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Palliation With Endoscopic Metal Stents May Be Preferable to Surgical Intervention for Patients With Obstructive Pancreatic Head Adenocarcinoma

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The aim of this study was to evaluate the efficacy of endoscopically placed metal stents in comparison with operative procedures, in patients with obstructive pancreatic head cancer. Endoscopic stenting techniques and materials for gastrointestinal malignancies are constantly improving. Despite this evolution, many still consider operative procedures to be the gold standard for palliation in patients with unresectable obstructive pancreatic head cancer. This is a retrospective study of 52 patients who were diagnosed with obstructive (biliary, duodenal, or both) adenocarcinoma of the pancreatic head. Twenty-nine patients (endoscopy group) underwent endoscopic stenting. Eleven patients (bypass group) underwent biliodigestive bypass. Twelve patients (Whipple group) underwent Whipple operation with curative intent; however, histopathology revealed R1 resection (palliative Whipple). T_4 disease was identified in 13 (44.8%), 7 (63.6%), and 3 (25%) patients in the endoscopy, bypass, and Whipple groups, respectively. Metastatic disease was present only in the endoscopy group (n = 12; 41.3%). There was no intervention-related mortality. Median survival was 280 days [95% confidence interval (95% CI), 103, 456 days], 157 days (95% CI, 0, 411 days), and 647 days (95% CI, 300, 993 days) for the endoscopy, bypass, and Whipple groups, respectively ($P = 0.111$). In patients with obstructive pancreatic head cancer, endoscopic stenting may offer equally good palliation compared with surgical double bypass. The numerically (not statistically) better survival after palliative Whipple might be

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explained by the smaller tumor burden in this subgroup of patients and not by the superior efficacy of this operation.

Key words: Palliation – Endoscopy – Metal stents – Biliodigestive bypass – Pancreaticoduodenectomy – Pancreatic adenocarcinoma

At presentation, patients given a diagnosis of pancreatic head adenocarcinoma will have approximately 10%, 35%, and 55% localized (upfront or potentially resectable), locally advanced, and metastatic disease, respectively.[1] Jaundice from mechanical obstruction of the common bile duct is the main presenting symptom in 80% of these patients. In addition, almost half of the patients will develop duodenal obstruction secondary to tumor overgrowth.[2] It is well documented that treatment of the malignant obstruction improves quality of life.[3]

The most widely used palliative treatment of malignant biliary obstruction is the endoscopic placement of metal stents, especially if the patient's estimated life expectancy exceeds 6 months.[4] Metal stents yield biliary patencies of almost 2 years.[5] On the other hand, when there is concomitant duodenal obstruction, literature favors surgical (biliodigestive bypass) over endoscopic palliation because of more durable intestinal patency rates,[6] despite metal stent placement having better short-term outcomes and being more cost efficient.[7] In addition, literature supports biliodigestive bypass at exploration even in asymptomatic patients, because approximately 20% of them will develop obstruction at a later point.[8,9]

Endoscopically placed biliary and duodenal metal stents exhibit a geometric progress of evolution because of substantial improvements in manufacturing technology and materials.[10] The fourth-generation metal stents used now in everyday practice are made of nitinol alloy and may be covered (partially or fully) with materials that improve patency rates.[11] In addition, biliary and duodenal stents may be used easily in combination for palliation of the same patient, without significant technical problems.[12] Furthermore, recent studies show that stent efficacy increases with synchronous use of chemotherapy or radiotherapy.[13] Moreover, metal stents that release chemotherapeutic agents have started being used in clinical practice.[14]

The aim of this study was to evaluate, in patients with unresectable obstructive pancreatic head adenocarcinoma, the efficacy of the newer endoscopic metal stents compared with the standard operative procedures.

Patients and Methods

This is a retrospective study of 52 patients who were given a diagnosis of obstructive pancreatic head adenocarcinoma and did not receive a potentially curative operation (R0 Whipple procedure). They were treated from January 2008 to December 2013 in a tertiary care facility. All patients had biliary obstruction. Four patients had concomitant duodenal obstruction as well. Depending on clinical condition (comorbidities, Eastern Cooperative Oncology Group status, age) and tumor characteristics (T status, M status), patients underwent either a palliative placement of partially silicone-covered nitinol stent(s) (Wallflex, Boston Scientific, Natick, Massachusetts) or a surgical exploration that resulted in a palliative operation (biliodigestive bypass or R1 Whipple procedure). To be more specific, patients received a palliative stent when at least one of the following conditions existed: (1) identifiable metastatic disease in cross-sectional imaging, (2) progression of disease after neoadjuvant chemoradiation, (3) age older than 80 years, (4) coronary or pulmonary disease that would prohibit the performance of an abdominal operation, and (5) unwillingness to undergo any major operative procedure. The rest of the patients received a laparotomy. At exploration, those with technically unresectable disease underwent a biliodigestive (double) bypass. Patients with technically resectable disease received a Whipple procedure that, after application of the Leeds Pathology Protocol[15] to the resected specimens, was characterized either as palliative (R1) or curative (R0). Patients with curative Whipple operation were excluded from this study. Overall, 29 patients were palliated with endoscopic placement of metal stents (group A), 11 patients received biliodigestive bypass (group B), and 12 patients underwent Whipple operation that was identified to be noncurative (group C).

The biliodigestive bypass consisted of a 60-cm Roux-en-Y hepaticojejunostomy and a retrocolic loop gastrojejunostomy. The Whipple procedure employed pancreaticogastrostomy, hepaticojejunostomy, and functional end-to-end gastrojejunostomy. Patients who were surgically explored after neo-

Table 1 Baseline characteristics of the 3 study groups[a]

	Metal stent(s): group A (n = 29)	Bypass: group B (n = 11)	R1 Whipple: group C (n = 12)	*P*
Demographics				
Age, y, median (minimum, maximum)	81 (34, 98)	70 (48, 77)	62 (40, 79)	<0.001
Female sex, n (%)	13 (44.8)	4 (36.4)	3 (25)	0.488
Clinical condition: Eastern Cooperative Oncology Group status 0, n (%)	18 (62.1)	8 (72.7)	12 (100)	0.141
Staging, n (%)				
T_3	16 (55.2)	4 (36.4)	9 (75)	0.175
T_4	13 (44.8)	7 (63.6)	3 (25)	
M_1	12 (41.4)	0 (0)	0 (0)	0.002
Adjuvant treatments, n (%)				
Neoadjuvant chemoradiation	0 (0)	3 (27.3)	3 (25)	0.014
Palliative chemotherapy	14 (48.3)	6 (54.5)	12 (100)	0.007

[a]Endoscopy group (group A) includes older patients with greater tumor burden and less chance of receiving adjunct treatments.

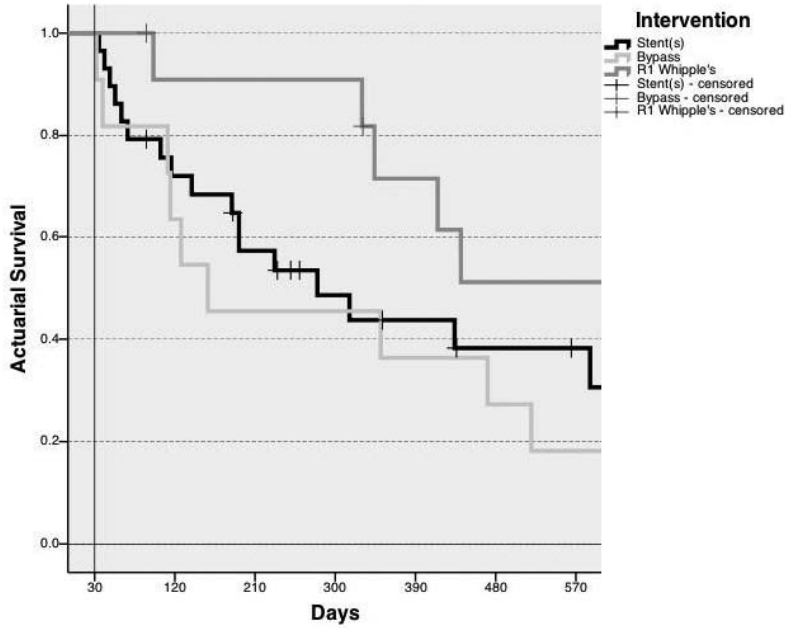
adjuvant chemoradiation received prior biliary decompression with plastic stent(s) (Advanix, Boston Scientific). Neoadjuvant chemoradiation consisted of 1000 mg/m^2 gemcitabine (Gemzar, Eli Lilly, Indianapolis, Indiana) on days 1 and 8 every 3 weeks, and of 38.5 Gy divided into 13 fractions. If clinical condition allowed, patients from all 3 groups received postintervention palliative chemotherapy. Patients' demographics, clinical condition, tumor characteristics, and adjunct (to intervention) treatments are depicted in Table 1. Median, minimum, and maximum follow-up times were 270, 32, and 1082 days, respectively.

Primary end points were intervention-related 30-day mortality and postintervention overall survival. Secondary end points included intervention related complications and biliodigestive patency rates. Complications were recorded and graded according to the Clavien-Dindo score.[16] Biliary patency was defined as absence of jaundice. Functional intestinal patency was defined as resumption of solid diet within the first 15 postintervention days. If resumption of diet was not possible, anatomic intestinal patency was investigated by computed tomography scan with oral Gastrografin.

Quantitative data were described by median and range. Nonparametric statistical analysis (Kruskal-Wallis one-way analysis of variance for 3 samples) was used for their comparisons. Qualitative data were described nominally. Nonparametric statistical analysis (Pearson χ^2 with Cramer V symmetric measures) was used for their comparisons. Kaplan-Meier survival curves were described by median and 95% confidence interval (95% CI). Log-rank (Mantel-Cox) test was used for their comparisons. Statistical significance level was set to $P \leq 0.05$. Statistical analysis was performed using SPSS for Mac, version 20.0.0 (SPSS Inc, Chicago, Illinois).

Results

There was no procedure-related (30-day) mortality for any of the 3 types of palliative intervention. Median postintervention overall survival times were 280 days (95% CI, 103, 456 days), 157 days (95% CI, 0, 411 days), and 647 days (95% CI, 300, 993 days) for the endoscopy, double bypass, and R1 Whipple groups, respectively. Mean postintervention overall survival times were 376 days (95% CI, 261, 490 days), 306 days (95% CI, 150, 463 days), and 571 days (95% CI, 394, 748 days) for the endoscopy, double bypass, and R1 Whipple groups, respectively. No statistically significant difference could be identified among the 3 modalities of palliative intervention (Fig. 1). Twelve patients in the endoscopy group had evidence of metastatic disease by cross-sectional imaging. No patients in the double bypass or the R1 Whipple group were diagnosed with metastatic disease at exploration. When these 12 group A patients with metastases were excluded from the analysis, median postintervention survival was 280 days (95% CI, 150, 409 days), 157 days (95% CI, 0, 411 days), and 647 days (95% CI, 300, 993 days) for the endoscopy, double bypass, and R1 Whipple groups, respectively. Mean postintervention survival was 361 days (95% CI, 222, 501 days), 306 days (95% CI, 150, 463 days), and 571 days (95% CI, 394, 748 days) for the endoscopy, double



Stent(s)	29	20	15	10	8	6	Numbers at risk
Bypass	11	7	5	5	4	3	
R1 Whipple's	12	10	10	10	7	5	

Fig. 1 Actuarial survival after palliative intervention in patients with unresectable obstructive adenocarcinoma of the pancreatic head. No statistically significant difference could be identified among the 3 modalities of palliative intervention (log-rank test: χ^2, 4.398; df, 2; $P = 0.111$).

bypass, and R1 Whipple groups, respectively. Again, no statistically significant difference could be identified among the 3 modalities of palliative intervention (log-rank test: χ^2, 4.348; df, 2; $P = 0.114$).

Excluding reinterventions for patency, there were 5 grade II procedure-related complications for the endoscopic stent placement group (1 transfusion of red blood cells, 2 initiations of parenteral nutrition, and 2 utilizations of synthetic opioids), 2 grade II procedure-related complications for the double bypass group (1 transfusion of red blood cells and 1 initiation of parenteral nutrition), and 4 grade II/IIIa procedure-related complications for the palliative Whipple group (1 transfusion of red blood cells, 1 initiation of parenteral nutrition, 1 reinsertion of nasogastric tube, and 1 percutaneous intra-abdominal collection drainage). No grade IV procedure-related complications were recorded.

Primary biliary and anatomic intestinal patency was achieved in 24 patients in group A. After endoscopic reinterventions (4 placements of new biliary metal stents, 1 placement of new duodenal stent), all patients in this group achieved secondary patency (biliary and anatomic intestinal). In addition, all patients in groups B and C enjoyed primary biliary and anatomic intestinal patency. On the other hand, 9 patients from the endoscopy group, 4 patients from the double bypass group, and 4 patients from the R1 Whipple group never reached functional intestinal patency (Table 2). Achievement of secondary biliary patency by all patients, regardless of the type of intervention, is reflected in the values of direct bilirubin. Median preintervention direct bilirubin levels were 10.0 mg/dL (95% CI, 8.6, 12.0 mg/dL), 6.0 mg/dL (95% CI, 4.8, 11.4 mg/dL), and 4.0 mg/dL (95% CI, 2.9, 5.1 mg/dL) for groups A, B, and C, respectively. On the other hand, median postintervention (at 4 weeks) direct bilirubin levels were 1.7 mg/dL (95% CI, 1.4, 2.0 mg/dL), 1.1 mg/dL (95% CI, 0.7, 2.1 mg/dL), and 1.0 mg/dL (95% CI, 0.7, 1.4 mg/dL) for groups A, B, and C, respectively.

Discussion

We have studied the palliative efficacy of endoscopic stent insertion compared with standardized surgical techniques (biliodigestive bypass and R1 Whipple procedure), in patients with unresectable obstructive pancreatic head adenocarcinoma. The main primary end point was overall survival. Patients who received an endoscopic stent insertion

Table 2 Patencies of the biliodigestive track after palliative intervention in patients with unresectable obstructive adenocarcinoma of the pancreatic head[a]

	Metal stent(s): group A (n = 29)	Bypass: group B (n = 11)	R1 Whipple: group C (n = 12)	*P*
Primary biliary and anatomic intestinal patency, n (%)	24 (82.7)	11 (100)	12 (100)	0.112
Secondary biliary and anatomic intestinal patency, n (%)	29 (100)	11 (100)	12 (100)	n/a
Functional intestinal patency, n (%)	21 (72.4)	7 (63.6)	8 (66.7)	0.845

n/a, not applicable.

[a]Biliary patency is defined as absence of jaundice. Functional intestinal patency is defined as resumption of solid diet. If resumption of diet was not possible, anatomic intestinal patency was investigated by computed tomography scan with oral Gastrografin.

were older, with more comorbidities and with a greater disease burden. In addition, they received less intense adjunct treatments (neoadjuvant or adjuvant chemotherapy or radiation). Survival was not statistically different among the 3 groups, although a trend toward higher survival for patients who underwent palliative Whipple procedure was observed.

No mortality from any intervention was observed in the patients in this study. This is expected for the endoscopy group and is consistent with the reported mortality rate for endoscopic retrograde cholangiopancreatography (ERCP). In a multicenter prospective survey of 13,000 procedures, Kapral *et al*[17] reported a mortality rate of 0.1%. In a Norwegian multicenter study with 2808 ERCPs, the overall mortality rate was 1.4%.[18] This is slightly higher because more than 91% of the ERCPs in this group were therapeutic (as they were in our study). On the other hand, zero mortality is an unexpected finding in the Whipple group. Obviously, this is attributed to the small number of patients who underwent R1 Whipple operations, and it is only a matter of time (and procedure number) until a postoperative fatality will occur. In fact, large cohorts in experienced centers show that postoperative mortality in Whipple patients is as low as 1.4%, but never zero.[19]

With respect to the overall survival, results in the endoscopy group are at least as good as those in the biliodigestive bypass group. In addition, overall survival in the endoscopy group was not statistically inferior to survival in the palliative Whipple group, despite the existence of a favorable trend for the latter. It is possible that the potential survival advantage for group C patients did not reach statistical significance because of the small sample size (type II error). However, we should not forget that these patients had a smaller tumor load, and that may have benefited from the adjunct therapies, which were administered to them much more commonly compared with the endoscopy or the double bypass groups. Another interesting observation is that that survival in the endoscopy group was not affected in a negative way by the presence of metastases. Perhaps patients with unresectable, obstructive, locally advanced disease have a much greater tumor burden, which we can identify by imaging studies (*i.e.*, undetectable systematic disease), and therefore they behave like patients with metastatic disease.

Complication rates were comparable among the 3 groups in this study. In the endoscopy group, the complication rate quoted excludes reinterventions for patency. Even then, we report a complication rate of 17%, which is higher than most reports in the literature, which are usually around 7%.[20,21] This observation may be explained by the fact that complications were recorded and graded according to the very detailed Clavien-Dindo score[16] applied in surgical procedures. For example, most authors do not include initiation of TPN as a complication after ERCP, whereas according to the Clavien-Dindo score, this is a grade II complication.

An important element for deciding which palliative procedure to use in a patient with unresectable obstructive pancreatic head adenocarcinoma is patency rate. We should emphasize that a 100% secondary anatomic patency rate was achieved with all 3 approaches in this study. Patency rate is where the main debate lies between endoscopy and surgical interventions.[6] In fact, biliary patency rates are less of a controversy now, because metal stents yield biliary patency rates of almost 2 years.[5] On the other hand, duodenal patency rates (especially the long-term ones) are where the debate still remains. Most surgeons feel that in cases of unresectability detected intraoperatively, a biliodigestive bypass should be constructed. Lillemoe *et al*[9] conducted a randomized study of 87 patients who were found intraoperatively to have unresectable disease. Patients were randomized to prophylactic gastrojejunostomy or observation. Their conclusion was that

19% of the control group demonstrated late gastric outlet obstruction. Van Heek *et al*[22] reached a similar conclusion, with 41.4% of the control group developing gastric outlet obstruction. We feel that the number of unnecessary gastrojejunostomies constructed for a potential 20% possibility of late gastric outlet obstruction is too high, especially because a good proportion of patients with advanced pancreatic cancer will not survive to develop such a complication. If gastric outlet obstruction develops, it can be dealt with promptly and successfully with endoscopic stent insertion, as we have demonstrated and as is supported by other authors, too.[5] Moreover, duodenal stenting has been shown to have shorter time to oral feeds, shorter hospital stay, and lower costs.[7] One thing is certain: technology will not cease to evolve. Stent patency rates will only get better as we move from the current fourth-generation metal stents to stents with more advanced alloys that are able to release locally chemotherapeutic agents.[14]

Obviously there are significant limitations to this study. It is a retrospective case series, and the number of patients in each group is small. Because of its retrospective nature, there is bound to be a mismatch in the patient characteristics among the 3 groups. The endoscopy group included significantly more elderly and frail patients compared with the surgical groups and particularly group C, whose patients had to be fit to undergo a Whipple operation. In addition, the endoscopy group patients had a greater tumor burden, as assessed by the T_4 and M_1 rates. These findings constitute a definite bias against the endoscopy group patients. Furthermore, bias against the endoscopy group patients consists of the use of adjunct therapies. A statistically significant number of patients in groups B and C received neoadjuvant chemotherapy with gemcitabine and radiotherapy. More patients in group C received adjuvant chemotherapy compared with patients in groups A and B. This is an expected difference, because patients in surgical palliation groups were younger, fitter, and, in the case of neoadjuvant therapy, without evidence of metastatic disease. Finally, an important limitation is the lack of data regarding pain management, a very important aspect of palliation adequacy.

In order to give definite recommendations for the preferred method of palliation in patients with unresectable obstructive pancreatic head adenocarcinoma, a large, randomized study of equivalency should be conducted. Such a study should investigate the palliative approach between two groups with similar tumor burden (*i.e.*, $T_3N_1M_0$). All patients should reach the operating room with curative intent; however, intraoperatively they will be deemed unresectable. Control group patients should undergo biliodigestive bypass, whereas study group patients should have no surgical intervention but only endoscopic metal stent placement (immediate or delayed) as required by their clinical condition.

In conclusion, it seems that in patients with obstructive pancreatic head adenocarcinoma, endoscopic stenting using newer metal stents offers equally good palliation compared with surgical double bypass. The same might be true, to a lesser extent, for patients who underwent palliative Whipple procedure. We anticipate that within the next few years, the evolution of endoscopic and minimally invasive techniques will render surgical palliation for obstructing tumors of the pancreatic head redundant.

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