

HIGHLIGHT ARTICLE

The Role of Biliary Drainage in Patients with Pancreatic Adenocarcinoma

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Summary

Pancreatic cancer is one of the leading causes of cancer deaths worldwide and constitutes a major public health problem. One of the most common symptoms associated with pancreatic adenocarcinoma is jaundice, caused by the obstruction of common bile duct. Endobiliary stenting is used to relieve these patients either preoperatively or merely for palliation and plastic or metal stents are usually endoscopically or percutaneously placed. Two interesting studies were presented at the 2014 ASCO Gastrointestinal Cancers Symposium. Strom *et al.* sought to investigate the effect of preoperative biliary drainage on recurrence and survival and they concluded that percutaneous biliary decompression was an independent predictor of worse overall survival and was associated with non-significant increase in hepatic recurrence (Abstract #314). Montero *et al.* presented the results of their study regarding the cost-effectiveness of metal stents in patients with inoperable pancreatic cancer and they concluded that placement of metal biliary stents is cost saving, improves overall survival and quality-adjusted survival compared with plastic stents (Abstract #260). Both studies concluded to useful results that along with the existing literature and formulated guidelines may help the provision of more effective, higher quality management of these patients.

Introduction

Pancreatic cancer is the 13th most common type of cancer worldwide and the fourth leading cause of cancer-related mortality in the United States [1]. During the year 2013, it is estimated that approximately 45,220 people were diagnosed with pancreatic adenocarcinoma and 38,460 died from it [2]. Despite the ongoing advances in diagnosis and treatment of pancreatic cancer, the overall five-year survival rate from all stages of the disease remains as low as 5% [3]. With the majority of patients presenting with inoperable, locally advanced tumors or metastatic disease [2], most of them will

appear with symptoms related to the disease. As most tumors are found in the head of the pancreas, jaundice due to bile duct obstruction is a common presenting symptom. It is estimated that 80% of patients with adenocarcinoma of the head of the pancreas, will suffer from obstructive jaundice at some time during the course of their disease and may require biliary drainage either preoperatively or merely for palliation.

What We Knew Before the 2014 ASCO Gastrointestinal Cancers Symposium

Preoperative biliary drainage, in patients with potentially resectable lesions, is a safe intervention to relieve disease related symptoms such as pruritus and cholangitis. It may improve liver function and can also be applied to maintain the patency of the common bile duct during neoadjuvant therapy or in patients whose surgical intervention is expected to be delayed. However, the role of preoperative biliary drainage performed using either percutaneous transhepatic or endoscopic techniques, remains controversial in terms of morbidity and mortality.

Key words Palliative Care; Pancreatic Neoplasms; Stents

Abbreviations ERCP: endoscopic retrograde cholangiopancreatography; NCCN: National Comprehensive Cancer Network

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Apart from the patients whom their disease stage is amenable to surgical intervention, a large proportion of patients will present with locally advanced, unresectable and metastatic disease. The majority of these patients will present with obstructive jaundice which, if left untreated, will result in malabsorption, cholestasis, progressive hepatic failure and early death. Therefore, alleviation of jaundice represents a critical component of palliation. In these patients palliation is best provided by endoscopic biliary stenting. Although in most cases metal stents are preferred over plastic ones, the debate continues in terms of efficacy and cost effectiveness.

What We Have Learned at the 2014 ASCO Gastrointestinal Cancers Symposium

Overall Survival with Preoperative Biliary Drainage in Patients with Resectable Pancreatic Cancer (Abstract #314) [4]

The role of preoperative biliary drainage remains a matter of controversy. This topic was the subject of an abstract presented by Strom *et al.* [4]. They conducted a study based on their institutional tumor registry to evaluate its role in recurrence and survival in patients with resectable pancreatic cancer. The study population included a total of 202 patients who were either operated without preoperative biliary drainage or subjected to drainage endoscopically (via ERCP) or percutaneously (via percutaneous transhepatic biliary drainage).

The three aforementioned groups differed

significantly in the mean pathologic tumor size (P=0.005), pathologic T3/4 (P=0.01) and pathologic N1 (P=0.007) status. In their results (Table 1), the authors showed that patients who underwent percutaneous transhepatic biliary drainage exhibited a non-significant increased rate of hepatic recurrences compared to the other groups of patients (P=0.20) and a worse median and 3-year survival compared to the patients that underwent ERCP or no biliary decompression at all (P=0.02). Percutaneous biliary drainage was also found to be an independent predictor of worse overall survival (P=0.005) using multivariate analysis. These results may suggest that patients that require preoperative percutaneous transhepatic biliary drainage may benefit from neoadjuvant therapy prior to the surgical intervention.

Cost-Effectiveness of Metal Stents in Pancreatic Cancer (Abstract #260) [5]

Patients with pancreatic adenocarcinoma usually present with locally advanced, unresectable or metastatic disease [2]. In this group of patients, biliary decompression may be required for palliation. Montero *et al.* presented the results of their study regarding the cost-effectiveness of metal stents in pancreatic cancer [5]. In the study were included patients with locally advanced pancreatic cancer, who underwent ERCP with metal or plastic stent placement. The results suggest that patients with metal stents had lower costs and greater overall and quality-adjusted survival. Specifically, the investigators found that metal stent implementation resulted in approximately \$1,500 saved per patient over a lifetime and fewer stents

Table 1. The results of the study of Strom *et al.* [4] (Abstract #314).

	Percutaneous transhepatic biliary drainage	Endoscopic retrograde cholangio-pancreatography	No biliary drainage	P value
Preoperative biliary procedures:				<0.001
- None or 1	27 (81.8%)	85 (86.7%)	114 (100%)	
- More than > 1	6 (18.2%)	13 (13.3%)	0	
Time from diagnosis to surgery (days):				<0.001
- Median (range)	29 (1-67)	16 (0-84)	13 (0-70)	
- Mean±SD	30±15	19±17	17±18	0.001
Pathologic tumor size (cm):				0.04
- Median (range)	2.5 (1.2-5.5)	2.9 (0.1-12.0)	3.1 (0.1-4.7)	
- Mean±SD	3.1±1.1	3.0±1.5	3.6±1.9	0.02
Tumor T stage:				0.02
- 1	1 (3.0%)	6 (6.1%)	9 (7.9%)	
- 2	5 (15.2%)	7 (7.1%)	29 (25.4%)	
- 3	27 (81.8%)	83 (84.7%)	73 (64%)	
- 4	0	2 (2.0%)	3 (2.6%)	
Nodes removed; median (range)	16 (0-29)	12 (1-45)	11 (0-49)	0.03
Tumor N stage:				0.003
- 0	6 (18.2%)	34 (34.7%)	56 (49.1%)	
- 1	27 (81.8%)	64 (65.3%)	58 (50.9%)	
Survival:				-
- Median	17.5 months	22.8 months	26.3 months	
- 3-year	18%	34%	41%	
- 5 year	3%	23.7%	27.2%	

SD: standard deviation

placed (mean number: 1.4 vs. 2.8). Moreover, metal stenting improved the overall survival by 0.07 months and the quality-adjusted survival by 0.10 months.

Discussion

Preoperative biliary drainage in patients with potentially resectable pancreatic cancer is mainly indicated for the alleviation of disease-related symptoms like pruritus and cholangitis. Although controversial, several studies have suggested that pancreatic surgery is associated with higher perioperative mortality when performed in the setting of hyperbilirubinemia and impaired liver function [6] and thus preoperative biliary decompression may be mandated. Nonetheless, a number of prospective and retrospective studies have failed to demonstrate decreased mortality in patients with preoperative biliary drainage [7, 8, 9, 10, 11, 12, 13]. A study by Povoski *et al.* showed that the risk of infectious complications, intra-abdominal abscess and death were increased with biliary drainage [14]. In another multicenter randomized trial, it was shown that preoperative biliary drainage resulted in 2-fold increased rate of serious complications compared with the patients that underwent surgery alone. However, no significant differences were found in surgery associated complications, length of hospital stay or mortality [15].

In the 2014 ASCO Gastrointestinal Cancer Symposium, Strom *et al.* presented the results of their retrospective study regarding the role of preoperative biliary drainage in patients with resectable pancreatic cancer [4]. Their findings are in line with the existing literature. They came to the conclusion that preoperative biliary decompression not only has no favorable effect on survival, but percutaneous transhepatic biliary drainage was found to be an independent prognostic factor associated with worse overall survival. However, there are some concerns regarding the study. First of all, the data derive from a retrospective analysis. Moreover, there are significant key differences between the study groups in terms of pathologic features with percutaneous transhepatic biliary drainage group patients presenting the most aggressive ones. Nonetheless, the authors acknowledge that the observed results regarding percutaneous transhepatic biliary drainage are likely attributed to multiple factors including more advanced disease stage, delayed surgical intervention, increased number of preoperative biliary procedures and increased rate of hepatic metastases, possibly from tumor seeding.

Therefore, it seems reasonable - as stated in the National Comprehensive Cancer Network (NCCN) guidelines - to implement preoperative biliary

decompression only in patients who present with jaundice and symptoms of cholangitis or fever, severe pruritus or in whom operation is expected to be significantly delayed (more than 1 week). Finally, although not the topic of this study, it should be mentioned that biliary drainage is necessary for patients with jaundice undergoing neoadjuvant therapy prior to surgery.

Biliary drainage, apart from its role in the preoperative period, also constitutes an important component of our armamentarium for the palliative management of the large proportion of patients with inoperable disease. Endoscopic approaches for palliation of pancreatic adenocarcinoma are rapidly expanding. However, it is still not clear which type of stent should be used.

To date, many trials have compared metal and plastic stents in patients with biliary obstruction due to pancreatic adenocarcinoma. Plastic stents become more frequently occluded, usually within 3 months of insertion resulting in recurrent cholangitis. On the contrary, metal stents are wider in diameter and thus less likely to become occluded. The results of a randomized controlled trial, that compared the patency of plastic and covered self-expanded metal stents, exhibited significantly prolonged patency for metal stents [16]. This study concluded that metal stents could be recommended in inoperable patients with malignant common bile duct strictures that survive a median of 4.5 months. Less costly plastic stents are preferable in the one third of patients who have distant metastases, although the cost in both cases was equal [16]. Similar were the results of a meta-analysis, published in the Cochrane database. The meta-analysis compared metal and plastic stents in patients with biliary obstruction due to pancreatic cancer and showed lower risk of recurrent biliary obstruction when metal stents were used [17].

Some institutions use plastic stents in patients with locally advanced or metastatic disease and short life expectancies, because of the lack of concern about long term patency. Many studies support that, since biliary self-expanding metal stents are significantly more expensive than plastic stents, their use should be reserved for patients whose estimated survival is greater than 3 to 4 months [18] and/or those patients without liver metastases [19]. However, the initial higher cost of metal stents might be balanced by a decreased need for repeat intervention due to lower occlusion.

The issue of cost/effectiveness of metal stents was the topic of an abstract presented in the 2014 ASCO Gastrointestinal Cancer Symposium by Montero *et al.* [5]. The authors found that placement of metal biliary stents in jaundiced patients with stage III pancreatic adenocarcinoma resulted in a modest

decrease in cost compared to plastic stents. This finding could, in part, be attributed to fewer stents being placed. Moreover, patients with metal stents were estimated to have 0.32 months of higher quality-adjusted life years. However, there are some specific limitations of the study, acknowledged by the authors themselves. Namely, the selection bias resulting from the used references for clinical inputs cannot be excluded, there is uncertainty around many of the parameters estimates, the cost inputs were based exclusively on United States data and, finally, they used utility weights for similar but not identical health conditions. Nonetheless, the study offers valuable information, useful for the appreciation of cost effectiveness of metal stents.

All the aforementioned data have been the basis for the formulation of guidelines regarding biliary drainage. According to the American Society for Gastrointestinal Endoscopy (ASGE) guidelines, endoscopic stent placement is recommended for the alleviation of obstructive jaundice in patients with unresectable or metastatic disease. Specifically, they propose plastic stents for patients with estimated life expectancy of less than 6 months and metal stents for those with life expectancy of more than 6 months [20]. More recently, the NCCN guidelines recommended the use of permanent self-expanding metal stents as the preferred method.

Conflicts of interest Authors report no conflict of interest

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