, even when the output of the tube is low. Several studies have demonstrated that the nasogastric tube can safely be removed immediately after surgery, since it appears unnecessary in many cases and may even adversely impact the postoperative course.[28–33] The four studies concerning patients after pancreatoduodenectomy were small retrospective cohort studies that did not start oral intake before day two or beyond, so future prospective studies are required to determine the effect of the omission of routine nasogastric drainage within an early oral feeding strategy after pancreatoduodenectomy. In addition, several studies investigating other topics addressed in the ERAS guidelines, which are hypothesized to enhance postoperative recovery, such as avoidance of prophylactic drainage,[34] the use of wound catheters instead of epidural analgesia,[35] or restrictive fluid regimens,[36,37] are currently ongoing in the Netherlands and the USA.

Delayed gastric emptying after pancreatoduodenectomy

The research presented in this thesis has mainly focused on the treatment of patients with primary or secondary (i.e. due to other postoperative complications) delayed gastric emptying.

Several risk factors of delayed gastric emptying in patients after pancreatoduodenectomy have been identified, such as preoperative diabetes, postoperative pancreatic fistulas and other postoperative complications.[38,39] However, to date the exact pathogenesis of delayed gastric emptying, especially primary delayed gastric emptying remains unknown. A better understanding of the mechanisms causing delayed gastric emptying may enable a more focused treatment or even prevention of this frequent and costly complication.[40] These mechanisms therefore require further investigation. Remarkably few studies have been performed to investigate the effect of prokinetic agents on the incidence of delayed gastric emptying.[41] A beneficial effect of intravenous use of motilin was found in one study,[42] but following studies have failed to show the same effect. Also cisapride was shown to accelerate gastric emptying,[43] but was withdrawn from the market due to drug-related, life-threatening cardiovascular complications. The most frequently investigated prokinetic agent is prophylactic or therapeutic erythromycin, which was associated with a decrease in the incidence of delayed gastric emptying,[44–46] but was, at least in the Netherlands, never incorporated in standard postoperative management protocols. Several novel drugs are in development, but convincing evidence for their efficacy remains to be established.[47] One non-pharmacological intervention that has shown promising results in gastrointestinal motility after surgery is chewing gum.[48,49] A randomized controlled trial investigated the effects of chewing gum treatment on prolonged ileus and delayed gastric emptying after pancreatoduodenectomy, but was terminated due to a radical change in postoperative care as well as surgical technique, and therefore had insufficient power to find statistically significant differences.[50] Further studies on chewing gum after pancreatoduodenectomy are therefore required, although its impact may be more on intestinal than gastric motility.

In the past decades various alterations of the surgical technique have been investigated to reduce the incidence of delayed gastric emptying, such as pylorus preservation versus classic Whipple resection or ante- versus retrocolic enteric reconstruction, but none was eventually found to have an impact on postoperative outcomes.[51,52] Currently there is an on-going trend towards subtotal stomach-preserving (or pylorus-ring-resecting) pancreatoduodenectomy, since it may improve intraoperative and short-term postoperative outcomes, especially delayed gastric emptying, compared to pylorus-preserving pancreatoduodenectomy. However, a recent meta-analysis failed to reach statistical significance for several important outcome measures, such as length of hospital stay.[53] Future well-designed randomized controlled trials, such as the currently ongoing trial in Germany,[54] are needed.

In the past years, minimally invasive approaches, such as laparoscopic and robot-assisted surgery, have become increasingly popular, also in pancreatic surgery. Minimally invasive surgery is thought to reduce the time to functional recovery after surgery and to decrease blood loss, pain, wound infections and delayed gastric emptying rates.[55–58]

In the Netherlands we are gradually introducing laparoscopic pancreatic surgery using a structured nationwide training program followed by a randomized controlled trial. The randomized trial on laparoscopic versus open distal pancreatotectomy (LEOPARD) has recently started,[59] and will soon be followed by a randomized trial comparing laparoscopic versus open pancreatoduodenectomy (LEOPARD-2). Thus far, however, the potential benefits of the minimally invasive approach seem to be controversial and a recent series even showed significantly higher postoperative morbidity, mainly due to higher pancreatic fistula rates,[60] which is associated with an increased risk of delayed gastric emptying.[38]

Identification and management of high-risk patients

In Chapter 2 we concluded that future prospective studies should aim to preoperatively identify those patients who are at high risk of requiring postoperative nutritional support. These patients could then receive a nasoenteral feeding tube during surgery, thereby minimizing both malnutrition and patient discomfort. With that in mind, we investigated such a high-risk group in Chapter 5. Because only half of this group actually required nasoenteral feeding, we concluded that relevant pre- or intraoperative predictive factors for the need for nutritional support after pancreatoduodenectomy seem difficult to identify. Therefore, future research should be focusing on preoperative dietary interventions, such as oral nutritional supplements or enteral nutrition. Currently, evidence of a positive effect of these interventions on postoperative outcomes is lacking for patients undergoing pancreatoduodenectomy.[3,61] According to nutritional guidelines, preoperative nutritional support should be administered for at least 10-14 days even if surgery has to be delayed.[1] In patients with preoperative obstructive jaundice, however, it was previously shown that early surgery is preferred over routine preoperative biliary drainage, despite the presumed increased risk of postoperative complications.[62] On the other hand, the window for improvement of a patient's nutritional status is increasingly elongated in the current era of advancing neo-adjuvant treatment options, such as chemoradiotherapy.

Implementation of electromagnetic guided nasoenteral feeding tube placement

This thesis has also answered several questions regarding the optimal technique for postoperative feeding tube placement. In Chapter 9 we have presented a high-quality multicenter randomized controlled trial, showing that electromagnetic guided placement is non-inferior to endoscopy in terms of effectiveness and has several advantages regarding logistics and costs. This trial may therefore have laid the foundation for (inter) national implementation of this technique ad first-choice option for nasoenteral feeding tube placement. However, currently electromagnetic guided placement is usually not embedded in standard care facilities and therefore requires an implementation process. In our experience, this process includes purchasing of the electromagnetic guided

system (e.g. by a user agreement as is customary in the Netherlands) and structured training of nurses. Electromagnetic guided placement procedures are usually performed by endoscopy nurses or members of a nutrition team. If volume permits, it may also be beneficial to train (surgical) ward nurses to perform these placements, as was recently initiated in the Academic Medical Center in Amsterdam, the Netherlands. This process, which will obviously have to be assessed and evaluated, could potentially further improve logistics and reduce costs.

Nasoenteral feeding tube placement in patients after pancreatoduodenectomy

Given the relatively small and single center subgroup included in the trial presented in Chapter 9, it is difficult to draw definitive conclusions on the application of electromagnetic guided placement in the subset of patients with an altered upper gastrointestinal anatomy. Future prospective studies should investigate whether an electromagnetic guided first approach is not disadvantageous for these patients since the success rates in this group are low. The most common reason for failure is the inability to pass the pylorus and to identify the efferent jejunal limb. The latter aspect may be countered with a new technique for bedside nasoenteral feeding tube placement. This involves a disposable feeding tube with an integrated real-time 3mm camera to visually aid the placement procedure.[63] However, the application of this technique remains to be investigated, especially in surgical patients with gastroparesis, who require post-pyloric tube placement, since the tubes were designed for nasogastric placement. Presumably, also with these tubes it will remain difficult to pass the pylorus because the tube is not rigid enough. Moreover, these tubes will also be associated with high costs, as is the case with electromagnetic guided tubes and it may be difficult for nurses, especially those without endoscopic experience, to correctly distinguish the anatomical markers of the different parts of the gastrointestinal tract to ensure correct placement.

Transhepatic feeding tube placement

Finally, although the results seem promising, the feasibility and additional value of transhepatic feeding tube placement, such as described in Chapter 10, requires further investigation outside the Academic Medical Center in Amsterdam. However, the procedure requires expertise in percutaneous transhepatic biliary drainage procedures and is only beneficial over traditional enteral access routes in a small subset of patients, so its application is likely to remain limited.

Altogether, many questions remain to be investigated. Some of the questions raised in this chapter are already being investigated by the Dutch Pancreatic Cancer Group (DPCG).[64] The DPCG is a national collaborative of delegates of all specialties involved in the treatment of

patients with pancreatic cancer, including many surgeons and hence it is an ideal platform for the conduct of large multicenter randomized controlled trials. Next to clinical research, the DPCG is also involved in clinical auditing, quality of life registry, an online expert panel and a nationwide pancreatic biobank, which will facilitate future fundamental and translation research. Together, these projects will improve health care in the Netherlands and increase the knowledge on pancreatic cancer and its treatment options to which this thesis made only a small contribution.

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Appendices

NEDERLANDSE SAMENVATTING

Het onderzoek dat beschreven staat in dit proefschrift heeft een aantal vragen over postoperatieve voeding beantwoord.

Voedingsstrategieën na pancreatoduodenectomie

In eerste instantie was het ons doel om vast te stellen wat de meest optimale voedingsstrategie na een pancreatoduodenectomie is. Daarvoor hebben we de postoperatieve uitkomsten bij het gebruik van verschillende strategieën met elkaar vergeleken. De huidige voedingsrichtlijnen geven tegenstrijdige aanbevelingen over hoe patiënten na deze operatie gevoed moeten worden. Bovendien zijn deze richtlijnen allemaal gebaseerd op studies bij patiënten die abdominale chirurgie ondergingen vanwege kanker in het algemeen en niet specifiek op studies bij patiënten na pancreatoduodenectomie.[1–3]

In **Hoofdstuk 2** hebben we systematisch de beschikbare literatuur over voeding na pancreaschirurgie onderzocht. Hierbij hebben we 15 studies geïdentificeerd die in totaal 3474 patiënten beschrijven en vijf verschillende voedingsstrategieën onderzocht hebben: orale voeding, sondevoeding via een nasoenterale voedingssonde, gastrojejunostomie of jejunostomie en parenterale voeding. De opnameduur was het kortst in de groepen die orale voeding of sondevoeding via een gastrojejunostomie kregen. Ook de tijd tot de hervatting van een normaal oraal dieet was het kortst in de groep met orale voeding. Dit is een meer specifieke voedingsgerelateerde uitkomst die minder afhankelijk is van andere postoperatieve parameters dan de opnameduur. Op basis van de literatuur leek er geen bewijs te zijn dat routinematige toediening van sonde- of parenterale voeding na pancreatoduodenectomie voordelen biedt ten opzichte van orale voeding.

Hoofdstuk 3 beschrijft een retrospectieve studie in een cohort van 129 patiënten na pancreatoduodenectomie. Uit deze studie bleek dat elk van de drie onderzochte voedingsstrategieën geassocieerd is met specifieke complicaties. Nasoenterale voedingssondes luxeren (dat wil zeggen krullen op in de maag of vallen uit) bij een derde van de patiënten en jejunostomieën kunnen leiden tot een potentieel levensbedreigende strangulatie van de darm. Parenterale voeding verdubbelt het risico op infecties. Er werd geen verschil tussen de drie groepen gezien in de tijd tot hervatting van een normaal oraal dieet, het optreden van complicaties of de opnameduur.

Op basis van de bevindingen in Hoofdstuk 2 en 3 was onze conclusie dat vroege orale voeding mogelijk de voorkeursstrategie na pancreatoduodenectomie zou moeten zijn. Daarom hebben we de observationele cohort studie, beschreven in **Hoofdstuk 4**, opgezet om te evalueren of een verandering in het postoperatieve voedingsbeleid van routinematige sondevoeding naar vroege orale voeding de klinische uitkomsten verbetert. De tijd tot hervatting van een normaal oraal dieet en de opnameduur waren significant

korter in het prospectieve cohort van 51 patiënten die vroege orale voeding ontvingen vergeleken met de 51 historische controles die nasoenterale sondevoeding ontvingen. Er werd geen negatief effect van vroege orale voeding gezien op de postoperatieve morbiditeit. Hieruit concludeerden wij dat vroege orale voeding, met sondevoeding op indicatie, de voorkeursstrategie is na een pancreatoduodenectomie. De helft van de patiënten die vroege orale voeding ontving kreeg alsnog sondevoeding op indicatie, omdat zij een vertraagde maagontlediging ontwikkelden na de operatie of vanwege ernstige postoperatieve complicaties.

De hypothese dat sommige subgroepen van patiënten, die een verhoogd risico hebben op preoperatieve ondervoeding en/of postoperatieve vertraagde maagontlediging, wellicht gebaat zijn bij routinematige sondevoeding in de postoperatieve periode werd verder onderzocht in **Hoofdstuk 5**. Preoperatieve symptomen van een maaguitgangstenose (dat wil zeggen braken, slikklachten, misselijkheid, gebrek aan eetlust en postprandiale klachten) zijn in eerder onderzoek geassocieerd met een drievoudig verhoogd risico op een vertraagde maagontlediging na pancreatoduodenectomie.[4–9] Wij hebben een opeenvolgend cohort van 78 patiënten met preoperatieve symptomen van een maaguitgangstenose onderzocht om te bekijken of de klinische uitkomsten na pancreatoduodenectomie bij deze patiënten verschillen tussen vroege orale voeding en routinematige sondevoeding. De toegepaste voedingsstrategie was in deze studie afhankelijk van de standaard strategie in dat ziekenhuis op dat moment en niet van de kenmerken van de patiënt. In de totale patiëntengroep was er geen verschil in de tijd tot hervatting van een normaal oraal dieet, het optreden van complicaties en de opnameduur tussen de twee voedingsstrategieën. Bij patiënten zonder postoperatieve complicaties was vroege orale voeding echter geassocieerd met een kortere tijd tot de hervatting van een normaal oraal dieet en een kortere opnameduur. Hieruit concludeerden wij dat ook bij patiënten met preoperatieve symptomen van een maaguitgangstenose vroege orale voeding de voorkeursstrategie is na een pancreatoduodenectomie.

Nasoenterale voedingssonde plaatsing

Ongeveer de helft van de patiënten uit de studies beschreven in Hoofdstukken 4 en 5 hadden uiteindelijk een indicatie voor sondevoeding omdat zij orale voeding niet konden verdragen. Hoewel voedingssondes binnen de orale voedingsstrategie niet meer routinematig peroperatief worden achtergelaten, hebben veel patiënten postoperatief toch een sonde nodig. Deze sonde wordt dan vaak endoscopisch geplaatst door een maag-darm-lever (MDL) arts. Blinde plaatsing is namelijk vaak niet succesvol en kan bovendien leiden tot complicaties door abusievelijke plaatsing in de luchtwegen.[10,11] Plaatsing onder doorlichting (fluoroscopisch) door radiologen is wel mogelijk, maar niet gebruikelijk in Nederland. Een endoscopische plaatsing is echter belastend voor zowel patiënten als

zorgverleners. Bovendien is in de afgelopen jaren de druk op endoscopieafdeling sterk toegenomen (onder andere door het bevolkingsonderzoek naar colonkanker).[12] Om deze reden hebben wij onderzocht of deze druk mogelijk verlicht kan worden door de taak van het plaatsen van nasoenterale voedingssondes te verplaatsen van MDL-artsen naar verpleegkundigen met het gebruik van een elektromagnetisch geleid plaatsingssysteem.
In **Hoofdstuk 6** hebben we systematisch de literatuur onderzocht over elektromagnetisch geleide, endoscopische en fluoroscopische nasoenterale plaatsing van voedingssondes. In totaal werden 28 studies geïncludeerd met in totaal 4056 patiënten die een plaatsing van een nasoenterale voedingssonde hadden ondergaan. De succespercentages van de drie verschillende plaatsingsprocedures waren onderling niet verschillend. Ook het aantal patiënten dat een herplaatsing moest ondergaan, wat een meer representatieve uitkomstmaat is voor de effectiviteit van de techniek, was niet verschillend tussen de drie groepen. De 16 studies die deze uitkomst rapporteerden gebruikten echter verschillende definities voor een herplaatsing. Proceduregerelateerde complicaties kwamen weinig voor bij alle drie de technieken. Sondegerelateerde complicaties betroffen voornamelijk de bekende complicaties van voedingssondes, namelijk luxatie en verstopping. Al met al leek elektromagnetisch geleide plaatsing even veilig en effectief als endoscopische of fluoroscopische plaatsing, maar was er wel sprake van een grote heterogeniteit tussen de studies. Bovendien waren de meeste studies uitgevoerd onder patiënten op de Intensive Care en had slechts één studie een rechtstreekse vergelijking gemaakt tussen elektromagnetisch geleide en endoscopische plaatsing.
In **Hoofdstuk 7** hebben we daarom elektromagnetisch geleide en endoscopische nasoenterale sondeplaatsing retrospectief met elkaar vergeleken in een groep van 249 volwassen patiënten die waren opgenomen op een gastro-intestinale chirurgische afdeling. Over het algemeen waren de succespercentages van beide technieken vergelijkbaar, behalve voor de kleine groep patiënten met een gewijzigde anatomie van de bovenste tractus digestivus (na een eerdere operatie). Binnen die groep lagen de succespercentages voor elektromagnetisch geleide plaatsing aanzienlijk lager dan bij endoscopie. Er werden geen significante verschillen gezien in sondegerelateerde complicaties. Daarom concludeerden wij dat elektromagnetisch geleide plaatsing aan het bed van de patiënt niet verschilt van endoscopische plaatsing wat betreft haalbaarheid en veiligheid bij patiënten met een normale anatomie. Aanvullend onderzoek naar de groep patiënten met een gewijzigde anatomie was echter noodzakelijk, omdat de aanwezigheid daarvan tot dusver werd beschouwd als een relatieve contra-indicatie voor elektromagnetisch geleide plaatsing.
Om het vermeende toegenomen risico op technisch falen en complicaties in de groep patiënten met een gewijzigde anatomie te onderzoeken, hebben we de prospectieve pilot studie onder 53 patiënten na pancreatoduodenectomie opgezet, die staat beschreven in

Hoofdstuk 8. De initiële plaatsingsprocedure was succesvol bij 58% van de 36 patiënten die een elektromagnetisch geleide plaatsing ondergingen, maar voor de 17 endoscopische procedures was het succespercentage eveneens slechts 53%. Er traden geen complicaties op tijdens de procedures en de sondegerelateerde complicaties waren voor beide technieken vergelijkbaar met de complicaties bij patiënten met een ongewijzigde anatomie. Alle voorgaande studies, inclusief degene die door ons zijn uitgevoerd, richtten zich voornamelijk op het technische succes van de plaatsingsprocedure. Hierbij werd niet gekeken naar de vermeende voordelen van elektromagnetisch geleide plaatsing zoals logistiek, patiëntgerapporteerde uitkomsten en kosten. **Hoofdstuk 9** beschrijft de CORE trial, een multicenter gerandomiseerde trial die als doel had om aan te tonen dat elektromagnetisch geleide sondeplaatsing niet inferieur is aan endoscopische plaatsing wat betreft effectiviteit bij chirurgische patiënten. Ook was het doel om de vermeende voordelen van elektromagnetisch geleide sondeplaatsing te objectiveren. Herplaatsing (bijvoorbeeld na een mislukte primaire plaatsing, luxatie of verstopping van de sonde) was nodig bij 36% van de patiënten in de elektromagnetisch geleide groep en bij 42% in de endoscopische groep, waarmee werd vastgesteld dat elektromagnetisch geleide plaatsing niet inferieur was aan endoscopie. Er waren geen significante verschillen tussen beide technieken in het succes van de procedure en het optreden van complicaties. Hoewel patiënten meer ongemak ervoeren tijdens elektromagnetisch geleide procedures, werd deze techniek sterker door hen aanbevolen. Bovendien had de elektromagnetisch geleide techniek logistieke voordelen ten opzichte van endoscopie en waren de kosten lager. Op basis van deze bevindingen concludeerden wij dat elektromagnetisch geleide plaatsing beschouwd kan worden als de voorkeurstechniek voor de plaatsing van nasoenterale voedingssondes.

Hoewel elektromagnetisch geleide sondeplaatsing een aantal voordelen biedt ten opzichte van endoscopie, blijft er een groep patiënten die langdurig sondevoeding moet krijgen. Zij hebben daardoor te lijden onder herhaaldelijke sondeplaatsingsprocedures en ongemak in de neus door de langdurige aanwezigheid van een sonde. Daarom wordt voor patiënten die langdurig sondevoeding moeten krijgen vaak aanbevolen om een jejunostomie of gastrojejunostomie te plaatsen. Deze sondes kunnen echter leiden tot complicaties,[13–16] zoals wij ook hebben laten zien in Hoofdstukken 2 en 3. In **Hoofdstuk 10** presenteren we een alternatieve techniek voor langdurige enterale toegang langs een reeds aanwezige percutane transhepatische galdrain. In deze retrospectieve cohort studie was deze techniek succesvol in 95% van de 40 initiële procedures en leidde enkel tot reeds bekende complicaties van voedingssondes (bijvoorbeeld luxatie of verstopping) en percutane transhepatische galdrains (bijvoorbeeld cholangitis, gallekkage en bloeding). Transhepatische voedingssondeplaatsing kan daarom overwogen worden als alternatief in een selecte groep patiënten die zowel een indicatie hebben voor langdurige

enterale toegang als voor galdrainage (bijvoorbeeld door een duodenumperforatie, voor perioperatieve galwegdecompressie dan wel bijvoeding of in verband met chirurgische complicaties).

Tabel 1 Samenvatting van de onderzoeksvragen en belangrijkste bevindingen van dit proefschrift

Hoofdstuk	
2	*Wat is de optimale voedingsstrategie na pancreatoduodenectomie wat betreft effectiviteit en veiligheid volgens de beschikbare literatuur?*
	Er is geen bewijs dat routinematige toediening van sonde- of parenterale voeding na pancreatoduodenectomie voordelen biedt ten opzichte van orale voeding. Vroege orale voeding lijkt de strategie van eerste keuze.
3	*Wat is het verschil in de effectiviteit en voedingsgerelateerde complicaties tussen sondevoeding via een nasoenterale sonde, sondevoeding via een jejunostomie of parenterale voeding na pancreatoduodenectomie?*
	Geen van de geanalyseerde strategieën was superieur wat betreft de tijd tot hervatting van een normaal oraal dieet, morbiditeit en mortaliteit. Elk van de strategieën was geassocieerd met specifieke complicaties. Nasoenterale sondes luxeren bij een derde van de patiënten, jejunostomieën kunnen, hoewel zeldzaam, leiden tot strangulatie van de darm en parenterale voeding leidt tot een verdubbeld risico op infecties.
4	*Leidt een wijziging van de routine voedingsstrategie van nasoenterale sondevoeding naar vroege orale voeding tot een verbetering van de postoperatieve uitkomsten na pancreatoduodenectomie?*
	De introductie van een vroege orale voedingsstrategie na pancreatoduodenectomie reduceert de tijd tot hervatting van een normaal oraal dieet en opnameduur, zonder negatieve uitwerking op de postoperatieve morbiditeit.
5	*Wat is het verschil in postoperatieve uitkomsten tussen vroege orale voeding en routinematige postoperatieve sondevoeding bij patiënten met preoperatieve symptomen van een maaguitgangstenose die een pancreatoduodenectomie ondergaan?*
	De klinische uitkomsten verschillen niet tussen postoperatieve vroege orale voeding en routinematige sondevoeding. Ook bij patiënten met preoperatieve symptomen van een maaguitgangstenose kan vroege orale voeding dus beschouwd worden als de voorkeursstrategie na pancreatoduodenectomie.
6	*Hoe effectief en veilig zijn elektromagnetisch geleide, endoscopische en fluoroscopische nasoenterale voedingssonde plaatsing bij volwassenen volgens de beschikbare literatuur?*
	Elektromagnetisch geleide plaatsing van een nasoenterale voedingssonde blijkt even effectief en veilig als endoscopie en fluoroscopie en verdient daarom waarschijnlijk de voorkeur boven de conventionele, duurdere procedures door MDL-artsen of radiologen. Gerandomiseerde studies ontbreken echter.

Hoofdstuk	
7	*Wat is het verschil in succespercentage tussen elektromagnetisch geleide en endoscopische plaatsing van nasoenterale voedingssondes bij chirurgische patiënten?*
	Elektromagnetisch geleide plaatsing van nasoenterale voedingssondes door gespecialiseerde verpleegkundigen aan het bed van de patiënt verschilt niet van endoscopische plaatsing door MDL-artsen wat betreft haalbaarheid en veiligheid bij chirurgische patiënten met een normale anatomie van de bovenste tractus digestivus.
8	*Bij patiënten die een pancreatoduodenectomie hebben ondergaan, hoe haalbaar en veilig is elektromagnetisch geleide voedingssondeplaatsing dan vergeleken met endoscopische plaatsing?*
	Elektromagnetisch geleide plaatsing van een nasoenterale voedingssonde was even succesvol en veilig als endoscopische plaatsing bij patiënten die een pancreatoduodenectomie hebben ondergaan.
9	*Is elektromagnetisch geleide plaatsing van nasoenterale voedingssondes door verpleegkundigen minstens net zo effectief als endoscopische plaatsing door MDL-artsen bij chirurgische patiënten die een nasoenterale voedingssonde nodig hebben?*
	Elektromagnetisch geleide plaatsing van nasoenterale voedingssondes door getrainde verpleegkundigen aan het bed van de patiënt is niet inferieur wat betreft de noodzaak tot herplaatsing van de sonde vergeleken met endoscopische plaatsing door MDL-artsen. Omdat elektromagnetisch geleide plaatsing logistieke voordelen heeft en de kosten lager zijn, kan dit beschouwd worden als de techniek van eerste keuze voor het plaatsen van nasoenterale voedingssondes.
10	*Is percutane transhepatische voedingssonde plaatsing haalbaar bij patiënten die zowel een indicatie hebben voor langdurige enterale toegang als voor galdrainage?*
	Percutane transhepatische voedingssonde plaatsing langs een reeds aanwezige percutane transhepatische galdrain was veilig en succesvol en kan worden overwogen in de selecte groep patiënten die zowel een indicatie hebben voor langdurige enterale toegang als voor galdrainage.

TOEKOMSTPERSPECTIEVEN

Het onderzoek dat beschreven staat in dit proefschrift heeft een aantal belangrijke vragen beantwoord over het perioperatieve beleid bij patiënten die gastro-intestinale (pancreas) chirurgie ondergaan. Er blijven echter nog veel vragen onbeantwoord.

Vroege orale voeding na pancreaschirurgie

Het onderzoek in Hoofdstukken 2 tot 5 heeft herhaaldelijk laten zien dat vroege orale voeding beschouwd kan worden als de voorkeursstrategie na een pancreatoduodenectomie. In veel ziekenhuizen is dit beleid momenteel geïmplementeerd en meerdere studies hebben de voordelen van vroege orale voeding binnen enhanced recovery after surgery (ERAS) of fast-track programma's laten zien.[17–23] Desondanks is het debat over de noodzaak voor ondersteunende voeding na pancreaschirurgie nog steeds gaande.[24–26] Idealiter zou het positieve effect van vroege orale voeding vergeleken met routinematige sondevoeding bevestigd worden in een gerandomiseerde studie. Een dergelijke trial is in 2012 geregistreerd in het Clinical Trials register,[27] maar tot op heden nog niet gestart met de inclusie van patiënten.

Andere aspecten van het postoperatieve herstel na pancreaschirurgie

De introductie van een vroege orale voedingsstrategie heeft de meeste patiënten na pancreatoduodenectomie verlost van het ongemak van een nasoenterale voedingssonde. Deze patiënten krijgen echter nog steeds een maagsonde gedurende de operatie, die vaak pas na een aantal dagen weer verwijderd wordt, zelfs als de drainproductie laag is. Een aantal studies hebben eerder al laten zien dat het veilig is om de maagsonde direct na de operatie te verwijderen.[28–33] De maagsonde is vaak niet nodig en kan zelfs een negatieve invloed hebben op het postoperatieve herstel. De vier studies over patiënten na pancreaschirurgie waren echter kleine retrospectieve cohort studies, die niet eerder dan de tweede postoperatieve dag begonnen met orale voeding. Toekomstige studies zouden zich dus moeten richten op de vraag wat het effect is van het achterwege laten van een postoperatieve maagsonde binnen een vroege orale voedingsstrategie na pancreatoduodenectomie. In aanvulling daarop zijn momenteel verschillende studies gaande in Nederland en de Verenigde Staten naar andere aspecten van de ERAS richtlijn, waarvan gesuggereerd wordt dat deze het postoperatieve herstel bespoedigen (zoals het vermijden van drains,[34] gebruik van wondkatheters in plaats van epidurale anesthesie, [35] en beperkte vochttoediening[36,37]).

Vertraagde maagontlediging na pancreatoduodenectomie

Het onderzoek beschreven in dit proefschrift heeft zich met name gericht op de behandeling

van patiënten met een primaire of secundaire (bijvoorbeeld door andere postoperatieve complicaties) vertraagde maagontlediging. Er zijn verschillende risicofactoren voor de ontwikkeling van een vertraagde maagontlediging bekend, zoals preoperatieve diabetes, postoperatieve pancreasfistels en postoperatieve complicaties in het algemeen.[38,39] Tot op heden is de exacte pathogenese van een vertraagde maagontlediging, met name de primaire variant, echter onbekend. Een beter begrip van het exacte mechanisme achter dit probleem zou een meer gerichte behandeling en mogelijk zelfs preventie van deze veel voorkomende en dure complicatie[40] mogelijk maken en behoeft dus nader onderzoek. Er zijn tot dusver opvallend weinig studies gedaan naar het effect van prokinetica op de incidentie van een vertraagde maagontlediging na pancreatoduodenectomie.[41] Eén studie heeft een positief effect aangetoond van domperidon,[42] maar daaropvolgende studies hebben dit effect niet kunnen bevestigen. Ook cisapride liet een positief effect op de maagontlediging zien,[43] maar is uit de handel genomen vanwege de cardiovasculaire bijwerkingen. Het meest frequent onderzochte prokineticum is profylactische dan wel therapeutische erytromycine. Hoewel is aangetoond dat toediening van erytromycine leidt tot een verlaagde incidentie van een vertraagde maagontlediging,[44–46] is de toepassing daarvan, in ieder geval in Nederland, nooit opgenomen in de postoperatieve protocollen. Er zijn een aantal nieuwe producten in ontwikkeling, maar overtuigend bewijs voor hun effectiviteit moet nog volgen.[47] Een niet-farmacologische interventie met mogelijk positieve effecten op de gastro-intestinale motiliteit is kauwgom.[48,49] Een gerandomiseerde trial naar het effect van kauwgom op het optreden van een ileus en/of vertraagde maagontlediging na pancreatoduodenectomie werd vroegtijdig beëindigd vanwege een radicale wijziging van het postoperatieve beleid en de chirurgische techniek, waardoor de studie onvoldoende power had om statistisch significante verschillen aan te tonen.[50] Nieuwe gerandomiseerde interventiestudies naar de effecten van kauwgom na pancreaschirurgie zijn daarom nodig, hoewel het mogelijk meer invloed heeft op de intestinale motiliteit dan op de maagontlediging.

In de afgelopen decennia zijn diverse variaties op de chirurgische techniek onderzocht om de incidentie van een vertraagde maagontlediging na pancreatoduodenectomie te verminderen, waaronder sparen van de pylorus versus klassieke Whipple resectie en ante- versus retrocolische reconstructie. Geen van deze technieken heeft echter uiteindelijk een bewezen effect op de postoperatieve uitkomsten.[51,52] Momenteel wordt in toenemende mate een subtotale maagsparende ('pylorus-ring resecting') pancreatoduodenectomie uitgevoerd. Vergeleken met pylorussparend opereren verbetert dit mogelijk de peroperatieve en korte termijn postoperatieve uitkomsten, met name het optreden van een vertraagde maagontlediging. Een recente meta-analyse liet echter geen statistisch significante verschillen zien voor diverse belangrijke uitkomstmaten zoals opnameduur.[53] Een goed opgezette gerandomiseerde studie, zoals momenteel gaande is in Duitsland,[54] is dus nodig om te onderzoeken of deze techniek daadwerkelijk de verwachte voordelen biedt.

In de afgelopen jaren hebben minimaal invasieve procedures, zoals laparoscopie en robotchirurgie, in toenemende mate aan populariteit gewonnen, ook binnen de pancreaschirurgie. De gedachte is dat minimaal invasieve chirurgie de tijd tot functioneel herstel verkort en leidt tot een reductie in bloedverlies, pijn, wondinfecties en het optreden van een vertraagde maagontlediging.[55–58] In Nederland wordt laparoscopische pancreaschirurgie momenteel stapsgewijs ingevoerd door middel van een gestructureerd trainingsprogramma gevolgd door een gerandomiseerde studie. Deze studie over laparoscopische versus open pancreasstaartresecties (LEOPARD) is recent gestart.[59] De trial voor laparoscopische versus open pancreatoduodenectomieën zal snel volgen (LEOPARD-2). Tot dusver lijken de potentiële voordelen van een minimaal invasieve benadering echter controversieel. Een recente studie liet een significant hogere postoperatieve morbiditeit zien, met name door een toename in pancreasfistels,[60] waarvan eerder al is aangetoond dat dit leidt tot een verhoogd risico op een vertraagde maagontlediging.[38]

Identificatie en behandeling van hoog risico patiënten

In Hoofdstuk 2 hebben we geconcludeerd dat er studies nodig zijn om in de preoperatieve fase die patiënten te kunnen identificeren die postoperatief ondersteunende voeding nodig hebben. Deze patiënten zouden dan peroperatief al een sonde kunnen krijgen, waardoor zowel het risico op ondervoeding als het ongemak voor de patiënt verminderd wordt. Met die gedachte hebben we in Hoofdstuk 5 een dergelijke hoog risico groep onderzocht. Omdat echter slechts de helft van deze patiënten uiteindelijk een sonde nodig bleek te hebben, kwamen wij tot de conclusie dat het lastig is om goede pre- of peroperatieve risicofactoren voor de noodzaak voor postoperatieve bijvoeding na een pancreatoduodenectomie te identificeren. Daarom zou toekomstig onderzoek zich wellicht meer moeten richten op preoperatieve voedingsinterventies bij hoog risico patiënten, zoals orale bijvoeding of sondevoeding. Momenteel is er namelijk geen bewijs dat deze interventies een positief effect hebben op de postoperatieve uitkomsten van patiënten die een pancreatoduodenectomie ondergaan.[3,61] Volgens de voedingsrichtlijnen moet preoperatieve bijvoeding gedurende minstens 10-14 dagen gegeven worden, zelfs als de operatie daardoor uitgesteld moet worden.[1] Bij patiënten met preoperatieve obstructieve icterus is echter in eerder onderzoek al eens aangetoond dat vroege chirurgie de voorkeur verdient boven preoperatieve galdrainage, ondanks het vermeende toegenomen risico op postoperatieve complicaties door de icterus.[62] Anderzijds wordt het tijdsframe waarbinnen peroperatieve interventies plaats kunnen vinden steeds groter in het huidige tijdperk van toenemende neo-adjuvante behandelingen.

Implementatie van elektromagnetisch geleide nasoenterale voedingssonde plaatsing

In dit proefschrift zijn ook een aantal vragen over de optimale techniek voor het postoperatief plaatsen van een nasoenterale voedingssonde beantwoord. In Hoofdstuk 9 hebben we een multicenter gerandomiseerde studie gepresenteerd die heeft aangetoond dat elektromagnetisch geleide plaatsing niet inferieur is aan endoscopie wat betreft effectiviteit en voordelen biedt op het gebied van logistiek en kosten. Deze trial kan daarom als basis dienen voor de (inter)nationale implementatie van deze techniek als voorkeurstechniek voor het plaatsen van nasoenterale voedingssondes. In de meeste ziekenhuizen is elektromagnetisch geleide plaatsing momenteel echter nog niet ingebed in de standaard zorg, dus dit vereist een implementatieproces. Onze ervaring is dat dit proces de aanschaf van het systeem (bijvoorbeeld in de vorm van een gebruikersovereenkomst met de fabrikant zoals gebruikelijk is in Nederland) en een gestructureerde training van verpleegkundigen of leden van een voedingsteam omvat. Als het volume het toelaat kan het mogelijk ook voordelig zijn om afdelingsverpleegkundigen te trainen in de uitvoer van deze procedure, zoals recent geïnitieerd is in het Academisch Medisch Centrum te Amsterdam. Dit proces, wat natuurlijk geëvalueerd moet worden, kan potentieel leiden tot een verdere reductie van logistiek en kosten.

Nasoenterale voedingssonde plaatsing bij patiënten na een pancreatoduodenectomie

Gezien de relatief kleine subgroep patiënten met een gewijzigde anatomie van de bovenste tractus digestivus in de trial in Hoofdstuk 9, is het niet goed mogelijk om harde conclusies te trekken over de toepassing van elektromagnetisch geleide plaatsing bij deze subgroep patiënten. Toekomstige studies moeten uitwijzen of een strategie waarin eerst elektromagnetisch geleide plaatsing geprobeerd wordt, en pas bij falen wordt overgegaan op endoscopie, niet nadelig is voor deze patiënten aangezien het succespercentage van de plaatsingsprocedures laag was. De meest voorkomende reden van niet slagen van de procedure was het feit dat de sonde niet voorbij de pylorus te manoeuvreren was of dat de afvoerende lis niet geïdentificeerd kon worden. Dat laatste probleem kan mogelijk verholpen worden met het gebruik van een ander systeem dat is ontwikkeld voor het plaatsen van voedingssondes aan het bed van een patiënt. Dit betreft een sonde voor eenmalig gebruik met een geïntegreerde 3-mm camera.[63] De toepassing van deze techniek moet echter nog onderzocht worden, met name bij patiënten met een gastroparese die een post-pylorische sonde moeten krijgen, aangezien de sondes zijn ontwikkeld voor plaatsing in de maag. Waarschijnlijk zal het ook met deze sondes moeizaam zijn om deze voorbij de pylorus te manoeuvreren omdat deze niet stug genoeg zijn. Bovendien zijn ook deze sondes kostbaar in gebruik, net als elektromagnetisch geleide sondes. Ook kan het voor verpleegkundigen, met name degenen zonder endoscopische ervaring, moeizaam zijn om onderscheid te maken tussen de verschillende delen van de tractus digestivus op basis van de videobeelden.

Transhepatische voedingssonde plaatsing

Hoewel de resultaten zoals gepresenteerd in Hoofdstuk 10 veelbelovend waren, moet ook de toepassing van transhepatische voedingssondes verder onderzocht worden buiten het Academisch Medisch Centrum te Amsterdam. De procedure vereist echter ervaring met het plaatsen van percutane transhepatische galdrains en biedt alleen voordelen ten opzichte van de traditionele routes voor de kleine subgroep patiënten die zowel een indicatie hebben voor langdurige enterale toegang als voor galdrainage, waardoor de toepasbaarheid van deze techniek waarschijnlijk beperkt zal blijven.

Al met al blijven dus veel vragen onbeantwoord. Een aantal van deze vragen wordt momenteel onderzocht door de Dutch Pancretic Cancer Group (DPCG). De DPCG is een nationale werkgroep waarin alle specialismen, die betrokken zijn bij de behandeling van patiënten met pancreaskanker, vertegenwoordigd zijn, waaronder veel chirurgen. Daarmee is de DPCG een ideaal platform voor de opzet en uitvoer van grote multicenter gerandomiseerde studies. Naast klinische studies richt de DPCG zich ook op auditing, kwaliteit-van-leven registratie, een online expertpanel en een nationale pancreasbiobank die toekomstig basaal en translationeel onderzoek kan faciliteren. Samen zullen deze projecten de gezondheidszorg in Nederland verbeteren, leiden tot een bevordering van de kennis over pancreaskanker en daarmee de behandeling van patiënten met pancreaskanker, waaraan dit proefschrift een kleine bijdrage heeft geleverd, verder optimaliseren.

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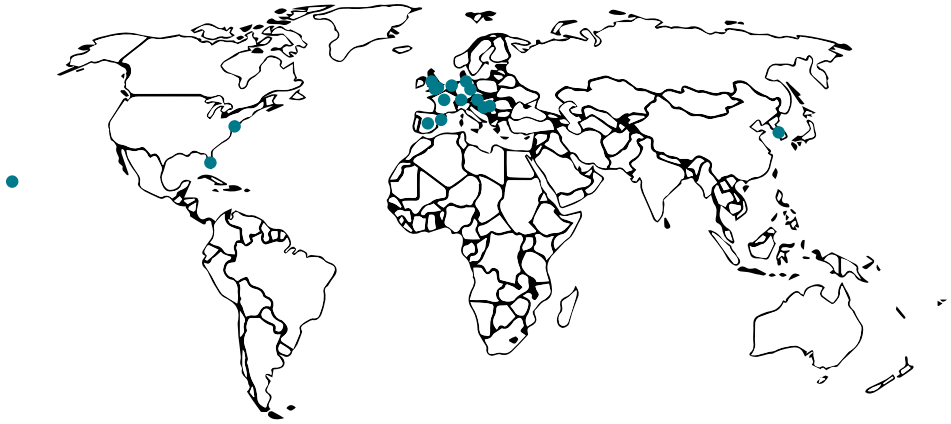

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LIST OF PUBLICATIONS

Gerritsen A, de Rooij T, Dijkgraaf MG, Busch OR, Bergman JJ, Ubbink DT, van Duijvendijk P, Erkelens GW, Klos M, Kruyt PM, Bac DJ, Rosman C, Tan AC, Molenaar IQ, Monkelbaan JF, Mathus-Vliegen EM, Besselink MG. Electromagnetic guided bedside placement of nasoenteral feeding tubes by nurses versus endoscopic placement by gastroenterologists (CORE): a multicenter, randomized, non-inferiority trial. Submitted

Gerritsen A, Damstra J, van Lienden KP, Busch OR, van Gulik TM, Boermeester MA, Laméris JS, van Delden OM, Besselink MG. Percutaneous transhepatic feeding tube placement: a single-center experience in 40 patients. Submitted.

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CURRICULUM VITAE

Arjanne (Arja) Gerritsen was born on August 27th 1986 in Amersfoort, the Netherlands. Until the age of 11, she lived in Nijkerk after which she moved to Beltrum. She graduated from secondary school (Gymnasium) at the Scholengemeenschap Manianum in Groenlo in 2004. In the same year she started medical school at Utrecht University. After her third year, she interrupted her studies for one year to fulfill a full-time position in the board of the Medical Students Association "Sams" in Utrecht. In 2011 she graduated from medical school and started working at the department of surgery of the St. Antonius Hospital in Nieuwegein (Dr. P.M.N.Y.H Go).

During the final stages of medical school she already started her research on nutrition after pancreatic surgery. In 2012 she started as a full time PhD student for the Dutch Pancreatic Cancer Group at both the University Medical Center in Utrecht (Prof.dr. I.H.M. Borel Rinkes and Dr. I.Q. Molenaar) and the Academic Medical Center in Amsterdam (Prof.dr. O.R.C. Busch and Dr. M.G.H. Besselink). Besides the work presented in this thesis, she also coordinated several studies on preoperative identification of benign pancreatic diseases and patient-reported outcomes in pancreatic cancer. She was also responsible for the establishment of the Dutch Pancreatic Biobank that will facilitate future research on pancreatic cancer and chronic pancreatitis. In 2015 she started working at the department of surgery of the Gelre Hospital in Apeldoorn (Dr. P. van Duijvendijk).