

A randomized trial comparing winged versus conventional plastic stents for malignant bile duct strictures



Authors

Lachlan Ayres¹, Danny Cheriyan^{1,2}, Ryan Scott³, Edward Kim¹, Terry Lee⁴, Joel Singer⁴, Fergal Donnellan⁵, Michael Byrne⁵, Alan Weiss⁵, Robert Enns^{1,6}, Jack Amar¹, Eric Lam¹, Jennifer Telford¹

Institutions

- 1 St. Paul's Hospital – Gastroenterology, Vancouver, Canada
- 2 Beaumont Hospital, Dublin – Gastroenterology, Dublin, Ireland
- 3 Belfast City Hospital – Gastroenterology, Belfast, United Kingdom of Great Britain and Northern Ireland
- 4 St Paul's Hospital – Medical Statistics, Vancouver, Canada
- 5 Vancouver General Hospital – Gastroenterology, Vancouver, Canada
- 6 University of British Columbia, Division of Gastroenterology, Department of Medicine, Vancouver, Canada

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Bibliography

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Corresponding author

Dr Lachlan Ayres, Department of Gastroenterology,
University of British Columbia, 1081 Burrard Street,
Vancouver, British Columbia V6Z 1Y6, Canada
lachlanayres@hotmail.com

ABSTRACT

Background and study aims Stent insertion at endoscopic retrograde cholangiopancreatography (ERCP) is an established therapy for managing malignant biliary obstruction. Conventional plastic stents with a tubular design are most commonly used despite limited patency. Plastic stents with a winged design may theoretically increase the duration of stent patency. The aim of this study was to compare stent patency of the winged versus conventional plastic stents in patients with malignant biliary obstruction.

Patients and methods A prospective, randomized subject-blinded trial was conducted. Patients with malignant biliary obstruction were randomized (1:1) to either a 10 French winged stent or 7 or 10 French conventional plastic stent. Strictures greater than 1 cm distal to the hilum were included. Patients were followed clinically to determine the frequency of stent failure until surgery, death or study closure.

Results Fifty-eight patients were enrolled. Following 9 exclusions, 49 patients were randomized to a winged (n=23) or conventional stent (n=26). Median time to stent failure was 89 (95% CI 26–NA) vs 143 (95% CI 33–266) days ($P=0.963$) for the winged and conventional group, respectively. Stent failure for the winged group occurred in 11 (48%) compared to 14 (54%) in the conventional group. Median survival was 123 (95% CI 81–189) vs 342 days (95% CI 123–704) ($p=0.084$) in the winged and conventional group respectively. There were no procedure related adverse events.

Conclusions Improvement in stent patency was not seen with the winged stent when compared to the conventional plastic stent.

Clinical trials number NCT01514214.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) and stent insertion is frequently performed to decompress the biliary tree in patients with malignant biliary obstruction. Both

plastic and metal stent insertion are effective methods of treating jaundice and improving quality of life [1–4].

Although self expanding metal stents (SEMS) offer more durable patency than plastic stents [2, 4–8], ERCP and plastic stent insertion is commonly performed for biliary decompres-

sion, often before a formal decision regarding surgical resection has been made.

The Viaduct™ stent (GI Supply, Camp Hill, Pennsylvania, United States) has a unique design with a winged perimeter, which channels flow of bile around the stent as well as through a narrow central lumen. Theoretically this may enhance flow (through the multiple channels) and biliary drainage, potentially increasing stent patency [9].

A recent study demonstrated the winged plastic stent to be inferior to SEMS in the setting of unresectable malignant biliary obstruction [10]. There have been no prospective randomized studies to date comparing the winged stent to conventional plastic stents.

The primary aim was to compare stent patency in the winged (Viaduct™) and conventional (polyethylene) stent groups in subjects with malignant bile duct strictures. Secondary goals were to evaluate the etiology of stent failure in the two treatment groups and to compare survival between the two groups.

Patients and methods

Patients

Patients referred to St Paul's Hospital and Vancouver General Hospital with biliary obstruction suspected or known to be secondary to malignancy were enrolled by the advanced endoscopy fellow. Inclusion criteria were: age ≥ 18 years; bile duct stricture confirmed at ERCP; malignant etiology confirmed on histology or cytology and stricture > 1 cm distal to the biliary hilum. Exclusion criteria were: inability to obtain consent; inability to tolerate procedure and circumstances where an alternative biliary stent was deemed critical by the treating endoscopist. The study protocol was approved by the Human Ethics Board at the University of British Columbia. Written, informed consent was obtained from all patients prior to ERCP. Clinical trials number NCT01514214.

Procedure

All ERCPs were performed by 1 of 9 experienced advanced endoscopists at 2 tertiary Vancouver hospitals using Olympus duodenoscopes and performed under conscious sedation. Randomization occurred following common bile duct (CBD) cannulation with successful placement of a guidewire proximal to the stricture. A random number generator was used to allocate subjects to stent group in a 1:1 fashion in blocks of four. The number sequence was generated by the primary investigator and was not concealed. The length of stent (and caliber for conventional stent) as well as stricture dilation prior to stent insertion was at the endoscopists' discretion. Stents were deployed in a standard transpapillary position. The endoscopist was not blinded to the stent type as there are obvious differences in appearance. Subjects were blinded to stent assignment.

Data collection

On the day of the procedure the following baseline and procedural data were collected: age, gender, prior stent therapy, imaging and laboratory results, stent type, calibre, length and success of stent deployment.

In addition to routine care, subjects were followed clinically with phone contact every 30 days (using a structured questionnaire) and by interrogation of electronic medical records to determine clinical progress relating to stent occlusion, stent change, repeat ERCP (or other biliary intervention), resection, palliative therapy and death. Stent change was performed on an as required basis.

Stent failure was determined at ERCP which was performed if there was clinical, biochemical or radiological suspicion of occlusion or migration. Stent migration was defined as stent migration above or below the stricture as assessed fluoroscopically or endoscopically. Stent failure was managed by ERCP and stent change using a conventional plastic or metal stent at the endoscopists' discretion. Patients were followed to stent failure, surgery, death or until study closure.

Statistical analysis

Estimates for stent patency in the winged stent group were extrapolated from the conventional stent literature [1–7]. Sufficient data were not available *a priori* to determine whether there is a difference, or the magnitude of difference, in stent patency, between conventional and winged stents. Therefore, we chose to calculate the study sample size to detect a 20% difference in stent patency between the 2 groups, as this was felt to be a clinically relevant difference. To determine a 20% difference in stent patency at 6 months, using a significance level of 5% and a power level of 80%, we estimated that 50 subjects would be required in each group.

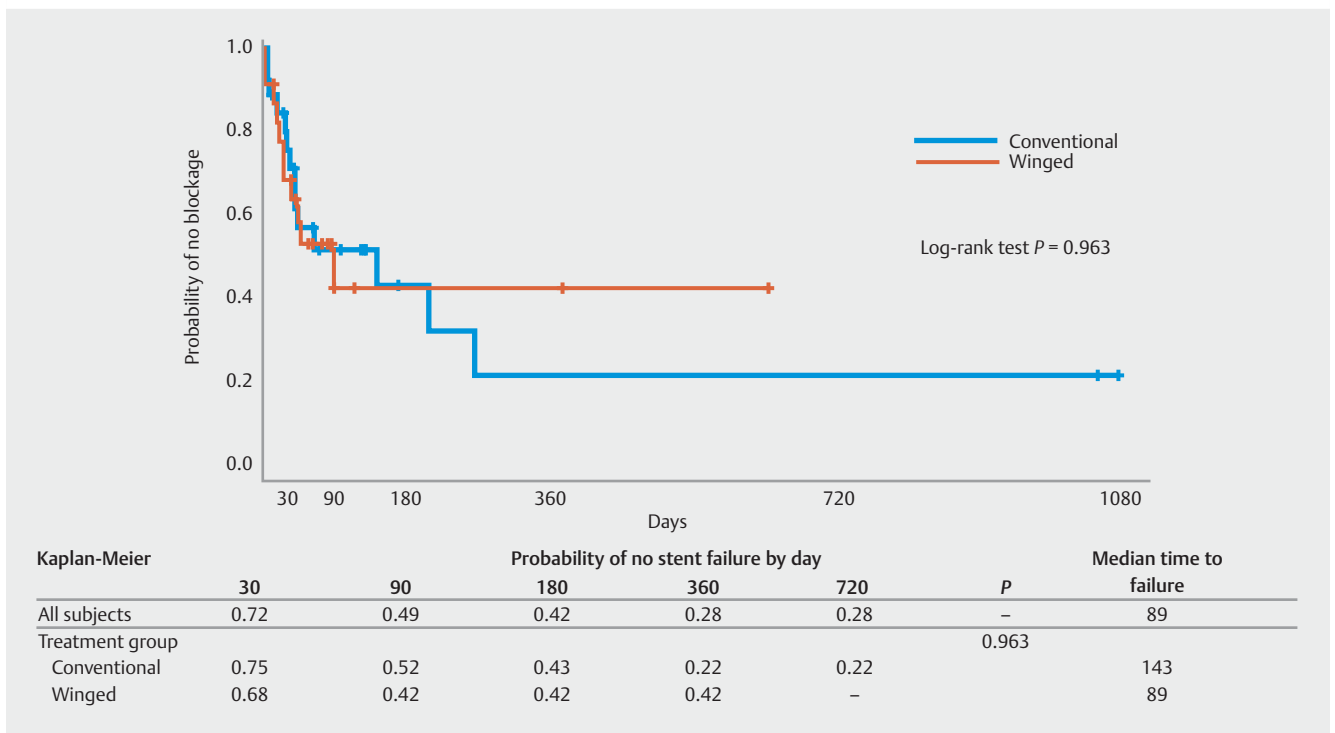
Stent patency was tested using the log-rank test and analyzed in an intention-to-treat fashion. Cumulative stent patency was estimated by Kaplan-Meier life-table analysis and the two groups compared by the log rank chi-square test. Patients who did not have a stent failure were censored at the time of surgery, time of death or time of the last follow-up, whichever occurred first. Time to death was compared between groups in a similar fashion with alive patients censored at the time of the last follow-up. We further examined the time to stent failure or death as a composite outcome using Kaplan-Meier curves. Patients who survived and did not have a failure or underwent surgical resection before a failure were censored at the time of the last follow-up. Cox regression was used to estimate the hazard ratio (HR) in the winged group versus the conventional group. Statistical analysis was performed using SAS 9.4 and R 3.2.0.

Results

Fifty-eight patients were enrolled between February 2012 and June 2015. Nine patients were excluded: failed common bile duct (CBD) cannulation (3), ampullary mass with no associated biliary stricture (2), 1 subject for each of the following: no biliary stricture on cholangiogram, obstructing duodenal stricture, benign stricture, a protocol violation with placement of a pig-tail stent. Thus of 49 patients 26 were randomized to conventional and 23 to the winged stent groups. There were no differences in the two groups at baseline (► **Table 1**). The most frequent cause of obstruction was pancreatic ductal adenocarcinoma $n = 33$ (67%). Follow up concluded January 2016.

► **Table 1** Patient baseline characteristics.

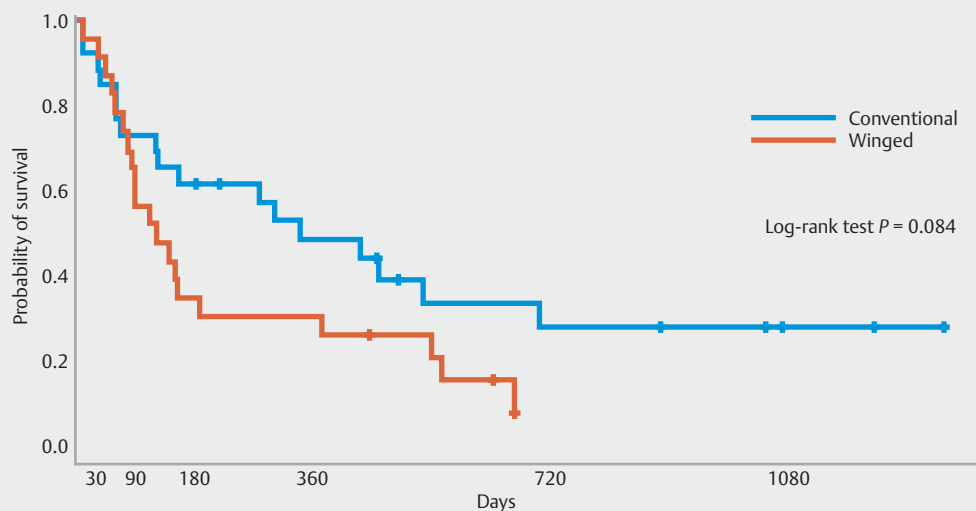
Variable	All n = 49 (%)	Treatment group		P
		Conventional n = 26 (%)	Winged n = 23 (%)	
Male, n (%)	27 (55)	13 (50)	14 (61)	0.445
Diagnosis, n (%)				0.417
Lymphoma	2 (4)	2 (8)	0 (0)	
Pancreatic cancer	34 (69)	15 (58)	19 (83)	
Pancreatic neuroendocrine tumor	2 (4)	1 (4)	1 (4)	
Cholangiocarcinoma	5 (10)	3 (12)	2 (9)	
Hilar hepatocellular carcinoma	1 (2)	1 (3)	0 (0)	
Metastatic obstruction	5 (10)	4 (15)	1 (4)	
Age				
Median	69	67.5	69.0	0.127
Range	(34–92)	(34–84)	(49–92)	
Bilirubin				
Median	173	178	166	0.845
Range	(11–404)	(11–387)	(30–404)	
CBD diameter (mm)				
Median	15	15.0	15.5	0.924



► **Fig. 1** Kaplan-Meier curve and table of time to stent failure. Patients who did not have stent failure were censored at the time of surgery, time of death or time of the last follow-up, whichever occurred first.

► **Table 2** Time to stent failure in 30-day blocks.

	Day					
	0	30	90	180	360	720
Treatment group conventional						
Number of patients at risk	26	17	9	4	2	2
Number of failures in between time point	0	6	5	1	2	0
Number censored in between time point	0	3	3	4	0	0
Treatment group winged						
Number of patients at risk	23	15	3	2	2	0
Number of failures in between time point	0	7	4	0	0	0
Number censored in between time point	0	1	8	1	0	2



Kaplan-Meier	Probability of survival by day					P	Median time to death
	30	90	180	360	720		
All subjects	0.94	0.65	0.49	0.40	0.18	–	156
Treatment group						0.084	
Conventional	0.92	0.73	0.62	0.48	0.28		342
Winged	0.96	0.56	0.35	0.30	–		123

► **Fig. 2** Kaplan-Meier survival curve and table showing probability of survival by day. Patients who did not die were censored at the time of the last follow-up.

Median time to stent failure was longer in the conventional stent group at 143 (95% CI 33–266) days compared to 89 (95% CI 26–NA) days for the winged group but not statistically significant ($P=0.963$; HR: 0.98, 95% CI: 0.44, 2.17) (► **Fig. 1** and ► **Table 2**). The higher confidence interval is non-applicable as there were no stent failures after 89 days. Five (19%) and 4 (17%) patients had a resection before stent occlusion in the conventional and winged group, with median times to surgery of 63 and 48 days, respectively.

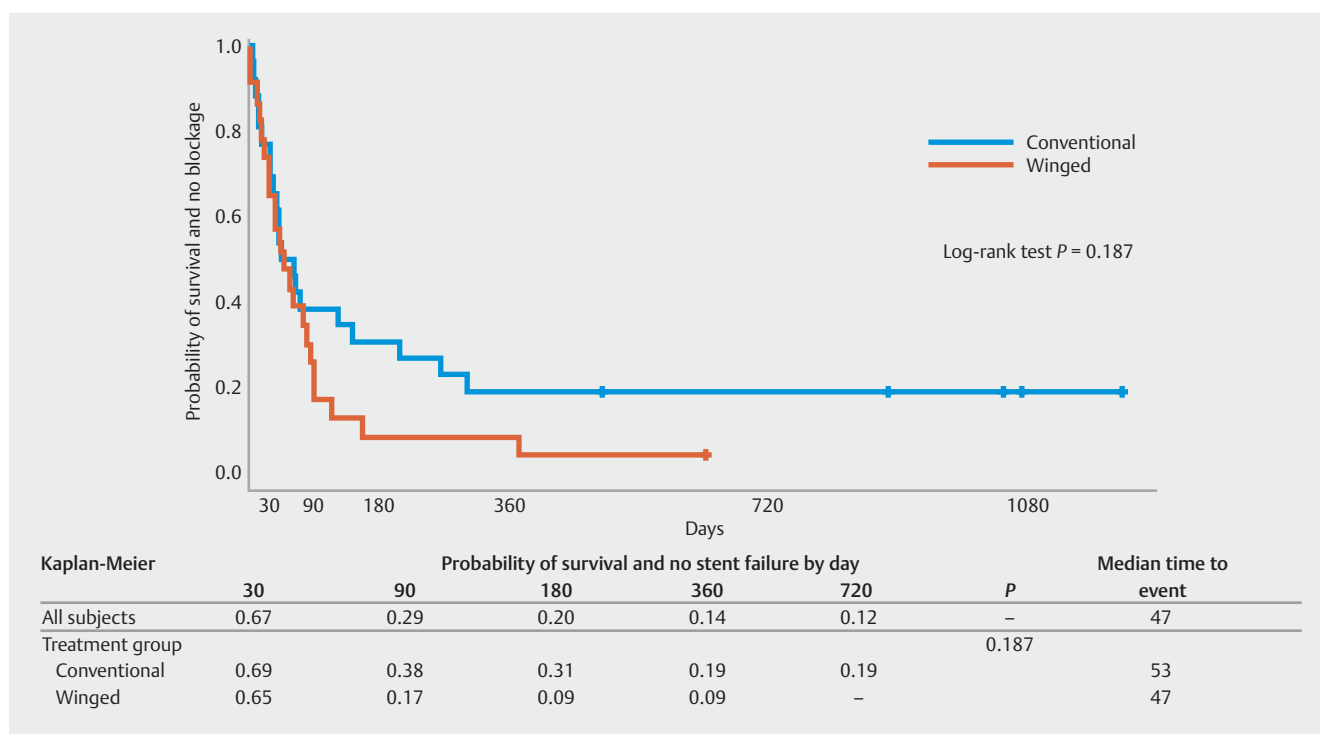
Median time to death was 342 days (95% CI 123–704) in the conventional stent group compared to 123 days (95% CI 81–189) for the winged group ($P=0.084$; HR: 1.78, 95% CI: 0.92,

3.45) (► **Fig. 2** and ► **Table 3**). To account for patients undergoing surgical resection and those who died before stent failure, the probability of stent failure or death was analyzed. The probability of the composite end-point was similar for the 2 groups in the first 50 days and was then higher for the winged group (► **Fig. 3** and ► **Table 4**). However, the difference between the Kaplan-Meier curves was not statistically significant ($P=0.187$; HR: 1.50, 95% CI: 0.82, 2.75).

In the conventional stent group 14 (54%) patients experienced stent failure due to occlusion 12 (46%) and migration 3 (12%) (in 1 patient the stent had occluded and migrated distally but was still in a transpapillary position). Figures for the

► **Table 3** Deaths occurring in 30-day blocks.

	Day					
	0	30	90	180	360	720
Treatment group conventional						
Number of patients at risk	26	24	19	16	11	5
Number of death in between time point	0	2	5	3	3	4
Number censored in between time point	0	0	0	0	2	2
Treatment group winged						
Number of patients at risk	23	22	13	8	7	0
Number of death in between time point	0	1	9	5	1	4
Number censored in between time point	0	0	0	0	0	3



► **Fig. 3** Kaplan-Meier survival curve and table showing time to stent failure or death. Patients who survived and did not have stent failure were censored at the time of the last follow-up.

winged group were broadly similar: 11 (48%) stent failures, 8 (35%) occlusion, and 1 (4%) migration. However there were also 2 (9%) instances of failed winged stent deployment (► **Fig. 4**).

The 2 occasions of winged stent deployment failure were classed as a stent failure in an intention to treat analysis. In 1 patient with pancreatic cancer, it was not technically possible to deploy a 7 French winged stent. The stent, guidewire and duodenoscope were withdrawn and the patient removed from the study. In the second patient, also with a pancreatic cancer, despite using a 10 French step dilator, the 7 French winged stent kinked during deployment. The duodenoscope, stent

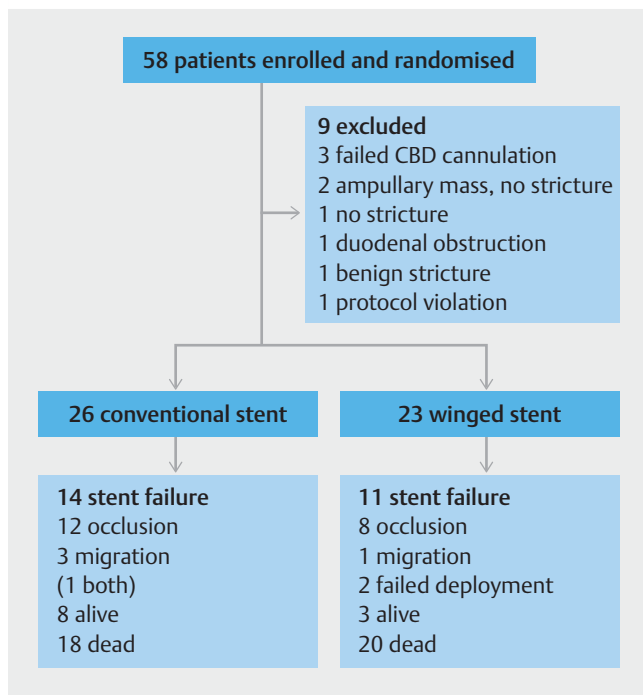
and guidewire were removed and a 10 French 7 cm conventional plastic stent was successfully deployed. There were no procedure related adverse events.

Discussion

This is the first prospective randomized trial comparing conventional, polyethylene plastic stents to a winged stent. Malignant biliary obstruction is typically managed with stent insertion at ERCP. The importance of durable stent patency without the need for repeated endoscopic intervention is self-evident. In

► **Table 4** Patients surviving with no stent failure in 30-day blocks.

	Day					
	0	30	90	180	360	720
Treatment group conventional						
Number of patients at risk	26	18	10	8	5	4
Number of events in between time point	0	8	8	2	3	0
Number censored in between time point	0	0	0	0	0	1
Treatment group winged						
Number of patients at risk	23	15	4	2	2	0
Number of events in between time point	0	8	11	2	0	1
Number censored in between time point	0	0	0	0	0	1

► **Fig. 4** Flow diagram of randomized patients.

our study we found the time to stent failure or death was not different between the 2 groups.

Outcomes using the winged stent design were first reported in 2006 [9]. This initial feasibility study of 5 patients with malignant biliary obstruction with limited follow-up of 2 weeks confirmed that all 5 patients had successful biliary decompression. Computer modelling data demonstrated that the winged stent has a larger surface area, higher flow velocity and higher flow rates than the conventional cylindrical plastic stents.

In 2012 a retrospective study [11] assessing a cohort of 346 patients with benign and malignant biliary strictures showed that early stent occlusion, defined as <90 days, was the same for winged and conventional stents. The winged stent group

experienced fewer episodes of cholangitis (10% vs 50% [$P=0.03$]) than the conventional stent group. In another retrospective study including 34 patients treated with a winged stent, stent failure was no different compared to conventional stents [12].

Similarly, this investigation found that there was no statistical difference between the 2 groups with respect to time to stent failure: the mean time to stent failure was 143 vs 89 days for conventional and winged stents, respectively.

In 2015 a randomized study comparing plastic winged stents to SEMs for palliative drainage was stopped after interim analysis revealed the mean time to stent failure was 51 days and 80 days respectively $P=0.022$ [10]. In some respects this result is to be expected as the diameter of SEMs at 10mm is much greater than the diameter of the winged plastic stents. The authors also noted that half of the winged stents requiring retrieval had adherent biliary sludge and are thus susceptible to occlusion through a similar mechanism as conventional plastic stents. This is contrary to one of the postulated advantages of the winged design that a larger surface area and higher flow rates would lead to a lower propensity for the adherence of a microbial film which is the initiating event in sludge formation and eventual occlusion [13]. In the above study survival was longer for the SEMs group 142 vs 74 days ($P=0.957$). Our study also showed a trend towards longer survival in the conventional stent group 342 vs 123 days ($P=0.084$). It is possible that a tendency to earlier stent failure in the winged stent group due to tumor ingrowth into the outer channels may in turn translate into shorter survival. This is speculative, however, as there was no statistical difference in the time to stent failure or survival between groups.

Of concern is the fact that on 2 occasions there was failure of stent deployment in the winged group. In ERCP practice, technical issues with stent deployment are typically only encountered in hilar or proximal strictures; however, both these events occurred in distal strictures. Although there is a learning curve with novel devices, the method of winged stent deployment (stent pushing catheter) is a basic ERCP skill, therefore the technical failure is most likely to be related to the stent. Another possi-

ble disadvantage of the winged design, as mentioned above, is susceptibility to tumor ingrowth into the outer channels, which cannot occur in conventional stents. It is not possible to reliably assess for this as a cause of stent occlusion when the stent is retrieved.

The fact that approximately half the patients with unresectable disease in each group required an unscheduled ERCP for stent failure suggests that to avoid the costs associated with hospital admission and a repeat ERCP, elective stent change should be considered. This finding also lends support to the recommendation that patients with life expectancy exceeding 3 months should be managed with SEMS insertion [14–16].

This study has several limitations. The most significant limitation is the small sample size which leads to a decrease in study power and the chance that a significant difference between the 2 stent groups exists but was not demonstrated. The intended sample size was not reached as a result of slow recruitment and difficulty maintaining stock of the winged stent due to manufacturer and supplier issues. A second limitation is that consecutive patients were not assessed for eligibility. This was due in part to the time limitations on the advanced endoscopy fellows enrolling patients and to winged stent supplies. The study was halted once the winged stent was no longer available for purchase in Canada. A further potential confounding factor was a degree of heterogeneity of conventional stent caliber: 3 patients in the conventional group had a 7 French stents inserted with patencies of 29, 64 and 208 days (mean 100) potentially bringing down the overall average for the conventional group. Malignant biliary obstruction is a common clinical scenario and management with ERCP and stent insertion is a routine procedure. As such these findings are broadly applicable.

Conclusion

In conclusion, this is the first randomized, prospective trial investigating winged versus conventional plastic stents in malignant biliary obstruction. There was no statistical difference in the time to stent failure or overall survival between the 2 groups.

Competing interests

None

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