ORIGINAL ARTICLE

A wait-and-see strategy with subsequent self-expanding metal stent on demand is superior to prophylactic bypass surgery for unresectable periampullary cancer

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Abstract

Background: A patient with unresectable periampullary malignancy found at laparotomy has traditionally received a prophylactic double bypass (biliary and duodenal), associated with considerable morbidity. With modern endoscopic treatments, surgical bypass has become questionable. This study aims to compare the two strategies. Sahlgrenska University Hospital (SU) performs a double bypass (DoB) routinely, and Skåne University Hospital Lund (SUL) secures biliary drainage endoscopically and treats only symptomatic duodenal obstruction (Wait and See, WaS).

Method: Between 2004 and 2013, 73 patients from SU and 70 from SUL were retrospectively identified. Demographics, tumour-related factors and postoperative outcomes during the remaining lifetime were noted.

Results: The DoB group had significantly more complications (67% vs. 31%, p = 0.00002) and longer hospital stay (14 vs. 8 days, p = 0.001) than the WaS-group. The two groups had similar proportion of patients in need of readmission. The DoB patients and the WaS patients with metallic biliary stents were comparable regarding their need of re-interventions and hospitalisation due to biliary obstruction. Surgical duodenal bypass did not prevent future duodenal obstructions.

Conclusion: Patients with unresectable periampullary malignancies can safely be managed with endoscopic drainage on demand and with lower morbidity and shorter hospital stay than with surgical prophylactic bypass.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer death and the tenth most common cancer diagnosed in the United States.[1] The overall five-year survival rate is less than 7%.[1] The only cure for pancreatic cancer is still surgery and at presentation only 15–20% are resectable.[2,3] Among the remaining patients, locally advanced or disseminated disease is found during the preoperative workup or finally at surgery, that was intended as a curative resection.

In patients with periampullary malignancies, 8–20% of the patients planned for radical resections are found to have unresectable disease during surgery.[4,5] The majority of these patients already have a biliary drainage procedure performed. Whether to perform prophylactic double bypass (hepaticojejunostomy and gastrojejunostomy) or wait until signs of GOO develop at the discovery of unresectable periampullary cancer is still debated.[6] Proponents of prophylactic surgical bypass quote that 75% will develop biliary obstruction[7] and up to 25% will develop GOO[7,8] when the disease progresses. Critics claim that 98% of patients without prophylactic bypass can be managed without surgery.[9]

The result of this paper was presented at the 22nd UEG Week in Vienna, Oct 18–22 2014.

Until now, recommendations have been to perform a double bypass at the time of surgery in patients with a life expectancy of more than 6–8 months since studies have shown that the surgical trauma does not lead to increased mortality or morbidity and diminishes episodes of cholangitis, icterus and GOO.[10,11]

The studies referred to are, however, more than ten years old and compare two groups that both underwent major surgery. No other prospective randomized studies have been produced. More recently, different bypass procedures have retrospectively been compared with laparotomy alone, indicating that the proportion of patients requiring re-intervention and total number of in-hospital days prior to death was similar regardless of the initial procedure.[12] Furthermore, there have been substantial developments in the field of self-expanding metallic stents (SEMS) and in the practice of using stents in patients with malignant obstruction. So the question is still, or once again, valid.

A Swedish prospective randomized multicentre study started in 2010 to determine whether to perform a prophylactic double bypass or await symptoms and conduct endoscopic treatment in patients with unresectable periampullary cancer. Due to difficulties related to the inclusion of patients, mainly due to problems with informed consent, this study was stopped in 2013.[13] Therefore, the present study was designed, based on power calculations of the halted RCT, to try to answer this clinically important question.

At Sahlgrenska University Hospital the approach to the perioperative finding of unresectable cancer has been to perform a double bypass, hepaticojejunostomy and gastrojejunostomy, over the last decade. At Skåne University Hospital Lund, on the other hand, the approach has been to treat only patients with symptoms of dysfunctioning biliary stent and/or GOO at the time of laparotomy and to wait until symptoms of GOO or biliary dysfunction develop in the remaining patients before performing endoscopic drainage and/or bypass procedures.

The aim of this study was to retrospectively analyse the postoperative complications and long-term follow-up for patients managed by the two different strategies to perioperative unresectable periampullary cancer at the two aforementioned tertiary referral centres.

Method

A retrospective search in the lists of planned pancreaticoduodenectomies, between January 2004 and December 2013, in the Surgery Planning Software was conducted. All included patients had surgery with the intent of performing a pancreaticoduodenectomy but had perioperative findings of locally advanced or metastasized tumours. Only patients with periampullary cancer were included. Endocrine cancers and benign findings were excluded. Patients who, after responding to oncologic treatment, were subjected to a second operation with curative intent were also excluded.

Metastatic disease was defined as histological proven liver or peritoneal metastases. Locally advanced disease was defined as the presence of lymph node metastasis above the celiac trunk or in the region below the left renal vein and aorta. Furthermore, invasion or encasement of celiac axis, hepatic artery, superior mesenteric artery or more than 2 cm of the portal vein were also defined as locally advanced disease. Involvement of locoregional lymph nodes and/or less involvement of the portal vein were not contraindications for resection.

Palliative procedures performed included biliary-enteric bypass (usually hepaticojejunostomy) and/or gastrojejunostomy.

Information about these patients was obtained from medical records including medical charts, operation records, pathology records and radiology records. Demographic data were collected as well as information regarding tumour size, TNM-grading, histopathological grading and oncological treatment given. Perioperative parameters were noted for all patients including reason of unresectability.

Postoperatively, data on complications, time to functioning oral food intake and length of primary hospital stay were obtained. All complications were classified according to the Clavien–Dindo classification.[14] Delayed gastric emptying (DGE) was graded according to the standards depicted by ISGPS.[15]

During follow-up, all readmissions due to obstructed biliary drainage or GOO syndrome were noted, including procedures and radiology performed as well as length of stay (LoS). Cholangitis was defined as a febrile episode treated with at least antibiotics, where the biliary tree was defined as the locus of infection or no other locus was defined. Readmissions for reasons other than biliary and/or duodenal obstruction were excluded. The type and length of palliative chemotherapy was noted.

This study was approved by the Regional Medical Ethics Committee in Gothenburg (005-14) with the participation of the Surgical Clinics of Skåne University Hospital at Lund and affiliated hospitals in the southern and west health care regions in Sweden.

Continuous data are presented as numbers and percentages, median and range as appropriate. Differences between groups were evaluated by the Chi square analysis, Fisher exact test, Mann–Whitney U-test and Kruskal–Wallis test. Survival analysis was performed using the Kaplan–Meier method. A p-value of <0.05 was considered significant. All analyses were performed using the SPSS statistical package (v22.0, SPSS Inc.®, Chicago, Ill).

Results

Between 2004 and 2013, 73 (51%) patients at Sahlgrenska University Hospital and 70 (49%) patients at Skåne University Hospital at Lund were found to be unresectable at the time of laparotomy. Demographics, histopathology and reason for unresectability are shown in Table 1. Palliative chemotherapy was

Table 1 Demographics, histopathology and reason for unresectability

Variable (n, % or median (range))	WaS, n = 70	DoB, n = 73	p-value
Age	70 (42–81)	66 (39–81)	***0.013***
Gender, (male)	46 (66%)	43 (59%)	0.490
Preoperative biliary drainage	54 (77%)	62 (84%)	0.287
ASA score			***0.049***
1	7 (10%)	8 (11%)	
2	34 (49%)	53 (73%)	
3	29 (41%)	12 (16%)	
Histopathology			
Pancreatic adenocarcinoma	50 (71%)	50 (68%)	0.501
Distal bile duct	11 (16%)	16 (22%)	
Ampullary	2 (3%)	1 (1%)	
Duodenum	4 (6%)	3 (4%)	
Unspecified cancer	3 (4%)	3 (4%)	
Tumour size (cm)	3.0 (1.0–7.0)	3.2 (1.3–9.0)	0.379
Stage			0.195
1	1 (1%)	3 (4%)	
2a	14 (20%)	9 (12%)	
2b	8 (11%)	3 (4%)	
3	17 (24%)	23 (32%)	
4	30 (43%)	35 (48%)	
Reason for unresectability			0.453
Locally advanced	41 (58%)	41 (56%)	
Peritoneal carcinomatosis	4 (6%)	4 (6%)	
Distant metastases	25 (36%)	28 (38%)	

Italicized bold values indicates statistically significant changes.

Table 2 Initial procedure and postoperative complications by strategy

Procedure or outcome	WaS n = 70	DoB n = 73	p-value
Operative procedure			
Wait and see	48 (69%)	0	
Double bypass	12 (17%)	59 (81%)	
Gastroenterostomy	10 (14%)	2 (3%)	
Hepaticojejunostomy	0	12 (16%)	
Patients with complications	**22 (31%)**	**48 (67%)**	***<0.001***
Complications, (Clavien–Dindo)			***0.017***
1	2	6	
2	17	25	
3a	1	8	
3b	1	6	
4a	0	2	
4b	0	0	
5	1	1	
Delayed gastric emptying	**12 (17%)**	**26 (36%)**	***0.017***
A	5 (7%)	12 (16%)	
B	5 (7%)	12 (16%)	
C	2 (3%)	2 (3%)	
Reoperation	**1 (2%)**	**4 (5%)**	0.366
Primary LoS	**8 (2–36)**	**14 (6–71)**	***0.001***

Italicized bold values indicates statistically significant changes.
NG, nasogastric tube; LoS, Length of stay. Delayed gastric emptying according to ISPGS classification.[15]
Numbers presented as median (range) or n (%).

administered to 42 (60%) of the patients in the WaS group as compared to 47 (64%) in the DoB group.

All patients in the DoB group underwent a prophylactic bypass procedure, most often a double bypass, while all asymptomatic patients in the WaS group (69%) were closed without a surgical bypass. The procedures performed are listed in Table 2. The operative time was longer for the DoB group (208 min [114–719] vs. 177 min [65–420], p = 0.107) than the WaS group, but not significant. The DoB group suffered from significantly higher blood loss (600 ml [100–5000] vs. 200 ml [0–900], p < 0.001) and a higher need of transfusion (32% vs. 14%, p = 0.017) than the WaS group.

Postoperative outcomes are shown in Table 2. Patients in the WaS group had their nasogastric tube removed significantly earlier (0 days [0–22] vs. 2 days [0–17], p < 0.001) and returned to a normal diet significantly faster (2 days [1–31] vs. 7 days [3–19], p < 0.001) than the DoB group.

The two groups have similar numbers of patients in need of readmission for biliary or gastric outlet symptoms during their remaining lifetime, 43 patients (61%) in the WaS group and 49 patients (67%) in the DoB group, p = 0.491. In total, counting both the length of primary hospital stay and that of readmissions, the WaS group still has significantly shorter total LoS with 18 days (3–74) compared with the DoB group with 24 days (8–53), p = 0.001.

Long-term outcomes by type of biliary drainage are shown in Table 3. The WaS group was further analysed by initial stent type (plastic vs. metal). Long-term outcomes for both groups with regard to delayed GOO syndrome are shown in Table 4.

There was no significant difference in overall survival between the two groups (WaS group median survival 330 days [15–1005] vs. 248 days [23–833] for the DoB group, p = 0.117).

Discussion

When patients are found to be unresectable at laparotomy, it is of major importance to provide the best quality of life during their short remaining lifetime. Non-therapeutic laparotomy has been

Table 3 Outcome regarding hospital stay and re-interventions for bile duct problems. The WaS patients who were only treated with stents are divided in two groups, depending on if the patients received plastic or metallic stents (SEMS) in the perioperative time

	WaS plastic n = 25	WaS SEMS n = 23	DoB, n = 73	p-value
Primary hospital stay	7 (3–39)	7 (3–27)	14 (6–71)	<**0.001**
Total LoS#	18 (3–74)	15 (5–73)	24 (8–53)	**0.001**
Patients readmitted due to cholangitis/ cholestasis	17	6	11 (15%)	**0.001**
Hospital days due to biliary related problems	10 (0–36)	4 (0–27)	4 (0–42)	**0.001**
ERC/PTC, post initial intervention	37	13	10	**0.001**

Italicized bold values indicates statistically significant changes.
Numbers presented as total numbers and median (range).
Total LoS, includes primary LoS and total LoS of readmissions.
ERC, endoscopic retrograde cholangiography; PTC, percutaneous transhepatic cholangiography.

Table 4 Outcome regarding gastric outlet obstruction (GOO)

	WaS, n = 70	DoB, n = 73	p-value
Gastric outlet obstruction	13 (18%)	9 (12%)	0.35
Endoscopic stent	7 (10%)	5 (7%)	0.55
Surgical bypass	6 (8%)	1 (1%)	0.06
Hospital stay due to GOO	15 (8–46)	17 (7–92)	0.473

Number of patients and days in median and range.

shown to be associated with significant morbidity, potential mortality, a decreased likelihood of receiving systemic treatment and decreased quality of life.[7,16]

When less invasive methods are available, routine bypass must be challenged. Palliation by non-surgical techniques is standardised practice when unresectable cancer is found during workup.[6] The double bypass procedure has a morbidity and mortality rate of 31–56% and 0–5% respectively.[10–12,17–19] Considering that not all patients will develop biliary or gastric obstruction, surgical bypass might even be unnecessary.

The results of the present study show that patients in the WaS group returned to normal diet significantly faster (2 vs. 7 days) and had a significantly shorter hospital stay (8 vs. 14 days) than patients in the DoB group. Furthermore, the patients in the DoB group suffered from significantly more complications postoperatively (67% vs. 31%). Similar results were recently shown by Spanheimer *et al.*, who also showed an overall survival that was significantly shorter in the bypass group.[17] Moreover, others have shown that postoperative complications have a significant impact on long-term survival.[18,20] In accordance with Lyons *et al.*, the two groups in this study have similar numbers of patients in need of readmission during their remaining lifetimes, 61% in WaS vs. 67% in DoB,[12] indicating that a prophylactic double bypass does not prevent future need for hospitalisation.

Most patients present with obstructive jaundice and receive biliary drainage during workup, plastic endoprosthesis in the majority. During the observed period there was a tendency in the WaS group to change all plastic stents to metallic stents in the perioperative time.

A Cochrane meta-analysis comparing surgical hepaticojejunostomy with plastic biliary stents showed no differences in technical or therapeutic success but a significantly higher risk of re-intervention due to recurrent biliary obstruction in the plastic stent group.[21] Additionally, metallic stents are shown to be superior to plastic stents regarding patency and reduced risk of recurrent biliary obstruction.[22–24] Artifon *et al.* demonstrated that the overall cost of care is lower and that the patients' quality of life score is better with metallic stents compared to surgical bypass.[25]

The current study shows that patients in the WaS group with metallic stent had a slightly higher proportion of readmissions due to biliary obstruction but a similar need of re-interventions and total hospital length of stay due to bile-related problems than the DoB patients. These results suggest that a metallic biliary stent has comparable benefits with surgical biliary bypass in the long run, with the benefit of faster recovery and a shorter hospital stay after initial laparotomy. A wait-and-see strategy is preferable if the biliary drainage is secured by a metallic stent.

A prophylactic gastrojejunostomy does not prevent or diminish future GOO according to this study, as also shown by Spanheimer *et al.*[17] All 70 patients in the WaS group are included in the analysis, since it is a part of the WaS strategy to supply symptomatic patients with a gastrojejunostomy at initial laparotomy. The patients in the two groups had similar proportions of late GOO and interventions to restore the ability to eat.

Duodenal SEMS is a safe and effective alternative to surgery.[26] Trials comparing SEMS and surgical bypass for patients with symptomatic GOO have shown significantly shorter LoS, lower costs,[27–30] faster relief of symptoms[26] and symptomatic relief to a higher extent[28,29] in favour of endoscopy. Published data has not shown any difference in the rates of technical success, delayed complications[26,27,29] or quality of life between the two treatments.[31] Recurrent GOO is more common after stent placement, as is the need of re-interventions accordingly.[29] However, it is also shown that for 75% of the endoscopically treated patients a single stent was both effective and sufficient during the remaining lifetime.[32]

Besides the obvious limitations of a retrospective study, data were recruited from two different hospitals. However, data from the Swedish National Quality Registry for pancreatic cancer show no differences in complications, LoS or overall management between the two hospitals.[33] Furthermore, the subdivision of the WaS group by plastic or metallic stent, gives two relatively small groups, although the outcome in the two groups are clearly significant.

This study shows that surgical biliary bypass and the use of metallic biliary stent have similar outcomes regarding the need for postoperative interventions due to biliary obstruction. Moreover, the data show that a surgical duodenal bypass does not prevent future gastric outlet obstruction. Considering the higher morbidity and longer postoperative stay after surgical bypass, the result of this study supports a wait-and-see strategy.

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Conflicts of interest

None declared.

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