Clinical issues in endoscopic interventions for pancreatico-biliary disorders

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Contents

Chapter 1

General introduction

In the Netherlands, yearly approximately 2100 patients are diagnosed with gastric cancer, 1500 with pancreatic cancer, 400 with hepatobiliary cancer and 90 with duodenal cancer.[1] The median survival of these patients with locally advanced unresectable disease is 8-12 months and only 3-6 months for those with metastatic disease at presentation.[2] Gastric outlet obstruction (GOO) is a common symptom in these patients and it has been found that 10-20% of patients with pancreatic cancer develop GOO.[3–5] GOO causes nausea, malnutrition and dehydration, resulting in a poor clinical condition at presentation.[5–7] Therefore, palliative treatment of GOO is mandatory as the clinical condition of these patients deteriorates rapidly, with consequently a short survival if left untreated. The aim of palliative treatment is to re-establish oral food intake and stabilize or even improve quality of life of these patients.

The main treatment modality for malignant GOO used to be gastrojejunostomy (GJJ). GJJ is associated with good functional outcome and relief of symptoms in most patients. Nevertheless, this treatment is associated with significant morbidity (13-55%) and mortality (2-36%).[5,8–11] More recently, endoscopic placement of metal stents in the duodenum has been introduced to treat patients with GOO. Self-expanding stents are already successfully applied at other sites of the gastrointestinal tract, for example in the palliative treatment of dysphagia from esophageal cancer.[12] Duodenal stents have been suggested to be a less invasive palliative treatment compared to GJJ, although stent placement has been associated with complications on the long term.[3,5] In addition, stent placement in the distal part of the duodenum may be difficult using a therapeutic endoscope, because of the short endoscope length and shaft flexibility which may cause looping of the scope in the stomach. The use of a colonoscope may overcome these problems.[13–16] Both treatments (stent placement and gastrojejunostomy) are frequently used for the palliation of GOO. It is however unclear which palliative treatment should be preferred in individual patients.

Endoscopic retrograde cholangiopancreaticography (ERCP) is a common procedure for pancreatico-biliary disorders. This procedure is however associated with morbidity in 5-10% of patients. Most common complications include pancreatitis (1-5%), cholangitis (1-5%), perforation (1-2%) and hemorrhage (1%).[17–19] Several studies have investigated possible risk factors for post-ERCP complications. The risk of post-ERCP complications depends on patient- and treatment-related characteristics, such as history of pancreatitis, female gender and younger age.[20–23] However, the relative contribution of these characteristics to morbidity and mortality after ERCP is unknown. Identification of risk factors for post-ERCP complications is of value for the recognition of high-risk patient groups. In addition, it will also help in detecting low-risk patient groups who could safely undergo an outpatient ERCP.

In many institutions, patients are admitted for an overnight observation to detect complications after ERCP. It has been suggested that ERCP can be performed on an outpatient basis in at least a subgroup of patients. As most complications occur within 2-4 hours, same-day discharge could be safe when a selective policy is used.[24] In contrast to hemorrhage and perforation, which are most often already detected during ERCP, the development of pancreatitis and cholangitis will usually take some more time after ERCP. Signs and symptoms suggesting pancreatitis or cholangitis are fever, severe pain, and increased levels of bilirubin and amylase, occurring within 24 hours after ERCP. A prognostic model that predicts the risk of pancreatitis and cholangitis, and may help predicting whether early discharge after ERCP is safe, is not available.

Aim of this thesis

The aim of this thesis is to compare stent placement with GJJ as palliative treatment in patients with GOO, with respect to medical effects (food intake, complications and survival), quality of life and costs. In addition, possible risk factors for (specific) post-ERCP complications are examined and a prognostic model that predicts the possibility of early discharge after ERCP is evaluated.

Outline of this thesis

In chapter 2, a literature overview is presented that compares stent placement with gastrojejunostomy in patients with GOO. In chapter 3, stent placement and GJJ are compared in a retrospective patient population. Chapter 4 describes the results of a multicenter randomized study in which stent placement and gastrojejunostomy are compared with regard to medical effects (food intake, complications and survival), quality of life and costs. Chapter 5 highlights the main problems of duodenal stent placement in the distal part of the duodenum or proximal jejunum, using a therapeutic gastroscope. In chapter 6 a literature overview is presented of outpatient ERCP. Chapter 7 describes the most important risk factors for post-ERCP complications. Chapter 8 describes a prognostic model that may help identifying patients who are eligible for early discharge after ERCP. Chapter 9 provides an overview of clinical issues regarding cystic neoplasms of the pancreas. In chapter 10, the results described in this thesis are summarized and discussed.

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Part I

Palliative treatment of malignant gastric outlet obstruction

Chapter 2

Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review

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Abstract

Background: Gastrojejunostomy (GJJ) is the most commonly used palliative treatment modality for malignant gastric outlet obstruction. Recently, stent placement has been introduced as an alternative treatment. We reviewed the available literature on stent placement and GJJ for gastric outlet obstruction, with regard to medical effects and costs.

Methods: A systematic review of the literature was performed by searching PubMed for the period January 1996 and January 2006. A total of 44 publications on GJJ and stents was identified and reported results on medical effects and costs were pooled and evaluated. Results from randomized and comparative studies were used for calculating odds ratios (OR) to compare differences between the two treatment modalities.

Results: In 2 randomized trials, stent placement was compared with GJJ (with 27 and 18 patients in each trial). In 6 comparative studies, stent placement was compared with GJJ. Thirty-six series evaluated either stent placement or GJJ. A total of 1046 patients received a duodenal stent and 297 patients underwent GJJ. No differences between stent placement and gastrojejunostomy were found in technical success (96% vs. 100%), early and late major complications (7% vs. 6% and 18% vs. 17%, respectively) and persisting symptoms (8% vs. 9%). Initial clinical success was higher after stent placement (89% vs. 72%). Minor complications were less frequently seen after stent placement in the patient series (9% vs. 33%), however the pooled analysis showed no differences (OR: 0.75, p=0.8). Recurrent obstructive symptoms were more common after stent placement (18% vs. 1%). Hospital stay was prolonged after GJJ compared to stent placement (13 days vs. 7 days). The mean survival was 105 days after stent placement and 164 days after GJJ.

Conclusion: These results suggest that stent placement may be associated with more favorable results in patients with a relatively short life expectancy, while GJJ is preferable in patients with a more prolonged prognosis. The paucity of evidence from large randomized trials may however have influenced the results and therefore a trial of sufficient size is needed to determine which palliative treatment modality is optimal in (sub)groups of patients with malignant gastric outlet obstruction.

Background

Gastric Outlet Obstruction (GOO) is a common symptom in patients with cancer of the distal stomach, duodenum and pancreas. The incidence of pancreatic cancer is 7.1 per 100,000 people of which approximately 15-20% patients will develop GOO.[1–4] Other causes are periampullary carcinoma, lymphoma and metastases to the duodenum or proximal jejunum.[1,3–5] Clinical symptoms of GOO include vomiting, nausea, malnutrition and dehydration. Most patients with GOO are therefore in a poor clinical condition at presentation and have a short life expectancy if left untreated.[3,6,7]

Traditionally, open gastrojejunostomy (GJJ) has been the standard palliative treatment in these patients. Open GJJ is associated with a good functional outcome and relieves symptoms in almost all patients. Nevertheless, early major complications and mortality have been reported to be substantial.[3,8,9] Most patients have delayed gastric emptying, which is defined as the inability to tolerate fluids for 8 days or more after treatment, which often causes a prolonged hospital stay.[10] In recent years, laparoscopic GJJ has been introduced as an alternative to open GJJ to relieve symptoms of malignant GOO. Laparoscopic GJJ has been reported to be less invasive and to be associated with a faster recovery compared to open GJJ, however mortality and morbidity of the procedure remain high.[3,6,11,12]

Palliative stent placement for GOO was first reported in the early 1990s.[13] Stents have already extensively been used at other sites of the gastrointestinal tract, for example for palliation of dysphagia from esophageal cancer.[14,15] Stent placement for GOO has been suggested to be less invasive with a faster relief of symptoms compared to open or laparoscopic GJJ. As a consequence, hospital stay should be shorter in the majority of patients with many of them being able to eat soft solids after 1-4 days. Technical and clinical success rates have been reported to be high and mortality related to the procedure is rare after stent placement.[16] A disadvantage of stent placement is however the high rate of late major complications caused by stent migration and occlusion.[1,3]

Limited data are currently available comparing stent placement and GJJ. In this study, we reviewed the available literature on stent placement and GJJ with respect to technical and clinical success, complications, hospital stay, survival and procedure-related costs.

Methods

A systematic review of the published literature was performed by searching PubMed for the period January 1996 until December 2005, combining the following search

terms: gastric outlet obstruction, duodenum, stent, gastrojejunostomy, surgical bypass and gastroenterostomy. A total of 166 studies were found using these search terms, of which 58 studies reported results on technical success, clinical success, complications, hospital stay, survival and costs for both treatment modalities. Fourteen publications were excluded for one or more of the following criteria: single case reports, abstracts, one of these treatments used in combination with a curative treatment modality or use of the same data in more than 1 article. In total, 44 studies were included (Table 1).

Definitions

For this review, we used the following definitions:

- **Technical success**: Adequate positioning and deployment of the stent or technical feasibility to perform a GJJ.
- **Clinical success**: Relief of symptoms and/or improvement of oral intake.
- **Major complications**: Life-threatening or severe complications such as perforation, stent migration, hemorrhage, fever, jaundice or severe pain, often requiring additional treatment and hospitalization. Major complications were divided in early ($\leq$7 days after treatment) or late ($>$7 days after treatment) complications.
- **Minor complications**: Complications which were not life-threatening or moderately severe, such as mild pain, wound infection, mild fever or occasionally vomiting without obstruction.
- **Persistent obstruction**: Persistence of obstructive symptoms after the intervention.
- **Recurrent obstruction**: Recurrent obstructive symptoms during follow-up.

Statistics

Technical and clinical success, complications, persistent and recurrent obstruction, hospital stay and survival rates were pooled. Odds ratios (OR) with 95% confidence interval (CI) were calculated for technical success, clinical success, early and late major complications, and minor complications using data from the randomized and comparative studies. Odds ratios were not calculated for a study when the event was detected in all patients. Calculations were done with SPSS 12.0 and RevMan 4.2. A $p<0.05$ was considered to be statistically significant.

Results

Study characteristics

A total of 44 studies were included in this review.[1,4–12,17–50] Study characteristics are shown in Table 1. Only two studies had a randomized design (with 27 and 18 patients included).[17,18] Stent placement was prospectively or retrospectively compared with GJJ in 6 studies.[6–8,19–21] Two retrospective studies compared laparoscopic GJJ with open GJJ.[35,36] Thirty-four studies evaluated either stent placement or GJJ. According to the Delphi criteria, we assessed the quality of the randomized and comparative trials with regard to: a) method of randomization, b) treatment allocation, c) similarity between groups, d) specification of eligible criteria, e) blinded outcome of assessor, care provider and patient, f) information on primary outcome, g) and intention-to-treat analysis.[51] Applying these criteria made clear that the quality of the trials was limited.

Table 1. Case series included

Author	Study type	Years	Inter-vention	N	Age	Impact factor
Mehta et al[17]	Randomized	Unknown	LGJJ	14	68	2
			Stent	13	70	
Fiori et al[18]	Randomized	2001-2002	OGJJ	9	70	1,4
			Stent	9	72	
Comparative studies						
Johnsson et al[19]	Prospective	1999-2004	OGJJ	15	72	2
			Stent	21	78	
Mittal et al[20]	Retrospective	1989-2002	LGJJ	14	68	5,1
			OGJJ	16	68	
			Stent	16	64	
Del Piano et al[7]	Retrospective	1997-2002	OGJJ	23	73	3,5
			Stent	24	75	
Maetani et al[8]	Retrospective	1993-2002	OGJJ	19	69	4
			Stent	20	72	
Wong et al[6]	Retrospectiev	1988-1998	OGJJ	17	*NS*	2
			Stent	6	*NS*	
Yim et al[21]	Retrospective	1994-1999	OGJJ	15	*NS*	3,5
			Stent	12	68	

Continued on next page

Table 1. Case series included (*Continued*)

Author	Study type	Years	Inter-vention	N	Age	Impact factor
Prospective studies						
Lillemoe et al[5]	Prospective	1994-1998	OGJJ	44	67	5,9
Van Heek et al[10]	Prospective	1998-2002	OGJJ	36	63	5,9
Jung et al[22]	Prospective	1999-2000	Stent	39	63	1,7
Pinto et al[24]	Prospective	2001	Stent	31	72	1
Kim et al[26]	Prospective	2000-2003	Stent	29	64	4
Holt et al[27]	Prospective	2000-2004	Stent	28	76	3,5
Schiefke et al[28]	Prospectiev	1999-2001	Stent	20	*NS*	3,5
Jung et al[23]	Prospective	1999-2000	Stent	19	65	2,4
Jeong et al[29]	Prospective	1999-2000	Stent	18	56	2,4
Lopera et al[30]	Prospective	2000-2001	Stent	16	58	1,7
Profili et al[31]	Prospective	1994-2000	Stent	15	65	1,2
Lee et al[32]	Prospective	1997-2000	Stent	11	68	1
Baere et al[33]	Prospective	1997	Stent	10	54	0,8
Bethge et al[34]	Prospective	1997	Stent	6	68	4,7
Espinel et al[1]	Prospective	1999-2000	Stent	6	76	1,4
Retrospective studies						
Brune et al[12]	Retrospective	1993-1995	LGJJ	16	67	2
Choi et al[35]	Retrospective	1999-2000	LGJJ	10	59	2
Bergamaschi et al[36]	Retrospective	1991-1996	LGJJ	9	*NS*	1,2
Alam et al[37]	Retrospective	1998-2000	LGJJ	8	67	2
Bergamaschi et al[36]	Retrospective	1991-1996	OGJJ	22	*NS*	1,2
Choi et al[35]	Retrospective	1998-2000	OGJJ	10	60	2
Telford et al[38]	Retrospective	1996-2003	Stent	176	65	3,5
Song et al[39]	Retrospective	2001-2004	Stent	102	58	1,7
Bessoud et al[11]	Retrospective	Unknown	Stent	72	62	1,7
Nassif et al[40]	Retrospective	1998-2001	Stent	63	73	4
Kim et al[26]	Retrospective	1995-1999	Stent	49	57	0,2
Adler et al[4]	Retrospective	1998-2001	Stent	36	61	4,7
Kaw et al[41]	Retrospective	1998-2001	Stent	33	62	2
Razzaq et al[9]	Retrospective	1996-2000	Stent	28	69	0,9
Park et al[42]	Retrospective	1996-1999	Stent	24	43	5,1
Aviv et al[43]	Retrospective	1998-1999	Stent	15	61	1,5
Feretis et al[44]	Retrospective	1993-1994	Stent	12	64	4
Soetiknoet al[46]	Retrospective	1995-1997	Stent	12	60	3,5
Yates te al[47]	Retrospective	1994-1996	Stent	11	71	4
Feretis et al[45]	Retrospective	Unknown	Stent	10	72	3,5
Nevitt et al[48]	Retrospective	1991-1997	Stent	8	63	2
Venu et al[49]	Retrospective	Unknown	Stent	8	66	4
Ely et al[50]	Retrospective	1998-200	Stent	5	65	2

NS not specified

Patient characteristics

A total of 1046 patients received a duodenal stent (mean age: 64 years) and 297 patients underwent GJJ (mean age: 67 years).

Biliary drainage some time before stent placement was performed in 76/579 (13%) patients, during stent placement in 34/579 (6%), and after stent placement in 31/579 (5%).[1,4,8,11,17,19,20,30,38–40,43,46] A biliary drainage procedure some time before GJJ was performed in 18/102 (18%) patients, during GJJ in 16/102 (16%) and after GJJ in 17/102 (17%).[8,12,17,19,20,37] Results on study outcomes are shown in Table 2.

Technical success

Stent placement was usually performed by endoscopy in combination with fluoroscopy. The stents that were used included enteral Wallstents and Niti-S stents, esophageal Memotherm stents, Ultraflex stents, Choo stents, Gianturco-Z stents, Song stent, Flamingo Wallstents and Endocoil stents. The surgical technique that was used for the GJJ included an open or laparoscopic procedure that was performed in an antecolic or retrocolic way.

Stent placement was technically feasible in 972/1012 (96%) patients and GJJ in 203/204 (99%) patients (Table 3). The main reasons for technical failure of stent placement were dislocation of the stent during the procedure, no passage of the guidewire through the stricture, failure to deploy or release the stent from the delivery system. The reason for technical failure to perform a GJJ was the finding of peritoneal carcinomatosis during the procedure.

Clinical success

Clinical success was 89% (890/1000 patients) after stent placement and 72% (79/110) after GJJ (Table 3). Information on food intake was available in most studies evaluating stent placement and in only one study that had included a small number of patients receiving a GJJ.[19] Based on the available data, we scored the results on food intake using the standardized Gastric Outlet Obstruction Scoring System (GOOSS) score, with 0=no oral intake, 1=liquids only, 2=soft foods and 3=solid food/full diet.[4] Food intake before the intervention was poor with no difference between patients undergoing stent placement or GJJ. The mean GOOSS score was 0 in 148/238 (62%) patients, 1 in 78/238 (33%) and 2 in 12/238 (5%). Following treatment with a stent or GJJ, food intake improved in the majority of patients. After stent placement, the GOOSS score was 0 in 18/306 (6%) patients, 1 in 68/306 (22%), 2 in 122/306 (40%) and 3 in 98/306 (32%). One week after GJJ, the GOOSS score was 0 in 5/14 (36%) patients, 1 in 7/14 (50%), 2 in 1/14 (7%) and 3 in 1/14 (7%).

Table 2. Results on technical and clinical success, hospital stay, complications, survival and 30-day mortality

Author	Intervention	N	Technical success	Clinical success	Hospital stay	Major complications		Minor complications	Survival (days)	30-day mortality (%)
						Early	Late			
Randomized studies										
Mehta et al[17]	LGJJ	14	93	*NS*	11	0	0	62	*NS*	23
	Stent	13	77	*NS*	5	0	0	0	*NS*	20
Fiori et al[18]	OGJJ	9	100	89	10	11	0	11	*NS*	*NS*
	Stent	9	100	100	3	11	0	11	*NS*	*NS*
Comparative studies										
Johnsson et al[19]	OGJJ	15	100	81	15	0	13	*NS*	99	27
	Stent	21	100	100	7	5	14	5	76	29
Mittal et al[20]	LGJJ	14	*NS*	*NS*	7	0	36	7	119	*NS*
	OGJJ	16	*NS*	*NS*	10	0	31	*NS*	120	*NS*
	Stent	16	*NS*	*NS*	2	0	0	0	56	*NS*
Del Piano et al[7]	OGJJ	23	100	56	24	0	30	61	70	30
	Stent	24	96	92	3	0	17	*NS*	96	0
Maetani et al[8]	OGJJ	19	100	84	30	26	0	5	79	16
	Stent	20	100	80	15	5	25	10	55	25
Wong et al[6]	OGJJ	17	*NS*	*NS*	15	*NS*	*NS*	*NS*	64	18
	Stent	6	*NS*	*NS*	4	*NS*	*NS*	*NS*	98	0
Yim et al[21]	OGJJ	15	*NS*	*NS*	14	*NS*	*NS*	*NS*	92	*NS*
	Stent	12	94	81	4	8	17	*NS*	94	*NS*
Prospective studies										
Lillemoe et al[5]	OGJJ	44	100	*NS*	9	0	0	32	249	0
Van Heek et al[10]	OGJJ	36	100	*NS*	11	0	21	25	216	3

Continued on next page

Table 2. Results on technical and clinical success, hospital stay, complications, survival and 30-day mortality (*Continued*)

Author	Intervention	N	Technical success	Clinical success	Hospital stay	Major complications		Minor complications	Survival (days)	30-day mortality (%)
						Early	Late			
Jung et al[22]	Stent	39	97	95	*NS*	8	28	3	134	10
Pinto et al[24]	Stent	31	100	90	*NS*	0	10	29	92	29
Kim et al[26]	Stent	29	90	96	18	0	29	*NS*	124	0
Holt et al[27]	Stent	28	93	93	7	0	21	*NS*	51	42
Schiefke et al[28]	Stent	20	100	100	*NS*	*NS*	*NS*	*NS*	144	*NS*
Jung et al[23]	Stent	19	95	100	*NS*	26	0	*NS*	*NS*	0
Jeong et al[29]	Stent	18	100	94	*NS*	6	22	11	85	*NS*
Lopera et al[30]	Stent	16	94	81	*NS*	19	0	13	84	*NS*
Profili et al[31]	Stent	15	100	93	*NS*	0	14	14	*NS*	0
Lee et al[32]	Stent	11	87	82	*NS*	0	0	64	*NS*	*NS*
Baere et al[33]	Stent	10	100	80	2	10	10	20	93	*NS*
Bethge et al[34]	Stent	6	100	100	*NS*	0	33	0	23	83
Espinel et al[1]	Stent	6	100	100	3	0	0	*NS*	98	0
Retrospective studies										
Brune et al[12]	LGJJ	16	100	81	7	6	0	19	87	0
Choi et al[35]	LGJJ	10	100	100	9	0	0	30	*NS*	*NS*
Bergamaschi et al[36]	LGJJ	9	*NS*	*NS*	10	*NS*	*NS*	*NS*	348	*NS*
Alam et al[37]	LGJJ	8	100	88	7	13	75	*NS*	*NS*	*NS*
Bergamaschi et al[36]	OGJJ	22	*NS*	*NS*	15	*NS*	*NS*	*NS*	294	*NS*
Choi et al[35]	OGJJ	10	100	100	13	0	10	70	*NS*	*NS*
Telford et al[38]	Stent	176	97	84	*NS*	*NS*	9	6	97	*NS*
Song et al[39]	Stent	102	99	84	*NS*	*NS*	9	2	92	2
Bessoud et al[11]	Stent	72	97	90	*NS*	1	14	1	120	*NS*
Nassif et al[40]	Stent	63	95	92	6	33	67	*NS*	210	*NS*

Continued on next page

Table 2. Results on technical and clinical success, hospital stay, complications, survival and 30-day mortality (*Continued*)

Author	Intervention	N	Technical success	Clinical success	Hospital stay	Major complications		Minor complications	Survival (days)	30-day mortality (%)
						Early	Late			
Kim et al[26]	Stent	49	100	92	7	17	10	70	18	*NS*
Adler et al[4]	Stent	36	100	97	*NS*	3	3	22	83	*NS*
Kaw et al[41]	Stent	33	97	88	*NS*	0	13	12	102	*NS*
Razzaq et al[9]	Stent	28	96	91	*NS*	*NS*	27	4	95	18
Park et al[42]	Stent	24	75	67	*NS*	4	38	*NS*	129	0
Aviv et al[43]	Stent	15	93	93	*NS*	13	20	*NS*	72	*NS*
Feretis et al[44]	Stent	12	100	92	*NS*	8	0	0	*NS*	0
Soetiknoet al[46]	Stent	12	100	75	2	*NS*	*NS*	25	*NS*	*NS*
Yates te al[47]	Stent	11	91	91	*NS*	*NS*	*NS*	63	77	*NS*
Feretis et al[45]	Stent	10	100	100	*NS*	0	20	*NS*	*NS*	*NS*
Nevitt et al[48]	Stent	8	100	88	*NS*	0	38	*NS*	141	0
Venu et al[49]	Stent	8	100	100	*NS*	0	10	0	*NS*	13
Ely et al[50]	Stent	5	100	100	*NS*	0	0	20	*NS*	*NS*

NS not specified

Table 3. Summary of the main study outcomes of stent placement and gastrojejunostomy in patients with malignant gastric outlet obstruction

	Stent	GJJ
Technical success (%)	972/1012 (96)	203/204 (99)
Clinical success (%)	890/1000 (89)	79/110 (72)
Complications (%)		
Early major complications	43/609 (7)	6/159 (4)
Late major complications	171/950 (18)	34/201 (17)
Minor complications	66/732 (9)	66/201 (33)
Persistent obstructive symptoms	43/535 (8)	10/106 (9)
Reintervention	147/814 (18)	1/138 (1)
Mean hospital stay (days, [range])	7 (2-18)	13 (7-30)
Mean survival (days, [range])	105 (23-210)	164 (64-348)

Complications

Early major complications were not different between stent placement (7%; 43/609) and GJJ (4%; 6/159)(Table 3). Early major complications after stent placement were mainly stent migration and dysfunction of the stent and after GJJ, jaundice and bleeding. In most patients with early major complications, a reintervention was performed. In addition, no differences in late major complications between stent placement (18%; 171/950) and GJJ (17%; 34/201) were found. The most commonly observed late complications after stent placement were stent migration and occlusion either by tumor in- or overgrowth or food. After GJJ, late major complications included leakage at the anastomotic site, fever and dysfunction of the GJJ.

Minor complications occurred more frequently after GJJ (33%; 66/201) than after stent placement (9%; 66/732). Minor complications after stent placement included mild pain in the upper abdominal region, vomiting or mild bleeding, whereas after GJJ delayed gastric emptying and wound infections were most frequently seen.

Persistent obstructive symptoms after treatment occurred in 43/535 (8%) patients after stent placement and in 10/106 (9%) following GJJ.

A reintervention for recurrent obstructive symptoms was more frequently performed after stent placement than after GJJ (18%; 147/814 vs. 1%; 1/138). Causes of recurrent obstruction after stent placement included stent occlusion by tumor in- and overgrowth or food.

Hospital stay and survival

Mean hospital stay was shorter after stent placement (7 days, n=324) than after GJJ (13 days, n=385). Mean survival after stent placement was 105 days (n=923) and after GJJ 164 days (n=246).

Costs

Total costs of stent placement and GJJ were compared in three non-randomized studies.[19–21] In the study by Yim et al.[21], mean total costs were $9,921 for stent placement and $28,173 for OGJJ. Only procedural costs were used in this calculation. In the study by Mittal et al.[20], information was collected on procedural and post procedural costs. Mean costs were $8,680 for stent placement, $20,060 for OGJJ and $16,552 for LGJJ. Johnsson et al.[19] included procedural costs, postoperative care, hospital stay and additional procedures. Mean costs were $8,163 for stent placement and $10,224 for OGJJ.

Odds ratios for available comparative and randomized studies

Odds ratios were analyzed for technical success, clinical success, early major complications, late major complications and minor complications using the two randomized studies [17,18] and 6 comparative studies. [6–8,19–21] The results showed no difference in technical success rate between stent placement and GJJ (OR: 0.22, CI: 0.02-2.1, p=0.2). The clinical success rate seemed however higher after stent placement than after GJJ (OR: 3.39, CI: 0.8-14.3, p=0.1). The results for early major and late major complications showed no clear differences between stent placement and GJJ (OR: 0.49, CI: 0.1-2.6, p=0.4 and OR: 0.74, CI: 0.1-4.0, p=0.7, respectively). Finally, no differences in minor complications between the two treatment modalities were found (OR: 0.75, CI: 0.1-5.0, p=0.8).

Discussion

This review summarizes the published results on duodenal stent placement and GJJ as palliative treatment modalities for GOO. There is a paucity of evidence to conclude that either one of these two treatment modalities gave better treatment results. The results of this review suggest however that patients with a duodenal stent have a shorter hospital stay, a more frequent and faster relief of obstructive symptoms, which may be associated with fewer minor complications than those treated with a GJJ. Nevertheless, patients after a GJJ have fewer recurrences of

obstructive symptoms and therefore the need for reinterventions is lower in GJJ patients than in those being treated with a stent.

The main objective of a palliative procedure in patients with malignant GOO is to restore the ability to eat. This review demonstrates that clinical success, defined as improvement of food intake and/or relief of symptoms, was more common after stent placement than after GJJ, with the OR also showing better, but statistically not significant, results after stent placement than after GJJ (OR=3.39, CI: 0.8-14.3, p=0.1). As stent placement is a less invasive treatment than GJJ, this may well explain why a faster relief of symptoms is seen with this treatment modality. In addition, the position of the anastomosis at the greater curvature after a GJJ may also contribute to the less favorable results following a surgical procedure. Nevertheless, our results are only based on studies with small patient numbers, and more and larger randomized studies are needed.

This review showed no differences in early and late major complications between stent placement and GJJ, which was confirmed by the ORs obtained from the randomized and comparative studies. Minor complications occurred more frequently after GJJ than after stent placement if all studies were compared. The OR however, did not indicate a difference between stent placement and GJJ (OR: 0.75, CI: 0.11-5.04, p=0.77). Remarkably, complication rates varied widely in the reviewed studies, which may have been caused by differences in patient age, clinical condition, sample size, operator experience and in the definitions used for complications in the different series and studies that were reviewed. In addition, it was not always possible to detect whether a complication was indeed associated with the treatment modality or with progression of the malignant disorder.

Recurrent obstructive symptoms, necessitating a reintervention, occurred more frequently after stent placement than after GJJ. The majority of recurrent obstructive symptoms after stent placement were caused by stent occlusion from either tumor in- or overgrowth, or food obstruction. Duodenal stent obstruction by tumor in- or overgrowth remains a problem, especially when non-covered stents are used. The use of covered stents in the duodenum may however lead to a higher incidence of stent migration and may also lead to an increased incidence of biliary obstruction and even pancreatitis due to obstruction of the common bile duct and/or pancreatic duct by the covered device.[23,25,29,30,42] Stent migration seems to occur in a shorter time period (range: 1-121 days) after stent placement than recurrent obstructive symptoms caused by tumor in- or overgrowth or food debris (range: 11-273 days). In addition, stent migration seems to occur at a shorter time period and more frequently after placement of a covered stent (19%) than after placement of a uncovered stent (6%).[11,23,24,26,29–31,39,42,47]

Our review suggests that initial costs are lower for stent placement than for a

surgical procedure. However, in the few studies that evaluated costs, reintervention and additional care costs were not taken into consideration.[19–21] As GJJ was found to be associated with a prolonged hospital stay, initial costs are likely to be higher following GJJ. Following stent placement however, a higher incidence of reinterventions for recurrent obstruction is likely to occur and this may result in more or less similar costs for GJJ and stent placement on the long term. A future cost-analysis study is needed that includes all costs of stent placement and GJJ involved in the whole period of time that these patients survive.

A number of issues are important to consider before concluding that either one of these treatment modalities is favorable in patients with a GOO. First, only 2 randomized trials and 6 comparative studies have so far been performed including small patient numbers. The prospective and retrospective design of most studies included in this review resulted in a minimal access to primary study outcomes and a comparison between potentially noncomparable patient populations. In most studies, no differentiation was made with respect to underlying malignancies. It is well known that survival in patients with GOO caused by pancreatic carcinoma is shorter than that in patients with gastric- or duodenal carcinoma.[52] Pancreatic cancer was the most common cause of GOO in various series. However, specific results for different types of patients were not available. Therefore survival rates may have been over- or underestimated depending on the type of patients that were included.

Secondly, several stent types were used in the different studies, whereas in some studies also more than one stent type was used. Again, specific data on outcome for individual stent types were often not available. Moreover, in several studies, esophageal stents rather than enteral stents were used. This could have influenced the complication rate, as esophageal stents are often covered, in contrast to enteral stents, resulting in an increased risk of stent migration.[53] Moreover, as esophageal stents, in contrast to enteral stents, cannot be placed through-the-scope, placement of these devices may have been technically more demanding. Only two studies compared open GJJ with laparoscopic GJJ. These comparative studies suggested that both hospital stay and time to restore the ability to eat were shorter after laparoscopic GJJ than after open GJJ. However additional, and preferably randomized studies are needed before a recommendation in favor of a laparoscopic procedure can be given in these patients.

Finally, publication bias (the selective reporting of studies with positive results) may result in overestimation of technical and clinical success rates and survival, and underestimation of complications and hospital stay. We assessed publication bias and found no clear effect of sample size or impact factor of the journal on the different endpoints (results not shown). Using the Delphi criteria to assess the

quality of the randomized and comparative trials, made clear that the quality of the assessed trials was limited.[51] In addition, the quality of the patient series was low because of small patient populations and minimal access to primary data. A high-quality trial may alter the interpretation of the benefit of the two treatment modalities. The results of this review should not be considered as a critical appraisal, but addresses the possible differences in treatment effects between stent placement and GJJ.

Conclusion

Despite the above-mentioned limitations, it seems reasonable to suggest that stent placement is associated with more favorable short-term results, whereas GJJ may be a better treatment option in patients with a more prolonged survival. The results of this review suggest that a trial with a sufficient number of patients is indicated in which patients with malignant GOO are randomized to stent placement or GJJ in order to define treatment guidelines for individual patients based on the underlying disorder and prognosis. In addition, a longer follow-up of patients is needed to assess the different endpoints, and, if indicated, to perform a cost-effectiveness analysis.

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Chapter 3

Gastrojejunostomy versus stent placement in patients with malignant gastric outlet obstruction: a comparison in 95 patients

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Abstract

Background: Gastrojejunostomy (GJJ) and duodenal stent placement are the most commonly used palliative treatment modalities for gastric outlet obstruction (GOO). In this retrospective study, we compared GJJ and stent placement with regard to medical effects.

Methods: Medical records of 95 patients who had undergone palliative treatment between 1994 and 2006 in a Dutch university hospital, were reviewed. Study outcomes were improvement of food intake, complications, persistent and recurrent symptoms, reinterventions, hospital stay and survival.

Results: Fifty-three patients were referred for duodenal stent placement and 42 patients underwent GJJ. There were no differences in technical and clinical success and the incidence of minor and early major complications and survival. Food intake improved more rapidly after stent placement than GJJ ($p=0.01$). The time to late major complications, recurrent obstructive symptoms and reintervention was significantly shorter after stent placement than GJJ ($p=0.004$, $p=0.002$ and $p=0.004$, respectively). Hospital stay was also shorter after stent placement than GJJ ($p<0.001$).

Conclusion: These findings suggest that stent placement is associated with better short-term outcomes and GJJ with better long-term outcomes. A large randomized controlled trial is however needed to systematically compare stent placement with GJJ with regard to medical effects, quality of life and costs.

Background

Patients with gastrointestinal malignancies may develop an obstruction at the level of the duodenum, which is caused by intrinsic, or extrinsic tumor growth. Studies have shown that 10 to 20% of patients with pancreatic cancer develop gastric outlet obstruction (GOO).[1–3] Other causes include periampullary tumors, lymphoma and metastases to the duodenum or jejunum.[4–6] Palliative treatment of GOO is mandatory as the clinical condition of these patients deteriorates rapidly due to dehydration and malnutrition.[2] The aim of palliative treatment is to re-establish oral food intake, and stabilize or improve the quality of life.

Initially, the main treatment for malignant GOO was a gastrojejunostomy (GJJ). However, this treatment is associated with significant morbidity (13-55%) and mortality (2-36%).[3,7–10] More recently, endoscopic placement of uncovered self-expanding metal stents in the duodenum is used to treat patients with GOO. Self-expanding stents are also successfully used for palliative treatment of malignant esophageal obstruction. Duodenal stents have been suggested to be a less invasive palliative treatment compared to GJJ.[1,11–13]. Currently, it is not clear which palliative treatment modality, either GJJ or stent placement, is preferable in individual patients with malignant GOO.

We therefore compared GJJ and stent placement in 95 patients with malignant GOO, who underwent either of these treatment modalities in our center. Study outcomes were technical and clinical success, complications, persistent and recurrent symptoms, reinterventions, hospital stay and survival.

Patients and methods

Patients

All patients had malignant GOO, which was confirmed by endoscopy or radiological studies. Inclusion criteria included: inoperable malignant carcinoma, due to metastatic disease and/or ingrowth into adjacent blood vessels as established by computed tomography, laparoscopy and/or laparotomy. All patients were symptomatic, i.e., had nausea, vomiting and/or inability to have a normal food intake. Patients were treated by duodenal stent placement or GJJ at the Erasmus MC Rotterdam, The Netherlands, in the period 1994 to 2006.

Open surgical procedure

Prior to the procedure, patients received an intravenous dose of 750 mg Cefazoline (Eli Lilly Nederland BV, Houten, The Netherlands). The abdominal cavity was

inspected during upper median laparotomy. Subsequently, a handmade side-to-side antecolic or retrocolic GJJ was performed using a jejunal loop 40-60 cm distal to Treitz ligament, which was anatomized with the posterior or anterior surface of the stomach. In case of either tumor ingrowth into or extrinsic compression of the common bile duct (CBD), a choledochojejunostomy or hepaticojejunostomy was performed additionally.

Laparoscopic procedure

Prior to the procedure, patients received an intravenous dose of 750 mg Cefazoline. To create a pneumoperitoneum, a Hasson trocar was placed below the umbilicus and two (12 mm) trocars were placed at the level of the left and right upper abdominal wall. A fourth (5 mm) trocar was placed in the left lower quadrant. After the abdominal cavity had been inspected, a stapled side-to-side antecolic GJJ was performed using a jejunal loop at 40-60 cm distal from Treitz ligament.

Endoscopic procedure

All stents were placed using a therapeutic upper GI endoscope (GIF-2T, Olympus Europe GmbH, Hamburg, Germany) after an intravenous dose of midazolam (Roche Nederland BV, Woerden, The Netherlands). The length of the stricture was determined endoscopically or fluoroscopically depending on whether the stricture allowed passage of the endoscope. A guide wire was then introduced through the stricture and the stent was advanced over the wire, so that both stent ends were 1-2 cm longer than the stricture. Endoscopy and fluoroscopy were used to inspect stent deployment. An upright abdominal X-ray was performed to assess whether a perforation had occurred. Within case of a biliary stricture initially a stent or drain was placed either endoscopically or percutaneously.

Data collection

Data were obtained from patient notes, radiology reports, endoscopy reports and/or surgical reports, and by telephone interviews with patients' general practitioners. Data that were collected included demographic information, procedural characteristics, and follow-up information on complications, persistent or recurrent symptoms, reinterventions, hospital stay and survival.

Primary outcome of the study was food intake, measured by the Gastric Outlet Obstruction Scoring System (GOOSS score), with 0=no oral intake, 1=liquids only, 2=soft solids and 3=full diet.[2] Data on food intake were available in almost all patients at the time of hospital discharge. Based on these data, clinical success was

defined as a relief of symptoms and improvement of oral intake so that at least intake of soft solids was possible (GOOSS score$\geq$2). Furthermore, in most patients, 20-day follow-up information on food intake was available. Secondary outcomes included technical success, complications, persistent and recurrent obstructive symptoms, re interventions, hospital stay and survival. Technical success of stent placement was defined as adequate deployment and positioning of the stent. For GJJ this was defined as technical possibility to create an anastomosis.

Complications were divided into early major, late major and minor complications. Major complications were defined as life-threatening or severe complications, for example perforation, stent migration, hemorrhage, fever, jaundice or severe pain. Major complications almost always required treatment and/or hospitalization. Early major complications were defined as occurring within 7 days after the intervention and late major complications as occurring more than 7 days after the intervention. Minor complications were defined as those that were not life-threatening or moderately severe complications and did not require hospital admission, for example mild pain, wound infection or mild fever. Persistent obstructive symptoms were defined as continuing symptoms up to or occurring within 4 weeks after the intervention. Recurrent obstructive symptoms were defined as symptoms occurring more than 4 weeks after treatment and most commonly were caused by tumor in- or overgrowth, food bolus obstruction, or stent migration. In case of multiple episodes of recurrent obstruction of the same origin occurred in one patient, only the first episode was used in the analysis. Reintervention was defined as each treatment for a complication or for persistent or recurrent obstructive symptoms.

Statistics

Clinical success was compared with the Mann-Whitney U test. The GOOSS score at different time points was compared by using a mixed model. The mixed model contained treatment as a fixed effect and the repeated measurement of food intake as a random effect. Survival was calculated and survival curves were constructed by Kaplan-Meier analysis and were compared with the log rank test. Complications, recurrent obstructive symptoms, and reinterventions were also calculated with Kaplan-Meier analysis and compared with the log rank test and presented as the time to non-fatal events (complications, recurrence and reintervention) with censoring of patients who died before developing the event. Tests were considered statistically significant if $p<0.05$. Calculations were performed with SPSS 12.0 and SAS 8.2.

Table 1. Characteristics of 95 patients with malignant gastric outlet obstruction treated with either gastrojejunostomy (GJJ) or duodenal stent placement (Stent)

Characteristics	GJJ (n=42)	Stent (n=53)
Mean (±SD) age in years	63.4 (11.0)	63.8 (11.9)
Male gender (%)	17 (40)	30 (57)
Prior radiation and/or chemotherapy (%)	11 (26)	18 (34)
Primary carcinoma (%)*		
Pancreas	40 (96)	31 (55)
Gallbladder	1 (2)	1 (2)
Duodenum	0	2 (4)
Stomach	0	5 (9)
Metastatic	1 (2)	13 (24)
Unknown	0	1 (2)

Results

Patient characteristics

Between 1994 and 2006, 95 patients (47 men, 48 women) were referred for palliative treatment for malignant GOO. Initially, patients were predominantly treated by GJJ, then later stents came into more common usage. Table 1 shows the baseline characteristics of both treatment groups. Forty-two patients underwent GJJ (mean age 63 ± 11 yrs, range 38-85 yrs) and 53 patients were referred for duodenal stent placement (mean age 64 ± 12 yrs, range 30-85 yrs). There were no statistically significant differences between the groups for age, gender, and administration of prior adjuvant radio- and/or chemotherapy. Significantly more pancreatic carcinoma (p=0.017) were seen in the GJJ group.

Technical success

It was technically feasible to perform either stent placement or GJJ in the majority of patients (49/53 (93%) vs. 42/42 (100%) respectively; p=0.5). Stent placement was unsuccessful in four patients. In three of these patients, the stricture could not be passed with a guidewire. One of these patients was treated with a GJJ. In the other two patients, no alternative treatment was performed. In the fourth patient, a perforation occurred during the procedure. This patient underwent a GJJ, with

oversewing of the perforation the same day. These four patients were not included in the further analyses.

A total of 50 stents were placed in 49 patients with one patient requiring double stent placement, as one stent could not cover the entire length of the tumor. Thirty-eight (78%) patients were treated with a 22 mm diameter enteral Wallstent (Boston Scientific, Natick, USA) with a length of either 60 (n=16) or 90 (n=22) mm. Nine (18%) patients were treated with an 22 mm diameter Wallflex stent (Boston Scientific, Natick, USA) with a length of either 60 (n=1), 90 (n=6), or 120 (n=2) mm. Finally, two (4%) patients received a 22x100 mm enteral Choostent (M.I.Tech Co., Ltd).

Laparoscopical GJJ was performed in 10 (24%) patients, whereas an open procedure was performed in the remaining 32 (76%) patients.

Biliary drainage

In case of CBD obstruction, patients were treated with a biliary Wallstent (n= 12) (Boston Scientific, Natick, USA), a plastic stent (n=3), a percutanous drain (n=4), a choledochojejunostomy (n=1) or a combination of these modalities (n=20).

In 19/53 (36%) patients with a duodenal stent, a procedure for CBD obstruction was performed prior to stent placement. During or after duodenal stent placement another two patients were treated for CBD obstruction. Following duodenal stent placement, 15 of these 21 (71%) patients had recurrent CBD obstruction (Table 2). In 17/42 (40%) patients treated with a GJJ, treatment for CBD obstruction was performed prior to GJJ. In 4/42 (2%) patients this was performed during GJJ, three of these patients had previously been treated with a plastic stent, and in 2/42 (5%) following GJJ. Recurrent CBD obstruction following GJJ occurred in nine of these 20 (48%) patients. The occurrence of recurrent CBD obstruction was not different between stent placement and GJJ (p=0.4)(Table 2).

Clinical success

Information on food intake during 20-day follow-up was available in 28/42 (67%) patients after GJJ and in 20/49 (41%) patients after duodenal stent placement. These were all patients who were admitted for a prolonged period. The ability to eat improved more rapidly after stent placement than after GJJ (p=0.01, Figure 1). After stent placement it took 3.6 $\pm$ 1.9 days before patients were able to eat at least soft solids, whereas this was 10.1 $\pm$ 4.8 days after GJJ. No difference was seen in the mean GOOSS score between the stent and GJJ group at 20 days after treatment (p=0.38). Information on food intake at the time of hospital discharge was in line with these results. This information was available in 40/42 (95%) patients after

Table 2. Number of patients with malignant gastric outlet obstruction treated with drainage of the common bile duct before, during or after gastrojejunostomy (GJJ) or duodenal stent placement (stent)

Biliary drainage	GJJ (%) (n=42)	Stent (%) (n=53)
No intervention	23 (55)	28 (53)
Drainage before intervention	17 (40)	19 (36)
Drainage during intervention	4 (2)[1]	1 (2)
Drainage after intervention	2 (5)	1 (2)
Recurrent CBD obstruction	9/20 (48)	15/21 (71)

[1] Three of these patients had previously been treated with a plastic stent

GJJ and in 40/49 (82%) patients after stent placement. Clinical success, defined as food intake of at least soft solids, was not different between stent placement and GJJ (75% vs. 59%; p=0.14).

Complications and reinterventions

Early major complications occurred at the same frequency after stent placement (n=3) and GJJ (n=4) (p=0.60). Early major complications in the stent group included extrinsic compression on the stent causing insufficient stent expansion and stent migration, whereas in the GJJ group hemorrhage, severe pain, cholangitis, and respiratory failure were seen.

More late major complications were seen in the stent group (after a follow-up of three months in nine patients (60%)) than in the GJJ group (after three months in four patients (22%)). The time to late major complications was significantly shorter after stent placement than GJJ (median: 147 vs. 513 days, p=0.004) (Figure 2). Late major complications after stent placement included stent occlusion due to a food bolus, tumor in- or overgrowth, stent migration, duodenal perforation and severe pain. After GJJ these included severe pain, anastomotic occlusion and jaundice caused by CBD obstruction.

Minor complications were seen after a follow-up of three months in 14 patients with a duodenal stent and in 13 patients with a GJJ. The most common minor complications after stent placement were mild pain, nausea and vomiting without obstruction and fever of unknown origin and after GJJ mild pain, wound infection and nausea and vomiting in the presence of an open anastomosis.

After treatment no difference was seen for persistence of obstructive symptoms

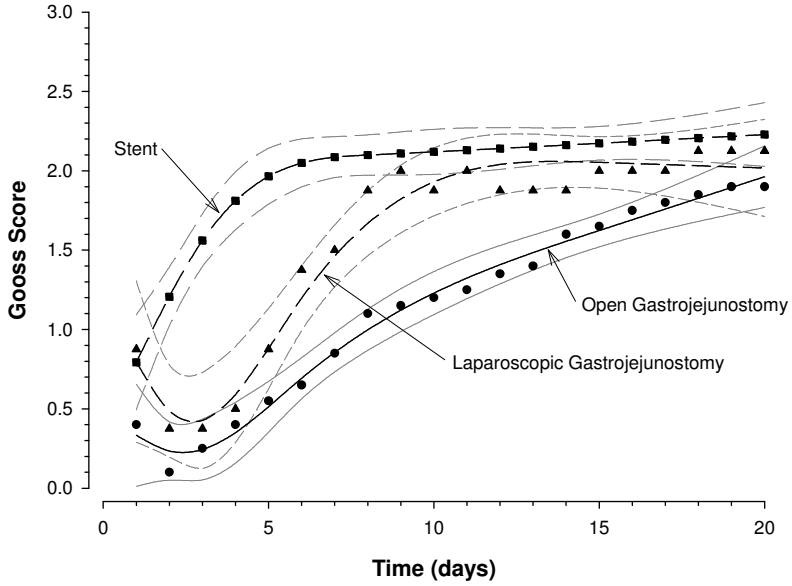

Figure 1. Gastric Outlet Obstruction Scoring System (GOOSS score) over a 20-day follow-up in 48 patients with malignant gastric outlet obstruction and treated with duodenal stent placement, open gastrojejunostomy or laparoscopic gastrojejunostomy

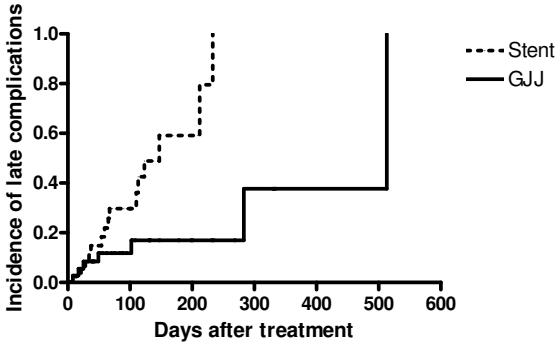

Figure 2. The incidence of late major complication censored for patients still alive after treatment with duodenal stent placement or gastrojejunostomy in patients with malignant gastric outlet obstruction

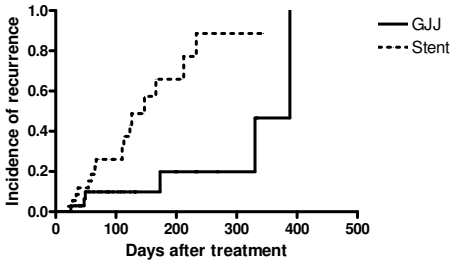

Figure 3. The incidence of recurrent obstructive symptoms censored for patients still alive after treatment with duodenal stent placement or gastrojejunostomy in patients with malignant gastric outlet obstruction

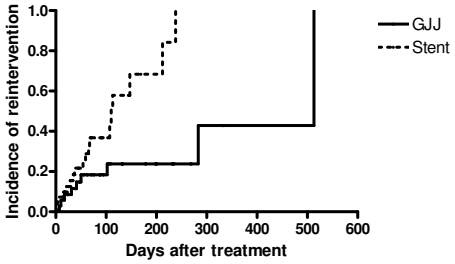

Figure 4. The incidence of a reintervention censored for patients still alive after treatment with duodenal stent placement or gastrojejunostomy in patients with malignant gastric outlet obstruction

between the stent and the GJJ group (n=13 vs. n=9, respectively). Persistence after GJJ was often caused by delayed gastric emptying. Recurrent symptoms occurred more frequently in patients treated with a stent (after three months in eight patients (47%)) than in those with a GJJ (after three months in three patients (17%)). The time to recurrent obstructive symptoms was shorter after stent placement than after GJJ (median: 147 vs. 388 days, p=0.002) (Figure 3). We also found that the time to a reintervention was shorter after stent placement than after GJJ (median: 110 vs. 513 days, p=0.004) (Figure 4). After three months of follow-up, a reintervention had been performed in 13 patients (92%) in the stent group and in six (40%) in the GJJ group.

Hospital stay and survival

Mean hospital stay was significantly shorter (6 $\pm$ 10.1 days (range 0-57)) after stent placement than after GJJ (18 $\pm$ 13.3 days (range 4-55)) ($p<0.001$) (Figure 5). Causes of prolonged hospital stay in both treatment groups included infections, pain, nausea, progressive disease and inability to eat at least soft solids (GOOSS score=2).

At day 30 the mortality rate was slightly higher in the stent group than in the GJJ group (17% vs. 7%, p=0.10). No difference was seen for median survival after stent placement or GJJ (70 days vs. 88 days, p=0.57). Three patients were still alive at day 100, 146 and 209 after stent placement (Figure 6).

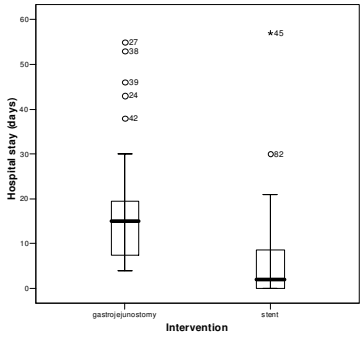

Figure 5. Hospital stay after treatment with duodenal stent placement or gastrojejunostomy in patients with malignant gastric outlet obstruction

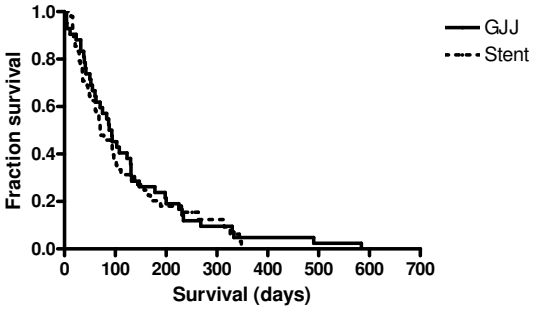

Figure 6. Survival after treatment with either duodenal stent placement or gastrojejunostomy in patients with malignant gastric outlet obstruction

Discussion

In this study, we compared stent placement with GJJ in 95 patients with malignant GOO. The results of this retrospective study show that both palliative treatment modalities were effective and safe. However, a more rapid improvement of food intake was seen after stent placement compared to a GJJ. This was also associated with a shorter hospital stay. Nevertheless, long-term results with regard to recurrent obstructive symptoms were better after GJJ. This was mainly due to the fact that complications and recurrent obstructive symptoms, necessitating a reintervention, developed sooner after stent placement than after GJJ.

The objective of palliative treatment in patients with GOO is to relief obstructive symptoms and to improve the ability to eat. This study demonstrates that food intake improved more rapidly after stent placement than after GJJ (Figure 1). However, 20 days after treatment, no difference in improvement of food intake was seen. Unfortunately, specified data on food intake during this 20-day follow-up were only available in 48 patients. As these patients were still admitted during this period, it may well indicate that the clinical condition was more favorable in those who were already discharged. Therefore, the quality of food intake might have been underestimated. A few small randomized and comparative studies have shown that results on food intake after stent placement or GJJ are similar. However, it is plausible that after stent placement patients are able to eat sooner than after GJJ as the integrity of the gastrointestinal tract is hardly affected by stent placement. In contrast to a GJJ for which a surgical approach is required.[4,10,14,15]

Three studies have suggested that laparoscopic GJJ is less invasive and is therefore associated with a shorter hospital stay and fewer early major complications than open GJJ.[16–18] Although we did not find a difference in hospital stay, complications rate, and survival between open GJJ and laparoscopic GJJ, food intake seems to improve more rapidly after laparoscopic GJJ than after open GJJ (Figure 1). This was also reported in a non-randomized comparative study by Mittal et al.[16]

Complications may affect quality of life and plays an important role in the total costs of care. This study shows that complications occur more rapidly after stent placement than after GJJ. In addition, a shorter time interval was seen for recurrent obstructive symptoms in the stent group compared to the GJJ group. Our results suggest that GJJ is associated with a more favorable long-term outcome, even though complications and reinterventions may be more severe and invasive than after stent placement. The most commonly performed reinterventions in the stent group were placement of a new stent or the endoscopic removal of obstructing food. In the GJJ group, reinterventions included surgical procedures for delayed gastric emptying by dilation of the anastomosis, persistent pain or occlusion of the anastomosis by an ileostomy. Reinterventions were performed in 20/49 (41%) patients after stent placement, whereas other studies have reported lower reintervention rates.[8,19–21] This could have been caused by patient selection. The reason for performing either stent placement or GJJ was not clearly stated in the medical records and is therefore unknown. Patients with a poor clinical condition may have been selected for stent placement, as this is a less invasive treatment than GJJ. In addition, the use of different stent designs and surgical techniques may also have played a role. Treatment for CBD obstruction is needed in 50% of the patients.[2,22] Jaundice caused by biliary obstruction reduces quality of life, particularly by impaired liver function, anorexia, malnutrition and pruritis. Therefore, biliary obstruction should be treated as soon as possible.[23] Finally, stent placement is associated with a learning curve, as illustrated by the occurrence of a perforation in the first duodenal stent patient. Nonetheless, our results did not show a statistically significant association between year of treatment and number of reinterventions needed (results not shown).

The difference in hospital stay between stent placement and GJJ was statistically significant. Other studies have also reported a shorter hospital stay after stent placement than after GJJ.[4,10,14,24] As these patients were treated between 1994 and 2006, this could have influenced the results. However, we found no relation between date of treatment and hospital stay. Nevertheless, we were unable to distinguish between a prolonged hospital stay caused by a complication of the procedure or a delay in ability to eat and a prolonged hospitalization caused by progressive disease. We therefore believe that the period of hospital stay that is attributed to the procedure, may have been overestimated in this study.

Median survival in this study was 70 days after stent placement and 88 days after GJJ. Median survival rates in other studies ranged from 7 to 141 days after stent placement and 70 to 249 days after GJJ.[1,4,8,15,16,19,20,25–27] Previous studies have suggested that survival rates were higher after GJJ than after stent placement. In contrast, our results do not indicate a statistically significant difference in survival rate between stent placement and GJJ. These differences may again result from differences between study groups. It has been shown that patients with a primary pancreatic carcinoma have a shorter survival than patients with a gastric- or duodenal carcinoma.[28] Pancreatic cancer patients were overrepresented in our study, particularly in those undergoing GJJ. Although we did not found a significant difference in survival between patients with pancreatic carcinoma and patients with gastric- or duodenum carcinoma, survival may have been underestimated in this group.

Results of previous studies suggest that initial costs are lower for stent placement than for a surgical procedure. However, in the few studies that evaluated costs, reintervention and additional care costs were not taken into consideration.[15,16,29] As GJJ was found to be associated with a prolonged hospital stay, initial costs are likely to be higher following GJJ. Following stent placement however, a higher incidence of reinterventions for recurrent obstruction is likely to occur and this may result in more or less similar costs for GJJ and stent placement on the long term. Because of the relatively short median survival of these patients it seems likely that stent placement could lead to annual savings of €1,45-1,90 million (600-800 patients) (unpublished results). A future cost-analysis study is needed that includes all costs of stent placement and GJJ involved in the whole period of time that these patients survive.

Despite the limitations of this retrospective study, the results suggest that duodenal stent placement and GJJ are effective and safe treatment modalities in patients with GOO. While stent placement is associated with better short-term outcomes, GJJ may have a more favorable long-term outcome. Our results indicate that adequate patient selection may be of great importance when considering a palliative treatment modality for malignant GOO. We suggest that a duodenal stent should be placed in patients in a poor clinical condition and a life expectancy of 2-3 months. GJJ should be reserved for patients with a better condition and therefore a longer life expectancy. However, in order to define definite guidelines for the palliative treatment of patients with GOO, a large randomized controlled trial is required in which patients are randomized between stent placement and GJJ. Follow-up of at least 1 year is needed to evaluate quality of life, complications, survival and costs/cost-effectiveness.

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Chapter 4

Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction: a multicenter randomized trial

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submitted

Abstract

Background: Both surgical gastrojejunostomy and endoscopic stent placement are commonly used for the palliation of obstructive symptoms due to malignant gastric outlet obstruction (GOO). It is however unclear which treatment is preferable. We performed a randomized, multicenter trial to compare the outcomes of these two modalities in patients with malignant GOO.

Methods: Twenty-one centers in the Netherlands agreed to participate, with 11 of these centers including 39 patients with GOO. Patients were randomized to gastrojejunostomy or stent placement and were followed until death. Primary outcome was the total area under the survival curve adjusted for the ability to eat at least soft solids (Gastric Outlet Obstruction Scoring System (GOOSS) score $\geq$2). Secondary outcomes were medical effects, quality of life and costs. Analysis was by intention-to-treat.

Results: Eighteen patients were randomized to GJJ (mean age 66 $\pm$ 11 years, 50% male) and 21 to stent placement (mean age 66 $\pm$ 13 years, 55% male). Food intake improved more rapidly after stent placement than after GJJ (GOOSS $\geq$2: 5 vs. 8 days; $p<0.01$) but long term (>60 days) relief of obstructive symptoms was better after GJJ. After GJJ, patients had more days with a GOOSS score $\geq$2 adjusted for survival than after stent placement (72 vs. 50 days; $p=0.05$). More major complications (6 in 4 vs. 0; $p=0.02$) and more recurrent obstructive symptoms (8 in 5 vs. 1 in 1; $p=0.02$) occurred after stent placement than after GJJ, resulting in more reinterventions after stent placement (stent: 10 in 7 vs. GJJ: 2 in 2; $p<0.01$). There was no difference in median survival (stent: 56 vs. GJJ: 78 days). Mean hospital stay was 8 days shorter after stent placement than after GJJ ($p=0.04$). Quality of life was maintained after both treatments with no differences between GJJ and stent placement, although pain scores decreased more rapidly after stent placement than after GJJ ($p=0.02$). Total costs of GJJ were higher compared to stent placement (€12,433 vs. €8,812; $p=0.049$).

Conclusions: Despite slow initial symptom improvement, GJJ gave better long-term relief of obstructive symptoms in patients with malignant GOO. Since GJJ was also associated with fewer complications and fewer recurrent obstructive symptoms on the long-term, this modality is the treatment of choice for relief of obstruction in patients with an expected life expectancy of 2 months or more. As stent placement was associated with a more rapid improvement of food intake, shorter hospital stay and lower costs, this treatment is preferable for patients expected to live shorter than 2 months.

Background

Malignant Gastric Outlet Obstruction (GOO) is most commonly seen in patients with pancreatic cancer of whom approximately 10-20% may develop obstructive symptoms in the course of the disease.[1–4] Other causes of GOO include periampullary carcinoma, lymphoma and metastases to the duodenum or jejunum.[5–7] Treatment of GOO is indicated as patients quickly develop a poor clinical condition due to vomiting, dehydration and malnutrition.[3] The aim of palliation is to maintain oral food intake and to stabilize or even improve the quality of life of these patients.

Traditionally, malignant GOO is treated with a surgically performed gastrojejunostomy (GJJ). This treatment modality is associated with a good functional outcome and relief of symptoms in 72% of patients.[8] However, it has also been reported to be associated with significant morbidity (13-55%).[4,9–12] Endoscopic placement of an uncovered self-expanding metal stent in the duodenum is increasingly being used to treat patients with GOO. Duodenal stent has been suggested to be a less invasive treatment with a faster relief of symptoms compared to GJJ.[1,13–15] Currently, it is not clear which palliative treatment, either GJJ or stent placement, is preferable in patients with malignant GOO.

We therefore performed a randomized study comparing GJJ with stent placement in patients with malignant GOO with respect to improvement of food intake, complications, persistent and recurrent obstructive symptoms, reinterventions, quality of life and costs.

Patients and Methods

Patients

Between January 2006 and May 2008, 77 patients with GOO were eligible to be included into the trial. Inclusion criteria included: 1) obstructive cancer extending from the distal one third of the stomach to the distal duodenum, 2) a Gastric Outlet Obstruction Scoring System (GOOSS) score of 0 (no oral intake) or 1 (liquids only) and 3) irresectable or metastatic disease. Exclusion criteria included: 1) evidence of other strictures in the gastrointestinal (GI) tract, 2) previous gastric, periampullary or duodenal surgery, 3) previous GJJ or duodenal stent placement as palliative treatment for the same condition, 4) a WHO performance score of 4 (patient is 100% of time in bed), and 5) unable to fill out quality of life questionnaires.

Procedures

Randomization was performed centrally at the Erasmus MC Rotterdam, using computer-generated lists. Patients were stratified for center and previous treatment of obstructive jaundice (defined as a treatment given 1 week or earlier prior to study inclusion).

Patients randomized to GJJ underwent an open or laparoscopic gastrojejunostomy, either antecolic or retrocolic, under complete anesthesia. Patients randomized to endoscopic stent placement received an Enteral Wallflex stent (Boston Scientific, Watertown, USA), with a diameter of 22 mm and a length of 60, 90 or 120 mm.[16] The stent was introduced over a guidewire and deployed under endoscopic and fluoroscopic monitoring.

Definitions

Food intake was measured by the standardized GOOSS score, with 0=no oral intake, 1=liquids only, 2=soft solids, 3=almost complete diet and 4=full diet.[3]

Complications were divided into early and late major complications and minor complications. Major complications were defined as life-threatening or severe complications, requiring treatment and/or hospitalization. Early major complications were defined as those occurring within 7 days after the intervention and late major complications as those occurring 7 days or later after the intervention. Minor complications were defined as those that were not life-threatening or moderately severe complications and did not require hospital admission.

Persistent obstructive symptoms were defined as continuing symptoms up to or occurring within 4 weeks after initial treatment. Recurrent obstructive symptoms were defined as symptoms occurring more than 4 weeks after treatment.[14] In case of multiple complications or recurrent obstructions of the same origin occurring in one patient, only the first episode was used in the analysis. Reinterventions were defined as treatments for a complication or for persistent or recurrent obstructive symptoms.

Data collection

Food intake was measured daily during the first 30 days after treatment and than weekly by patient diaries. Health Related Quality of Life (HRQoL) was assessed with standardized quality of life questionnaires i.e., the EORTC QLQ-C30, the EuroQol-5D, the EQ-VAS and the pancreatic-cancer specific EORTC QLQ-PAN26, which can also be used in patients with GOO.[17–19] In addition, the burden of intervention, patient preference, pain and nausea were measured by self-developed questionnaires,

which were also used in previous studies.[20] Total medical costs included initial costs of treatment, hospital stay, reinterventions, medical services and extramural health care. All costs are reported in Euro.

Patients were followed-up by home visits of a specially trained research nurse at 14 days, 1 month and then monthly after randomization. During these visits the diaries were checked and the HRQoL questionnaires were completed. Use of medical services, food supplements and extramural health care were registered during the home visits by a standardized checklist. If indicated, patients were readmitted for clinical investigation and/or treatment. All clinicians completed standardized case record forms during control visits, reinterventions and admissions of patients.

Ethics

The study was conducted according to the principles of the Declaration of Helsinki and 'Good Clinical Practice' guidelines. The protocol was approved by the Medical Ethical Committee of the Erasmus MC University Medical Center Rotterdam and the local Ethical Committees of the participating centers. Prior to randomization, written informed consent was obtained from all patients.

Statistical analysis

Analyses were undertaken on an intention-to-treat basis with follow-up until death of all patients. The sample size calculation was based on the total time that patients were unable to eat at least a soft diet after both procedures. Time was log transformed. Assuming that patients with a stent were 1.8 days earlier able to eat a soft diet after treatment, 2x74 patients were calculated to be needed for an 84% power at the 5% level (t-test).

The GOOSS score at different time points was compared by using a mixed model, with treatment as fixed effect and repeated measurement of food intake as random effect. Friedman's supersmoother was used to smoothen the GOOSS adjusted survival curve.

Quality of life was scored according to standardized scoring algorithms to obtain scores for the various multi-item scales of the QLQ-C30 and QLQ-PAN26 and the index and VAS score for the EQ-5D. For each item, a total score was determined and linearly transformed resulting in a scale range of 0 to 100, with a higher score representing more symptoms. A better health status for the EQ-5D was represented as a lower score and for the VAS as a higher score. We compared quality of life scores with analysis of repeated measurements. For each scale, a model was fitted that included day and treatment group as fixed factors, and the baseline measure and interaction between day and treatment group as covariates.

Complications, reinterventions and survival between both treatments were compared with Kaplan-Meier curves and log-rank tests, whereas costs were compared with the Mann-Witney U test. We regarded two-sided p-values <0.05 as significant. Calculations were performed in SPSS (version 12.0, SPSS Inc. Chicago, IL), SAS (version 8.2, SAS Institute Inc. Cary, NC) and R (version 2.0.7, Statistical Computing, Vienna).

Role of the funding source

The funding source had no role in the study design, data collection, analysis and interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Patient characteristics

Figure 1 shows the trial outline and Table 1 the baseline patient characteristics for the two groups. Of the 77 patients eligible for the study, 38 patients refused to participate, as they preferred stent placement over GJJ. In total, 39 patients from 11 centers were randomized to GJJ or stent placement. No significant differences in baseline characteristics between the two treatment groups were found.

Food intake

Food intake improved more rapidly after stent placement than after gastrojejunostomy. After stent placement patients needed a median of 5 days to restore their ability to eat (GOOSS $\geq$2) whereas this was 8 days after GJJ ($p<0.01$). Starting at 30 days, a decrease in food intake was noticed in patients treated with a stent. After 60 days, food intake results were significantly better after GJJ than after stent placement ($p=0.05$). In addition, patients after GJJ had more days with a GOOSS $\geq$2 adjusted for survival than after stent placement (72 vs. 50 days; $p=0.05$) (Figure 2).

Complications and reinterventions

Table 2 shows technical problems, complications and reinterventions in both treatment arms. Technical problems occurred in 2 patients during GJJ and in 5 patients during stent placement. During GJJ, the procedure failed in 1 patient because of

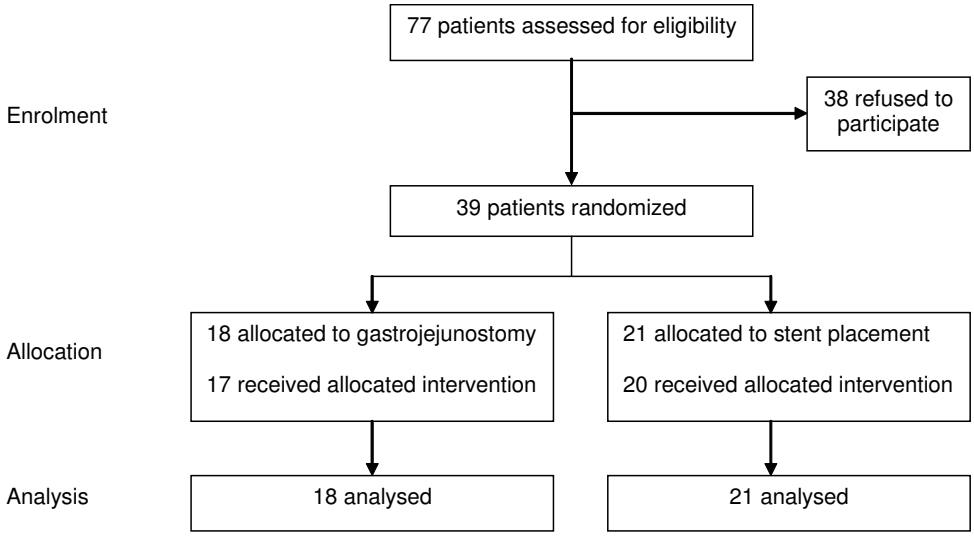


Figure 1. Trial profile

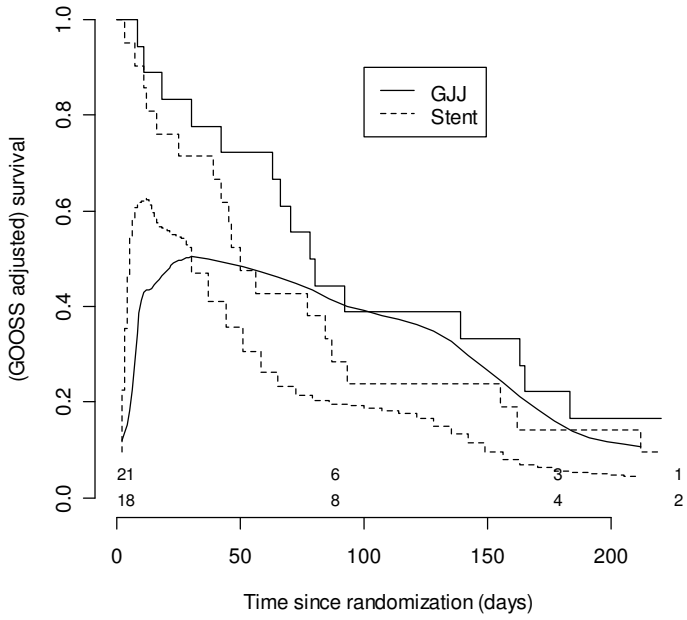


Figure 2. Kaplan Meier curve of the survival and Gastric Outlet Obstruction Scoring System (GOOSS score) adjusted for survival after stent placement and gastrojejunostomy

Table 1. Characteristics of 39 patients with malignant gastric outlet obstruction randomized for gastrojejunostomy (GJJ) or duodenal stent placement (Stent)

Characteristics	GJJ (n=18)	Stent (n=21)
Mean (±SD) age in years	66 (11.0)	66 (13)
Male gender (%)	9 (50)	11 (52)
Mean (±SD) GOOSS score before treatment	0.9 (0.7)	0.9 (0.8)
Location underlying cancer (%)		
Pancreas	13	15
Bile duct	1	0
Duodenum	1	3
Stomach	1	2
Papilla	1	0
Extrinsic due to metastases	1	1
Location of obstruction		
Proximal stomach	3	3
Bulbus	6	9
Descending part of duodenum	8	8
Horizontal part of duodenum	1	1
Mean obstruction length (cm, (±SD))	3.6 (1.3)	4.2 (1.8)
Percentage ingrowth (%, (±SD))	81 (22)	82 (24)
Indictation for palliative treatment (%)		
Irresectable	11 (59)	16 (76)
Metastases	8 (47)	10 (50)
Poor medical condition	2 (12)	0 (0)
Mean (±SD) WHO score	1.7 (0.9)	1.9 (0.9)

metastases in the peritoneal cavity. This patient did not undergo further treatment. In another patient, the small bowel was perforated during GJJ. This patient fully recovered. During stent placement 4 patients required additional stent placement during the same procedure to fully bridge the stricture. In one patient, stent placement failed because of inability to pass the stricture endoscopically. This patient was treated with GJJ. Major complications occurred more frequently after stent placement than after GJJ (6 in 4 patients vs. 0; p=0.02). One early major complication occurred after stent placement. This consisted of stent migration 3 days after stent placement, which was treated with additional stent placement. No early major complications were seen after GJJ (p=0.3).

Three patients randomized to stent placement developed 5 late major complications. In one patient obstruction by food debris occurred after 58 days and by

Table 2. Complications, recurrent and persistent obstructive symptoms, and reinterventions after gastrojejunostomy and stent placement

	GJJ (n=18)	Stent (n=21)	p-value
Technical problems	2	5	0.6
Major complications	0	6 in 4 patients	0.02
Minor complications	6 in 5 patients	4 in 4 patients	0.8
Persistent obstructive symptoms	3 in 3 patients	3 in 3 patients	0.9
Recurrent obstructive symptoms	1 in 1 patients	8 in 5 patients	0.02
Reinterventions	2 in 2 patients	10 in 7 patients	<0.01

tumor in- or overgrowth after 73 and 148 days. In the second patient, tumor in- or overgrowth occurred after 28 days. In the third patient obstruction by food debris occurred after 133 days. No late major complications were observed after GJJ. Late major complications occurred more frequently after stent placement than after GJJ ($p=0.04$).

Five patients randomized to GJJ developed 6 minor complications and 4 patients randomized to stent placement developed 4 minor complications ($p=0.9$). Minor complications after stent placement included bacterial infection ($n=1$) after additional treatment with GJJ for unsuccessful stent placement, and delayed gastric emptying ($n=3$) After GJJ, urinary tract infection ($n=1$), wound infection ($n=2$), delayed gastric emptying ($n=2$) and paralytic ileus for 9 days ($n=1$) were seen.

Persistence of obstructive symptoms occurred in 3 patients after GJJ and in 3 patients after stent placement ($p=0.9$). After GJJ one patient died within 4 weeks, and after stent placement 2 patients died within 4 weeks without improvement of food intake. Recurrent obstructive symptoms occurred in 1 patient after GJJ and in 5 patients after stent placement, with 2 patients developing multiple episodes of recurrent obstructive symptoms. Recurrent obstructive symptoms occurred more frequently after stent placement than after GJJ ($p=0.02$).

Reinterventions for delayed gastric emptying and for recurrent or persistent obstructive symptoms occurred more often after stent placement than after GJJ (10 in 7 patients vs. 2 in 2 patients; $p<0.01$). After stent placement, reinterventions included endoscopy with cleansing of the stent if necessary ($n=4$), second stent placement ($n=4$) and GJJ ($n=2$). After GJJ, the 2 patients underwent endoscopy for evaluation of recurrent obstructive symptoms, however, no indication for additional treatment was found.

Treatment for jaundice

Fourteen patients randomized for GJJ were also treated for jaundice. Ten patients underwent endoscopic biliary drainage prior to GJJ, whereas in 2 patients a choledochojejunostomy was performed during the GJJ procedure. During follow-up, another two patients developed jaundice of which one patient developed jaundice at three different episodes after initial treatment (range: 33-67 days). These two patients were treated by a percutaneously placed drain or endoscopic stent placement in the CBD respectively.

Fifteen patients randomized to stent placement were treated for jaundice, i.e., ten patients prior to duodenal stent placement, 2 during stent placement and four patients for jaundice that developed after duodenal stent placement. One of the latter patients developed cholangitis 15 days after stent placement and underwent endoscopic stent placement in the CBD. Another patient developed jaundice 5 days after stent placement and died 11 days after treatment due to progressive malignant disease. The third patient developed jaundice 31 and 54 days after treatment and was treated by a percutaneously placed drain. The last patient received a CBD stent prior to stent placement, but developed recurrent jaundice 14 days after duodenal stent placement, which was treated by a percutaneously placed drain.

Hospital stay and survival

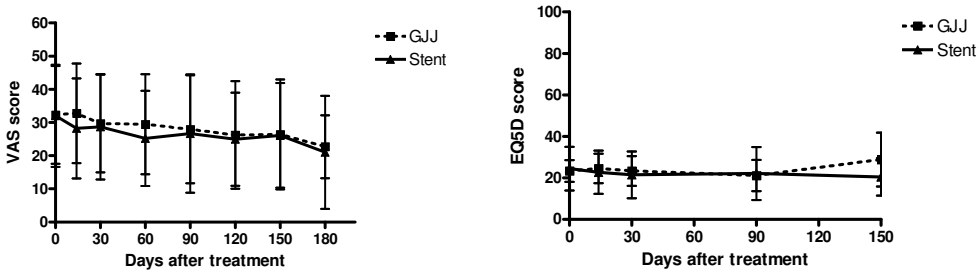
Hospital stay was shorter after stent placement than after GJJ (7 vs. 15 days, $p=0.04$). Median survival was 56 days after stent placement and 78 days after GJJ ($p=0.19$, Figure 2). By August 2008, all patients had died from progressive malignant disease.

Quality of life

HRQoL scores remained stable after both treatments. During follow-up, no significant differences were observed in quality of life scores at baseline and during follow-up in each treatment group for the EORTC QLQ-C30, EuroQol-5D (including the VAS-score), and EORTC QLQ-PAN26 questionnaires (Figure 3).

While pain and nausea symptoms diminished during follow-up in both treatment groups, pain scores decreased more rapidly after stent placement than after GJJ ($p=0.02$).

Patient satisfaction and patient preferences were not different between patients in the GJJ and stent placement group ($p=0.7$). Reasons for preferring stent placement included a shorter time to restore the ability to eat and a shorter hospital stay. On the other hand, GJJ was preferred because of fewer complications on the long



(a) (b)

Figure 3. Overall quality of life. (a) VAS score after treatment, with 95% CIs during follow-up, (b) EQ-5D score after treatment, with 95% CIs during follow-up

term and fewer reinterventions. Burden of treatment was not different between GJJ and stent placement (p=0.3).

Costs

Total medical costs on a per patient basis were lower for stent placement than for GJJ (€8,812 vs. €12,433, p=0.049) (Table 3). Higher costs for GJJ were largely due to a longer hospital stay after initial treatment (€7070 vs. €3240, p<0.001). Costs during follow-up were similar for GJJ and stent placement, except for the use of tube or additional drink feeding, with patients after GJJ using this more often than after stent placement (€130 vs. €109, p=0.04).

Discussion

This study compared the two most commonly used palliative treatments for malignant GOO, i.e. GJJ and duodenal stent placement. Stent placement resulted in a more rapid improvement of food intake, shorter hospital stay and lower total costs. At longer follow-up, GJJ had better results with regard to food intake and fewer major complications, recurrent obstructive symptoms and reinterventions.

The primary aim of palliative treatment in patients with malignant GOO is relief of obstructive symptoms and improvement of food intake. This study demonstrates that the median time to restore the ability to eat at least soft solids (GOOSS score $\geq$2) was 8 days after GJJ and 5 days after stent placement, which confirms that stent placement is more effective on the short term. These results are comparable

Table 3. Medical costs of gastrojejunostomy and stent placement

Average cost per patient (€)	GJJ (n=18)	Stent (n=21)	p-value
Initial costs			
Treatment[1]	1245	1573	<0.001
Hospital stay[2]	7070	3240	<0.001
Costs during follow-up			
Intramural care[3]	1753	1679	0.9
Medical procedures[4]	538	641	0.9
Diagnostic procedures	98	135	0.5
Curative procedures	440	506	0.7
Extramural care[5]	1557	1468	0.8
Medication	270	211	0.03
Symptom medication	140	102	0.4
Tube feeding/drink feeding	130	109	0.04
Total costs per patient	12.433	8812	0.049

[1] Includes initial treatment costs (including second stent placement during initial stent placement and GJJ because of failed stent placement or not functioning of the stent)

[2] Includes hospital stay after initial treatment

[3] Includes additional hospital stay and visits to outpatient clinics

[4] All medical procedures during follow-up

[5] Includes visits to family practitioner, nursing care at home and nursing homes

to results reported in a recent review on duodenal stent placement, in which it was reported that patients were able to eat after a mean time of 4 days after stent placement.[21] In addition, another study reported a statistically significant difference in time to restore the ability to eat between GJJ and stent placement (9 vs. 1 days).[22] Our results also show that after a follow-up of 60 days, more patients in the GJJ group had a GOOSS score $\geq$2, which suggests that the surgical procedure was particularly more effective after a longer follow-up. This is at least partly explained by the fact that GJJ is a more invasive procedure requiring a longer recovery time for the gastric and bowel function to adapt to the new anatomical situation compared to stent placement. In addition, the occurrence of complications and recurrent obstructive symptoms may have affected the food intake results. Following stent placement, more patients developed recurrent obstructive symptoms. However, as obstructive symptoms occurred in only 5/21 (24%) of the stented patients, it seems unlikely that this had caused the inferior long term results of food intake

in this group. Alternatively, we suggest that this may have been caused by subtotal obstruction of the stent, caused by food debris and/or tissue in- or overgrowth, in addition to a relatively large capacity of the stomach to accumulate food. Consequently, stented patient may only seek medical attention when complete obstruction occurs, resulting in a clear cut picture with typical symptoms of GOO (i.e. nausea, vomiting and dehydration).

Late major complications and reinterventions occurred more frequently after stent placement than after GJJ, suggesting a more favorable long term outcome after GJJ. The most common complication was stent obstruction by hyperplastic and/or tumor in- or overgrowth, which is one of the main concerns with non-covered metal stents. Although not used in this study, covered duodenal stents have been shown to be associated with an increased risk of stent migration.[7,23–26] Therefore, we advocate the use of uncovered stents in this position, until newer design covered stents indeed have been shown to be no longer prone to migration.

Until now, reviews have not reported differences in complication rates between GJJ and stent placement.[8,27] This is at least partly, due to different definitions used. For example, Hosono et al. did not differentiate between major and minor complications.[27] On the other hand, a retrospective, comparative study using similar definitions reported almost similar results as were reported in the current trial.[28] The use of uniform definitions in future studies may improve comparability between separate studies. In addition, we defined stent obstruction also as a major complication in contrast to previous studies. We realize that this can be disputed. Some authors consider upper endoscopy with additional stent placement in case of recurrent obstruction to be a non-invasive treatment and therefore not a major complication.[9,21,27,29] However, we do believe that reinterventions, regardless what type, are burdensome to patients, particularly in those with progressive malignant disease.

Apart from food intake over time and complications, we also studied persistence of obstructive symptoms, as this is a common symptom after palliative treatment in patients with malignant GOO. Our results showed that this was not different between the two palliative treatments. This was also reported in a previous review and a retrospective, comparative study.[8,28] Persistence of obstructive symptoms likely occurs as a consequence of impaired gastric motility, possibly due to progressive neural infiltration by tumoral tissue. This explains why no difference in the occurrence of persistent obstructive symptoms was found between the two treatment modalities.

Placement of a duodenal stent at the level of the ampulla of Vater may prevent access to the common bile duct by ERCP for treatment of jaundice and cholangitis. In 1/4 patients, who developed symptoms of CBD obstruction following duodenal

stent placement, a stent was placed endoscopically in the CBD, whereas in 2/4 patients a percutaneous procedure was preferred. This highlights the importance to consider placement of a CBD stent at an early stage, preferably prior to duodenal stent placement.[30,31]

Previous studies have suggested that an open surgical procedure for performing a GJJ was associated with a higher risk of complications, a longer hospital stay and longer time to resume a light diet, compared to a laparoscopic procedure.[32–34] In our study, GJJ was performed as an open procedure in 16 patients and laparoscopic in 2 patients. Although it seems likely that the short term effects of laparoscopic GJJ are better compared to open GJJ, both procedures have only been evaluated and compared in small populations. Therefore, a large randomized trial comparing both surgical procedures is indicated.

Apart from medical effects, we measured quality of life during follow-up. Health-related quality of life is important in patients diagnosed with incurable progressive disease.[35] The results of this study clearly demonstrate that HRQoL scores between the two palliative treatments during follow-up were not different. Results of palliation of GOO from the perspective of patients have not previously been reported. Only Mehta et al. reported higher physical health scores 1 month after stent placement compared to GJJ.[36] As QoL scores remained stable over time in patients treated with either GJJ or stent placement, it can be concluded that both modalities probably effectively palliate obstructive symptoms from the perspective of patients.

Finally, we measured total costs of both palliative treatments. We found that total costs were higher for GJJ compared to stent placement, which was similar to the findings of Johnsson et al.[37] Higher costs of GJJ were largely due to a prolonged initial hospital stay compared to stent placement. Nevertheless, in our opinion, costs should not be the predominant argument for a preference of stent placement over GJJ. As stent placement was associated with better results at the short term and GJJ had more favorable results on the long term, the prognosis of individual patients should be leading if one considers either stent placement or GJJ in this patient group with a dismal prognosis.

Here, we report the largest randomized study comparing stent placement with GJJ for GOO so far. Other studies randomized 18 and 27 patients respectively.[36,38] However, as the sample size of our study was still small, this may well have affected our results. The relatively small size of the study was largely due to the fact that 50% of patients eligible for this study refused participating, with the majority of them preferring stent placement. In our opinion, this emphasizes that a randomized trial between an endoscopic procedure on the one hand and a surgical procedure one the other hand is difficult to perform. This is likely to be due to the expected

invasiveness by patients of the surgical procedure. As our sample size calculation was based on a smaller difference in time to restore food intake, we were still able to find a borderline statistical significant p-value in favor of GJJ for the primary outcome. Therefore, our results can well be used when a decision needs to be made which palliative treatment modality, either stent placement or GJJ, should be used in individual patients with malignant GOO.

Based on the results of this study, we recommend GJJ as the primary treatment in patients with an expected survival of 2 months or more, whereas stent placement is the preferred modality for patients who are expected to live shorter than 2 months.

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Chapter 5

Use of a colonoscope for distal duodenal stent placement in patients with malignant obstruction

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Abstract

Background: Stent placement in the distal duodenum or proximal jejunum with a therapeutic gastroscope can be difficult, because of the reach of the endoscope, loop formation in the stomach, and flexibility of the gastroscope. The use of a colonoscope may overcome these problems. The objective of this study is to report our experience with distal duodenal stent placement in 16 patients using a colonoscope.

Methods: Multicenter, retrospective series of patients with a malignant obstruction at the level of the distal duodenum and proximal jejunum and treated by stent placement using a colonoscope. Main outcome measurements are technical success, ability to eat, complications, and survival.

Results: Stent placement was technically feasible in 93% (15/16) of patients. Food intake improved from a median Gastric Outlet obstruction Scoring System (GOOSS) score of 1 (no oral intake) to 3 (soft solids) (p=0.001). Severe complications were not observed. One patient had persistent obstructive symptoms presumably due to motility problems. Recurrent obstructive symptoms were caused by tissue/tumor ingrowth through the stent mesh (n=6 [38%]) and stent occlusion by debris (n=1 [6%]). Reinterventions included additional stent placement (n=5 [31%]), gastrojejunostomy (n=2 [12%]), and endoscopical stent cleansing (n=1 [6%]). Median survival was 153 days.

Conclusion: Duodenal stent placement can effectively and safely be performed using a colonoscope in patients with an obstruction at the level of the distal duodenum or proximal jejunum. A colonoscope has the advantage that it is long enough and offers good endoscopic stiffness, which avoids looping in the stomach.

Introduction

Patients with gastrointestinal malignancies may develop an obstruction at the level of the duodenum. The largest group consists of patients with pancreatic cancer, who develop in 10-20% of cases a gastric outlet obstruction (GOO).[1–3] Other causes of GOO include periampullary carcinoma, lymphoma, primary duodenal carcinoma as well as metastases to the duodenum.[4–6]. Palliative treatment of GOO is mandatory as it is associated with a rapid deterioration of the clinical status due to vomiting, dehydration and malnutrition.[2]

Stent placement is a commonly used palliative treatment, because this modality is less invasive compared to a surgically performed gastrojejunostomy. In addition, results of small randomized trials concluded that stent placement superior over gastrojejunostomy.[7,8] Stent placement in patients with a malignant obstruction at the level of the distal stomach or proximal duodenum (superior, descending and first half of the horizontal part) is routinely performed with a therapeutic gastroscope. However, stent placement in the distal part of the duodenum (second half of the horizontal part and ascending part of the duodenum) or proximal jejunum with a therapeutic gastroscope can be difficult. The main factors limiting the use of a gastroscope for distal duodenal stenting are the relatively short endoscope length, and shaft flexibility which may cause looping of the scope into the stomach. The use of a colonoscope may potentially overcome these problems.[6,9–11]

In this series, we report our experience with distal duodenal stent placement in 16 patients using a colonoscope.

Patients and methods

Patients

All patients with a malignant obstruction at the level of the distal duodenum and proximal jejunum and treated by stent placement using a colonoscope at the Erasmus MC-University Medical Center Rotterdam, The Netherlands, the University Medical Center Utrecht, The Netherlands and Istituto Clinico Humanitas, Milan, Italy in the period 2001 to 2006 were included. Data were obtained from the clinical records and endoscopy report databases at both centers, and by telephone interviews with patients and/or their treating physicians or general practitioners. Information that was collected included demographic information, procedural characteristics, and follow-up information on complications, persistent and recurrent obstructive symptoms, re-interventions and survival.

Endoscopic procedure

All stents were placed using a colonoscope after an intravenous dose of midazolam (Roche, Basel, Switzerland), or propofol (AstraZeneca, Zoetermeer, The Netherlands). The length of the stricture was determined using contrast fluoroscopy of the duodenum during the procedure. A guide wire was then introduced through the stricture and the stent was advanced over the wire. Stent length was chosen to aim at a length of 1-2 centimeters more than the stricture. Endoscopy and fluoroscopy were used to follow stent deployment. Immediately after the procedure, an upright abdominal X-ray was performed to assess that no perforation had occurred during the procedure.

Follow-up information

Food intake was measured by the standardized Gastric Outlet Obstruction Scoring System (GOOSS score), with 1=no oral intake, 2=liquids only, 3=soft solids and 4=full diet.[2] The GOOSS score was measured before and one week after stent placement. Based on this score, clinical success was defined as relief of symptoms and improvement of oral intake until at least soft solids (GOOSS=3) one week after the procedure. Technical success of stent placement was defined as adequate positioning and deployment of the stent with complete bridging of the stenosis.

Complications included life-threatening or severe complications, for example perforation and stent migration. Persistent obstructive symptoms were defined as continuing obstructive symptoms occurring within 2 weeks after the intervention, whereas recurrent obstructive symptoms were defined as symptoms occurring more than 2 weeks after treatment. A re-intervention was defined as a treatment for a complication, or persistent or recurrent obstructive symptoms.

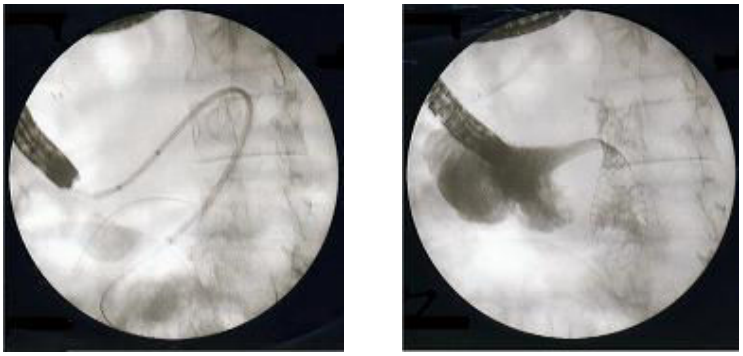
Statistics

The GOOSS score before and one week after stent placement was compared with the Wilcoxon rank sum test. Survival was calculated by Kaplan-Meier analysis. Calculations were performed with SPSS 12.0. A two-sided p-value <0.05 was considered statistically significant.

Results

Patient characteristics

In the period 2001-2006, enteral Wallstents (Boston Scientific, Natick, MA) (n=12) or Wallflex stents (Boston Scientific) (n=4) were placed using a colonoscope in 16



(a) (b)

Figure 1. Distal duodenum stent placement using a colonoscope. a) Introduction of the guidewire and advancing the stent introduction system over the wire. b) Partly deployed stent at the duodenojejunal flexure (Treitz ligament)

patients (11 men, 5 women). Table 1 shows the baseline characteristics of these patients (mean age: 70.1 ± 9.4 years). Obstruction was caused by pancreatic cancer (n=8), duodenal cancer (n=2), colorectal cancer (n=2), lymphoma (n=1) and metastases from renal cell (n=1), lung (n=1) and liver cancer (n=1). Sites of obstruction were the second half of the horizontal and ascending part of the duodenum (n=10), duodenojejunal flexure (n=5) and proximal jejunum (n=1). Main study outcomes are shown in Table 2.

Technical success

In 9 patients, initial stent placement using a gastroscope was unsuccessful. In all these patients a GIF-1T145 gastrocope (Olympus America Inc., Center Valley, PA, USA) had been used. Therefore, this endoscope was changed for a colonoscope (CF0165 or CF0180 colonoscope, Olympus Japan Inc.). In the following 7 patients, we primarily used a colonoscope (CF0165 or CF0180 colonoscope, Olympus Japan Inc.). Stent placement with a colonoscope was technically feasible in 93% (15/16) of patients (Figure 1). In one patient, persistent obstructive symptoms were present after the procedure. It was found that the primary stent had not completely bridged the tumor. In this patient, a second stent was placed one day later.

Food intake

Food intake improved in all patients (improvement of median GOOSS score from 1 (before stent placement) to 3 (one week after) (p=0.001)). One patient was only

Table 1. Characteristics of 16 patients treated with distal duodenum stent placement using a colonoscope

Pat	Age	Gender	Obstruction site	Technical success	GOOSS score		Complications	Recurrent obstruction	Persistence	Reintervention	Survival (days)
					Before	After					
1	67	F	Horizontal part	Yes	1	3	No	Tissue/Tumor ingrowth at day 92 and 242	No	Stent placement (2x)	365
2	55	F	Ascending part	Yes	1	4	No	No	No	No	184
3	87	M	Horizontal part	Yes	2	3	No	No	No	No	184
4	73	M	Horizontal part	Yes	3	4	No	No	No	No	120
5	69	M	Horizontal part	Yes	2	4	No	No	No	No	153
6	71	M	Ascending part	Yes	2	4	No	Tissue/Tumor ingrowth at day 63	No	Stent placement	168
7	76	F	Horizontal part	Yes	2	3	No	Tissue/Tumor ingrowth at day 241	No	Gastrojejunostomy	243
8	81	M	Ascending part	Yes	2	3	No	Tissue/Tumor ingrowth at day 273	No	Stent placement	302
9	78	M	Proximal jejunum	Yes	2	4	No	Debris in stent at day 21	No	Endoscopy	273
10	81	M	Ascending part	Yes	2	3	No	No	No	No	138
11	51	M	Ascending part	Yes	2	3	No	Obstructive symptoms at day 30	No	Gastrojejunostomy	165
12	66	M	Horizontal part	Yes	2	3	No	Tissue/Tumor ingrowth at day 54	No	Stent placement	111
13	66	F	Horizontal part	Yes	2	4	No	No	No	No	13
14	64	M	Horizontal part	Yes	1	4	No	No	No	No	26
15	71	M	Horizontal part	No	1	3	No	No	No	No	21
16	66	F	Horizontal part	Yes	1	2	No	No	Yes	No	18

Table 2. Main outcomes of duodenum stent placement using a colonoscope in 16 patients with an obstruction in the distal duodenum or proximal jejunum

Main outcomes	Patients (n=16)
Technical success (%)	15 (93)
Clinical success (%)	15 (93)
Complications (%)	0 (0)
Recurrent obstruction (%)	7 (44)
Persistent obstruction (%)	1 (6)
Reinterventions (%)	8 (50)*
Median survival (days ±SD)	153±27

* one patient had tissue/tumor ingrowth at day 92 and 242, for which 2 stents were placed

able to drink liquids one week after stent placement (GOOSS score: 2). Clinical success was therefore considered to be 94% (15/16).

Complications

Severe complications were not observed during the follow-up period. Recurrent obstructive symptoms occurred in 7 patients after a median of 240 days (range 13 to 270) due to tissue/tumor ingrowth (n=7) and stent occlusion by debris (n=1). One patient suffered twice of tumor ingrowth, 92 days and 242 days after initial stent placement.

Persistence of obstructive symptoms occurred in one patient with motility problems. This patient refused additional treatment and died 18 days after stent placement from progressive tumor growth.

Reinterventions were only performed for recurrent obstructive symptoms and included stent placement (n=5), gastrojejunostomy (n=2) and endoscopical cleansing of the stent (n=1). Subsequent gastrojejunostomy was performed in two patients with tumor overgrowth because a second stent could not be placed.

Survival

The 30-day mortality rate was 25% (4/16). Median survival was 153 days, with 4 patients still being alive at the end of our follow-up period (January 1, 2007).

Discussion

The results of this study show that distal duodenal/proximal jejunal stent placement using a colonoscope is safe and effective. It was demonstrated that a colonoscope was a good alternative for a gastroscope in this situation.

In the first 9 patients, stent placement was initially performed with a gastroscope. However, stent placement failed because of looping of the gastroscope in the stomach resulting in inability of the endoscope to reach the malignant stricture. For that reason, the gastroscope was changed for a colonoscope.

In our experience, when a therapeutic gastroscope is used for stent placement in the distal part of the duodenum or proximal jejunum, three potential problems may occur. First, the length of the gastroscope may be insufficient because of looping in the stomach. Looping is more likely to occur if the stomach and proximal duodenum are dilated particularly if the stricture in the duodenum/jejunum has existed for a prolonged period of time. Second, when looping occurs, the resulting friction between the stent and the working channel of the endoscope may prevent the stent from being advanced out of the endoscope. Third, even when the stent can be advanced close to an often angulated stricture, the ability to maintain the gastroscope in a stationary position in the duodenum is reduced. The resistance offered by an angulated stricture may result in a retrograde force pushing the gastroscope back into the stomach, even if a super-stiff guidewire is advanced through the endoscope. The colonoscope is obviously longer, provides more stiffness in these cases and avoids looping in the stomach, resulting in a stable position close to a stricture distal in the duodenum and proximal jejunum. In addition, Ross et al. reported the use of double balloon enteroscopy in combination with a colonoscope. The technical advantages of this technique may allow endoscopic stent placement in patients with a single point of obstruction that is beyond the reach of conventional endoscopes and existing stent delivery systems.[12] In our opinion, a newly designed endoscope with specifications for duodenal stent placement should provide the following features: 1) a large working channel which makes stent placement over the guidewire possible, 2) adequate stiffness of the endoscope without increasing the diameter, and 3) sufficient length of the endoscope to reach distal strictures.

To the best of our knowledge, stent placement for obstructions in the distal duodenum or proximal jejunum using a colonoscope has not previously been reported, although Baron et al. already mentioned the usefullness of this technique.[13] We compared our results with those summarized in a recent systematic review summarizing stent placement for malignant strictures in the distal stomach or proximal duodenum.[14] Results on food intake, technical success, complications and persistent symptoms were not different. However, mean survival after stent placement was

longer in our study population (184 vs. 85 days). This difference may result from differences in clinical condition. Unfortunately, this was not clearly stated in the medical records and is therefore unknown. In addition, recurrent obstructive symptoms appeared to have occurred more frequently in our patient population (44% vs. 22%), most often due to tissue/tumor ingrowth. This can probably be explained by the fact that Dormann et al. included results of both uncovered and covered stents.[14] Remarkably, 13% (80/606) patients in this review were treated with a covered esophageal stent placed in the distal stomach/proximal jejunum. A clear drawback of uncovered stents in the duodenum is the occurrence of hyperplastic tissue or tumor growth through the mesh of the stent.[15–17] In the present study, we only used uncovered stents, whereas a second uncovered stent for tissue or tumor ingrowth was performed for six occluded stents in 5 patients. The use of covered stents in the duodenum may overcome this problem of tissue/tumor ingrowth. The evidence for the safe use of covered stents in the duodenum is however conflicting in that on the one hand this design may prevent tissue or tumor ingrowth, but, on the other hand, covered stents are more likely to migrate than uncovered stents.[6,18] In addition, the longer survival in our patient series compared to that in the review by Dorman et al. may also have resulted in a higher incidence of recurrent obstructive symptoms. In this regard, it is important to emphasize that patients with a good prognosis could potentially have more benefit from a laparoscopic gastrojejunostomy as this palliative treatment has been suggested to be associated with a lower incidence of recurrent obstructive symptoms compared to stent placement.[19] If one has to decide on the most optimal treatment option, it could well be that patients with a poor clinical condition may have more benefit from stent placement, whereas gastojejunostomy should be reserved for those with an expected longer survival. Nevertheless, a large randomized trial has not been performed yet.

Finally, stent placement in the distal duodenum has the advantage that malignant biliary obstruction occurring after duodenal stent placement is not precluding the possibility to perform biliary drainage by ERCP at a later time point. Biliary obstruction occurs in 2-8% of patients after stent placement in the proximal duodenum.[1,2,20,21] It is often difficult or even impossible to cannulate the papilla through the mesh of an uncovered stent. Therefore, in many centers, prior to stent placement in the proximal duodenum, a stent is placed in the common bile duct.[22]

Our results indicate that duodenal stent placement can effectively and safely be performed using a colonoscope in patients with an obstruction at the level of the distal duodenum or proximal jejunum. A colonoscope has the advantage that it is long enough and offers good endoscopic stiffness, which avoids looping in the stomach.

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Part II

Treatment of pancreatico-biliary disorders: complications of ERCP

Chapter 6

Endoscopic retrograde cholangiopancreatography as an outpatient treatment: a review

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Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP) on an outpatient basis could be as safe as on an inpatient basis and may also reduce medical costs. The objective of this study is to review the available literature to determine safety of ERCP performed on outpatient basis.

Methods: A review of the published literature was performed by searching PubMed, the Cochrane Library, EMBASE and Web of Science. Main outcome measurements are patient and treatment characteristics, complications, prolonged hospital admissions and readmissions.

Results: Eleven studies were included in this review, of which five were comparative studies, five prospective studies and one retrospective study. A total of 2483 patients underwent ERCP on an outpatient basis and 2320 patients were admitted overnight after ERCP in these series. Complications were seen in 184/2483 (7%) outpatients, of which 72% (107/149) presented within 2-6 hours, 10% (15/149) within 6-24 hours and 18% (27/149) more than 24 hours after ERCP. Three percent (82/2320) of inpatients developed a complication, of which 95% (78/82) presented within 24 hours and 5% (4/82) more than 24 hours after ERCP. Prolonged hospital stay after ERCP was indicated in 6% (148/2483) of the designated outpatients, whereas 3% (74/2149) of outpatients and $<$1% (4/2320) of inpatients were readmitted after discharge.

Conclusion: This review shows that with a selective policy, ERCP on an outpatient basis seems as safe as when performed on an inpatient basis.

Background

In many institutions, patients are admitted for an overnight observation to detect complications after endoscopic retrograde cholangiopancreatography (ERCP). Results from several studies have shown that 7-10% of the patients develop a complication after ERCP.[1] Risk factors for the development of post-ERCP complications are well established and largely depend on treatment and patient characteristics. For instance, patient-related risk factors include for example sphincter of Oddi dysfunction and history of post-ERCP pancreatitis, whereas treatment-related risk factors include biliary sphincterotomy and moderate to difficult cannulation.[2] The most commonly reported complication after ERCP is the development of pancreatitis (1-5%).[3] Other complications are cholangitits (1-5%), hemorrhage (1%) and perforation (1-2%).[4,5]

Recently, it has been suggested that ERCP can be performed on an outpatient basis. Since most complications occur within 2-4 hours, same-day discharge could therefore be safe.[6] In addition, cost containment is nowadays a high priority in many hospitals. ERCP on an outpatient basis could reduce the use of medical health care resources. So far, only one randomized study has been performed in which outpatients and inpatients were compared with respect to complications and costs.[7] This publication is however only available in the Spanish language.

We aimed to review the available literature to determine safety of ERCP performed on an outpatient basis. The main outcomes were patient and treatment characteristics of patients undergoing ERCP, complications, prolonged hospital admissions and readmissions.

Patients and methods

A review of the published literature was performed by searching PubMed, the Cochrane Library, EMBASE and Web of Science in the period January 1980 to May 2007, combining the following search terms: ERCP, outpatient, ambulatory daycare and same-day discharge. A total of 102 studies were found using these search terms of which 17 studies reported results of ERCP on an outpatient basis. Six publications were excluded because they were only available in the Spanish language (n=2) or only the abstract (n=4) was available. This resulted in a total of 11 studies to be included in this review. In 8 articles complications were defined according to consensus criteria.[5,6,8–13] In the other 3 articles no defintion for complications was given.[1,14,15]

In- and exclusion criteria outpatients

The articles included in this review used similar criteria for patients to be eligible to undergo ERCP on an outpatient basis. The criteria included: a relative good health (ASA I or II), no deteriorating illnesses, no evidence of cholangitis or sepsis, corrected coagulopathy, living within 30 minutes driving distance from the hospital, not already being admitted to the hospital, and escorted by a second person.

Definitions

For this review, we used the following definitions:

- **Prolonged hospital stay**: hospital admission longer than 2-6 hours in outpatients and longer than 24 hours in inpatients.
- **Readmission**: readmission after initial discharge in outpatients (admitted for a maximum of 2-6 hours) and inpatients (admitted for a maximum of 24 hours).
- **Complications within the observation period**: complications within 2-6 hours after ERCP in outpatients and within 24 hours in inpatients.

Statistics

Data of the included studies on patient and treatment characteristics, complications and hospital (re)admission were pooled. Pooled odds ratios (OR) were determined for complications using results from the comparative studies. A forest plot was made to examine consistency of study results. In the forest plot, ORs were represented as a box with 95% CI on both sides of the box, with the size of the box representing the weight of each trial. ORs were not available when the event was present or absent in all patients. The statistical analysis focused on results from the comparative studies, and considered outcomes reported per study. Calculations were done with SPSS 12.0 and RevMan 4.2.

Results

Study characteristics

A total of 11 studies were included in this review, of which five comparative studies, five prospective studies and one retrospective study. Study characteristics are shown in Table 1. A total of 2483 patients underwent ERCP on an outpatient basis (mean

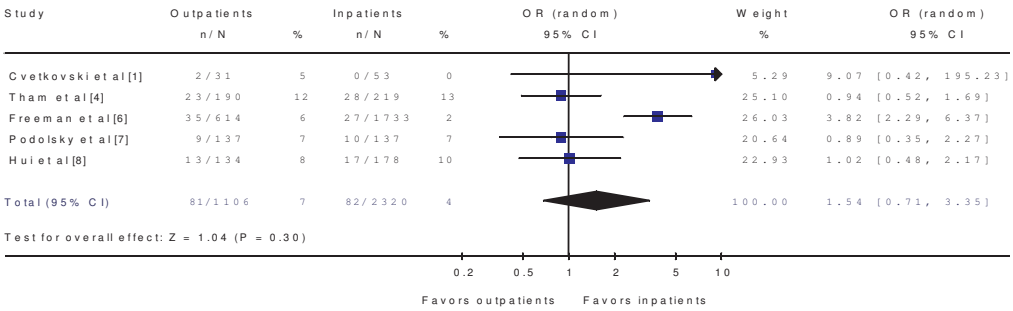

Figure 1. Odds ratios (OR) and 95% confidence interval (CI) of complications after ERCP in patients undergoing ERCP either with a 2-6 hours observation period (outpatients) or with an overnight observation (inpatients)

age: 61, range 52-76 years) and 2320 patients had an overnight observation after ERCP (mean age: 68, range 61-78 years).

Indications for ERCP in inpatients and outpatients are shown in Table 2. Most patients underwent ERCP for treatment of common bile duct stones (outpatients: 38% (947/2483); inpatients: 53% (311/587)).

In total, 2908 ERCP procedures were performed in 2483 outpatients, while 2407 ERCP procedures were performed in 2320 inpatients. The most commonly performed ERCP procedure was biliary sphincterotomy in 39% (1128/2908) of the outpatient procedures and in 82% (1965/2407) of the inpatient procedures. Other less frequently performed procedures were stone extraction and dilation (Table 3).

Complications

Seven percent (184/2483) of the outpatients developed a complication after ERCP, including post-ERCP pancreatitis in 4% (108/2483), hemorrhage in 1% (26/2483), cholangitis in 1% (21/2483) and other complications, such as perforation, pain or cholecystitis in 1% (29/2483). Three percent (82/2320) of the inpatients developed a complication after ERCP, including post-ERCP pancreatitis in 1% (29/2320), hemorrhage in 1% (15/2320), cholangitis in $<$1% (5/2320) and other complications in 1% (33/2320) (Table 4). OR was analyzed for complications using the 5 comparative studies (Figure 1).[1,6,8–10] The frequency of complications was not statistically significant between ERCP on an outpatient or inpatient basis (7% vs 4%, OR: 1.54, CI: 0.71-3.39, p=0.3).

Complications in outpatients occurred within 2-6 hours in 72% (107/149), of which at least 82% (88/107) occurred within 4 hours. Ten percent (15/149) of the

Table 1. Characteristics and outcomes on complications, prolonged hospital admission and readmission of the included case series

Author	Inclusion period	N	Intervention	n	Complications (%)	Prolonged admission	Readmission	Impact factor
Comparative studies								
Cvetkovski et al[1]	1996-1007	84	Outpatients	31	2 (5.0)	2	0	2.0
			Inpatients	53	0 (0.0)	0	0	
Tham et al[6]	*NA*	409	2 hour observation	190	23 (11.6)	26	5	2.0
			Overnight observation	219	28 (13)	28	*NA*	
Freeman et al[8]	1992-1994	2347	Same-day discharge	614	35 (5.7)	27	35	2.0
			Overnight observation	1733	27 (1.6)	27	*NA*	
Podolsky et al[9]	1996-1997	716	2-4 hour observation	137	9 (6.6)	9	0	2.0
			Overnight observation	137	10 (7.3)	10	*NA*	
Hui et al[10]	1996-2000	312	6 hour observation	134	13 (9.7)	13	2	1.7
			Overnight observation	178	17 (9.6)	13	4	
Prospective studies								
Ho et al[5]	1994-1997	415	2 hours observation	415	39 (9.4)	29	12	2.0
Mehta et al[11]	*NA*	209	1-4 hours observation	209	15 (5.7)	7	2	4.8
Mahnke et al[12]	2003-2004	419	Outpatients	334	18 (5.4)	18	*NA*	*NA*
Elfant et al[14]	1994	97	1-3 hours observation	97	5 (5.1)	1	2	5.1
Fox et al[13]	*NA*	82	Outpatients	82	11 (13.4)	2	7	1.7
Retrospective study								
Duncan et al[15]	20 months	240	2 hours observation	240	14 (5.8)	14	9	1.7

NA not available

Table 2. Indications for ERCP in out- and inpatients

Diagnosis	Outpatients (n=2483)(%)*	Inpatients (n=587)(%)*
Common bile duct stones	947 (38)	311 (53)
Malignant stricture	399 (16)	112 (19)
Pancreatitis	256 (10)	3 (1)
Sphincter of Oddi dysfunction	214 (9)	6 (1)
Benign biliary stricture	123 (5)	1 (<1)
Papillary stenosis	70 (3)	21 (4)
Cholangitis	60 (2)	25 (4)
Ampullary neoplasm	31 (1)	2 (<1)
Pancreatic carcinoma	24 (1)	42 (7)
Pancreatic stones	16 (1)	0 (0)
Other	446 (18)	64 (11)

* Patients could have more than one indication for ERCP

complications occurred within 6 to 24 hours and 18% (27/149) more than 24 hours after ERCP. Complications in inpatients occurred within the observation period of 24 hours in 95% (78/82) and more than 24 hours after ERCP in 5% (4/82) (Table 4).

Hospital (re)admission

Prolonged hospital stay after ERCP occurred in 6% (148/2483, range 2-14%) of the outpatients (Table 4). This was largely due to the development of complications during or shortly after ERCP. Nine outpatients were admitted for a period longer than 24 hours for observation of symptoms or adverse events that developed during or shortly after ERCP, which however did not progress to complications. Readmission occurred in 3% (74/2149, range 0-6%) of outpatients. Hospital admission was longer than 24 hours in 3% (78/2320) of inpatients because of complications. Four inpatients (<1%) were readmitted for complications after initial discharge.

Costs

Only one study determined costs related to ERCP on an outpatient basis.[6] The additional costs for admitting a patient for an observation after ERCP in this study was $805 for each 24 hours being admitted. The estimated cost savings for 100 patients undergoing an outpatient ERCP would therefore be $805 x 84 (which is the number of patients who would not have required routine admission after the

Table 3. Procedures performed during ERCP in patients undergoing ERCP on an out- and inpatient basis

ERCP procedure	Outpatients[1] n(%)	Inpatients[2] n(%)
Biliary sphincterotomy	1128 (39)	1965 (82)
Biliary or pancreatic sphincterotomy[3]	339 (12)	131 (5)
Stent placement	782 (27)	197 (8)
Stone extraction	126 (4)	4 (<1)
Dilation	104 (4)	6 (<1)
Other[4]	312 (10)	104 (4)
Diagnostic	117 (4)	0 (0)

[1] 2908 ERCP procedures performed in 2483 outpatients

[2] 2407 ERCP procedures performed in 2320 inpatients

[3] Some studies did not distinguish between biliary and pancreatic sphincterotomy

[4] ERCP unsuccessful in 50 (2%) outpatients and 11 (<1%) inpatients; difficult cannulation in 49 (2%) outpatients and 59 (2%) inpatients

procedure in this study) resulting in $676,20 per patient undergoing ERCP on an outpatient basis.

Discussion

The results of this review show limited evidence that ERCP on an outpatient basis is as safe as ERCP on an inpatient basis. However, our results do suggest that with a selective policy, outpatient ERCP could well be an option and is likely to reduce costs of medical care. Despite the variation in complications and hospital (re)admission rates between different studies, the larger series showed similar tendencies in results for outpatients and inpatients if outpatient ERCP was performed with a selective policy. This suggests that complications resulting in prolonged hospital stay did not differ for ERCP performed on an outpatient or inpatient basis.[5,8,9] Moreover, delayed complications, leading to a readmission, were rarely seen in the majority of series.[1,9–11] Although the results of the comparative studies suggest a trend towards more complications after ERCP on an outpatient basis compared to ERCP on an inpatient basis, this effect may be due to the small patient populations of the comparative studies.

Our results show that 10% of the outpatients with a post-ERCP complication, developing between 6 and 24 hours after ERCP, needed readmission for treatment

Table 4. Complications and hospital (re)admission in patients after an ERCP on an out- and inpatient basis

	Outpatients (%)	Inpatients (%)
Total complications after ERCP	184/2483 (7)	82/2320 (3)
Pancreatitis	108/2483 (4)	29/2320 (1)
Hemorrhage	26/2483 (1)	15/2320 (1)
Cholangitis	21/2483 (1)	5/2320 (1)
Other	29/2483 (1)	33/2320 (1)
Complications within observation period[1]	107/149[2] (72)	78/82 (95)
Complications within 6-24h	15/149 (10)	*NA*
Complications after 24h	27/149 (18)	4/82 (5)
Prolonged hospital admission[3]	148/2483 (6)	78/2320 (3)
Readmission[4]	74/2149 (3)	4/2320 (<1)

[1] Complications within 2-6 hours after ERCP in case of outpatients and within 24 hours in case of inpatients

[2] Of which at least 88 complications developed within 4 hours after ERCP

[3] Hospital admission longer than 2-6 hours in case of outpatients and longer than 24 hours in case of inpatients

[4] Readmission after initial discharge in case of outpatients (admitted for 2-6 hours) and inpatients (admitted for a maximum of 24 hours

NA not available

or observation. Unfortunately, it is unknown whether these patients already had one or more risk factors for developing post-ERCP complications. Several studies have suggested that patient and treatment characteristics may influence the risk for post-ERCP complications. For example, a previous episode of pancreatitis, multiple attempts to cannulate the common bile duct, or sphincter of Oddi dysfunction (SOD) are such risk factors.[2,16–18]

The reviewed studies did not state that patients were systematically followed-up after ERCP. Although it is unlikely that patients did not contact the treating physician, either directly of through consultation of the hospital where the patient was admitted for this complication, it is still possible that the complication rate in outpatients may have been underestimated. In all studies, patients and their escorts were given detailed information when to notify the hospital, particularly if any symptoms suggestive of a complication, such as pain, fever or melena, developed.

Four inpatients died shortly after ERCP. Three patients died after a complication unrelated to the ERCP and one patient from pancreatitis.[6,12,15] None of the studies

reported post-ERCP mortality in outpatients.

So far, only one randomized trial has been performed.[7] Of this Spanish study, only an abstract in the English language was available. A total of 122 patients were randomized between ERCP on an outpatient (n=60) or an inpatient (n=62) basis. All patients underwent sphincterotomy for biliary or pancreatic disease. The total complication rate was 3% (3 inpatients and 1 outpatient). The authors concluded that ERCP with sphincterotomy could be safely performed on an outpatient basis.

A number of issues are important to consider before concluding that ERCP on an outpatient basis is as safe and effective as when performed on an inpatient basis. First, no randomized trials were available for this review. The prospective and retrospective design of the included studies resulted in a limited access to the study outcomes. The lack of randomized trials could have resulted in non-comparable patient groups. Patients may have different risk factors for post-ERCP complications and also treatment characteristics play an important role in the development of post-ERCP complications. For example, there may be a difference in risk for post-ERCP complications between pancreatic stent placement and biliary stent placement or between pancreatic and biliary sphincterotomy. Unfortunately, most reviewed studies did not distinguish between these treatments.[5,10–12,15] In addition, patients undergoing high risk ERCP procedures (i.e. pancreatic therapy), associated with SOD or with concurrent comorbity were already scheduled for 24 hour postprocedural observation in some studies.[5,11–13,15] This could have influenced the results on complications after ERCP.

Second, in the majority of the reviewed studies, the timing of a complication after ERCP was not reported. With this information, it would have been possible to establish whether an observation period longer than 24 hours could have detected a post-ERCP complication at an early and therefore more favorable stage. Hui et al reported that most outpatients developed post-ERCP complications within 6 hours after the procedure (85% (11/13)). Two patients developed complications 3 and 4 days after ERCP, respectively.[10] In addition, Freeman et al reported that 79% of complications occurred within 6 hours after ERCP.[8] These results indicate that ERCP on an outpatient basis with an observation period of 6 hours could be safe.

Finally, apart from the timing, only a few studies reported on the severity of complications.[8,10,12] In addition, it is unknown whether the prognosis of outpatients who needed readmission within 24 hours after ERCP because of complications was worse as compared to inpatients with a complication within 24 hours.

In this decennium, hospitals are facing high costs related to advanced medical care. One way to reduce these high costs could be to make medical care more efficient. As physicians expect an increased risk of complications after ERCP, an overnight observation after ERCP is common. This policy, however, causes un-

necessary high medical health costs and inefficient use of medical resources in the majority of patients. A solution is to shift from inpatient to outpatient treatments, reserving admission only for those with (a high risk of) complications.

Despite the limitations of this review, the results show that ERCP on an outpatient basis seems to be safe when this is performed with a selective policy. We suggest that patients are likely to be eligible for ERCP on an outpatient basis if they: 1) do not have an increased risk for post-ERCP complications (i.e., previous history of pancreatitis, sphincter of Oddi dysfunction or difficult cannulation), 2) have a relative good health status (American Society of Anesthesiologists (ASA) physical status classification I or II), 3) have a corrected coagulopathy, 4) stay within 30 minutes driving distance from the hospital, 5) are not already being admitted to the hospital, and 6) are escorted by a second person. These patients should be observed for 4 hours, as almost 60% of all complications occur within 4 hours after ERCP. Moreover, using the criteria mentioned above will exclude patients with a high risk for post-ERCP complications, which will decrease the incidence of complications in the outpatient group. In addition, amylase and lipase levels should be measured 4 hours after ERCP, because elevated levels in combination with pain could indicate post-ERCP pancreatitis. Elevated amylase and lipase levels may however occur in a number of conditions. For example, sensitivity of elevated amylase levels is limited in patients with hypertriglyceridemia or alcohol abuse.[19,20] All other patients not fulfilling these criteria, should be admitted for an overnight observation after ERCP. Nevertheless, a randomized trial of sufficient size is needed to determine differences between outpatient and inpatient ERCP, with respect to patient and treatment characteristics, complications, patient preferences and costs, in order to define definite criteria for performing ERCP on an outpatient basis.

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Chapter 7

Predictors of complications after Endoscopic Retrograde Cholangiopancreatography: a multivariable analysis

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submitted

Abstract

Background: Various studies have evaluated risk factors for complications following Endoscopic Retrograde Cholangiopancreatography (ERCP), but their relative importance is unknown. The objective of this study was to determine risk factors for post-ERCP complications.

Methods: Risk factors were identified from a literature review. In a single-center retrospective analysis (2001-2006), these risk factors were evaluated in a multivariable logistic regression and odds ratios (ORs) were calculated.

Results: From the 16 reviewed studies, risk factors were revealed for overall post-ERCP complications, pancreatitis and cholangitis. Our retrospective database included 1372 ERCPs performed in 588 patients. In these procedures, 76 (6%) complications occurred, i.e., pancreatitis in 34 (2%), cholangitis in 31 (2%), perforation in 6 (0.4%) and hemorrhage in 5 (0.4%). Multivariable analysis showed that primary sclerosing cholangitis (PSC) (OR 2.2; $p=0.02$) and sphincterotomy (OR 2.2; $p<0.01$) were important predictors for overall complications. Significant preditors for post-ERCP pancreatitis were pancreas divisum (OR 10.5; $p=0.05$), PSC (OR 4.6; $p<0.01$), age$<$60 years (OR 4.9; $p=0.03$) and female gender (OR 2.1; $p=0.05$). For post-ERCP cholangitis, placement of an expandable metal stent (OR 3.9, $p=0.05$) and sphincterotomy (OR 2.8; $p=0.01$) were important predictors.

Conclusions: Our results identified several patient- and procedure-related factors that are associated with complications in ERCP. The next step is to prospectively establish whether these risk factors can be used to identify the group of patients that requires specific preventive measures and post-procedural observation on the one hand, and to select patients for early discharge after ERCP on the other hand.

Background

Endoscopic retrograde cholangiopancreatography (ERCP) is a common procedure for the evaluation and treatment of biliary and pancreatic duct disorders. This procedure is however associated with a relatively high morbidity rate. In published series, complication rates varying between 0.8% and 45% have been reported.[1−6] Pancreatitis is the most frequently observed complication after ERCP (1-5%), resulting in morbidity and occasional mortality.[2] Other major complications include cholangitis (1-5%), retroperitoneal perforation (1-2%), and hemorrhage (1%).[6,7]

Several retrospective and prospective trials have evaluated risk factors for the development of post-ERCP complications. Identification of these risk factors may be essential for the recognition of high-risk patient groups for whom protective endoscopic or pharmacologic measures should be considered. It may, on the other hand, also be helpful in detecting low-risk patients eligible for outpatient ERCP. Recent studies have used multivariable analyses to identify risk factors that are independently associated with post-ERCP complications. Reported risk factors included a history of post-ERCP pancreatitis, sphincter of Oddi dysfunction (SOD), balloon dilation of the sphincter, difficult or repeated cannulation of the common bile duct (CBD), female gender, and younger age.[1−4,8−14] However, their relative contribution to morbidity and mortality after ERCP is unknown.

The objective of this study was to examine risk factors for post-ERCP complications, i.e. pancreatitis and cholangitis, which could help clinicians to identify high- and low risk patient groups for post-ERCP complications. We compared results from the literature with those from a multivariable analysis in a retrospective patient population.

Patients and methods

Systematic review

A systematic review of the published literature was performed by searching PubMed, EMBASE, the Cochrane Library and the Web of Science in the period January 1985-September 2007, using the following search terms: ERCP, pancreatitis, cholangitis and hemorrhage and these were combined with risks and multivariate analysis. In addition, we also checked reference lists of obtained studies to identify additional relevant reports. A total of 725 studies were found using these search terms, of which 17 reported univariable and/or multivariable analyses of risk factors for post-ERCP complications.[1−5,8,10−19] One study was excluded, because the confidence intervals were not reported. Therefore, a total of 16 studies were included.

Patients

From our endoscopy database, all ERCP procedures performed between January 2001 and January 2006 at the Erasmus MC-University Medical Center Rotterdam, the Netherlands, were listed. Patients referred from other medical centers were excluded from further analysis because of uncertainty with regard to the completeness of the 30-day follow-up data according to our strict definitions.

Procedure

All ERCP procedures were performed by experienced gastroenterologists assisted by a fellow. A standard abdominal X-ray was made immediately after each procedure. The study setting was an academic tertiary referral center with a liver transplantation program and a medium-high ERCP volume averaging between 650 and 800 ERCP's per annum over the last 10 years, performed by a limited number of dedicated endoscopists. All patients were admitted overnight after the procedure. Medical records were reviewed for any adverse events during admission, i.e. post-ERCP complications, fever, high blood pressure and high pulse rate. Pre- and post-ERCP levels of bilirubin, alkaline phosphate, gamma-glutanyltranspeptide, AST, ALT and amylase were collected. Complications after admission were obtained from our complication registry.

Definitions

A procedure related complication was defined as any event occurring during the 30-day period after ERCP that negatively affected the health status of a patient for any period of time. Each major complication was graded into categories of severity as proposed by Cotton et al.[20]

- **Pancreatitis** was defined as an amylase concentration of at least three times the normal level, 24 hours or more after ERCP.
- **Cholangitis** was defined as a fever, which was present for over 24 hours after ERCP.
- **Hemorrhage** was defined as clinical evidence of bleeding during or after the ERCP procedure associated with a hemoglobin drop of at least 3 g/dl. Immediate minor hemorrhage was carefully noted, but according to the Cotton definition, this was not considered to be a complication.
- **Perforation** was defined as the radiological presence of contrast or air outside the confines of the bile duct and duodenum during or after ERCP or on a routinely made abdominal X-ray immediately after the procedure.

In patients with active pancreatitis or cholangitis at the time of ERCP, symptoms compatible with these conditions in the post-procedural phase of the study were not scored as procedural complications. Similarly, when progression of the underlying disease resulted in death in such a patient within 30 days, this was also considered to be unrelated to the procedure.[5]

Statistics

Forest plots were constructed using odds ratios (ORs) and 95%-confidence interval (CI) of the risk factors for complications if these were evaluated in more than 2 reviewed studies. ORs were pooled and forest plots were created using StatsDirect (StatsDirect statistical tools. ©1990-2007 StatsDirect Limited, UK). A Z-test was used to test whether pooled ORs differed from 1, indicating a significant effect on the development of (specific) post-ERCP complications. A two-sided p-value$<$0.05 was considered to be significant. An inconsistency (I^2) test was used to detect inconsistency between the results of the reviewed studies. Inconsistency is part of the variability between studies due to true heterogeneity rather than chance. An I^2 test is an intuitive and simple expression of the inconsistency of results of studies. It does not inherently depend upon the number of studies included. In this test 0% indicates no observed heterogeneity, while higher percentages indicating increasing heterogeneity.[21]

For the analysis of the patient population, explanatory risk factors for complications detected in the reviewed literature were applied. Logistic regression was performed, using Statistical Package for Social Science program (SPSS 12.0.1, SPSS Inc., Chicago). Factors that had a p-value$<$0.5 in univariable analysis were entered into a stepwise logistic regression model to estimate adjusted ORs. In the multivariable analysis, a p$<$0.05 was considered to be significant.

Results

Systematic review

Overall complications

Eight studies reported risk factors for overall post-ERCP complications (pancreatitis, cholangitis, perforation and hemorrhage), resulting in pooled ORs of 4 risk factors for overall complications. Significant risk factors for overall complications were suspected SOD (OR 4.4; CI 2.4-8.0), precut sphincterotomy (OR 2.0; CI 1.6-2.6) and female gender (OR 1.3; CI 1.0-1.7). Younger age was not a significant risk factor for post-ERCP complications (OR 1.2; CI 1.0-1.5) (Table 1, Appendix: Figure 1).

Inconsistency values were high for younger age (70%), gender (58%) and SOD (48%) and relatively low for precut sphincterotomy (15%).

Table 1. Pooled odds ratios of predictors for overall post-ERCP complications from the literature review and odds ratios from univariable and/or multivaribale analysis of a retrospectively collected database

Predictors	Literature review	Retrospective population	
		Univariable analysis	Multivariable analysis
	OR (CI)	OR (CI)	OR (CI)
Patient variables			
Suspected SOD	4.4 (2.4-8.0)*	*NA*	*NA*
Female gender	1.3 (1.0-1.7)*	1.6 (0.9-2.2)*	1.3 (0.8-2.1)
History of pancreatitis	*NA*	0.9 (0.5-1.7)	*NS*
Younger age (<60 years)	1.2 (1.0-1.5)	1.3 (0.8-2.2)*	1.7 (0.7-3.8)
Age (continuous)	*NA*	1.0 (1.0-1.02)*	1.0 (1.0-1.0)
Cholangitis at presentation	*NA*	0.4 (0.2-1.0)*	0.5 (0.2-1.2)
Antibiotic use	*NA*	0.7 (0.4-1.5)*	0.8 (0.4-1.6)
Cirrhose	*NA*	1.3 (0.4-3.6)	*NS*
PSC	*NA*	1.8 (1.0-3.3)*	2.2 (1.1-4.4)*
Previous ERCP	*NA*	0.7 (0.4-1.2)*	0.9 (0.5-1.7)
Treatment variables			
Therapeutic ERCP	*NA*	1.7 (0.8-3.8)*	1.4 (0.6-3.1)
Precut sphincterotomy	2.0 (1.6-2.6)*	1.9 (0.8-4.2)*	1.6 (0.6-4.2)
Sphincterotomy	*NA*	2.3 (1.4-3.9)*	2.2 (1.3-3.9)*
Balloon dilation CBD	*NA*	1.5 (0.7-3.0)*	1.6 (0.8-3.3)
Difficult cannulation	*NA*	1.6 (0.9-2.7)*	1.3 (0.7-2.4)

* p-value<0.5 in univariable analysis, and/or p-value<0.05 in multivariable analysis

NA not applicable

NS not significant in univariable analysis

Post-ERCP pancreatitis

A total of 13 studies evaluated risk factors for post-ERCP pancreatitis, resulting in pooled ORs of 10 risk factors for post-ERCP pancreatitis. Significant risk factors for post-ERCP pancreatitis were suspected SOD (OR 3.6; CI 2.3-5.5), history of post-ERCP pancreatitis (OR 3.6; CI 2.7-4.9), difficult cannulation (OR 3.2; CI 2.0-5.0), precut sphincterotomy (OR 2.4; CI 1.6-3.7), pancreas divisum (OR 2.2; CI 1.4-3.4),

younger age (OR 2.1; CI 1.4-3.1), female gender (OR 1.9; CI 1.4-2.4), and multiple pancreatic duct contrast injections (OR 1.6; CI 1.3-2.0). Pancreatic sphincterotomy (OR 1.6; CI 0.7-3.9) and small diameter CBD (OR 1.5; CI 0.7-3.0) were not found to be significant risk factors for post-ERCP pancreatitis (Table 2, Appendix:Figure 2). Inconsistency was high for a small CBD duct (89%), pancreatic sphincterotomy (85%), younger age (78%), suspected SOD (66%) and difficult cannulation (55%), and was below 50% for precut sphincterotomy (39%), female gender (35%), multiple pancreatic duct contrast injections (26%), history of post-ERCP pancreatitis (19%), and pancreas divisum (0%).

Cholangitis

Three studies evaluated a limited number of risk factors for cholangitis.[5,10,15] None of these risk factors were evaluated in more than 2 studies and therefore no forest plots were constructed. Possible risk factors were jaundice at presentation (OR 4.8; CI 1.6-14.3), a small volume center (OR 4.7; CI 1.9-11.7), endoprosthesis placement (OR 3.1; CI 1.8-5.2) and female gender (OR 2.8; CI 1.2-6.6). Antibiotics use (OR 0.9; CI 0.5-1.6) and obstruction of the CBD at the end of ERCP (OR 0.3; CI 0.0-1.7) were not found to be significant risk factors (Table 3).

Retrospective patient population

A total of 588 patients (58% male, mean age 56.5 $\pm$ 17) were included in this study, who in total underwent 1372 ERCP procedures (Table 4). Most patients were referred for ERCP because of (suspicion of) malignant CBD obstruction or choledocholithiasis. Of the 1372 ERCPs performed, 367 (27%) were procedures on patients with virgin papillas, in 199 procedures (15%) no therapeutic intervention was performed. In 130 procedures (10%) selective cannulation of the CBD was not achieved. Precut sphincterotomy was performed in 74 (5%) procedures, and standard sphincterotomy in 225 (16%). Placement of a plastic endoprosthesis was performed in 702 (51%) procedures, self expandable metal stent (SEMS) placement in 52 (4%), balloon dilation of the CBD in 130 (10%) and removal of CBD stones in 186 (14%).

A total of 76 (6%) complications occurred after ERCP, of which pancreatitis was the most frequently seen after 34 (2%) ERCP procedures, followed by cholangitis after 31 (2%), perforation during 6 (0.4%) and hemorrhage after 5 (0.4%) (Table 5).

Table 2. Pooled odds ratios of predictors for post-ERCP pancreatitis from the literature review and odds ratios from univariable and/or multivaribale analysis of a retrospectively collected database

Predictors	**Literature review**	**Retrospective population**	
		Univariable analysis	**Multivariable analysis**
	OR (CI)	OR (CI)	OR (CI)
Patient variables			
Younger age (<60 years)	2.1 (1.4-3.1)*	4.0 (1.5-10.5)*	4.9 (1.2-19.6)*
Age (continuous)	*NA*	1.0 (1.0-1.1)*	1.0 (1.0-1.0)
Female gender	1.9 (1.4-2.4)*	1.8 (0.9-3.5)*	2.1 (1.0-4.6)*
History of pancreatitis	3.6 (2.7-4.9)*	1.4 (0.6-3.2)*	1.8 (0.7-4.7)
PSC	*NA*	3.4 (1.6-7.2)*	4.6 (1.8-11.5)*
Suspected SOD	3.6 (2.3-5.3)*	*NA*	*NA*
Small diameter CBD	1.5*NS*	*NA*	*NA*
Pancreas divisum	2.2 (1.4-3.4)*	6.7 (0.8-57.5)*	10.5 (1.0-112.8)*
Cholangitis at presentation	*NA*	0.2 (0.0-1.3)*	0.2 (0.0-1.6)
Previous ERCP	*NA*	0.6 (0.3-1.2)*	0.6 (0.2-1.3)
Treatment variables			
Precut sphincterotomy	2.4 (1.6-3.7)*	1.1 (0.3-4.7)	1.3 (0.3-6.1)
Multiple PD contrast injections	1.6 (1.3-2.0)*	*NA*	*NA*
Pancreatic sphincterotomy	1.6*NS*	*NA*	*NA*
Therapeutic ERCP	*NA*	1.3 (0.5-3.7)	*NS*
Sphincterotomy	*NA*	1.9 (0.9-4.1)*	1.5 (0.5-4.0)
Placement of endoprothese	*NA*	0.8 (0.4-1.7)	*NS*
Balloon dilation CBD	*NA*	2.1 (0.9-5.2)*	2.2 (0.8-5.8)
Stone removal	*NA*	2.0 (0.9-4.5)*	1.9 (0.7-4.9)
Difficult cannulation	3.2 (2.0-5.0)*	1.1 (0.5-2.6)	*NS*

* p-value<0.5 in univariable analysis, and/or p-value<0.05 in multivariable analysis

NA not applicable

NS not significant in univariable analysis

Table 3. Pooled odds ratios of predictors for post-ERCP cholangitis from the literature review and odds ratios from univariable and/or multivaribale analysis of a retrospectively collected database

Predictors	**Literature review**	**Retrospective population**	
		Univariable analysis	**Multivariable analysis**
	OR (CI)	OR (CI)	OR (CI)
Patient variables			
Age (continuous)	*NA*	1.0 (1.0-1.0)*	1.0 (1.0-1.0)
Younger age (<60 years)	*NA*	0.6 (0.3-1.3)*	0.7 (0.2-2.5)
Female gender	2.8 (1.2-6.6)*	0.7 (0.3-1.6)*	0.7 (0.3-1.6)
Small center	4.7 (1.9-11.7)*	*NA*	*NA*
Jaundice at presentation	4.8 (1.6-14.3)*	0.7 (0.3-1.8)*	0.6 (0.2-1.6)
Antibiotic use	0.9*NS*	1.6 (0.5-5.3)*	0.7 (0.3-2.2)
Previous ERCP	*NA*	1.5 (0.6-3.8)*	1.4 (0.5-3.8)
Previous precut	*NA*	2.3 (0.9-5.6)*	2.2 (0.9-5.8)
Treatment variables			
Obstruction of CBD at end ERCP	0.3*NS*	*NA*	*NA*
Placement expandable stent	*NA*	2.8 (0.8-9.6)*	3.9 (1.0-15.7)*
Difficult cannulation	*NA*	1.2 (0.5-2.9)	*NS*
Sphincterotomy	*NA*	2.1 (1.0-4.7)*	2.8 (1.2-6.4)*
Precut sphincterotomy	*NA*	1.2 (0.3-5.2)	*NS*
Placement of endoprothesis	3.1 (1.8-5.2)	1.3 (0.6-2.7)*	1.8 (0.8-3.9)

* p-value<0.5 in univariable analysis, and/or p-value<0.05 in multivariable analysis

NA not applicable

NS not significant in univariable analysis

Table 4. Characteristics of the ERCP procedure

Characteristics	N
Number of procedures	1372
Number of patients	588
Diagnostic procedures	199 (15%)
Failed procedures	130 (10%)
First time ERCPs	367 (27%)
Procedures	
Sphincterotomy	225 (16%)
Precut sphincterotomy	74 (5%)
Plastic endoprosthesis placement	702 (51%)
Metal stent placement	52 (4%)
Balloon dilation of CBD	130 (9%)
Removal of CBD stones	186 (14%)
Ampullary resection	8 (1%)

Table 5. Severity of post-ERCP complications in a retrospective population (1372 ERCPs performed in 588 patients)

Complications	Mild (%)	Moderate (%)	Severe (%)	Total
Pancreatitis	12 (31)	21(54)	6 (15)	39
Cholangitis	15 (44)	17 (50)	2 (6)	34
Perforation	4 (67)	0 (0)	2 (33)	6
Hemorrhage	1 (20)	2 (40)	2 (40)	5

Uni- and multivariable analysis

Uni- and multivariate analyses were only performed for overall complications, and the two most frequent complications, i.e. pancreatitis and cholangitis. We found 12 risk factors to be significantly associated with an increased or decreased risk for overall post-ERCP complications in our patient population in univariable analysis (Table 1). In addition, 11 patient- and procedure-related risk factors for post-ERCP pancreatitis (Table 2) and 10 for cholangitis were identified (Table 3).

In the multivariable analysis, only PSC (OR 2.2; CI 1.1-4.4) and sphincterotomy (OR 2.2; CI 1.3-3.9) remained significant risk factors for overall post-ERCP complications. Risk factors in multivariable analysis for the development of post-ERCP pancreatitis were pancreas divisum (OR 10.5; CI 1.0-112.8), PSC (OR 4.6;

CI 1.8-11.5), age below 60 years (OR 4.9; CI 1.2-19.6) and female gender (OR 2.1; CI 1.0-4.6). For cholangitis this was SEMS placement (OR 3.9; CI 1.0-15.7) and sphincterotomy (OR 2.8; CI 1.2-6.4).

Discussion

ERCP is a well established procedure in the management of (obstructive) biliary and pancreatic disease. The procedure is however associated with a considerable morbidity rate varying from 0.8-45% in different studies.[1–6] This is the first study with a complete overview of all possible risk factors for (specific) post-ERCP complications. The pooled ORs obtained from the literature firstly indicated the magnitude of the effect of individual risk factors on the development of post-ERCP complications. Secondly, a multivariable analysis of our ERCP population resulted in the detection of previously unrecognized risk factors.

As was expected, the results from the literature and our multivariable analyses overlapped partially. However, some of our results for specific risk factors for post-ERCP complications differed from those found in the literature.

Female gender was a significant risk factor in the pooled ORs for overall post-ERCP complications, as well as for pancreatitis and cholangitis specifically. However, this association was not found in all studies.[4,14,15,17,18] In our cohort, female gender was only significant in the univariable analysis for pancreatitis. Several studies have suggested that women may be at a higher risk for (specific) post-ERCP complications regardless of the clinical context or technical difficulty of the ERCP, due to a higher prevalence of SOD.[3,10,13] Yet, the prevalence of presumed SOD was low in our population and may explain the difference between literature and our analyses. Therefore, female gender seems to be a likely risk factor for post-ERCP complications.

Precut sphincterotomy has also been reported to be a significant risk factor for overall post-ERCP complications and in particular for pancreatitis. In our series, this could not be confirmed, in spite of a considerable precut sphincterotomy rate. The risk of precut sphincterotomy for the development of post-ERCP complications has been reported to be operator-dependent. In our center, precut sphincterotomy was only performed by highly experienced endoscopists and therefore the level of experience might be a likely explanation for the observed difference between our data and those reported in the literature.[2,3,15] Furthermore, precut sphincterotomy in itself might be a representative of difficult cannulation. As difficult cannulation was not a significant risk factor in our database, this may also explain this difference.

A history of pancreatitis has also been reported as an individual risk factor for the development of post-ERCP pancreatitis, as was confirmed in our literature

review. However this was not the case in our population. A history of pancreatitis is probably not a really strong risk factor for recurrent pancreatitis, as in several studies this factor was found to be only significant in univariable but not in multivariable analysis.[1,12,14]

The multivariable analysis in our patient population established additional risk factors, which were not evaluated in the reviewed studies. For example, PSC as underlying condition was found to be a risk factor for post-ERCP pancreatitis. Previous studies had suggested that performing an ERCP in patients with PSC is a risk factor for post-ERCP complications.[22,23] This is explained by the more difficult cannulation and multiple manipulation of the papilla during ERCP in PSC patients with often multiple, difficult to pass strictures. In addition, younger age was confirmed to be a risk factor for pancreatitis in our multivariable analysis. Freeman et al. have suggested that this may be caused by the fact that many analyses failed to include potentially confounding variables, such as increased bilirubin levels.[13] Nevertheless, the progressive decline in pancreatic exocrine function with aging may also protect older patients from pancreatic injury as a consequence of ERCP.

There are limitations in our study that might explain differences between the pooled ORs from the literature and our multivariable analyses. As not all published data on patient- and treatment characteristics were available in our database, we were not able to analyze all possible risk factors. For example, the incidence of suspected SOD was low in our population, largely due to the fact that SOD is considered to be not an important explanation for signs and symptoms caused by SOD in the Netherlands. Against this background, sphincter of Oddi manometry is an uncommon procedure in our country. According to the reviewed literature, SOD is a well established risk factor for post-ERCP complications.[1,2,5,12–14,17,18]

Furthermore, although all medical records were reviewed for a follow-up period of 30 days after ERCP, the possibility remains that patients had symptoms and/or signs of post-ERCP complication while already having been discharged from the hospital. By including only procedures in patients that were treated in our hospital this confounder was limited. As a result, we analyzed a relatively small number of patients undergoing ERCP. As the occurrence of hemorrhage and perforation was low, a logistic regression for possible risk factors of these complications could not be performed. Only a few studies have been able to investigate risk factors for these complications. It was found that hemodialysis, coagulopathy, cholangitis at presentation and younger age were likely factors predicting hemorrhage during ERCP.[3,5,12,17,19] Precut sphincterotomy, juxtapapillary diverticulum, small diameter of distal CBD, suspected pancreatic or biliary malignancy, intramural contrast injections, previous gastric surgery, stricture of the pancreatic duct and suspected cholangitis were associated with an increased risk of perforation.[5,9,10,15,17]

Various studies only investigated risk factors in a pre-selected patient group, for example patients who had a sphincterotomy during ERCP, resulting in investigating non-comparable patient groups.[3,12,17,19] In addition, the definition of risk factors differed between the reviewed studies, for example for difficult cannulation. The difficulty of cannulation is not easily quantifiable and several interactions with time for and methods of cannulation may occur, which may have resulted in an over- or underestimation of the effect of this risk factor and may explain the differences between the literature and our multivariable analyses.

Heterogeneity between studies was influenced by the size of the populations from the reviewed studies, which varied widely from 372 to 5264 ERCP procedures. However, no similarity was seen in outcomes between the larger studies. In addition, only a few studies evaluated risk factors for cholangitis after ERCP, which affected the outcomes of the pooled ORs.

Finally, we evaluated a large number of variables related to a limited number of endpoints. This so-called over-fitting may result in false-positive findings of significance and unreliable estimates of the magnitude of any association identified and may therefore have resulted in over- or underestimation of the effect of risk factors. For example, we found a significant effect of pancreas divisum and placement of a SEMS in the literature as well as in our population. However, as both these factors are thought to have a protective effect on post-ERCP complications, it may well be that the effect we found was overestimated. In addition, the effect of pancreas divisum may also be related to the increased risk for post-ERCP complication of minor papilla cannulation.[2,3]

In conclusion, this study shows risk factors for (specific) post-ERCP complications. Female and younger patients are at higher risk for these complications, especially when treated in a small center, as well as those with PSC, SOD, a pancreas divisum, or a history of pancreatitis, and those undergoing (precut) sphincterotomy, multiple PD contrast injections and in whom cannulation of CBD was difficult. The next step is to prospectively establish whether these risk factors can be used to identify patients who require specific preventive measures and/or need close post-procedural observation on the one hand, and select those patients with a low risk of ERCP complications for which early discharge after ERCP should be considered on the other hand.

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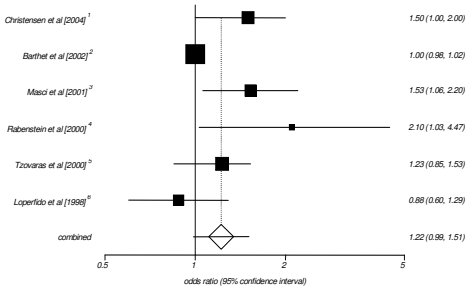
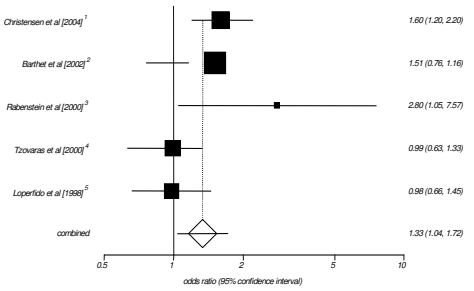
Appendix



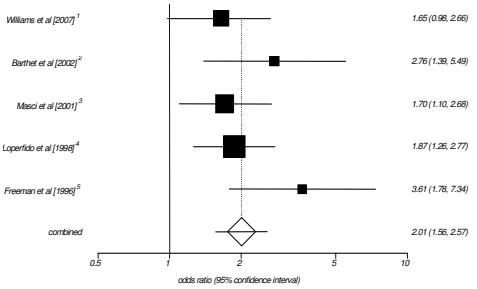
(a) **Age as risk predictor**

[1] <40 years
[2] Continous
[3,4,5] <60 years
[6] <70 years
[2,3] Multivariable analyses
[1,4,5,6] Univariable analyses



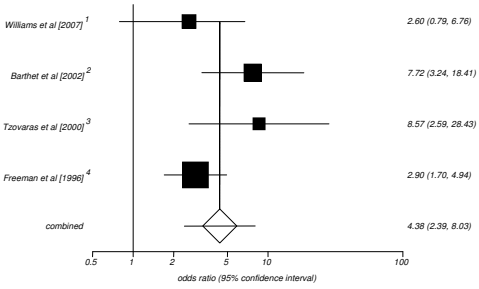
(b) **Gender as risk predictor**

[1] Multivariable analysis
[2,3,4,5] Univariable analyses



(c) **Precut sphincterotomy as risk predictor**

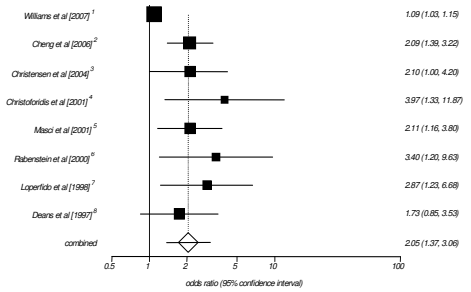
[2,3,5] Multivariable analyses
[1,4] Univariable analyses



(d) **SOD as risk predictor**

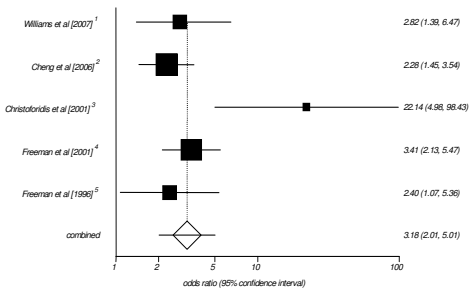
[2,4] Multivariable analyses
[1,3] Univariable analyses

Figure 1. Odds ratios (OR) and 95% confidence interval (CI) of age, gender, precut-sphincterotomy and sphincter of Oddi dysfunction (SOD) as predictors for post-ERCP complications in general



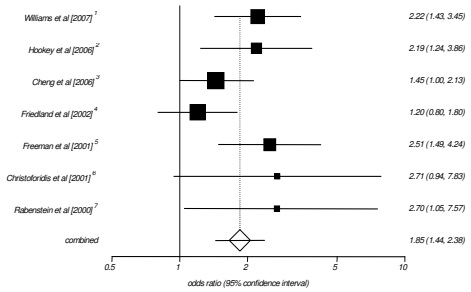
(a) **Age as risk predictor**

[1] per 5 year decrease
[2,5,6] <60 years
[3] <40 years
[4] <50 years
[7] <70 years
[8] <55 years
[1,3,4,5,7] Multivariable analyses
[2,6,8] Univariable analyses



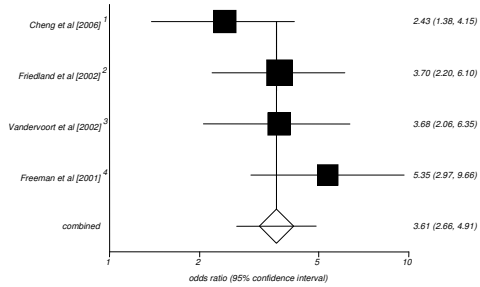
(b) **Difficult cannulation as risk predictor**

[1] >1 vs 1
[2] easy: 1-8 attempts, moderate/difficult: >8
[3] difficult: >3 attempts
[4,5] easy: <5 attempts, moderate: 6-15, difficult: >15 attempts
[1,3,4,5] Multivariable analyses
[2] Univariable analysis



(c) **Gender as risk predictor**

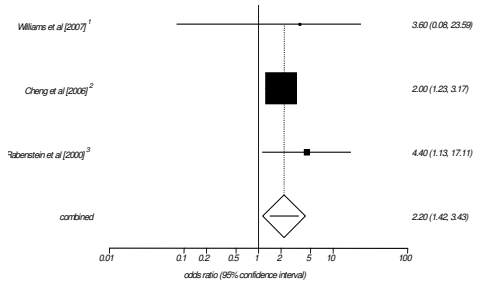
[1,2,5,6] Multivariable analyses
[3,4,7] Univariable analyses



(d) **History of post-ERCP pancreatitis as risk predictor**

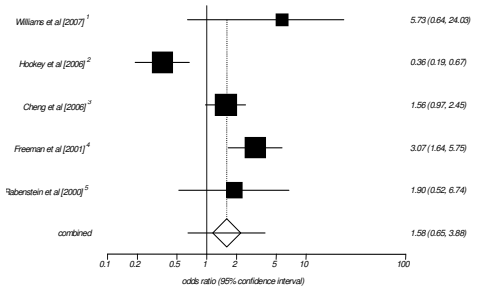
[4] Multivariable analysis
[1,2,3] Univariable analyses

Figure 2. Odds ratios (OR) and 95% confidence interval (CI) of age, difficult cannulation, gender, history of post-ERCP pancreatitis, pancreatic divisum, pancreatic sphincterotomy, multiple PD contrast injections, precut-sphincterotomy, small diameter CBD and sphincter of Oddi dysfunction (SOD) as predictors for post-ERCP pancreatitis



(e) **Pancreatic divisum as risk predictor**

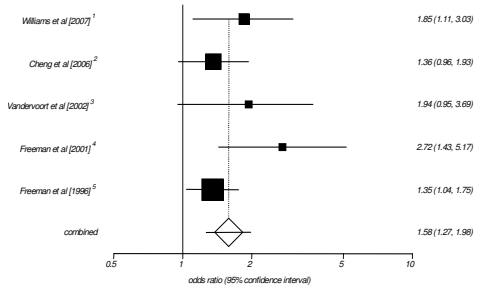
[1,2,3] Univariable analyses



(f) **Pancreatic sphincterotomy as risk predictor**

[2,4] Multivariable analyses

[1,3,5] Univariable analyses



(g) **Multiple PD contrast injections as risk predictor**

[1,4] >1 PD injections

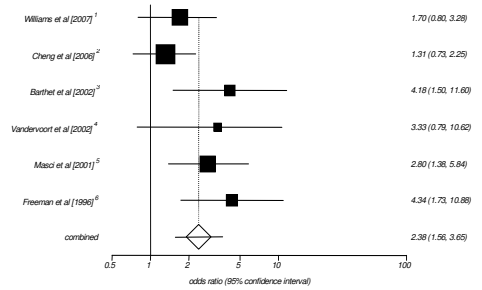
[2] ≥2 PD injections

[3] >5 PD injections

[5] >4 PD injections

[4,5] Multivariable analyses

[1,2,3] Univariable analyses

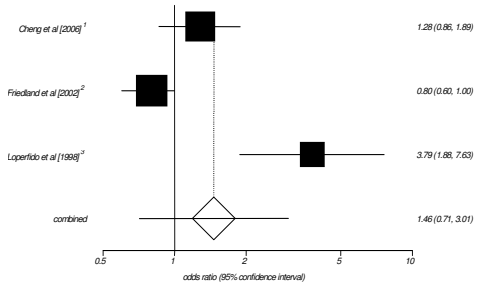


(h) **Precut-sphincterotomy as risk predictor**

[3,5,6] Multivariable analyses

[1,2,4] Univariable analyses

Figure 2. Odds ratios (OR) and 95% confidence interval (CI) of age, difficult cannulation, gender, history of post-ERCP pancreatitis, pancreatic divisum, pancreatic sphincterotomy, multiple PD contrast injections, precut-sphincterotomy, small diameter CBD and sphincter of Oddi dysfunction (SOD) as predictors for post-ERCP pancreatitis (*Continued*)



(i) **Small diameter CBD as risk predictor**

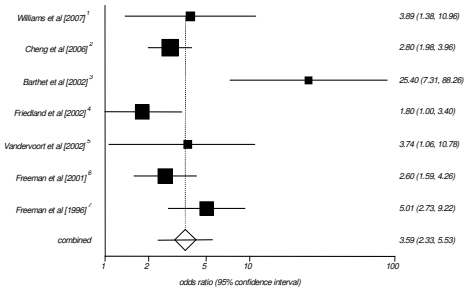
[1] <5 mm

[2] bile duct diameter

[3] not defined

[3] Multivariable analysis

[1,2] Univariable analyses



(j) **SOD as risk predictor**

[3,6,7] Multivariable analyses

[1,2,4,5] Univariable analyses

Figure 2. Odds ratios (OR) and 95% confidence interval (CI) of age, difficult cannulation, gender, history of post-ERCP pancreatitis, pancreatic divisum, pancreatic sphincterotomy, multiple PD contrast injections, precut-sphincterotomy, small diameter CBD and sphincter of Oddi dysfunction (SOD) as predictors for post-ERCP pancreatitis (*Continued*)

Chapter 8

Identification of risk groups for complications after ERCP: evaluation of a prognostic early discharge model

Suzanne M. Jeurnink, Ewout W. Steyerberg, Peter D. Siersema, Ernst J. Kuipers

submitted

Abstract

Background: Patients are often admitted for overnight observation after endoscopic retrograde cholangiopancreatography (ERCP) as this procedure has a morbidity rate of 5-10%. Nevertheless, it has been suggested that selective early discharge of 3-6 hours after ERCP is safe. Although several studies have evaluated risk factors for post-ERCP pancreatitis and cholangitis, a simple prognostic model that could predict the risk of pancreatitis and cholangitis is not available.
Objective: To determine the appropriate observation period for early discharge and to develop a prognostic model that determines which patients can be safely discharged shortly after ERCP.
Methods: In a prospective patient population with a follow-up of 30 days after ERCP time to complications was determined. The prognostic model was composed of risk factors for pancreatitis and cholangitis from a literature review and evaluated in a prospective patient population (274 procedures in 220 patients).
Results: Twenty-seven (10%) complications occurred in 274 procedures, including 14 patients with pancreatitis, 12 with cholangitis and 1 with hemorrhage. Pancreatitis and cholangitis occurred within 4.1 hours after ERCP, and 90% (23/26) of complications were diagnosed within 6 hours after ERCP. A score of 3 or less in the prognostic model was associated with a low to intermediate risk for pancreatitis and cholangitis (8%, 20/252), while a score of 4 or above was associated with a high risk (27%, 6/16).
Conclusion: This prognostic scoring system may aid clinicians to identify patients at high risk for post-ERCP pancreatitis or cholangitis. Patients may safely be discharged 6 hours after ERCP if they have a low to intermediate score and no complications during the observation period nor having undergone a high risk procedure for perforation and hemorrhage.

Background

Endoscopic retrograde cholangiopancreatography (ERCP) is an effective procedure for biliary and pancreatic diseases. Patients are commonly admitted for an overnight observation after ERCP, since 5-10% of the patients develop a complication after this endoscopic procedure.[1–6] Pancreatitis and cholangitis are the most frequent complications of ERCP, resulting in substantial morbidity and occasional mortality. Other complications are hemorrhage (1%) and retroperitoneal perforation (1-2%).[3,7] Various risk factors for the development of post-ERCP complications have been reported, including patient- and treatment-related characteristics. Well known patient-related risk factors for the development of post-ERCP pancreatitis include sphincter of Oddi dysfunction (SOD) and a history of post-ERCP pancreatitis, whereas treatment-related risk factors include precut sphincterotomy and difficult cannulation.[2,6,8–11]

A recent review suggested that an observation period of 4 hours should be as safe and effective as an inpatient ERCP when performed with a selective policy.[12] Early discharge can lead to a decrease in the burden of ERCP for patients and a cost reduction. A selective policy should distinguish patients with a low risk for post-ERCP complications from patients with a high risk. So far, only Friedland et al. presented a prognostic model to predict the risk for post-ERCP pancreatitis.[13] However, this model did not take other common ERCP complications, in particular cholangitis, hemorrhage and perforation, into account. Knowledge of risk factors for perforation and hemorrhage is rare, as these occur in only 1-2% of patients. Nevertheless, it is known that high risk procedures such as papillectomy, first time balloon dilation and (precut) sphincterotomy in patients with coagulation disorders are associated with a higher risk of perforation and hemorrhage. In addition, these complications are most often detected during or directly after ERCP, for example immediate hemorrhage during ERCP, a hemoglobin drop of at least 3g and free air on X-ray.

We aimed to determine the appropriate period for early discharge and to develop and evaluate a prognostic model for post-ERCP pancreatitis and cholangitis, which could help clinicians selecting patients who are eligible for safe early discharge after ERCP.

Patients and methods

Patients

All patients undergoing an ERCP at the Erasmus MC-University Medical Center Rotterdam between April 2006 and April 2008 were asked to participate in a prospective

study with a follow-up of 30 days after ERCP. A researcher obtained and recorded data on patient- and treatment characteristics and complications after ERCP. Detection of complications after discharge from the hospital was done by telephone interviews with patients 7 and 30 days after ERCP and by diaries for pain and nausea scores. Patients referred from another hospital were excluded because of limitations with respect to complete 30-day follow-up data. All patients gave written informed consent.

Procedure

All ERCP procedures were performed by experienced gastroenterologists assisted by a clinical fellow. The study setting was an academic tertiary referral center with a liver transplantation program and an ERCP volume of 650-800 ERCPs per annum, performed by a limited number of dedicated endoscopists.

Risk factors

Risk factors for post-ERCP pancreatitis and cholangitis were obtained from a literature review on risk factors for post-ERCP complications. Two experienced clinicians, specialized in ERCPs, selected the most important risk factors of this review for post-ERCP pancreatitis and cholangitis to be included in a prognostic model.[9]

Definitions

A complication of ERCP was defined as any event occurring during the 30-day period after the procedure that negatively affected the health status of a patient. Each major type of complication was graded into categories of severity as proposed by Cotton et al.[14]

- **Pancreatitis** was defined as a maximal post-procedural serum amylase level of at least three times the upper limit of normal, 24 hours or more after ERCP
- **Cholangitis** was defined as a fever, for over 24 hours.
- **Hemorrhage** was defined as clinical evidence of bleeding during or after the ERCP procedure associated with a hemoglobin drop of at least 3g/l. Immediate minor hemorrhage was carefully noted, but according to the Cotton definition, this was not considered to be a complication.
- **Perforation** was probable if based on clinical findings, and definite if a retroperitoneal leak of contrast was observed during the ERCP procedure or the presence of free air on abdominal X-ray.

In patients with active pancreatitis or cholangitis at the time of ERCP, the subsequent decline of the clinical condition was not graded as a complication. Similarly, where disease progression or death occurred in such a patient within 30 days, this was considered unrelated to the procedure.[6]

The time after which complications occurred was defined by the time first signs of pancreatitis, cholangitis, hemorrhage or perforation occurred, i.e. fever, severe abdominal pain, hemoglobin drop, free air on CT and elevated bilirubin or amylase. These measurements were obtained from the patient records and patient interviews.

Statistics

Each risk factor in the prognostic model was nominated a value that represented the magnitude of the effect on the development of pancreatitis or cholangitis, based on the typical odds ratio (OR) in the review. Risk factors were evaluated using logistic regression in the prospective patient population using SPSS software (version 12.0.1, SPSS Inc., Chicago). A Kaplan-Meier curve was used to determine the time to complications. A two-sided p value$<$0.05 was considered statistically significant.

Results

Prospective patient population

The prospective study enrolled 274 ERCPs performed in 220 patients (59% male, mean age 60 $\pm$ 14) (Table 1). Most common indications for ERCP were choledocholithiasis and stenosis of the anastomosis after liver transplantation. Placement of an endoprosthesis and a (precut) sphincterotomy were the most frequently performed procedures during ERCP.

Twenty-seven patients (10%) developed post-ERCP complications during 30-day follow-up, including 14 (5%) patients with pancreatitis. Pancreatitis was mild in three patients, moderately severe in eight and severe in three. Cholangitis occurred in 12 (5%) patients and was mild in three patients and moderately severe in nine patients. One (0.1%) patient developed a mild hemorrhage after ERCP. Three patients developed an immediate minor hemorrhage during the procedure. In none of the patients retroperitoneal perforation was observed (Table 2).

Time to complication

Overall post-ERCP complications (pancreatitis and cholangitis) occurred within a mean time of 4.1 hours after treatment. The mean time to developing pancreatitis was 4.2 hours after treatment and for cholangitis 4.1 hours (Table 2). Our results

Table 1. Procedure characteristics in a prospective population of 204 patients

Characteristics	Number (%)
Number of procedures	274
Number of patients	220
Gender (%male)	129 (59)
Age (±SD)	60 (±14)
Diagnostic procedures (%)	59 (22)
Virgin ERCPs (%)	77 (28)
Indication	
CBD stones	62
Stenosis of the anastomosis after LTx	42
Malignant CBD obstruction	29
Chronic pancreatitis	28
PSC	21
Acute pancreatitis	11
PBC	2
Other	79
Procedures	
(Precut) sphincterotomy	67
Placement of a plastic endoprothesis/stent	149
Balloon dilation of the CBD	41
Removal of CBD stones	46
Ampullary resection	7

show that 90% (23/26) of complications were detected within 6 hours after treatment. Complications occurring more than 6 hours after ERCP were cholangitis after 7 and 16 hours and one case of pancreatitis after 17 hours (Figure 1).

Prognostic model

The prognostic model for pancreatitis and cholangitis included 8 risk factors. All these factors were evaluated in the prospective patient population by multivariable logistic regression. Risk factors included (precut) sphincterotomy (OR 1.6, CI 0.6-4.0), suspected SOD (undefinable), younger age (<60 years) (OR 1.0, CI 0.4-2.4), primary sclerosing cholangitis (PSC) (OR 1.9, CI 0.5-8.0), female gender (OR 0.6, CI 0.2-1.5), history of pancreatitis (OR 1.4, CI 0.5-3.7), pancreas divisum (OR 2.6, CI 0.2-30.5) and difficult cannulation (>10 min attempting to cannulate) (OR 2.0, CI 0.7-5.6). The points selected for each of the risk factors were derived from the coefficients of the regression analysis from the review, with one point for each of the

Table 2. Severity of (specific) post-ERCP complications and time to the development of post-ERCP pancreatitis or cholangitis in a prospective population (n=274 ERCPs)

Complication	Time to complication (hr ±SD)	Mild (%)	Moderate (%)	Severe (%)	Total (%)
Overall	4.1 (4.1)	7 (26)	17 (63)	3 (11)	27 (10)
Pancreatitis	4.2 (3.9)	3 (21)	8 (58)	3 (21)	14 (5)
Cholangitis	4.5 (4.4)	3 (25)	9 (75)	0 (0)	12 (5)
Hemorrhage	0.0	1 (100)	0	0	1 (0.1)

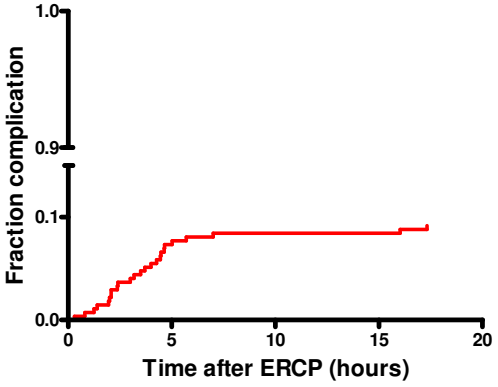


Figure 1. Time (hours) to development of pancreatitis or cholangitis after ERCP in a prospective patient population

following risk factors: (precut) sphincterotomy, SOD, younger age, female gender, history of pancreatitis, pancreas divisum and difficult cannulation and 2 points for PSC.[10] For example, a 58-year-old female patient with PSC and undergoing an ERCP with precut sphincterotomy has a score of 5 *(1+1+2+1)* (Table 3).

Patients were scored as high risk (overall score >3) or low to intermediate risk (overall score ≤3). In the low to intermediate risk patient group, complications occurred in 8% (20/252). In the high risk group complications occurred in 27% (6/22) (Table 4).

Table 3. Combined scores for a prognostic model for pancreatitis and cholangitis and ORs from the literature and a multivariable analysis of a retrospective (n=1372) and prospective (n=255) patient population

Characteristics	Score
(Precut) sphincterotomy	+1
SOD	+1
Younger age (<60)	+1
PSC	+2
Female gender	+1
History of pancreatitis	+1
Pancreas divisum	+1
Difficult cannulation*	+1

* defined as more than 10 min of attempting to cannulate

Discussion

An overnight observation after ERCP is burdensome to patients, requires the availability of clinical facilities, and is associated with costs. Early discharge after ERCP is therefore attractive, however this can only be applied safely and effectively when performed with a selective policy. A guideline for early discharge after ERCP is however yet not available.

Cholangitis, pancreatitis, hemorrhage and retroperitoneal perforation are the most common severe post-ERCP complications resulting in prolonged hospital admission. Hemorrhage and retroperitoneal perforation are frequently observed during or immediately after the ERCP and most often occur during high risk procedures. In contrast, pancreatitis and cholangitis are often not as easily recognized and may manifest some time after ERCP. Our prognostic model can help clinicians to distinguish between high and low to intermediate risk patient groups and may support in the decision whether patients are safely eligible for early discharge after ERCP.

In our population, complications occurred in 10% of patients including pancreatitis in 5%, cholangitis in 5% and hemorrhage in 0.1% of patients. These outcomes are largely comparable to previous studies.[8,14,15] Nevertheless, the incidence of cholangitis is somewhat higher in our population, probably due to differences in definition and a relatively small population sample.[6] As definition for cholangitis we used the Cotton criteria, whereas others defined cholangitis as a fever for over 48 hours or as septic illness occurring in a jaundiced patient.[15,16]

The first signs of pancreatitis or cholangitis occurred within a mean time of 4.1

Table 4. Post-ERCP pancreatitis or cholangitis by score

Score	ERCPs without cholangitis or pancreatitis	ERCPs with cholangitis or pancreatitis (%)	Risk groups
0	38	3 (7)	**Low to intermediate risk group:**
1	84	11 (12)	252 patients (92% of total)
2	70	5 (6)	8% risk
3	40	1 (7)	
4	15	5 (25)	**High risk group:**
5+	1	1 (50)	22 patients (8% of total)
			27% risk

hour after ERCP, with 90% of complications being detected within 6 hours. Only a few studies have so far reported results on time to complications after ERCP. Hui et al. reported that 85% of patients undergoing outpatient ERCP developed a complication within 6 hours.[17] In addition, Freeman et al. reported that 79% of complications were detected within 6 hours after ERCP.[18]

Our model distinguished patients with a low to intermediate score from patients with a high score in the prognostic model for post-ERCP pancreatitis or cholangitis, resulting in 8% of all patients being at high risk. These results are comparable to the results of the prognostic model developed by Friedland et al., who found that 7% of all patients undergoing ERCP were at high risk for post-ERCP pancreatitis.[13]

Friedland et al. were the first to create a simple prognostic model for post-ERCP pancreatitis composed of the following risk factors: pain during the procedure, cannulation of the pancreatic duct, history of pancreatitis and difficult cannulation. This model was based on a multivariable analyses of a retrospectively collected database and therefore missed various important risk factors known from other studies, such as SOD, gender and precut sphincterotomy. In addition, the model was validated in the same database used to determine risk factors for the prognostic model.[13] Evaluating the model in another population would however have been needed to provide evidence that the model was generally applicable.

Using the data from the systematic review resulted in an accurate model, as this review gave a complete overview of all possible risk factors for post-ERCP pancreatitis and cholangitis. Nevertheless, using these data also has some limitations.

The risk factors in the systematic review were derived from several studies and

therefore risk factors from non-comparable patient groups were included. For example, in some studies only patients undergoing sphincterotomy or patients with SOD were evaluated.[5,10,11] Another disadvantage of our approach could be that the use of a relatively large number of risk factors may result in overfitting. Overfitting can result in false-positive findings of significance and unreliable estimates of the magnitude of any association identified.

The selected risk factors for the prognostic model were evaluated in a prospective population. Comparing the ORs from the prospective population with the ORs from the review showed large differences in significance, as none of the selected risk factors from the literature had a significant effect on the development of complications in the prospective population. Nonetheless, the magnitude of these risk factors was comparable for most risk factors. These differences made it more difficult to distinguish between high and low risk patients. It seems likely that this is mainly due to the relatively small population included in the prospective study.

A few studies have suggested that the size of a center and the experience of a gastroenterologist could influence the risk of post-ERCP complications. Therefore, our model should only be used in patients treated in hospitals performing more than 150 ERCPs per year and/or with inexperienced gastroenterologists.[16] As Loperfido et al found an OR of 2.9 for the effect of small center on developing a post-ERCP complication, adding an additional score of 1 point could make this model also applicable for patients treated in small volume centers or by inexperienced gastroenterologists. More research is however needed to confirm the magnitude of the effect of this additional risk factor.

Despite the limitations of this study, our results show that this prognostic model may help clinicians to identify patients with a high risk for developing pancreatitis or cholangitis after ERCP. We suggest that patients may safely be discharged 6 hours after ERCP if they have a low to intermediate score and no complications during the observation period, or having undergone a high risk procedure for perforation and hemorrhage. All other patients should be admitted for an overnight observation after ERCP.

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Chapter 9

Facts and current issues of mucinous cystic neoplasms of the pancreas

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Digestive and Liver diseases. 2008, Nov;40(11):837-846

Abstract

Pancreatic cystic lesions are uncommon and consist of pseudocysts, congenital cysts and cystic neoplasms including mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs) and serous cystic neoplasms (SCNs). MCNs are large septated cysts without connection to the ductal system, characterized by the presence of thick-walled ovarian-type stroma and mucin. They occur predominantly in women and often are malignant. Therefore, surgical resection is recommended. IPMNs are neoplasms with tall, columnar, mucin-containing epithelium involving the main pancreatic ducts or major side branches. IPMNs occur in men and women in their 60s and 70s and may differentiate into malignant neoplasms. Therefore, surgical resection is mandatory. SCNs appear as multiple cysts lined with cubic flat epithelium containing glycogen-rich cells with clear cytoplasm. They mainly occur in women in their 50s and are generally benign. Therefore, a conservative approach is recommended. As both MCNs and IPMNs have a high malignant potential, it is important to differentiate between the various pancreatic cystic lesions. Several imaging techniques and tumors markers have been evaluated. Nonetheless, definitive guidelines to differentiate between SCNs, MCNs and IPMNs are still poorly defined. A number of management issues regarding these neoplasms are still under debate, for example which imaging technique to use, differentiation between malignant or benign lesions and the preferred treatment modality for each pancreatic cystic neoplasm. Further research may lead to a definitive guideline for the diagnosis and treatment of MCNs, IPMNs and SCNs.

Introduction

Tumors of the pancreas generally have a poor prognosis, with the majority being highly malignant. Although cystic lesions of the pancreas are uncommon, pancreatic cystic neoplasms are currently increasingly being diagnosed, probably because of the wider availability of imaging procedures. Many patients are asymptomatic (up to 40-75%), with the cystic mass discovered only incidentally during diagnostic investigation of unrelated upper abdominal symptoms. When a patient is symptomatic, the presentation is usually non-specific and related to the mass effect of the neoplasm.[1]

Four types of cystic neoplasms of the pancreas have been described, i.e., (1) serous neoplasms, (2) mucinous neoplasms, (3) intraductal papillary cystic neoplasms and (4) papillary cystic neoplasms.[2–5] The cells of origin of the different types of pancreatic cystic neoplasms and their biologic aggressiveness vary tremendously and therefore need a selective management approach.[1] In this review we present an overview of the clinical problems of cystic neoplasms of the pancreas, with specific emphasis on mucinous pancreatic neoplasms.

Cystic mucinous tumors

Epidemiology

MCNs of the pancreas are relatively rare and occur predominantly in women. Nonetheless, MCNs represent 40-50% of cystic neoplasms of the pancreas. MCNs cover 10-15% of pancreatic cysts and mucinous cystadenocarcinomas 1% of pancreatic neoplasms in the US.[1,3,5–8] Patient ages range widely (35-90 years), with an average that seems to depend on the degree of malignancy of the neoplasm. Patients with mucinous cystadenocarcinomas appear to be approximately 15 years older than those with a mucinous cystadenoma, suggesting a time-dependent degeneration.[1,2,9,10] Although MCNs are more common in the body and tail of the pancreas, they also occur in the head region. The average size of a MCN is greater than 5 cm.[1,11]

Clinical presentation

Symptoms in MCN are non-specific. It has been reported that, even among asymptomatic patients, 18% already have early or invasive cancer, 42% have a potentially malignant lesion and 40% a benign lesion.[12] The most frequently reported symptoms are abdominal pain, weight loss, back pain, jaundice, a palpable mass and postprandial fullness.[2,6,8–10,12,13] The duration of symptoms ranges from a few days of abdominal discomfort and pain to a 5-year history of an abdominal mass.[10]

Table 1. Histological classification of cystic neoplasms of the pancreas

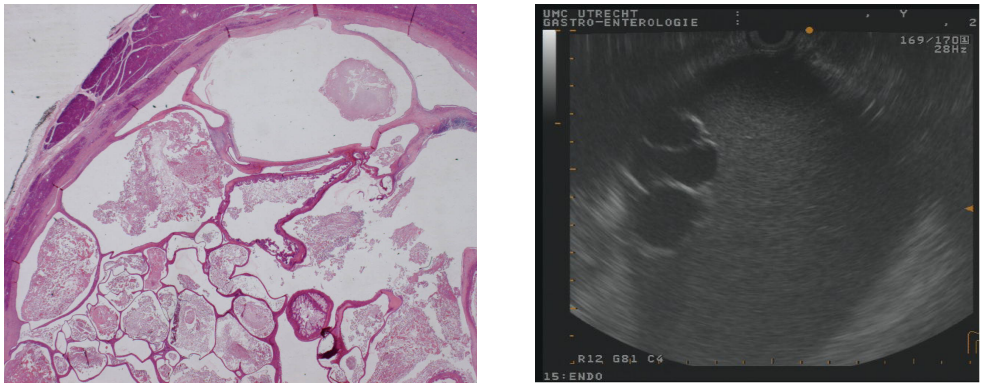
Classification
Serous microcystic cystadenoma
Serous oligocystic adenoma
Serous cystadenocarcinoma
Mucinous cystadenoma
Mucinous cystadenoma-borderline
Mucinous cystadenocarcinoma
Non invasive
Invasive
Intraductal papillary mucinous adenoma
Intraductal papillary mucinous tumors-borderline
Intraductal papillary mucinous carcinoma
Non invasive
Invasive

Physical examination usually discloses an abdominal mass, frequently in the left upper quadrant, that is firm, round, often tender, and moves upon respiration.[6] The presence of symptoms in patients with MCN increases the likelihood of a malignant MCN, but the absence of symptoms does not necessarily exclude this.

Classification and pathology

MCNs occur in several sub-types, i.e. mucinous cystadenoma (mild epithelial dysplasia), mucinous cystic borderline tumors (moderate epithelial dysplasia) and mucinous cystadenocarcinomas (high grade dysplasia), suggesting a gradual malignant transformation of the epithelial lining (Table 1).[2–5,9,14,15] According to the World Health Organization (WHO) classification, MCNs are defined as large thick-walled, septated cysts ($<$6) without connection to the ductal system, characterized by the presence of ovarian-type stroma (Figure 1a). This stroma is not only morphologically similar to that of the ovarian cortex, but also expresses estrogen and progesterone receptors that are detectable by immunohistochemistry. This distinctive mesenchym helps distinguish MCNs from other almost similar neoplasms, especially IPMNs, and may explain the higher incidence in females than in males.[14,16] The cysts often have septa and may have an eccentric solid component.

As stated above, MCNs contain columnar epithelium and may exhibit a broad range of dysplasia. The benign form contains a single layer of benign-appearing, mucin-secreting columnar epithelium resembling pancreatic duct epithelium. The



(a) (b)

Figure 1. (a) Histological picture of a MCN demonstrating multiple small cysts containing mucin and a thick wall consisting of ovarian-type stroma surrounding the entire lesion. (b) EUS picture showing a large thick-walled cystic lesion containing three smaller cysts with a more hypoechogenic content.

intracystic fluid is more viscous than in SCNs and contains mucus.[2,9]

Macroscopically, MCNs are characterized by being round with a smooth surface and a fibrous pseudocapsule. The internal surface of unilocular tumors is usually smooth and glistening. Multilocular tumors often have papillary projections and mural nodules. The cyst contents can be mucinous, hemorrhagic, or necrotic, and cyst fluid varies from clear to turbid, with variable color.[8,9] One of the most notable features of MCN is the frequent concurrence or juxtaposition of apparently benign and obviously malignant epithelium.[6]

Pathogenesis

A specific serum tumor marker, able to discriminate between different types of cystic neoplasms, is not yet available. However, some serum markers may help to distinguish MCNs from other pancreatic cystic neoplasms and may predict malignancy. As the cyst fluid is often rich in mucin-related glycoproteins and oncoproteins such as carcinoembryonic antigen (CEA), a positive CEA serum marker status and/or the presence of more than two positive serum markers (CEA, Ca 19-9 or Ca 125) has a good specificity for differentiating pseudocysts from MCNs and may even suggest the presence of a potentially malignant MCN.[3,17] An intracystic CEA concentration $>$250 ng/ml fairly reliably identifies a mucinous neoplasm, whereas a value of $<$5 ng/ml is rather specific for excluding a diagnosis of MCN. Other tumor markers

(CA 19-9, CA 72-4, CA 125 and CA15.3) may be present in higher concentrations in MCNs, but their diagnostic and discriminatory value remains limited.[1,13]

K-*ras* mutations occur early in MCN and seem to increase in frequency when malignant cellular features show signs of invasiveness. Nuclear p53 immunoreactivity indicates a malignant transition of the epithelium. Similarly, it has been noted that the expression of the DPC4 gene product is frequently lost in invasive MCNs.[9,18]

Imaging

Cross-sectional imaging usually shows the cysts to have thick, irregular walls with papillary excrescences or septae extending into the cysts. Although MCNs often have been misdiagnosed as pancreatic pseudocysts in the past, MCNs usually lack the extracystic, inflammatory component. Calcifications are uncommon, but when present (<20%) they tend to be located in an eggshell distribution within the peripheral cyst walls, which increases the probability of a malignant MCN. The presence of an eccentrically located mass within the cystic area, a recognizable pericystic mass/reaction, extrahepatic biliary obstruction, metastatic cystic liver lesions, or ascites raises the suspicion of a (invasive) mucinous cystadenocarcinoma. In the absence of these features, differentiation of benign MCNs from non-invasive proliferative MCNs is difficult. However, multiple papillary invaginations on CT, US, or endoscopic US (EUS) signify the proliferative nature of the mucinous epithelial lining. Interestingly, the height/diameter of mural nodules may be related with the probability of malignant degeneration. It should be emphasized, however, that a definite preoperative distinction between benign and malignant MCNs cannot be made accurately.[1,19]

Radiological investigation enhances two patterns of MCNs: the macrocystic multilocular and the macrocystic unilocular. The former is often located in the body or tail of the pancreas, appearing on US images as a sharply defined mass surrounded by a variably thickened wall (Figure 1b). Thin septae delimit cystic spaces and calcifications are a common finding. On CT scan, the precontrast phase can easily detect calcifications. The density of the content depends on the amount of mucin or blood from previous intracystic bleeding. The macrocystic unilocular pattern is less specific and simulates any kind of pancreatic cystic mass both on US and CT scan images. As a consequence, differentiation is not easy in cases with just one thin-walled cyst, without calcifications or parietal nodules.[2,4]

From a radiological point of view, a thickened wall, the presence of papillary proliferations arising from the wall or septa, evidence of peripheral calcifications as well as invasion of surrounding vascular structures are considered the clearest signs of malignancy.[2]

Management

As MCNs can dedifferentiate and transform into cystadenocarcinomas, it is generally agreed that all MCNs should be resected because of the risk of latent or overt malignancy. The standard procedure for MCNs in the head of the pancreas is a pylorus-preserving pancreatoduodenectomy. For MCNs in the body or tail region a segmental central resection or a spleen-preserving resection can be considered if there is no indication that the neoplasm has an invasive component. In many patients, a distal pancreatectomy with splenectomy is the best treatment. Other procedures, such as enucleation, duodenum-preserving subtotal pancreatic head resection or even segmental resection of the neck or body of the pancreas, although technically feasible, may be suboptimal operative options, because of the limitations in the preoperative and even intraoperative recognition of an underlying invasive malignancy.[1,11]

Intraductal papillary mucinous tumors

Epidemiology

Intraductal papillary mucinous neoplasms (IPMNs), first described in 1982 by Ohashi et al.[20], occur most frequently in the sixth and seventh decades of life (range 30-94 years), originally affecting males more often than females (ratio 2.2:1), however more recent reports show an equal gender distribution.[2,21–24] A retrospective study from Asia found a male predominance, which raises the question of whether or not geographic factors are involved in the pathogenesis of IPMNs. IPMNs account for less than 10% of all pancreatic neoplasms and are found in the head (50%), tail (7%) and uncinate process (4%) of the pancreas with the remainder (39%) spread throughout the pancreas.[21,24–26]

Clinical presentation

Approximately 20% of patients with IPMN present with acute pancreatitis of mild to moderate severity.[2,21,25] IPMN can be mistaken for idiopathic pancreatitis when patients have a large, dilated pancreatic duct. However, patients with IPMN are typically older compared to patients with chronic pancreatitis and have no history of prolonged pancreatopathy.[1] Patients with IPMN experience symptoms of epigastric discomfort or pain (70-80%), nausea and vomiting (11-21%), backache (10%), weight loss (20-40%), diabetes, and jaundice.[21,24–27] When invasive carcinoma coexists in IPMN, as it does in up to 40% of patients, a symptom profile similar to that of pancreatic ductal adenocarcinoma (pain, jaundice, weight loss, malaise) may

be present.[1]

It has been suggested that weight loss has two different pathogenetic mechanisms and is related to the stage of the disease. In the early phase, the hyperproduction of mucin obstructs normal pancreatic secretion, causing pain related to meals. Consequently, the patient stops eating in order to avoid pain. In a more advanced stage, weight loss is more often due to the production of neoplastic factors responsible for cachexia. Jaundice may be the result of viscous mucin obstructing the ampulla, the size of an IPMN being large enough to cause compression of the common bile duct (CBD), or when mural nodules involve the CBD and/or ampulla. Persistent occlusion of the main pancreatic duct with viscid mucin may result in exocrine and/or endocrine pancreatic insufficiency. In addition, hyperamylasemia is often present for many years. It should be realized however that most patients with IPMN do not present with any symptoms as a result of inactive mucin production and/or location of the tumor in the body or tail of the pancreas.[24–26]

Classification and pathology

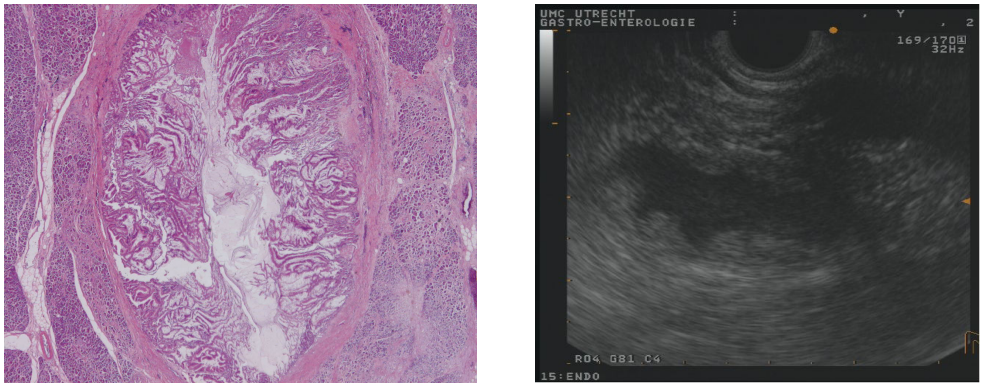
According to the WHO classification, IPMNs are defined as neoplasms with tall, columnar, mucin-containing epithelium with or without papillary proliferation and extensively involving the main pancreatic ducts (Figure 2a) or major side branches. In addition, IPMNs lack the ovarian stroma characteristic of MCNs. IPMNs are divided into IPMN adenoma, IPMN borderline and intraductal papillary mucinous carcinoma (Table 1).[15,21,22,28–34]

An IPMN adenoma is characterized by an epithelium that is comprised of tall columnar mucin-containing cells that show no or only low-grade dysplasia. The epithelium maintains a high degree of differentiation in adenomas. The time between the development from IPMN adenoma to invasive cancer is estimated to be 3-6 years.[24]

IPMN borderline is characterized by moderate dysplasia. The epithelium shows moderate loss of polarity, nuclear crowding, nuclear enlargement, pseudostratification and nuclear hyperchromatism. Papillary areas maintain identifiable stromal cores, but pseudopapillary structures may be present as well.

Intraductal papillary mucinous carcinomas are characterized by severe dysplastic epithelial changes (invasive or not). Severe dysplasia is manifested cytologically by loss of polarity, loss of differentiated cytoplasmic features including diminished mucin content, cellular and nuclear pleomorphism, nuclear enlargement and the presence of mitosis. Severely dysplastic cells may lack mucin.[23,28]

Because of their connection to the pancreatic ducts, IPMNs can be divided in three types depending on the site and extent of involvement, i.e., in the main pancreatic duct, one of the branch ducts or combined.[11,23–25,28] Using this classification,



(a) (b)

Figure 2. (a) Histologic picture of a large duct IPMN. Note the numerous papillary structures inside the lumen of the main pancreatic duct. (b) EUS image of an IPMN showing cystic dilatation of the main pancreatic duct with mural nodular/papillary structures inside the lumen.

one-quarter originates from the main duct, half from one the branch ducts and the remaining quarter has a combined origin, with the majority of IPMNs occurring in the head of the pancreas.[22] Most, if not all, branch-type IPMNs are benign, while main-duct and mixed type IPMNs are frequently malignant.[25]

Branch type IPMNs affect one or more branches of the pancreatic duct, which consequently show cystic dilatation. The dilated duct may contain solitary or multiple tumors and/or viscid mucin. The presence of large and an increased number of mural nodules indicate an increased probability of malignancy. When IPMNs are large enough to cause compression of the main pancreatic duct, obstructive pancreatitis may result, but also jaundice due to compression on the common bile duct may occur.[25,35]

Main duct type IPMNs are characterized by a diffusely or partially dilated main pancreatic duct filled with excessive mucin. IPMNs are predominantly found in the pancreatic head and only occasionally in the tail. The probability of malignancy increases when the main pancreatic duct is dilated >1 cm and mural nodules (>1 cm) are present. Several years of main duct obstruction with viscid mucin and mural nodules may result in chronic pancreatitis, in which case the entire pancreas is markedly fibrotic.[35]

Any combination of the branch type and main duct type is denoted as mixed-type IPMN. Mixed-type IPMNs are an advanced form of the branch type, in which the IPMN has spread to the main pancreatic duct, or an ultimate form of the main duct type, in which the IPMN has involved the branch ducts as well.[25,35]

Etiology and pathogenesis

The etiology of IPMN is unclear. There is no genetic or familial tendency, although an association has been described with familial adenomatous polyposis, Peutz-Jegher's syndrome, and other nonpancreatic tumors.[27,36] The genetic changes from the development of IPMN adenoma to IPMN invasive carcinoma have not been entirely established but are thought to be distinct from those associated with pancreatic ductal carcinoma development.[22,27,36]

Telomerase is responsible for cell immortality and is known to be activated in most human malignancies. Its activity has been found to be predominantly present in IPMNs with severe cellular atypia and may therefore be a useful diagnostic tool in the distinction between adenoma and intraductal carcinoma.[37]

A leading feature of many IPMNs is excessive mucin production. The expression of mucin glycoproteins (MUCs) in IPMNs has recently been typed by in situ hybridization and immunocytochemistry. It was demonstrated that most IPMNs produce MUC2, while MUC1 was not expressed, except in those cases that showed an invasive tubular component resembling ductal carcinoma. In addition, a third, mixed type, coexpressing both MUC1 and MUC2, has been distinguished. This type included the recently reported oncocytic subtype of IPMN. In addition, it has been reported that the expression of proliferating-cell nuclear antigen (PCNA), p53 and vascular endothelial growth factor (VEGF) becomes stronger as the malignant potential progresses. However, no clear differences were shown between patients with malignant and benign IPMNs. Other findings have indicated that matrix metalloproteinase-7 (MMP-7) may play a significant role in the progression from noninvasive to invasive cystadenocarcinoma.[18,22,25,38]

Recent research showed that IPMN is associated with frequent point mutations in the K-*ras* gene, thereby establishing these mutations as a genetic marker in IPMN. However, the exact role of these mutations remains unclear.[25]

Another molecular alteration is the loss of heterozygocity (LOH) in 9p21 (p16) and LOH in 17p13 (p53) seen in adenomas and borderline neoplasms, but with a 100% incidence in invasive carcinomas. Interestingly, all cases with LOH in 17p13 (p53) were concomitant with LOH in 9p21 (p16). Probably, K-*ras* mutation is a key event leading to subsequent genetic alterations in the development of IPMNs, including inactivation of the tumor suppressor p16 and p53 genes or gene products.[1]

Imaging

The primary imaging modality used to detect and evaluate IPMNs is a CT scan. CT scanning has significantly improved recognition of IPMNs. With non-contrasted images it is possible to identify ductal ectasia and, by distending the duodenal lu-

men with water, it is possible to recognize the protruding papilla. The presence of calcifications may be due to associated CP, or, when centrally located in the duct, results from deposits of calcium within the mucin. Multiplicity of cysts and associated downstream dilatation of the main pancreatic duct, when present, distinguish IPMNs from other cystic pancreatic neoplasms.[2,11,25]

Significant ductal dilation with normal or increased parenchymal thickness may indicate the presence of malignancy, which is supported by the presence of papillary proliferations (Figure 2b). The coexisting cystic ectasia of the collateral ducts and a protruding papilla makes the diagnosis of diffuse forms easier. In segmental forms, the CT picture is non-specific. If the pattern is of a cystic mass, most commonly in the tail, communication with the pancreatic duct should confirm the diagnosis. The demonstration of communication with the main duct is mandatory if the diagnosis is to be precise.

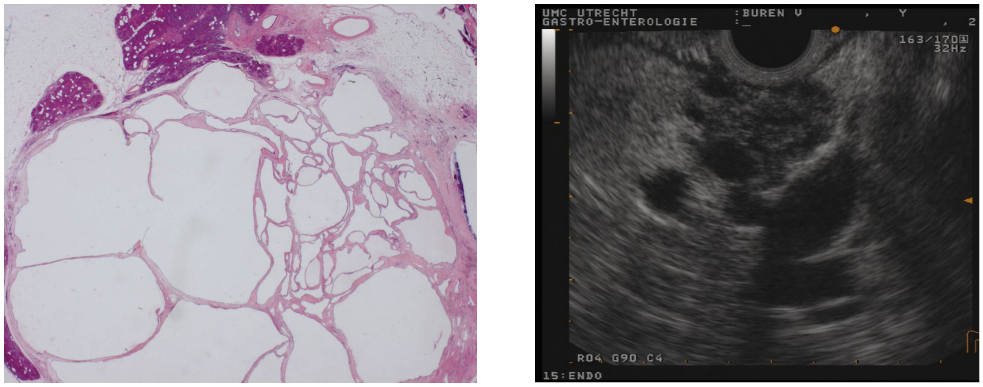
Until recently this information was only available with ERCP. In addition, the finding of viscous fluid oozing from the ampulla of Vater is a classic endoscopic finding in patients with IPMN.[25] Typical ERCP findings of IPMN include a diffusely or segmentally dilated pancreatic duct without strictures, dilation of side branches, and filling defects secondary to mucus or mural nodules. The papilla is patulous and resembles 'fish-eyes', frequently with mucus extruding from the orifice.[26]

ERCP and EUS are important secondary diagnostic tools for evaluation. EUS detection of a dilated main duct in the absence of an obstructing mass or a history that may explain a postinflammatory stricture should arouse the suspicion of segmental IPMN. In its diffuse form, the whole duct is dilated to different degrees and, unlike the segmental form, it is common to find ectasia of the duct, typically in the head. In this case it is not always easy to establish whether the whole duct is affected or the neoplasm is associated with dilation of the upstream duct because of obstruction.[2,24]

Management

As IPMNs manifest a much greater malignant potential than other cystic neoplasms of the pancreas, surgical resection is usually considered mandatory for the following reasons: 1) operation is still the option that gives the best chance of cure; 2) no reliable criteria and investigatory tools are available to differentiate non-invasive from invasive IPMNs; 3) treatments other than surgery give worse outcomes, especially for non-invasive IPMNs; and 4) operative mortality and morbidity is acceptably low in experienced hands. Partial pancreatectomy is the most common treatment for main-duct and some symptomatic large (>3 cm) branch-duct IPMNs of the pancreas.[24,25]

The extent of pancreatic resection for IPMN, however, remains as yet unclear,



(a) (b)

Figure 3. (a) Histologic picture of a mixed micro-macrocystic serous cystadenoma. Note the absence of both mucin as well as a wall with ovarian stroma. (b) EUS picture of a multicystic lesion with multiple cystic spacings (honeycomb-like structure) just below the transducer (serous cystadenoma).

because the long-term outcomes are not defined clearly.[1,11,25] Recurrence of IPMN following resection in patients with invasive IPMN has been reported in several studies (range 7-22%) after a follow-up of 2 to 25 months.[21,29,31] The overall 5-year survival for IPMNs is 36% to 77%. The 5-year survival of surgical resection for non-invasive IPMNs has been reported to range from 77% to 100%, while the 5-year survival of surgical resection for IPMNs with invasive carcinoma has been reported to vary between 27% and 60%.[22,24]

Serous Cystic Tumors

Epidemiology

Serous cystic neoplasms (SCNs) are generally benign.[2,6,39] These neoplasms mainly occur in women in their 50s (65%) and represent approximately 30% of primary cystic neoplasms of the pancreas.[2,3,11,40] SCNs are most frequently detected in the head of the pancreas (>50%) and have a mean size of approximately 7 cm.[1–3]

Clinical presentation

The most frequently reported symptoms are abdominal discomfort and low-grade pain. Weight loss, palpable mass, jaundice and obstruction of the upper gastroin-

testinal tract are rare and are related to extensive growth of the lesion.[1,2,12,39] A history of acute or chronic pancreatitis is absent except in the rare patient in whom SCN causes an episode of acute pancreatitis, presumably due to partial pancreatic duct obstruction.[1]

Classification and pathology

According to the WHO classification, SCNs are divided in serous microcystic adenomas, serous oligocystic adenomas and serous cystadenocarcinomas (Table 1). Serous microcystic adenomas are defined as benign pancreatic neoplasms composed of innumerable small cysts lined by clear cells. The appearance of serous oligocystic adenomas is similar to that of the serous microcystic adenomas, but these have fewer cystic spaces. Serous cystadenocarcinomas have the same histologic features as serous microcystic adenomas, but with metastases to or invasion into adjacent organs.[1,3,15]

SCNs appear as multiple cysts lined with cubic flat epithelium with cells with clear glycogen-rich cytoplasm without mucin (Figure 3a).[1,2,16,41] The malignant counterparts of SCNs are serous cystadenocarcinomas, but these are extremely rare. Therefore, SCNs of the pancreas should be considered (and managed as) benign neoplasms.[1]

Pathogenesis

SCNs are characterized by the absence of mucin, lack of immunoreactivity for cytokeratins AE1 and AE3, and positive staining with the periodic acid-Schiff reaction for glycogen. Cystic fluid analysis should not demonstrate an increased amylase concentration as is seen in pancreatic pseudocysts. In addition, increased levels of Ca 19-9 or CEA, as is found in pancreatic ductal cancers with cystic necrosis and MCNs, are also not present. A suspicion of malignant SCN should arise in the presence of Von Hippel-Lindau (VHL) syndrome, a genetic condition associated in 15-30% of cases with serous cystadenocarcinoma.[2,3,13]

Imaging

SCNs have three morphologic patters: polycystic, oligocystic and honeycomb. The polycystic form is characterized by a bosselated collection of multiple, small ($<$2 cm) cysts, usually greater than six in number. A central fibrous scar with a characteristic stellate pattern of calcification occurs in up to 30% of these neoplasms. The honeycomb pattern is characterized by numerous, subcentimeter cysts that cannot be depicted as individual cysts by cross-sectional imaging. The oligocystic pattern is the

least common, occurring in less than 10% of patients. The characteristic findings of stromal hypervascularity with a predominance of small cystic areas, combined with an idolent course, lack of metastases or local invasion, and an appropriate clinical setting, permits the diagnosis of SCN to be made with an accuracy approaching 90-95%.[1,2,4,39]

The diagnosis of SCN is easily made when (endoscopic) US shows a mass with multilobulated borders, no posterior acoustic enhancement and an internal honeycomb architecture due to the presence of multiple septa which delimit small cystic spaces (Figure 3b).[1,2,39]

On CT, microcystic tumors appear as a mass that is neither enhanced nor affecting or deforming the profile of the gland. When calcifications are present, the location is almost always central, and they are punctuate or globular, as opposed to the lamellar calcifications seen in MCNs. The presence of central calcification in correspondence with scars or septa definitively characterizes a cystic mass as SCN.

MRI demonstrates in the microcystic pattern the presence of small fluid content within the dense septa of a sponge-like mass but has the disadvantage that it is insensitive to calcifications. In macro-microcystic cases the two components are easily recognizable.[1,2,39]

Management

To label a pancreatic mass as a SCN is clinically relevant because this tumor, unlike other cystic tumors of the pancreas, is most frequently benign. Therefore, whenever possible, a conservative approach is recommended.[2] When the diagnosis of a SCN is made with certainty, management is determined by symptoms, progression and location of the lesion. Symptomatic and enlarging serous cystadenomas should be resected. Lesions in the body or tail of the pancreas require a distal pancreatectomy while those in the head of the gland are resected by pancreaticoduodenectomy. Small, asymptomatic, and non-enlarging serous cystadenomas can be observed since the risk of malignant change is small. The optimal interval for repeating an imaging study in such patients is however unknown.[1−3] Although rare, if a malignant SCN is suspected, this should be resected.[3,41,42]

Current Issues

A number of issues regarding pancreatic cystic neoplasms are still under debate and require further study.

First, although imaging techniques are improving and the awareness of these cystic neoplasms is high, differentiation between SCNs, MCNs and IPMNs is still

difficult and the possibility of misdiagnosing is as high as 10%. Differentiation between serous and mucinous neoplasms is important, because the latter is potentially malignant. Guidelines may help to differentiate between SCNs, MCNs and IPMNs (Table 2), however, available criteria are not all reliable. For example, positive mucin-staining of the cystic fluid excludes SCNs. However, the absence of mucin does not necessarily exclude the presence of MCNs. In addition, the absence of communication between a cyst and the pancreatic duct has been used by some as a criterion for diagnosing MCNs and to differentiate them from IPMNs. However, this criterion is unreliable as demonstration of such a communication depends on several factors, including quality of the imaging modality and the thoroughness of the pathologist. Moreover, some MCNs may communicate with the pancreatic duct as well.[14] MCNs are often characterized by the presence of ovarian stroma. Whether the presence of ovarian stroma is mandatory for a diagnosis of MCNs remains controversial. Opponents argue that the absence of ovarian stroma cannot be the only criterion for ruling out a MCN. They argue that ovarian stroma can sometimes be observed in only a small part of the cystic wall and thus may be missed if the pathological examination is less than complete.[14,43] In addition, some have suggested that MCNs may lose their ovarian stroma with malignant transformation.[35,43] Others have argued however that the presence of ovarian stroma should be a prerequisite for a diagnosis of MCN, as in the absence of another definitive marker, it is currently impossible to determine if a mucin-producing neoplasm is indeed a MCN. Furthermore, exceptions to this rule would lead to misclassification of IPMNs and MCNs.[14,16]

Second, as the variety of cystic pancreatic neoplasms is broad, differentiation between malignant and benign neoplasms is difficult. This differentiation is however of great importance to the management of the neoplasm. Many techniques are available for differentiation between malignant and benign lesions, for example cytologic analysis, cystic fluid examination for amylase and tumor markers, 18F-FDG-PET scan and EUS (Table 2).[12,13,24,44] Combining several techniques is necessary since not a single technique has been proven to be able to definitely detect malignancy.[7] For example, several studies have reported a positive correlation between tumor diameter and differentiation.[45] Though, in other reports, tumor diameter was of no significance in the differentiation between benign and malignant MCNs.[4,9,16] In addition, 18F-FDG-PET scan is often combined with CT or serum glucose levels. A PET scan analyzes the metabolic activity of tissues. As most malignant tumors have a higher metabolic activity than benign tumors, this technique may be helpful in the differentiation between malignant and benign pancreas neoplasms.[46–50] Cyst fluid analysis of CEA and amylase is another method to differentiate between benign and (pre)malignant pancreatic cystic neoplasms. A recent review of the literature

suggested that CEA levels>800 ng/mL strongly suggest a mucinous cystadenoma. CEA levels <5 ng/mL or CA 19-9 levels <37 U/mL may be associated with a serous cystadenoma or a pseudocyst. Finally, amylase levels <250 U/L nearly excludes the presence of a pseudocyst.[51] The loss of an ovarian-like stromal differentiation and p53 positivity seem to be associated with malignant behavior of MCNs. It has even been suggested that a correlation is present between pancreatic MCNs and its counterparts in the ovary, liver, and retroperitoneum related to the embryogenesis of the respective tissues of origin.[9] Patients with IPMN have also been suggested to be genetically predisposed to the development of malignant tumors in a variety of organs, including stomach, colon, breast, pancreas and others.[35] A cystic structure and the presence of mucin-secreting epithelium are not sufficient to classify a neoplasm as MCN because IPMNs with duct ectasia and mucin hypersecretion may have the same characteristics. A clear distinction between these two tumors requires precise definition, because both types of lesions have the potential to become malignant. In addition, MCNs are difficult to distinguish from pseudocysts.[9] Many investigators have assessed whether the use of molecular biologic factors, such as RAS and p53, is helpful in distinguishing between benign and malignant IPMNs. Further genetic and morphologic studies are needed to refine the histologic grading of IPMNs, as there is still no consensus on grading of the density of the cytoplasm, shape of epithelial cells, expression of MUC1 and MUC2, oncogenes and tumor suppressor genes.[37]

Third, the major unsolved issue is to obtain a definite preoperative diagnosis as various cystic neoplasms require a different treatment. As most IPMNs are resectable and curable, it is important to define the characteristics of invasive IPMN adenocarcinoma. Most studies have reported an excellent prognosis for patients who undergo surgery for benign tumors. In contrast, a wide variation in 5-year survival rates has been reported (0-82%) for patients treated for malignant IPMN.[2,18,28,37,38] There is considerable controversy regarding the treatment of pancreatic cystadenomas. Most authors recommend resection whenever possible because of the difficulty in determining which tumors are potentially or definitely malignant.[3,28] Treatment of MCNs mainly depends on the type of differentiation. It remains therefore unclear, which patients with MCN require a complete resection and a close follow-up for potential recurrence. It has been suggested that a regular follow-up program with surveillance using imaging tests and/or serum tumor markers may not be necessary to detect local recurrences or additional primary neoplasms.[8] Nevertheless, others believe that all MCNs should be considered as mucinous cystadenocarcinomas of low-grade malignant potential because recurrences after resection occurred in 7% of 60 patients who had MCN without dysplasia.[52] Surgical resection is the treatment of choice for most IPMNs, particularly at a stage that invasive carcinoma is demonstrated but no evidence of metastases is found. The prognosis becomes worse once

Table 2. Clinical features for differentiation of serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), and intraductal pancreatic mucinous neoplasms (IPMNs)

Feature	SCN	MCN	IPMN
Age	Perimenopausal	Perimenopausal	Elderly
Sex (%female)	>95%	>95%	Around 30%
Location	>50% in head	Mostly in body and tail	>60% in head
Clinical features	Usually found incidentally, but may cause adbominal pain and a palpable mass if large	Usually found incidentally but may cause abdominal pain and a palpable mass if large	History of pancreatitis, abdominal pain, or found incidentally
Calcification	Yes	Rare	No
Morphology/EUS findings	Microcystic with a honeycomb appearance; rarely has a macrocystic component; central calcification	Macrocystic, occasionally septated; peripheral calcifications, solid components and regional adenopathy when malignant	Dilated main pancreatic duct or side branches; may appear as a septated cyst; may have a solid component
Fluid characteristics	Thin, clear to serosanginous, stains positive for glycogen	Viscous or stringly, clear, stains positive for mucin	Viscous or stringly, clear, stains positive for mucin
Communication with pancreatic duct	No	Rare	Yes, but not always demonstrable
Main pancreatic duct	Normal or deviated	Normal or deviated	Normal or dilated
Malignant potential	Almost none	Yes	Yes

invasive carcinoma has developed.[28,29] The management of patients whose cystic lesion cannot be diagnosed with certainty presents a great problem. Most experienced physicians recommend resection for even moderately suspicious lesions in the body and tail of the pancreas, and for highly suspicious lesions in the head of the gland.[3] Controversy still also exists regarding the extent of pancreatectomy that should be performed in patients with pancreatic IPMNs. Total pancreatectomy appears to be a logical choice, but on the other hand, this procedure is associated with a higher risk of postoperative complications and often results in brittle diabetes.[25]

Finally, there is ongoing debate on the prognosis of these neoplasms. While some have the opinion that MCNs may recur and/or metastasize after complete removal, others are quite convinced that the prognosis is excellent once the tumor has been completely removed. Recent studies based on extensive tumor sampling have however clarified this. It was shown that recurrence and tumor-related death were features of deeply invasive MCNs only.[14,18] Still, it remains unclear whether similar predictions can be made with regard to IPMNs. As IPMNs are slowly growing neoplasms, recurrences may become evident at a late stage and be underestimated after short-term follow up. The ability to stratify patients into low- and high-risk categories would allow more objective, evidence-based recommendations on when and how to resect a lesion.

Conclusion

Cystic neoplasms are currently increasingly being diagnosed, because of a wider variety in imaging techniques. MCNs and IPMNs have a malignant potential, whereas SCNs are generally benign. Differentiation between benign, premalignant and malignant neoplasms is of great importance, because treatment and prognosis is highly dependent on these characteristics. CT and 18F-FDG-PET scan seem to be the examinations of choice for a correct prediction of tumor type. High concentrations of CEA may differentiate mucinous from serous neoplasms and low amylase levels may exclude the presence of a pseudocyst. In addition, endoscopic US may be useful to detect the morphologic criteria of small tumors. Surgical resection should be performed in patients with symptomatic SCAs, all mucinous cystic neoplasms, and cystic tumors that are not clearly defined. Nonetheless, further research is required to define the optimal differentiation technique and treatment strategy for SCNs, MCNs and IPMNs.

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Chapter 10

General discussion

Palliative treatment of malignant gastric outlet obstruction

In the first part of this thesis, the results of a randomized study comparing the two most widely used palliative treatment options for malignant gastric outlet obstruction (GOO), i.e., gastrojejunostomy (GJJ) and duodenal stent placement, are reported. Our aim was to compare these two palliative treatments with regard to medical effects (ability for food intake, complications and survival), quality of life and costs. Using the data from this study, we proposed a more evidence-based treatment guideline for the palliative treatment of patients with malignant GOO.

Main conclusions on the palliative treatment of malignant GOO:
The data of this study led to the following conclusions:

- Clinical success was similar for GJJ and stent placement.
- Food intake improved more rapidly after stent placement than after GJJ.
- During long-term follow-up, food intake was better after GJJ than after stent placement.
- Stent placement was associated with more major complications and reinterventions compared to GJJ, largely due to a higher incidence of stent obstruction by food debris and tumor/tissue ingrowth through the meshes of the stent.
- Both methods had a similar effect on the quality of life.
- Total costs were higher for GJJ than for stent placement, largely due to a longer hospital stay after surgery.
- Endoscopic stent placement in the distal part of the duodenum can be difficult, because of looping of the gastroscope. For this purpose, a colonoscope is recommended, as it is longer than a therapeutic gastroscope, and offers good endoscopic stiffness, which avoids looping in the stomach.

Based on these results, we recommend GJJ as the preferred treatment for malignant GOO in patients with an expected life expectancy of more than 2 months, as this treatment is associated with better long term results. Stent placement is preferred for patients who do not want to undergo surgery and those with a short life expectancy ($<$2 months) as this treatment is less invasive and associated with a faster relief of obstructive symptoms.

Perspectives and future research of palliative treatment of malignant gastric outlet obstruction

Stent placement

In this thesis we evaluated stent placement in a literature review, a retrospective study and in a multicenter randomized trial. The results of these studies supported each other, with regard to improvement of food intake, hospital stay and survival. However, there were some differences in incidence of complications, especially between the randomized and retrospective studies on the one hand and the literature review on the other hand. This was mainly due to the difference in the definition of complications. We defined recurrent obstruction by tumor/tissue ingrowth or food debris also as major complications. Although previous reported studies did not do so, we adopted this strategy given the fact that stent obstruction requires renewed endoscopic intervention, which is burdensome for patients in the palliative phase, and can be associated with weight loss and a decline in quality of life. Therefore, we recommend that future studies adopt a similar strategy whereby the use of uniform definitions will improve the interpretation and comparison of different studies.

Differences in the frequency of complications between the randomized and retrospective study and the literature review may also be explained by the use of various materials and stent designs. The most common complication on the long term after placement of an uncovered duodenal stent placement is tissue in- or overgrowth. Although covered stents were developed to prevent tissue ingrowth, they are also known for the high incidence of migration on the short term.[1–3] The duodenal stents designed by Song et al. are fully or partially covered with the ends flared to a wider diameter. This design has been suggested to overcome tumor ingrowth. In addition, partially covered stents may also be associated with a lower incidence of stent migration than fully covered stents.[4,5] Another study investigated the advantages of coaxial stent placement of covered stents. This is based on the idea that efficient delivery systems for covered stents are not available yet. Coaxial stent placement was suggested to contribute to a decreased migration rate, leading to fewer cases of recurrent obstruction.[2]

One of the other new stent designs is the D-Weave Niti-S™stent (Taewoong Medical, Seoul, Korea), made of a single piece of extruded nitinol wire woven in a novel configuration, rather than the usual braided design. The new design achieves an improved flexibility with a high expansible force and a low longitudinal resistance and has been suggested to prevent both perforation and migration. Preliminary studies have already shown promising results.[6–8] Currently, an ongoing trial is being performed in the Netherlands to determine safety and efficacy of this new stent. Future research should compare different stent designs in randomized controlled tri-

als. Companies developing new stent designs should aim at integrating the benefits of both covered and non-covered stents to reduce complication rates.

Gastrojejunostomy

In a literature review, a retrospective study, and a prospective randomized study, we evaluated the results of GJJ for gastric outlet obstruction in patients with inoperable malignancy. This showed that GJJ is a safe and effective palliative treatment and associated with good long term outcomes when looking at complications and food intake. Therefore, we suggest that GJJ is the preferred standard palliative treatment for malignant GOO.

Despite the good long term outcome, the retrospective study and literature review also showed that GJJ was associated with a higher incidence of minor complications and a long recovery period compared to duodenal stents. A less invasive surgical technique could lead to better short term outcomes without interfering with the good long term outcomes of GJJ, as is laparoscopic gastrojejunostomy (LGJ). LGJ is associated with a lower incidence of complications, shorter hospital stay and a fast relief of obstructive symptoms, compared to open GJJ.[9–11] Unfortunately, LGJ has only been investigated in relatively small populations. Therefore, large randomized trials are needed, comparing LGJ and GJJ with regard to food intake, hospital stay, complications and burden of treatment.

Another less invasive technique to perform GJJ is by natural orifice transluminal endoscopic surgery (NOTES). Recent studies have suggested that NOTES is less invasive than an open surgical procedure and has a short recovery period. An obvious advantage of NOTES is that the abdominal wall is not incised, preventing complications, such as wound infections. In addition, NOTES may result in lower stress levels and a faster recovery.[12,13] Despite the promising results of NOTES, this technique is still in an early stage and therefore safety and efficacy of this new combined surgical-endoscopic technology should be evaluated before it is implemented as the standard treatment for malignant GOO.[14,15]

Endoscopic ultrasound (EUS) is an upcoming technique that may guide minimally-invasive surgical therapy. This technique has constantly been improved over the last few years and aims not only at reduced scaring, shorter hospital stay and fast recovery, but has also led to new transgastric endoscopic procedures without percutaneous access to the abdominal cavity. EUS has the unique ability to puncture organs through the gastrointestinal tract, for example accessing the small bowel through the gastric wall without direct viewing.[16]

Stent placement versus gastrojejunostomy

We performed a multicenter randomized trial comparing GJJ and duodenal stent placement in 21 hospitals. For an accurate power to detect a difference in food intake, we had calculated to require 148 patients. Nevertheless, we were only able to randomize 39 patients. This was due to two reasons. First, recruiting patients in a randomized trial comparing a surgical with a non-surgical treatment modality turned to be difficult, as most patients had a strong preference for the non-surgical intervention. Second, the recruitment of patients was a time-consuming process when implemented correctly. As became clear, time is sparse in a clinical setting and in most hospitals research nurses are not available to perform all the necessary procedures to randomize patients. In future, randomized trials, comparing a surgical and a non-surgical intervention, this should be taken into consideration. A specialized nurse practitioner could be of great help in including patients and completing follow-up in such trials.

Despite the small sample size, our results showed statistically significant differences in the number of days patients were able to eat at least soft solids, complications, and costs between GJJ and stent placement. Therefore, we consider our results to be of great importance for the the decision which palliative treatment should be preferred in individual patients with malignant GOO.

Besides our recommendations on the palliative treatment of malignant GOO, our studies also resulted in some interesting perspectives, important for future studies. In our randomized trial, a specialized trained nurse followed all patients to complete quality of life questionnaires and to give advice during follow-up. As many of these patients in the palliative setting were not routinely followed-up in the outpatient clinic, it became clear that these visits were well appreciated by our patients. A recent study compared follow-up by nurse-led home visits with visits to the clinic in patients who had undergone resection of esophageal cancer. It was concluded that patients after curative esophageal cancer surgery can safely be followed up by a specialist nurse. In addition, it was found that this was less costly and did not adversely affected quality of life, patient satisfaction and medical outcome. Currently, a randomized trial is being conducted in our center comparing follow-up by home visits with outpatient clinic visits in patients in a palliative stage of pancreatic-, esophageal- or hepatocellular cancer. Main outcomes are quality of life, medical effects, satisfaction and costs.

Another perspective from this study was the observation that malnutrition had a negative impact on quality of life and health status, potentially affecting the development and severity of complications after palliative treatment.[17,18] Therefore, the nutritional status prior to treatment and during the recovery period is of great importance. In our study, health status was scored using the WHO performance

score. Although the WHO performance score had no effect on outcomes in our study, recent studies showed a relationship between nutritional status and complication rate after gastrointestinal surgery.[19,20] A currently ongoing trial investigates the effect of specific food supplements in patients with esophageal cancer undergoing curative surgery, with regard to health status, complications and quality of life.

From the first part of this thesis we can conclude that GJJ should be recommended as the initial palliative treatment of malignant GOO. Duodenal stent placement is preferred for patients who do not want to undergo surgery, and those with an expected short survival. Both GJJ and stent placement are however not optimal in achieving fast and long term relief of obstructive symptoms with minimal invasiveness. Stent placement is a noninvasive treatment, with a fast relief of symptoms and short hospital stay. Nevertheless, during long-term follow-up, food intake decreases and there is a high incidence of complications. GJJ on the other hand is an invasive treatment with a relatively long recovery period. The relief of symptoms is however maintained on the long term and there is a low incidence of complications. Future studies should investigate whether the results of GJJ and stent placement can be improved by refinements in surgical techniques or new stent designs. In addition, a prognostic model that distinguishes between patients with a relative long and short expected survival, may contribute to patient selection for GJJ and stent placement. In this way, optimal results will be achieved in the treatment of individual patients with malignant GOO.

Treatment of pancreatico-biliary disorders: complications of ERCP

The second part of this thesis reports the results of a study on complications after ERCP. Our aim was to examine possible risk factors for post-ERCP complications and to evaluate a prognostic model that could help to determine which patients are eligible for early discharge after ERCP. Using the data from this study we were able to detect the most important risk factors for post-ERCP complications and to develop a prognostic model for outpatient ERCP.

Main conclusions on post-ERCP complications:
The data of this study resulted in the following conclusions:

- Various patient- and treatment characteristics may increase the risk of post-ERCP complications.

- The most important risk factors for post-ERCP complications were (precut) sphincterotomy, female gender, young age, primary sclerosing cholangits (PSC), pancreas divisum, history of pancreatitis, sphincter of Oddi dysphunction (SOD) and difficult cannulation.
- A prognostic model that validates the effect of these risk factors was able to detect patients at high risk for pancreatitis and cholangitis.
- Patients with a low to intermediate score in the prognostic model, and without a high risk procedure for perforation or hemorrhage, or complications during observation, were found to be eligible for early discharge after ERCP.
- Early discharge after ERCP should be defined as an observation period of 6 hours after ERCP, as 90% of complications were shown to occur within this period.

In general, we conclude that the use of a prognostic model and a selective policy may distinguish between patients eligible for early discharge and patients who need an overnight observation. Patients with a low to intermediate score in the prognostic model, without complications during the observation period, high risk procedures for perforation and hemorrhage, hemorrhage during ERCP or free air on X-ray examination indicating retroperitoneal perforation may safely be considered for early discharge 6 hours after ERCP.

Perspectives and future research of the treatment of pancreaticobiliary disorders

Our recommendation for early discharge after ERCP is based on results from the literature and a prospective follow-up study. Nevertheless, a randomized trial is necessary to conclude whether this is indeed safe, may lead to a cost reduction and will maintain or improve quality of life in patients. In our experience, such a randomized trial was difficult to perform in our unit because of various logistical problems. In addition, as this is an academic hospital, most of the patients undergoing ERCP did not fulfil the criteria for early discharge. The ideal setup should include a randomized trial comparing patients following the standard follow-up after ERCP and patients with a follow-up that depends on the outcome of our prognostic model.

Knowledge of risk factors of post-ERCP complications may have several patient- and procedure effects. First of all, it may increase the quality of the information provided by clinicians to patients. In addition, early discharge after ERCP may increase quality of life and therefore reduce the burden of this treatment. A currently ongoing trial investigates the burden of ERCP by questionnaires on pain, burden and satisfaction during a 7 day follow-up after ERCP.

Second, knowledge of risk may also lead to an increase of preventive measures as clinicians will be more aware when patients are at high risk for post-ERCP complications. These preventive measurements will reduce severity of complications and may even prevent complications to occur. A common preventive measure is for example the placement of a small diameter plastic stent in the pancreatic duct to reduce the risk and/or severity of pancreatitis.[21,22] An ideal stent would be biodegradable with an adequate radial force and diameter for a sufficient period of time. Some studies have investigated various materials for use in biodegradable stents, such as polylactide (PLA).[23−25] Nevertheless, the ideal stent for the pancreatic duct or CBD duct has not been developed yet, as none of the evaluated materials met the requirements.

Another way to prevent post-ERCP complications is by drug treatment. Several pharmacological agents have been investigated for the prevention of post-ERCP pancreatitis. The most widely investigated compound of prophylaxis against post-ERCP pancreatitis is somatostatin and its synthetic analogue, octreotide. Somatostatin acts by inhibiting pancreatic secretion, alters the cytokine milieu, has anti-inflammatory activity and protects pancreatic cells. Nevertheless, even large randomized studies were not able to prove a definitive reduced risk due to non-representative and/or small patient groups. To date, a number of other pharmacologic agents have been studied, for example nitroglycerine, antibiotics and diclofenac. Unfortunately, none of these studies showed a clearly reduced risk of post-ERCP pancreatitis.[26−29]

Several new techniques have been developed to improve therapeutic ERCP procedures, for example cholangioscopy, which has been developing rapidly during recent years.[26,30,31] Cholangioscopy is achieved by passing a small caliber endoscope through a conventional endoscope and allows direct visualization and targeted tissue sampling of lesions within the bile duct. Recent studies concluded that cholangioscopy is highly accurate in diagnosing and excluding malignancy and also seems to be an excellent way to remove bile duct stones.[32−34] Nevertheless, additional trials are needed to investigate the safety and efficacy of this new technique.

From the second part of this thesis we conclude that there are several patient- and treatment characteristics affect the risk of post-ERCP complications. An ERCP on an outpatient basis is safe and effective when our prognostic model is combined with a selective policy.

Nevertheless, there are still new techniques and pharmacological agents being developed, in order to reduce the risk of post-ERCP complications. It remains to be investigated what the effect of these developments is on the incidence of post-ERCP complications. In addition, randomized trials comparing standard follow-up with a

6 hour observation after ERCP is needed to investigate the safety and efficacy of our recommendations.

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Summary

In the Netherlands, yearly approximately 2100 patients are diagnosed with gastric cancer, 1500 with pancreatic cancer, 400 with hepatobiliary cancer and 90 with duodenal cancer.

Gastric Outlet Obstruction (GOO) is a common symptom in patients with pancreas-, hepatobiliary- or duodenum cancer. GOO causes malnutrition, dehydration and nausea resulting in a fast decline of the clinical condition of these patients. Palliative treatment is therefore mandatory and aims at relief of obstructive symptoms and maintains or even improves the quality of life. Traditionally, gastrojejunostomy (GJJ) was the standard palliative treatment in patients with GOO. Recently, endoscopic stent placement has been introduced as an alternative treatment. We reviewed the available literature on stent placement and GJJ with regard to medical effects and costs. In total, 44 studies were identified of which 2 randomized, 6 comparative and 36 retrospective and prospective studies. A total of 1046 patients received a stent and 297 patients underwent GJJ. Our results showed that stent placement was associated with a faster relief of obstructive symptoms and a shorter hospital stay. Nevertheless, patients after GJJ had fewer recurrent obstructive symptoms and therefore the need for reinterventions was lower. The findings of this review suggested that stent placement was associated with more favorable short-term results, whereas GJJ may be a better treatment option in patients with a more prolonged survival **(Chapter 2)**.

In a retrospective study we compared GJJ with stent placement in 95 patients with malignant GOO, with regard to medical effects. Fifty-three patients were referred for duodenal stent placement and 42 patients underwent GJJ at the Erasmus MC in the period 1994-2006. Primary outcome was food intake, measured by the Gastric Outlet Obstruction Scoring System (GOOSS), with a score of 0=no oral intake, 1=liquids only, 2=soft solids and 3=full diet. Secondary outcomes were complications, recurrent and persistent obstructive symptoms, hospital stay and survival. We found that both palliative treatments were safe and effective. However, after stent placement food intake improved more rapidly (stent: 3.6 days, GJJ: 10.1 days, $p<0.01$) and hospital stay was shorter (stent: 6 days, GJJ: 18 days, $p<0.01$). Nevertheless, late major complications, recurrent obstructive symptoms and reintervention occurred more often after stent placement than after GJJ. From this retrospective comparable study we concluded that GJJ was preferable to stent placement as the initial palliative treatment for patients with malignant GOO. Stent placement may be reserved for patients with a short life expectancy **(Chapter 3)**.

Chapter 4, describes the largest randomized study on stent placement and GJJ

performed at this moment. Between January 2006 and May 2008, 39 patients were randomized to GJJ (n=18) or duodenal stent placement (n=21). In this randomized trial, 21 hospitals were participating of which 11 included patients. Main outcomes were medical effects (food intake, complications and survival), quality of life and costs. Food intake improved more rapidly after stent placement than after GJJ (5 vs. 8 days; $p<0.01$). However, long term relief of obstructive symptoms was better after GJJ. Major complications occurred more often after stent placement than after GJJ (6 in 4 patients vs. 0; $p<0.01$), including stent obstruction by food debris and tumor in- or overgrowth. We did not found a significant difference in recurrent and persistent obstructive symptoms. Nevertheless, recurrent obstructive symptoms (8 in 5 vs. 1 in 1, $p=0.02$) and reinterventions (10 in 7 patients vs. 2 in 2 patients; $p<0.01$) occurred more often after stent placement than after GJJ. Hospital stay was shorter after stent placement than after GJJ (7 vs. 15 days, $p=0.04$). There was no difference in survival (stent: 56 vs. GJJ: 78 days; $p=0.15$). Quality of life was measured by standard quality of life questionnaires on day 0, 14, 30 and then monthly. We did not found a difference in quality of life during follow-up or between stent placement and GJJ. Though, pain symptoms decreased more rapidly after stent placement than after GJJ ($p=0.02$). Total costs were lower for stent placement than for GJJ (stent: €8,812 vs. GJJ: €12,433, $p=0.04$), mainly due to higher costs for prolonged hospital stay after GJJ.

This randomized study showed that despite slow improvement, GJJ gave better long-term relief of obstructive symptoms in patients with malignant GOO. Therefore, we concluded that GJJ was preferred as the initial treatment for relief of obstruction in patients with an expected survival of 2 months or more. Because stent placement was associated with a rapid improvement of food intake, short hospital stay and lower costs, this treatment was preferable for those patients expected to live shorter than 2 months.

Duodenal stent placement in the distal duodenum or proximal jejunum with a therapeutic endoscope is difficult, because of the reach of the endoscope, loop formation in the stomach, and flexibility of the gastroscope. The use of a colonoscope may overcome these problems. When using a therapeutic gastroscope for stent placement in the distal part of the duodenum or proximal jejunum, we experienced three problems. First, the length of the gastroscope may be insufficient, because of looping in the stomach. Looping is more likely to occur if the stomach and proximal duodenum are dilated, particularly if the stricture in the duodenum/jejunum has existed for a prolonged period of time. Second, when looping occurs, the resulting friction between the stent and the working channel of the endoscope may prevent the stent from being advanced out of the endoscope. Third, even when the stent

can be advanced close to an often angulated stricture, the ability to maintain the gastroscope in a stationary position in the duodenum is reduced. The resistance offered by an angulated stricture may result in a retrograde force pushing the gastroscope back into the stomach, even if a super-stiff guidewire is advanced through the endoscope. The colonoscope is obviously longer, provides more stiffness in these cases and avoids looping in the stomach, resulting in a stable position close to a stricture distal in the duodenum and proximal jejunum. We retrospectively studied 16 patients to report our experiences with distal duodenal stent placement using a colonoscope. We found that the main outcomes (food intake, complications and survival) were comparable to other studies on duodenal stent placement using a therapeutic gastroscope. The results of this study showed that distal duodenal/proximal jejunal stent placement using a colonoscope is safe and effective. Therefore, we suggested that a colonoscope was a good alternative for a therapeutic gastroscope in this situation **(Chapter 5)**.

In many institutions, patients are admitted for an overnight observation to detect complications after endoscopic retrograde cholangiopancreatography (ERCP). However, an overnight observation could be burdensome to patients and early discharge may lead to cost reduction. We reviewed the available literature to determine safety of ERCP performed on an outpatient basis in **Chapter 6**. In total, eleven studies reported results on in- and outpatient ERCP. In 2320 outpatients, 2407 ERCPs were performed and 2908 ERCPs were performed in 2483 inpatients. We did not found a significant difference in complication rate between in- and outpatients. Complications in outpatients occurred within 2-6 hours in 72% of which at least 82% within 4 hours. Ten percent occurred within 6 to 24 hours and 18% more than 24 hours after ERCP. The results showed that ERCP on an outpatient basis was safe when performed with a selective policy. Patients were likely to be eligible for ERCP on an outpatient basis if they: 1) do not have an increased risk for post-ERCP complications (i.e., previous history of pancreatitis, sphincter of Oddi dysfunction or difficult cannulation), 2) have a relative good health status (American Society of Anesthesiologists (ASA) physical status classification I or II), 3) have a corrected coagulopathy, 4) stay within 30 minutes driving distance from the hospital, 5) are not already being admitted to the hospital, and 6) are escorted by a second person. These patients should be observed for 4 hours, as almost 60% of all complications occur within 4 hours after ERCP.

An ERCP is a common procedure for the treatment of biliary and pancreatic disorders. This procedure is however associated with a relatively high morbidity rate of 5-10%. Several retrospective and prospective trials have determined possible risk

factors for the development of post-ERCP complications. However, the relative importance of these risk factors is unknown. In **Chapter 7** we evaluated possible risk factors for post-ERCP complications from literature. In addition, results from the literature were compared with results from a multivariable analysis in a retrospective patient population. A total of 16 studies reported results on uni- and multivariable analyses of risk factors for post-ERCP complications. The retrospective database included 1372 ERCP procedures. Our results identified various patient- and procedure characteristics that predict the development of complications after ERCP. Patients were at higher risk for pancreatitis and cholangitis when the following risk factors were present: female gender, younger age, (precut) sphincterotomy, PSC, SOD, pancreas divisum, difficult cannulation of CBD and/or history of pancreatitis.

Most common complications after ERCP are pancreatitis, cholangitis, retroperitoneal perforation and hemorrhage. In the previous chapter the most important risk factors and the magnitude of their effect were established. In **Chapter 8** we developed and evaluated a prognostic model that distinguished between high- and low risk patient groups in order to determine which patients are safely eligible for early discharge after ERCP. This model was based on the results of chapter 7.

Hemorrhage and retroperitoneal perforations can often be detected during or directly after ERCP. Nevertheless, symptoms of pancreatitis and cholangitis occur most often 3 to 6 hours after ERCP. We evaluated our prognostic model in a prospective patient population. In the prospective patient population 27 (10%) complications occurred in 274 procedures, including pancreatitis (n=14), cholangitis (n=12) and hemorrhage (n=1). A score of 3 or less in the prognostic model was associated with a low to intermediate risk for pancreatitis and cholangitis (8%, 20/252), a score of 4 or above was associated with a high risk (27%, 6/16). Pancreatitis and cholangitis occurred within a mean time of 4.1 hours after ERCP, with 90% of complications diagnosed within 6 hours after ERCP. Our results showed that this scoring system might only help clinicians to identify patients at high risk for post-ERCP pancreatitis or cholangitis. Patients with a low to intermediate score, without complications during 6 hour observation, high risk procedures for perforation and hemorrhage, hemorrhage during ERCP and free air on CT indicating retroperitoneal perforation, are safely eligible for early discharge after ERCP. The observation period for early discharge should be 6 hours, as 90% of the complications occur within this time period.

Tumors of the pancreas generally have a poor prognosis, with the majority being highly malignant. Although cystic lesions of the pancreas are uncommon, pancreatic cystic neoplasms are currently increasingly being diagnosed, probably because

of the wider availability of imaging procedures. Pancreatic cystic lesions consist of pseudocysts, congenital cysts and cystic neoplasms including mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs) and serous cystic neoplasms (SCNs). In **Chapter 9** we have given a literature overview on cystic lesions of the pancreas, emphasized on mucinous neoplasms, regarding the epidemiology, clinical presentation, classification, etiology, imaging and treatment. Cystic neoplasms, including MCNs and IPMNs, had a high malignant potential, whereas SCNs were generally benign. A CT seemed to be the examination of choice for a primary definition of tumor type. In addition, cyst fluid CEA may differentiate between mucinous and serous neoplasms. Furthermore, surgical resection should be performed in all patients with mucinous neoplasms.

In the **General Discussion (Chapter 10)**, we concluded that this thesis demonstrates that gastrojejunostomy is the preferred palliative treatment in patients with malignant GOO. Duodenal stent placement should be reserved for those with a poor prognosis ($<$2 months). In addition, in patients with a distal duodenal obstruction, a colonoscope may be a good alternative for stent placement. Future research should investigate whether new stent designs may improve results after stent placement and whether natural orifice transluminal endoscopic surgery (NOTES) is a good alternative for GJJ.

This thesis also demonstrated that a prognostic model, composed of patient- and treatment related risk factors, may help clinicians to detect patients at high risk for post-ERCP complications. In addition, this model may also help to determine which patients are safely eligible for early (6 hours) discharge after ERCP, when combined with a selective policy. The development of new techniques and pharmacological agents may reduce the risk of post-ERCP complications.

Samenvatting

In Nederland worden jaarlijks ongeveer 2100 patiënten gediagnosticeerd met maagkanker, 1500 patiënten met alvleesklierkanker, 400 patiënten met hepatobiliaire kanker en 90 patiënten met duodenumkanker.

Patiënten met alvleesklier-, galweg- of duodenumkanker ontwikkelen vaak een maligne duodenumstenose. Een maligne duodenumstenose leidt tot passageklachten, dehydratatie en misselijkheid, waardoor de gezondheidsstatus van deze patiënten snel verslechtert. Een palliatieve behandeling is gericht op het verlichten van de passageklachten en het behouden of zelfs verbeteren van de kwaliteit van leven. Tot voorkort was een gastrojejunostomie (GJJ) de standaard palliatieve behandeling voor patiënten met een maligne duodenumstenose. Sinds kort is het plaatsen van een stent in het duodenum een goed alternatief. In **Hoofdstuk 2** wordt een literatuuroverzicht gegeven waarin stentplaatsing en GJJ met elkaar worden vergeleken. In totaal werden er 44 studies gevonden, waaronder 2 gerandomiseerde studies, 6 vergelijkende studies en 36 retrospectieve en prospectieve studies waarin de uitkomsten van stentplaatsing en/of gastrojejunostomie werden gerapporteerd. In totaal kregen 1046 patiënten een stent en 297 patiënten ondergingen een GJJ. Onze resultaten lieten zien dat na stentplaatsing de voedselinname sneller verbeterde en de ziekenhuisopname korter was dan na GJJ. Na GJJ ontstonden er echter minder hernieuwde passageklachten waarvoor een herhaalde behandeling nodig was vergeleken met stentplaatsing. De resultaten van dit literatuuroverzicht lieten zien dat stentplaatsing was geassocieerd met goede resultaten op korte termijn, terwijl GJJ betere resultaten op lange termijn behaalde en hierdoor de voorkeur zou hebben in patiënten met een goede prognose.

In een retrospectief onderzoek werd stent plaatsing vergeleken met GJJ bij 95 patiënten met een maligne duodenum vernauwing. Uitkomstmaten waren voedselinname, complicaties, herhaalde en aanhoudende passageklachten, herhaalde behandelingen, ziekenhuisopname en overleving. Drie-en-vijftig patiënten kregen een stent en 42 patiënten hebben een GJJ ondergaan in het Erasmus MC tussen 1994 en 2006. Voedselinname werd bepaald aan de hand van de Gastric Outlet Obstruction Scoring System (GOOSS) score, met een score van 0=geen voedselinname, 1= alleen vloeibaar voedsel, 2= zacht voedsel en 3= volledig dieet. Onze resultaten lieten zien dat beide palliatieve behandelingen veilig en effectief waren. Echter, voedsel inname verbeterde sneller na stentplaatsing (stent: 3.6 dagen, GJJ: 10.1 dagen, $p<0.01$) en ook de ziekenhuisopname was korter (stent: 6 dagen, GJJ: 18 dagen, $p<0.01$), vergeleken met GJJ. Desalniettemin, ernstige complicaties, herhaalde passageklachten en herhaalde behandelingen kwamen vaker voor na stentplaatsing dan na GJJ. Uit dit retrospectieve onderzoek werd geconcludeerd dat stentplaatsing was

geassocieerd met goede resultaten op korte termijn. GJJ leek betere resultaten op lange termijn te hebben. Uitkomsten van deze retrospectieve studie ondersteunen de conclusie uit de literatuurstudie, waarbij stent plaatsing de voorkeur zou moeten hebben bij patiënten met een slechte prognose. Patiënten in een betere conditie zouden meer voordelen hebben van een GJJ **(Hoofdstuk 3)**.

In **Hoofdstuk 4** worden de resultaten van een multicenter gerandomiseerd onderzoek tussen stentplaatsing en GJJ beschreven. Dit is hiermee de grootste gerandomiseerde studie tot nu toe gerapporteerd. In de periode januari 2006 tot mei 2008 werden patiënten met een maligne duodenum vernauwing gerandomiseerd voor stentplaatsing en GJJ. In totaal namen er 21 ziekenhuizen deel, waarvan 11 ziekenhuizen 39 patiënten hebben gerandomiseerd voor GJJ (n=18) of stent plaatsing (n=21). De follow-up bestond uit thuis bezoeken door een gespecialiseerde verpleegkundige die na 14 en 30 dagen en daarna maandelijks de patiënt bezocht. In dit onderzoek werd gekeken naar medische effecten (voedselinname, complicaties en overleving), kwaliteit van leven en kosten.

Hoewel er een snellere verbetering van de voedselinname na stent plaatsing optrad (5 vs. 8 dagen; $p<0.01$), was de verbetering van voedselinname over de gehele periode beter na GJJ. Ernstige complicaties kwamen vaker voor na stentplaatsing dan na GJJ (6 in 4 patiënten vs. 0; $p<0.01$), waaronder stent obstructie door een voedselbrok en tumor in- of doorgroei. Er was geen significant verschil in het voorkomen van persisterende klachten tussen stentplaatsing en GJJ. Echter, na stentplaatsing hadden meer patiënten herhaalde obstructieklachten (8 in 5 vs. 1 in 1; $p=0.02$) en vonden er meer herhaalde behandelingen plaats dan na GJJ (10 in 7 patiënten vs. 2 in 2 patiënten; $p<0.01$). De ziekenhuisopname was korter na stentplaatsing dan na GJJ (7 vs. 15 dagen; $p=0.04$). Er was geen verschil in overleving (stent: 56 vs. GJJ: 78 dagen; $p=0.19$). De kwaliteit van leven werd gemeten met behulp van gestandaardiseerde vragenlijsten op dag 0, 14, 30 en daarna maandelijks. Gedurende de follow-up bleven de scores voor de EQ-5D, QLQ-PAN26 en QLQ-C30 gelijk vergeleken met de baseline. Wij vonden geen significant verschil in kwaliteit van leven tussen stentplaatsing en GJJ. Wel namen de pijnsymptomen sneller af na stentplaatsing dan na GJJ ($p=0.02$). Totale kosten waren lager voor stentplaatsing dan voor GJJ (€8,812 vs. €12,433; $p=0.04$). Dit verschil werd voornamelijk veroorzaakt door een langere ziekenhuisopname na GJJ.

De resultaten van deze studie lieten zien dat GJJ gemiddeld gezien de voorkeur heeft bij patiënten met een maligne duodenum stenose. Patiënten waarvan wordt verwacht dat zij korter zullen leven dan 2 maanden, zouden meer profijt hebben van stentplaatsing, aangezien dit een minder invasieve behandeling is met goede korte termijn resultaten.

Het plaatsen van een stent in het distale gedeelte van het duodenum of het proximale gedeelte van het jejunum met behulp van een therapeutische gastroscoop kan problemen opleveren door de korte lengte en de flexibiliteit van de gastroscoop. Het gebruik van een colonoscoop kan deze problemen voorkomen. Wanneer men een gastroscoop gebruikt voor het plaatsen van een stent in het distale duodenum of proximale jejunum kunnen de volgende 3 problemen ontstaan. Ten eerste is de lengte van de gastroscoop onvoldoende om de vernauwing te bereiken, doordat de scoop uitbocht in de maag. Uitbochten van de scoop gebeurt met name wanneer de maag en het proximale duodenum sterk zijn gedilateerd. Ten tweede kan het uitbochten van de scoop leiden tot frictie tussen de stent en het werkkanaal, waardoor de stent niet kan worden opgevoerd. Ten derde kan het uitbochten van de scoop leiden tot instabiliteit van de scoop. De scoop kan hierdoor niet in de juiste positie worden gehouden tijdens het ontplooien van de stent, doordat de scoop terug wordt geduwd in de maag. Een colonoscoop is langer en biedt meer weerstand tegen het uitbochten. Hierdoor is het makkelijker om de scoop in de juiste positie te houden, dicht bij de vernauwing.

In **Hoofdstuk 5** zijn 16 patiënten retrospectief vervolgd. Alle patiënten hebben een duodenum stent gekregen met behulp van een colonoscoop. De resultaten van ons onderzoek waren vergelijkbaar met resultaten uit eerdere onderzoeken naar het plaatsen van een stent met behulp van een therapeutische gastroscoop. Het plaatsen van een stent met behulp van een colonoscoop was daarom veilig en effectief. Wij adviseren dan ook om een colonoscoop te gebruiken wanneer een stent wordt geplaatst in het distale duodenum of proximale jejunum, gezien de lengte en betere stabiliteit.

In veel ziekenhuizen worden patiënten na een endoscopische retrograde cholangiopancreatografie (ERCP) een nacht ter observatie gehouden om complicaties tijdig te detecteren. Het voorstel is echter om patiënten eerder te ontslaan na een ERCP, aangezien een overnachting belastend kan zijn voor patiënten en vroeg ontslag kan leiden tot kostenreductie. In **Hoofdstuk 6** werd een overzicht van de literatuur gegeven, waarin ERCP in dagbehandeling wordt vergeleken met een ERCP met opname. Wij vonden 11 onderzoeken die resultaten publiceerden over ERCP in dagbehandeling en met opname. In totaal werden 2407 ERCPs met dagbehandeling uitgevoerd bij 2320 patiënten en 2908 ERCP's met ziekenhuisopname bij 2483 patiënten. Er was geen verschil in het aantal complicaties na ERCP tussen beide groepen (dagbehandeling: 7%, ziekenhuisopname: 4%, OR: 1.54, CI: 0.71-3.39). Twee-en-zeventig procent van de complicaties na een ERCP in dagbehandeling ontstonden binnen 2 tot 6 uur, waarvan minstens 85% binnen 4 uur. Tien

procent van de complicaties ontstond binnen 6 tot 24 uur en 18% meer dan 24 uur na ERCP. De uitkomsten van dit literatuuroverzicht lieten zien dat een ERCP in dagbehandeling veilig en effectief was wanneer een selectief beleid werd toegepast. Patiënten kwamen in aanmerking voor vroeg ontslag na een ERCP wanneer zij: 1) geen verhoogd risico hebben op post-ERCP complicaties (bijv. voorgeschiedenis met pancreatitis, moeizame cannulatie), 2) in goede conditie verkeren (American Society of Anesthesiologists (ASA) physical status classification I of II), 3) geen stollingsstoornissen hebben, 4) op 30 minuten afstand van het ziekenhuis verblijven, 5) niet reeds zijn opgenomen, en 6) worden begeleid door een tweede persoon.

Een ERCP wordt frequent gebruikt bij klachten die worden veroorzaakt door aandoeningen van de alvleesklier of galwegen. Deze behandeling leidt echter in 5-10% van de patiënten tot een complicatie. Verschillende prospectieve en retrospectieve onderzoeken hebben de patiënt- en behandelings-gerelateerde risicofactoren voor het ontstaan van post-ERCP complicaties onderzocht. Echter, de relatieve bijdrage van deze factoren aan het ontstaan van complicaties is onbekend. In **Hoofdstuk 7** onderzochten wij alle mogelijke risicofactoren voor post-ERCP complicaties aan de hand van gegevens uit de literatuur en aan de hand van een multivariabele analyses in een retrospectieve patiëntenpopulatie. In totaal vonden we 16 publicaties, waarin resultaten van uni- en multivariabele analyses werden gerapporteerd. De retrospectieve database bestond uit 1372 ERCP behandelingen. Onze resultaten lieten zien dat verschillende patiënt- en behandelingskenmerken invloed hadden op het ontstaan van post-ERCP complicaties. Patiënten hadden een groter risico wanneer de volgende risicofactoren aanwezig waren: vrouwelijk geslacht, jonge leeftijd, (precut) papillotomie, PSC, SOD, pancreas divisum, moeizame cannulatie en voorgeschiedenis met pancreatitis.

De meest voorkomende post-ERCP complicaties zijn pancreatitis, cholangitis, perforatie en ernstige bloedingen. Ernstige bloedingen en perforaties kunnen vaak tijdens of direct na de ERCP worden gediagnosticeerd. Symptomen voor pancreatitis en cholangitis treden echter pas 3 tot 6 uur na de behandeling op. In Hoofdstuk 7 is de relatieve bijdrage van de verschillende risicofactoren in kaart gebracht. In **Hoofdstuk 8** hebben we aan de hand van deze resultaten een prognostisch model opgesteld waarmee onderscheid kon worden gemaakt tussen hoog en laag risico patiënten voor post-ERCP complicaties. Het prognostisch model werd geëvalueerd in een prospectieve populatie. In totaal werden er 255 ERCP's uitgevoerd, waarna 27 (10%) complicaties ontstonden waaronder pancreatitis (n=14), cholangitis (n=12) en één ernstige bloeding. Een score van drie punten of minder in het model was geassocieerd met een laag tot gemiddeld risico op post-ERCP pancreatitis en cholangitis. Een

score van 4 punten of hoger was geassocieerd met een hoog risico. Pancreatitis en cholangitis ontstonden gemiddeld 4.1 uur na ERCP, waarvan 90% gediagnosticeerd werd binnen 6 uur na ERCP. Onze resultaten lieten zien dat dit prognostische model clinici kan helpen om patiënten met een hoog risico te identificeren. Patiënten met een laag tot gemiddeld risico en die geen complicaties binnen 6 uur na ERCP hebben, hoog risico behandeling ondergaan voor ernstige bloedingen of perforaties, bloeding tijdens ERCP hebben of waarbij vrij lucht wordt gezien op CT, komen in aanmerking voor een ERCP in dagbehandeling. Deze dagbehandeling bestaat uit een observatie periode van 6 uur, aangezien 90% van de complicaties binnen dit tijdsbestek werd gediagnosticeerd.

Patiënten met alvleesklierkanker hebben vaak een slechte prognose. Hoewel cysteuze afwijkingen in de alvleesklier niet vaak voorkomen, worden steeds meer afwijkingen gevonden door het frequente gebruik en vernieuwingen van beeldvorming. Cysteuze afwijkingen van de alvleesklier komen met name voor als pseudocysten, congenitale cysten en cysteuze neoplasma's waaronder mucineuze cysteuze neoplasma's (MCNs), intraductale papillaire mucineuze neoplasma's (IPMNs) en sereuze cysteuze neoplasma's (SCNs). In **Hoofdstuk 9** wordt een overzicht gegeven van de literatuur, waarin met name de mucineuze alvleesklierafwijkingen centraal staan. Er werd dieper ingegaan op de epidemiologie, klinische presentatie, classificatie en pathologie, etiologie en pathogenese, beeldvorming en behandeling. Uit deze literatuurstudie bleek dat cysteuze neoplasma's, zoals MCNs en IPMNs, vaak (pre)maligne aandoeningen waren, terwijl SCNs vaak benigne waren. Een CT scan was de meest aangewezen techniek om het type tumor te bepalen. Daarnaast kon het CEA gehalte in de vloeistof van een cyste onderscheid maken tussen MCNs en SCNs. Bij patiënten met een mucineus neoplasma was operatieve verwijdering hiervan de aangewezen behandeling.

In de discussie **(Hoofdstuk 10)** concluderen wij dat dit proefschrift aantoont dat GJJ de voorkeur heeft als palliatieve behandeling bij patiënten met een relatieve goede prognose. Stentplaatsing heeft de voorkeur bij patiënten met een overleving <2 maanden, gezien de goede resultaten op korte termijn. Stentplaatsing bij patiënten met een distale duodenum vernauwing kan het beste worden verricht met behulp van een colonoscoop. Toekomstige studies zullen echter moeten onderzoeken of nieuwe typen stents de resultaten van stentplaatsing kunnen verbeteren. Daarnaast moet onderzocht worden of 'natural orifice transluminal endoscopic surgery' (NOTES) een goed alternatief is voor GJJ.

Een prognostisch model, opgebouwd uit patiënt- en procedure gerelateerde risicofactoren kan artsen helpen bij het identificeren van patiënten met een hoog risico

voor post-ERCP complicaties. Daarbij kan dit model, in combinatie met een selectief beleid, worden gebruikt bij het identificeren van patiënten die in aanmerking komen voor vroegtijdig ontslag (binnen 6 uur) na ERCP. De ontwikkeling van nieuwe technieken en medicijnen kunnen bijdragen aan het verlagen van het risico op post-ERCP complicaties.

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Curriculum vitae

Suzanne Maria Jeurnink was born on October 18th 1980 in Schalkhaar. She completed her secondary school in 1999 at the Geert Grote College in Deventer. In 1999 she started to study Nutrition and Health at Wageningen University and Research Center (the Netherlands), where she specialized in Public Health and Human Nutrition. In November 2004 she obtained her Master of Science degree. From May 2005 to November 2005 she worked at the department of Nutrition and Health at Unilever, Vlaardingen. In November 2005 she started the work presented in this thesis at the Department of Gastroenterology and Hepatology at the Erasmus MC University Medical Center, Rotterdam (Supervisors: Prof. dr. E.J. Kuipers and Prof. dr. P.D. Siersema). In September 2008 she started the Selective Medical Master Utrecht (SUMMA) at the University Medical Center Utrecht. During this master she will be trained as a physician within 4 years.