Title: Biliary Stenting in Patients With Pancreatic Cancer: Results From a Population-Based Cohort Study

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ABSTRACT

Objectives: We aimed to describe management of biliary obstruction in the context of pancreatic cancer within a population-based cohort.

Methods: We examined management of biliary obstruction in 1863 patients diagnosed with pancreatic cancer in 2010/2011. We used descriptive statistics and logistic regression to describe patterns of biliary stent usage, complications and duration of patency, associations between preoperative stenting and surgical outcomes, and between patient factors and management of jaundice.

Results: Almost half of the people in the cohort (N=909) were jaundiced within 12 months of diagnosis. Two-thirds of these had at least one stent inserted. Preoperative stenting, mostly with plastic stents, occurred for 72% of patients who experienced jaundice prior to an attempted resection but was not associated with surgical outcomes. Seventy percent of the jaundiced patients who did not have an attempted resection were stented. Metal stents were less frequently replaced within 30 days than plastic (9% vs 42%). Living in a rural area was associated with reduced likelihood of having jaundice managed.

Conclusions: Plastic stents were still used frequently, despite guidelines recommending metal in most contexts. Patients living in rural areas were less likely have biliary obstruction managed. This work highlights the need to monitor current practice.

Keywords

Biliary obstruction; pancreatic cancer; biliary stent; jaundice; population based.

INTRODUCTION

Pancreatic cancer has the worst prognosis of any cancer and is the 4th most common cause of cancer death in developed countries.[1] Biliary obstruction (BO) is a common sequela of pancreatic cancer, especially if the tumor is in the head or neck of the pancreas. The prevalence of symptomatic BO in patients with cancer of the head of the pancreas has been reported to be as high as 70%.[2] BO can have significant impacts on quality of life, causing impaired gastrointestinal absorption, pruritis, deranged liver function, and possibly cholangitis. It is therefore important to relieve these obstructions in patients with pancreatic cancer.

Biliary obstructions may be managed surgically with biliary-enteric anastamosis as part of a potentially curative resection or palliative bypass, or by insertion of a stent into the biliary tree. Stents may be plastic or metal and can be inserted endoscopically or percutaneously. The approach to managing BO differs according to a number of factors, such as cancer stage and symptoms. The United States National Comprehensive Cancer Network (NCCN) guidelines for BO management in pancreatic cancer recommend different approaches according to clinical context (Table 1, supplementary table).[3]

One of the contentious issues regarding best practice management of BO for patients with pancreatic cancer relates to the harms and benefits of preoperative stenting for the patient with a resectable tumor. Meta-analyses[4-7] investigating this issue have generally concluded that preoperative biliary drainage (PBD) via stenting should not be routinely performed, with no difference in mortality but increased morbidity associated with PBD. However, preoperative stent placement is recommended for patients with cholangitis, significant pruritis, coagulopathy, renal insufficiency or for whom surgical resection is significantly delayed.[3]

There is also debate about the relative merits of plastic and metal stents. Metal stents have been found to have lower rates of migration and longer term patency,[8] but plastic stents are easier to insert and replace and have traditionally been regarded as more cost effective. However a recent analysis found that the initial placement of metal stents was more cost effective and associated with a better quality of life than plastic stents for patients with an overall survival of more than 6 months.[9] Differences in patency duration and mortality, morbidity and re-intervention rates have been investigated with meta-analyses.[10-12] These

demonstrate that metal stents are superior to plastic, due to longer patency resulting in fewer endoscopic interventions. Nevertheless, the NCCN guidelines[3] and guidelines from the European Society of Gastrointestinal Endoscopy (ESGE)[13] both advocate plastic stents when the diagnosis of malignancy is uncertain and possibly for those with poor prognosis (<3 months in NCCN or <4 months in ESGE). The NCCN recommend metal stents over plastic in the preoperative setting, with the caveat that level 1 evidence is not yet available to answer this question.

The aims of this study were to describe stenting practices and explore outcomes associated with different management practices in a large population-based cohort.

Methods

Patients and data collection

Patients were selected for inclusion based on notifications to the Queensland (QLD) Cancer Registry (QCR) and the New South Wales (NSW) Cancer Registry (Cancer Institute NSW) from 1 July 2009 to 30 June 2011 and 1 July 2009 to 31st December 2010, respectively. Patients who were at least 18 years old with a histological diagnosis of pancreatic ductal adenocarcinoma or a clinical diagnosis with unknown histology were included. Trained research nurses reviewed the medical records of eligible patients to obtain information about clinical presentation, investigations, patient comorbid and functional status, diagnosis, staging, management and outcomes. A detailed description of the study population and data collection has been published.[14]

Data collected regarding biliary stenting included date of insertion, clinical indication, insertion method (endoscopic or percutaneous), type (plastic or metal) and associated complications arising within 30 days.

We restricted this analysis to patients with jaundice (as an indicator of BO) either at the time of diagnosis or during the subsequent 12 months.

Outcomes

The aim of this work was primarily to describe patterns of biliary stent usage in Australian patients with BO due to pancreatic cancer. We compared prevalence of complications and duration of patency by stent

type. Time to stent replacement was calculated as time from placement of one stent to the time of placement of a subsequent stent.

For patients who had an attempted resection, we were also interested in whether PBD was associated with whether or not resection was completed and the risk of post-operative complications.

Exposure variables

We investigated factors associated with whether or not patients with BO and no attempted tumor resection underwent biliary decompression. Factors included age, sex, stage, comorbidity (measured by the Charlson comorbidity index), socioeconomic status (determined using the Socio-Economic Indexes for Areas (SEIFA) which assigns SES based on residential location [15]), and remoteness of place of residence (measured using the Accessibility/Remoteness Index of Australia (ARIA) [16]).

Statistical analysis

This is primarily a descriptive study. Most data are presented as percentages of patients with a specific symptom, complication or undergoing a particular procedure, with chi-squared tests or Fisher's exact test being used to assess the statistical significance of differences where appropriate. Logistic regression was used to estimate crude and adjusted odds ratios (OR and AOR, respectively) for binary outcomes. We used directed acyclic graphs to guide selection of potential confounders, and confounders that changed the effect estimate of interest by at least 10% were retained in the relevant model. Patients could receive more than one stent so to account for clustering within patients, mixed effects models were used to estimate the time to replacement and associations between stent type and complications using generalized estimating equations with an exchangeable correlation matrix.

All statistical analyses were performed using Stata (Statacorp, Texas) version 14.0. We used a significance level of $P < 0.05$.

Results

We were notified of 2090 potentially eligible cases. We could not identify medical records for 87 of these and 140 were ineligible. Of the 1863 people in the study cohort, almost half (N=909, 49%) were jaundiced during the study period (Figure 1), 713 (38%) at diagnosis and 196 (11%) in the 12 months

following diagnosis. Most patients with jaundice (75%) did not undergo an attempted resection. Approximately half (N=423, 47%) of the jaundiced patients had one stent inserted, 23% (N=207) had more than one stent inserted and 8% (N=72) had biliary bypass surgery.

We captured 992 stent insertions in the study period: 712 initial and 280 replacement stents. Most (N=902, 92%) were inserted endoscopically rather than percutaneously (N=83, 8%) (the method was not stated for 7 cases). Metal stents were more likely than plastic to be inserted percutaneously (14% vs 1%).

Preoperative stenting occurred for 72% of the 222 people who experienced jaundice prior to an attempted resection. Most stents (84%) were plastic. The median time between stent insertion and surgery was 32 days (range 3-240 days); in 43% of cases the time was less than 4 weeks. Thirteen per cent of people required their first stent replaced prior to surgery; 90% of stents requiring replacement were plastic. Stenting prior to attempted resection was not associated with whether the resection was able to be completed; the tumor could not be removed for approximately a quarter of patients irrespective of preoperative stent insertion (Figure 1). Three quarters of all patients found to have inoperable tumors at laparotomy underwent biliary bypass surgery.

Among patients who had a completed resection, the occurrence of at least one post-operative complication was similar for patients who did and did not have a BO (47% and 44%, respectively), and did not differ according to preoperative treatment of BO (Table 1). In multivariable analysis there was no difference in the prevalence of overall complications between these groups after adjustment for age, comorbidities or surgeon volume (data not shown). Among those with preoperative BO the percentages of people who experienced an anastomotic leak were 12% for those that were stented prior to surgery compared with only 2% of those who were not stented but the difference was not statistically significant ($P = 0.07$). The length of time between stent insertion and surgery was not associated with complications (≤ 4 weeks versus > 4 weeks: 49% versus 47%, $P = 0.83$).

Of the jaundiced patients who did not have an attempted resection, 70% (N=470) had stenting as the only form of biliary decompression and 4% (N=26) underwent biliary bypass surgery (Figure 1). The initial stent type was metal in 57% of patients where the stent type was known (N=427, 91%). Thirty-eight per cent of initial stents were replaced (18% of metal compared with 71% of plastic) and the percentage of

metal stents replaced within 30 days was much lower than that of plastic stents (9% vs 42%: OR 0.14, 95% CI 0.05-0.41). The median time to replacement was 91 days for metal stents and 35 days for plastic, and the median time from first stent placement to death was 137 days for metal stents and 170 days for plastic. The odds of having a complication were higher after insertion of a plastic compared with a metal stent (OR=1.9, 95% CI 1.3-2.7) (Table 2). The most common complications were persisting jaundice, cholangitis and stent occlusion, all of which occurred more frequently after a plastic stent.

Approximately a quarter (26%) of palliative patients with BO did not receive stenting or surgical bypass. People who were elderly (>85 years), or who lived in more geographically remote (AOR 2.5, 95% CI 1.5-4.1) or socioeconomically disadvantaged (AOR 2.0, 95% CI 1.1-3.7) areas had a greater likelihood of not receiving palliative biliary decompression (Table 3). While people with more advanced disease and shorter life expectancy were also less likely to be treated, these factors did not explain the associations with sociodemographic factors. When place of residence and SES were modelled together, the association persisted for geographically remote areas (AOR 2.1, 95% CI 1.2-3.7) but was no longer significant for socioeconomically disadvantaged areas (AOR=1.6, 95% CI 0.8-3.1). Higher medical comorbidity was not associated with not being treated.

Discussion

This study examined the use of stents for patients with symptomatic malignant BO in Australia. Almost half of our cohort overall had jaundice or developed it during the 12 months following diagnosis. Pre-operative biliary decompression did not influence whether or not a planned resection was able to be completed or the occurrence of postoperative complications.

In the group receiving palliation only, over 40% of initial stents were plastic and, compared to those treated with metal stents, a higher proportion experienced complications. Patients living in rural areas were less likely to receive palliative biliary decompression.

The incidence of symptomatic BO in this cohort is lower than the 70% commonly quoted in the literature.[17] This may be partly because we only used jaundice to identify BO, whereas BO can occur without jaundice. At diagnosis, 38% of patients were jaundiced, somewhat lower than the results from

the SYMPTOM study, a prospective cohort study, which reported 55% of people had jaundice at diagnosis.[18]

For patients with potentially resectable disease, the theoretical advantage of PBD is the correction of the impaired coagulation and immunologic function associated with cholestasis.[19] Data on the benefits of PBD are contradictory[20-23] and the general consensus is that it should not be routinely performed.[4-7, 24] Current international guidelines do, however, suggest it may be appropriate when patients have cholangitis, intractable pruritis or other severe complications from BO.[3] An Australian consensus statement advises that "patients with lesions in the pancreatic head may need metal (not narrow plastic) stenting prior to operative intervention".[25] Despite this, PBD was widely used in our study, with a clear preference for plastic stents (84%). The latter may be explained, in part, by the relatively short time (median 32 days) between stent insertion and surgery, which makes longer term patency less important.

Meta-analyses have found that post-operative complications may be increased by PBD.[4-7] Amongst those with preoperative BO, we found no statistically significant association between PBD and either surgical success or post-operative complications. Higher rates of anastomotic leakage in PBD have been reported elsewhere[26] and may be attributed to bile duct mucosal inflammation associated with stenting; we found a suggestion that PBD might be associated with leakage but this was not statistically significant. One meta-analysis found higher levels of morbidity in those with PBD who had fewer than 4 weeks between preoperative drainage and pancreaticoduodenectomy compared with no PBD; there was no difference when there was more than 4 weeks between stent insertion and surgery.[24] In our study time from stenting to surgery was not associated with the risk of complications. Our findings suggest that PBD was not deleterious and, in the Australian context, may allow time to complete the staging work-up that is standard practice to avoid unnecessary laparotomies.

For palliative patients endoscopic stenting was used much more frequently than biliary bypass surgery. This is consistent with the NCCN guidelines which state that a self-expanding metal stent is preferable to bypass for patients with locally advanced or metastatic disease unless biliary bypass was performed at the time of laparotomy or laparoscopy. However these guidelines were established prior to the advent of the newer more efficacious chemotherapeutic regimens. With longer survival resulting from the use of these

regimens and the increasing difficulty of replacing stents as the tumor progresses locally, bypass may still have a role in some patients.

Despite consensus reports and guidelines[3, 13, 27] generally recommending that metal rather than plastic stents be used in the palliative setting, our data suggest relatively extensive use of plastic stents in Australia in 2010/11 for the palliation of malignant BO. Guidelines do allow for plastic being appropriate when the diagnosis is uncertain or if the prognosis indicates less than four months survival[3, 13] but the similar survival times we observed for people treated with the two stent types suggests that choice of stent type was not strongly influenced by prognosis.

Our results regarding the benefit of metal stents concur with the literature. We found that metal stents were much less likely to require replacement (OR for 30 day replacement was 0.14) and had a median patency duration of 91 days, compared with 35 days for those who were initially given a plastic stent. A meta-analysis of randomized controlled trials demonstrated the 30-day occlusion rate was significantly lower for metal compared with plastic stents (OR 0.27),[12] and a trial comparing plastic and metal stents reported a median of 108 days to occlusion for metal stents and 54 days for plastic stents.[8]

In the palliative setting, approximately a quarter (26%) of people received no intervention for BO, with higher cancer stage and associated shorter life expectancy appearing to influence the decision to forgo treatment. These factors did not explain the association we observed between place of residence and decompression. We and others have previously shown that surgical and chemotherapeutic management varies according to sociodemographic factors,[28,29,30,31] and our results suggest that management of BO is subjected to the same forces.

It is important to note that our findings are based on data collected in 2010/11 and practices may have changed in subsequent years. Another limitation is that we did not ascertain the date when a decision was made to pursue palliation in those who did not have an attempted resection. Consequently, we cannot rule out the possibility that decisions regarding stenting, including type, were made at a time when the patient was still under consideration for surgery.

A major strength of our study is that it is population-based, with data collected from multiple centres within both the private and public hospital systems of QLD and NSW. Furthermore, we collected detailed data on up to 3 stents insertions per person, including complications arising within 30 days of insertion. Our study is the first to provide a comprehensive insight into the management of BO in Australia, and the results are likely to be relevant to other jurisdictions, particularly those where treatment is not based on insurance status.

In conclusion, these results show that stenting prior to surgery occurred frequently and often with plastic stents, despite a consensus statement suggesting metal should be used in this context. Plastic stents were still used frequently for palliative patients, possibly due to an incorrect perception that they are more cost effective. Patients living in rural areas were less likely to receive management of BO. This work highlights the need to monitor current practice.

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FIGURE LEGEND

Figure 1: Management of patients with symptomatic biliary obstruction [numbers in boxes are N (%)] (*Missing data in 6 cases)

Table 1: Post-Operative Complications for all Patients With Completed Resection (With or Without Biliary Obstruction) and for Subgroups According to Pre-Operative Biliary Obstruction and Preoperative Stenting[†]

Post-operative complication	Completed resection (total=279) N (%)	Completed resection *without* pre-operative biliary obstruction (total=115) N (%)	Completed resection *with* pre-operative biliary obstruction (total=164) N (%)			
			All	With pre-operative stent (total=117)	Without pre-operative stent (total=47)	*P* value[‡]
Any complication	128 (46)	51 (44)	77 (47)	56 (48)	21 (45)	0.71
Sepsis	38 (14)	17 (15)	21 (13)	15 (13)	6 (13)	1.00
Anastomotic leak	28 (10)	13 (11)	15 (9)	14 (12)	1 (2)	0.07
Wound infection	27 (10)	12 (10)	15 (9)	10 (9)	5 (11)	0.77
Delayed gastric emptying	27 (10)	7 (6)	20 (12)	13 (11)	7 (15)	0.60
Gastric outlet obstruction	15 (5)	6 (5)	9 (5)	8 (7)	1 (2)	0.45
Haemorrhage	14 (5)	5 (4)	9 (5)	8 (7)	1 (2)	0.45
Fistula	13 (5)	5 (4)	8 (5)	7 (6)	1 (2)	0.44
Respiratory tract infection	16 (6)	7 (6)	9 (5)	7 (6)	2 (4)	1.00
No complication	147 (53)	60 (54)	87 (53)	61 (52)	26 (55)	0.71

[†] Data regarding post-operative complications missing for 4 cases

[‡]P-value for comparison of complication rate for those with and without pre-operative stenting. Chi-squared test used for 'any complication' and 'no complication'; Fisher's exact test used for specific complications (yes or no).

Table 2: Complications Following Stent Placement for Patients who did not Have a Resection Attempt: Total and by Type of Stent

	Proportion of total stent insertions[*,†] N (%)	By stent type Metal N (%)	Plastic N (%)	Odds ratio[‡] (95% confidence interval)	*P* value
Stents inserted	666 (100)	442 (66)[§]	224 (34)[§]	-	
Any complication[‖]	145 (22)	79 (18)	66 (29)	1.9 (1.3-2.7)	0.001
Persisting jaundice	68 (10)	33 (7)	35 (16)	2.0 (1.2-3.3)	0.01
Cholangitis	63 (9)	34 (8)	29 (13)	1.8 (1.1-3.0)	0.03
Occlusion	39 (6)	14 (3)	25 (11)	3.9 (2.0-7.4)	<0.001
Pancreatitis	17 (3)	9 (2)	8 (4)	1.7 (0.7-4.4)	0.25
Sepsis	10 (2)	7 (2)	3 (1)	0.8 (0.2-3.3)	0.81
Perforation	6 (1)	3 (<1)	3 (1)	2.0 (0.4-10.0)	0.40
Haemorrhage	4 (1)	3 (<1)	1 (<1)	0.7 (0.1-6.3)	0.71
Bile leak	4 (1)	2 (<1)	2 (<1)	2.0 (0.3-14.2)	0.50
Other	15 (2)	-		-	

* 102 patients with missing data excluded

† Note that this is number of stents and not number of people; people may have had more than one stent

‡ Odds ratios estimated using generalized estimating equations with an exchangeable correlation matrix to allow for multiple stents per person

§ Row %, all others are column %

‖ One stent event may be associated with more than one complication

Table 3: Association Between Demographic / Disease Characteristics and Biliary Decompression for Jaundiced Non-Surgical Patients (Total n = 680)

		Biliary decompression N (%)	**No intervention** N (%)	**Adjusted OR (95% CI)***
Total (N=674)†		496 (74)‡	178 (26)‡	-
Sex	Men	269 (54)	102 (57)	1.0
	Women	227 (46)	76 (43)	0.8 (0.6-1.2)
Deceased at 3 months	No	383 (77)	96 (54)	1.0
	Yes	113 (23)	82 (46)	6.7 (4.5-9.9)
Age at diagnosis (years)	≤ 64	113 (23)	39 (22)	1.0
	65 - 74	134 (27)	43 (24)	0.9 (0.6-1.5)
	75 - 84	176 (35)	49 (28)	0.8 (0.5-1.3)
	≥ 85	73 (15)	47 (26)	1.8 (1.1-3.1)
TNM Stage	Stage I & II	185 (37)	36 (20)	1.0
	Stage III	57 (11)	6 (3)	0.6 (0.2-1.4)
	Stage IV	219 (44)	120 (67)	3.3 (2.1-5.1)
	Undetermined stage	*35 (7)*	*16 (9)*	-
Charlson Comorbidity	Low (0)	197 (40)	67 (38)	1.0
Index	Medium (1)	157 (32)	60 (34)	1.0 (0.7-1.6)
	High (≥2)	139 (28)	51 (29)	1.0 (0.7-1.6)
	Unknown	*4 (1)*	*0 (0)*	-
Place of residence	Major cities	343 (69)	106 (60)	1.0
	Inner regional	103 (21)	37 (21)	1.2 (0.8-1.8)
	Outer regional/Remote	46 (9)	33 (19)	2.5 (1.5-4.1)
	Unknown	*4 (1)*	*2 (1)*	-
Socio-economic status	Least disadvantaged	83 (17)	20 (11)	1.0
	Second	108 (22)	32 (18)	1.3 (0.7-2.5)
	Third	95 (19)	33 (19)	1.5 (0.8-2.9)
	Fourth	102 (21)	44 (25)	2.0 (1.1-3.7)
	Most disadvantaged	104 (21)	47 (26)	2.0 (1.1-3.7)
	Unknown	*4 (1)*	*2 (1)*	-

OR: Odds ratio; CI: Confidence Interval.

* Adjusted for age and comorbidity

† Management unknown for 6 cases

‡ Row %, all others are column %