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Use of stents in patients undergoing chemotherapy for borderline resectable pancreatic cancer-causing biliary obstruction while awaiting surgery: A cost-effectiveness analysis

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ABSTRACT

Background and study aims Biliary stenting is indicated to relieve obstruction from borderline resectable pancreatic cancer while patients receive preoperative neoadjuvant therapy. We compared the cost-effectiveness of plastic versus metal biliary stenting in this setting.

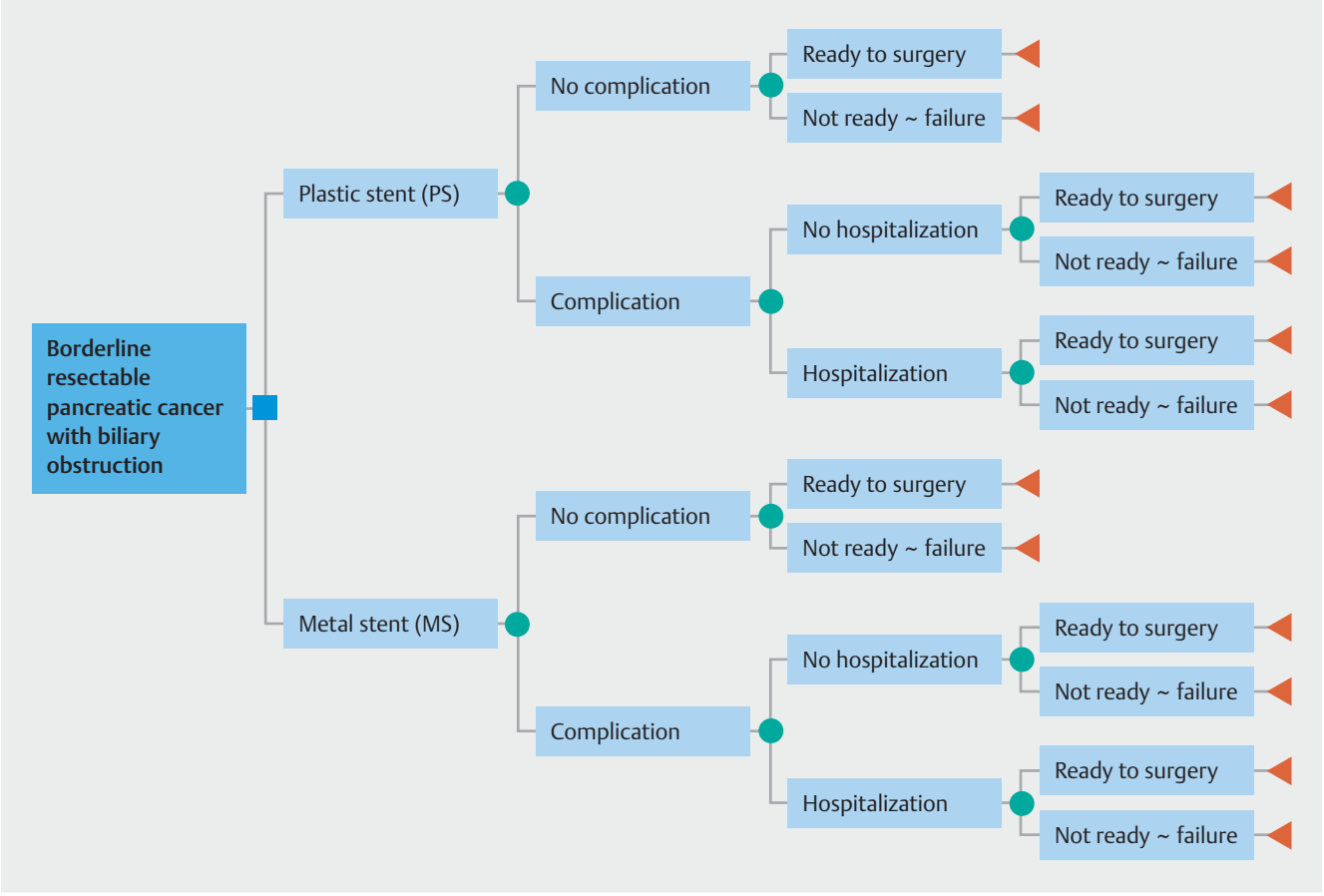
Methods A decision tree analysis compares two competing types of biliary stents (initially metal vs. initially plastic) to treat malignant distal biliary obstruction while receiving neoadjuvant therapy with different scenarios including possible complications as bridge till the patient undergoes curative surgical attempt. Using published information, effectiveness was chosen as the probability of successfully reaching a state of being ready for surgery once chemotherapy was completed. Costs (2018 US$) were based on national data. A third-party payer perspective was adopted, and sensitivity analyses were performed over a time-horizon of one year.

Results Initially inserting a metal versus a plastic biliary stent was more efficacious with a higher probability of reaching the readiness for surgery endpoint (96 % vs. 85 %), on average 18 days earlier while also being less expensive (US$ 9,304 vs. US$ 11,538). Sensitivity analyses confirmed robustness of these results across varying probability assumptions of plausible ranges and remained a dominant strategy even when lowering the willingness-to-pay threshold to US$ 1,000.

Conclusions Initial metal stenting to relieve malignant biliary obstruction from borderline resectable pancreatic cancer in patients undergoing neoadjuvant therapy prior to surgery is a dominant intervention in economic terms, when compared to initially inserting a plastic biliary stent as it results in a greater proportion of patients being fit for surgery earlier and at a lower cost.

Introduction

The burden of pancreatic cancer has increased over the last decade with a present age-standardized incidence of 5.7 per 100,000 person-years and an estimated 441,000 deaths globally [1]. Pancreatic cancer has a low 5-year survival rate of only 9.3 % based on the United-States Surveillance, Epidemiology, and End Results program [2]. Surgery represents the only modality to achieve cure and, unfortunately, a majority of patients present at an advanced stage when it is no longer an option.



▶ **Fig. 1** Decision model structure.

Once biliary obstruction and jaundice due to pancreatic cancer develops, stenting is indicated for palliation [3]; in this context, the superiority of metal over plastic biliary stents has been demonstrated [4, 5] as cost-effectiveness [6–8].

More recently, the use of neoadjuvant therapy prior to surgery has been advocated in cases of resectable and borderline resectable pancreatic cancer [9]. The aims of such therapy are earlier treatment of micro-metastatic disease, better tolerance of systemic therapy prior to surgery, improved selection of patients without rapidly progressive disease for surgical resection, as well as lower rates of positive resection margins [10, 11].

In these patients, the increased upfront costs of metal biliary stenting needs to be weighed against any possible costs of increased complications due to the shorter stent patency duration of plastic stents with resulting interruptions in the chemotherapy protocol leading to a delay or cancellation of subsequently planned surgery. Based on available literature, there exists uncertainty as to the cost-effectiveness of metal versus plastic stents for biliary drainage in the setting of neoadjuvant therapy. Indeed, some studies have suggested the superiority of initially inserting a metal biliary stent in this setting [12–15], while a retrospective study from Japan showed no difference in the effectiveness of both stents [16], and a US randomized controlled trial (RCT) demonstrated similar cost-effectiveness comparing both approaches [17]. We thus aimed to better characterize the cost-effectiveness of initial plastic versus metal biliary stent placement in patients with a resectable or borderline resectable pancreatic cancer causing biliary obstruction in whom pre-operative neoadjuvant therapy is planned.

Methods

Model design and patient population

The decision analysis software TreeAge Pro 2018 (Williamstown, Massachusetts, United States) was used to design a decision tree (▶ **Fig. 1**) comparing two competing types of stents to treat malignant distal biliary obstruction. The target population was adult patients with borderline resectable pancreatic cancer. Possible clinical management scenarios following the insertion of the biliary stent were included in the model. The overall time horizon was up to 1 year, with the duration of successive specific health states leading to respective terminal nodes for each approach that are based on available data from the literature. If there was no complication at any time after the initial stent insertion at index endoscopic retrograde cholangiopancreatography (ERCP), the patient ended the planned chemotherapy and reached the terminal node identifying the individual as ready for the surgery or not, also noting the time elapsed between initial stent insertion and this decision. For the patient who suffered a complication following initial stent insertion,

the model then included a possible admission. In such a patient, a second ERCP was performed and the original stent was replaced by a metal expandable stent (fully or partially covered), regardless of the type of initial stent that was inserted (metal or plastic). The patient then proceeded to the terminal node of either "ready for surgery" or "not ready for surgery" based on the observed outcomes for such patients as reported in studies identified by our comprehensive literature review. In the former case, the time elapsed to reach this decision from initial stent insertion also was tabulated. The model assumed chemotherapy and follow-up of the patient every 15 days throughout the process until the final health status (when the patient reaches the terminal node). If there was an admission, chemotherapy was suspended during the hospital length-of-stay and was restarted again 1 week after the end of hospitalization.

Outcomes of effectiveness

The primary outcome of effectiveness was the cumulative probability for each strategy across all its possible clinical paths with which the patient is deemed a surgical candidate (i. e.: after having completed chemotherapy and repeat staging), or not. The secondary outcome of effectiveness was the mean time in days elapsed between initial stent insertion and a decision that the patient was indeed ready for surgery, if that was the case. Death was not considered in the model as there exist no data to suggest that either stenting strategy provides a survival benefit [12–17].

Data sources and analytical framework

A comprehensive literature search was performed from 1978 to February 2019 using OVID MEDLINE, EMBASE, Cochrane Library, and ISI Web of Knowledge databases with validated search terms specified for pancreatic cancer and stenting (**Appendix 1**). Additional relevant studies were identified from cross-referencing and hand-searches of references of the retrieved articles. All human adult studies published in English were considered.

The computed average duration of management from initial stent insertion until the final reassessment of the patient for surgery following chemotherapy was based on the mean duration (in days) of those patients who enrolled in a prospective randomized study [17] and reached this desired endpoint. All probabilities are derived from the literature.

National mean hospital costs and length-of-stay are provided by the National Inpatient Sample 2015 which is a US-wide database collecting more than 7 million hospitalization records across 47 states. Hospitalizations of adult patients identified with the ICD-9-CM code '576.1' (cholangitis – used as it is the most common complication noted requiring admission, which also usually has the most consequential length of stay and impact amongst all possible complications in this setting on subsequent time to readiness for surgery) are selected to represent the hospitalisations in the model. Physician fees and drug prices are the national amounts provided by Centers for Medicare and Medicaid Services 2018. For chemotherapy drug costs, the respective average body surface of patients for an upper gastrointestinal category is used, weighted by the proportion of individuals developing pancreatic cancer in North America in 2016 [18]. Stent prices and ERCP facility fees were provided by Boston Scientific Inc. (Marlborough, Massachusetts, United States).

The willingness-to-pay (WTP) threshold is defined as the pre-fixed maximum dollar value that is deemed acceptable spending for a treatment for biliary obstruction in borderline resectable pancreatic cancer. It is fixed at US$ 50,000 as previously done in such analyses [6, 19–21]. Adopting a third-party payer perspective, only direct costs were considered. All costs are expressed in 2018 US$ using, when necessary, the US consumer price index for medical services.

Presentation of results

Results were reported as average costs, effectiveness, and cost-effectiveness ratios per individual treatment. The effectiveness measure used in reporting cost-effectiveness was the probability of being ready for surgery once chemotherapy was completed. One-way deterministic sensitivity analysis, including Tornado analyses, was performed on all the variables of the model. Possible relevant tipping points beyond the variable bounds identified by threshold analyses are presented.

A probabilistic sensitivity analysis also was performed, exploring further the uncertainty around the point estimates. The Monte-Carlo analysis runs 100,000 simulations varying simultaneously all model assumptions across their respective ranges. The resulting cost-effectiveness acceptability curve graph and scatter plot graph including the incremental cost-effectiveness report were generated. The reporting of our results followedthe CHEERS Statements recommendations (http://www.resource-allocation.com/content/11/1/6).

Results

Reported variables and their determination

The search string used to identify the relevant studies is included in Appendix. Twenty-six input variables were required to construct the model (▶ **Table 1**). Probabilities were extracted from six studies [12–17]. Drug chemotherapy costs were based on the Folforinox regimen (oxaliplatin, leucovorin, irinotecan, fluorouracil [22]). Costs for metal stenting represent a weighted average of biliary fully covered (80 %) and uncovered (20 %) metal stents. The range around the point estimate for each variable was set at ± 30 % of its respective baseline value and the WTP was fixed at US$ 50,000. We associated β distributions to probabilities and normal distributions to the length of the chemotherapy cycles, delays of suspension after the end of hospitalization, and frequency of follow-up throughout the process until the terminal nodes, while γ distributions were applied for all other variables [23].

The cost-effectiveness analysis (▶ **Table 2**) suggests that choosing a metal stent at the initial insertion is associated with an average cost per patient of US$ 9,304 across an average length of clinical management of 170 days, yielding a 96 % probability for the patient to eventually be ready for surgery. The initial plastic stent option is associated with both a more

▶ **Table 1** Model assumptions.

Category	Description	Baseline	Units	Low	High	Source (Ref Number)
Probability	Admission if complication post initial insertion	39.024	%	27	51	Literature [15]
Probability	Complication (MS)	23.809	%	16	31	Literature [12–17]
Probability	Complication (PS)	71.429	%	50	93	Literature [12–17]
Probability	Being ready for surgery if complication (MS)	83.333	%	58	100	Literature [12–17]
Probability	Being ready for surgery if complication (PS)	78.667	%	55	100	Literature [12–17]
Probability	Being ready for surgery if no complication (MS)	100	%	70	100	Literature [12–17]
Probability	Being ready for surgery if no complication (PS)	100	%	70	100	Literature [12–17]
Percentage	Distribution of fully-covered/uncovered for MS	80	%	56	100	Expert author consensus
Physician fees	Anesthesia	221.89	2018 US$	155	289	CMS
Physician fees	Inpatient consultation	76	2018 US$	53	99	CMS
Physician fees	Outpatient consultation	69	2018 US$	48	90	CMS
Physician fees	ERCP first insertion	488.69	2018 US$	342	636	CMS
Physician fees	ERCP second insertion	510.11	2018 US$	357	664	CMS
Physician fees	Inpatient follow-up	39.96	2018 US$	27	52	CMS
Physician fees	Patient visits (outside initial ERCP and any admission)	79.90	2018 US$	55	104	CMS
Price per cycle	Neoadjuvant chemotherapy[1]	170.17	2018 US$	119	222	CMS
Procedure fees	Endoscopic Retrograde Cholangio-Pancreatography	1,849	2018 US$	1,294	2,404	Boston Scientific Inc.
Unit price	Fully covered MS (10 French × 60 mm)	2,400	2018 US$	1,680	3,120	Boston Scientific Inc.
Unit price	PS (10F × 70 mm)	105	2018 US$	73	137	Boston Scientific Inc.
Unit price	Uncovered MS (10F × 60 mm)	1,600	2018 US$	1,120	2,080	Boston Scientific Inc.
Per diem	Hospitalization for procedure or stent-related complication	2,961.19	2018 US$	2,072	3,850	NIS
Duration	Length-of-stay for procedure or stent-related complication NIS2015	4.9	Days	3	6	NIS
Duration	Chemotherapy cycle	15	Days	10	20	Expert author consensus
Duration	Delay in chemotherapy after hospitalization (postponement)	7	Days	5	9	Expert author consensus
Duration	Frequency of follow-up	15	Days	10	20	Expert author consensus

MS, metal biliary stent; ERCP, endoscopic retrograde cholangiopancreatography; PS, plastic biliary stent; CMS, Centers for Medicare and Medicaid Services; NIS, National Inpatient Sample (Healthcare Cost and Utilization Project).
[1] For a typical adult patient with borderline resectable pancreatic cancer with a body-surface area of 1.79 m^2.

expensive average cost per patient of US$ 11,538 and a lower effectiveness of 85 % (in the probability of reaching the readiness for surgery outcome), while achieving this endpoint, on average, 18 days later. The initial metal stent option therefore dominates the initial plastic stent approach, being both less costly and more effective.

The Tornado diagram shows that the model is sensitive to some specific variables (hospitalization costs for procedure or stent-related complication, and a number of probabilities including the readiness for surgery after complications, of complications following plastic stent insertion, and of hospitalization). More specifically, the one-way sensitivity analysis shows

▶ **Table 2** Cost-effectiveness analysis report.

Strategy	Cost (2018 US$)	Incremental cost (2018 US$)	Effectiveness	Incremental effectiveness	Cost-effectiveness ratio (2018 US$) (CER)	Incremental CER (2018 US$)
Metal stent (MS)	9,304		0.9603		9,689	
Plastic stent (PS)	11,538	2,233	0.8476	-0.1127	13,612	–19,816

The willingness-to-pay is fixed at US$50,000.

▶ **Table 3** Threshold values analysis.

Variables	Units	Baseline value	Threshold value and resulting interpretation		
Unit price of fully-covered MS	2018 US$	2,400	Above	6,333	PS is still less effective but becomes less expensive than MS
Per diem hospitalization cost	2018 US$	2,961	Below	508	PS is still less effective but becomes less expensive than MS
Unit price of uncovered MS	2018 US$	1,600	Above	17,774	PS is still less effective but becomes less expensive than MS
Length-of-stay for procedure or stent-related complication hospitalization	days	5	Below	1	PS is still less effective but becomes less expensive than MS
Complication rate (post initial MS)	%	24	Above	48	PS is still less effective but becomes less expensive than MS
Complication rate (post initial PS)	%	71	Below	48	PS is still less effective but becomes less expensive than MS
Probability of being ready for surgery after a complication (MS)	%	83	Below[1]	36	PS becomes more effective but is still more expensive than MS

MS, metal biliary stent; PS, plastic biliary stent.
[1] Staying 0.19 (below 0.19, PS since preferred)

that if the probability of reaching the health state of being ready for surgery after a complication following the initial stent insertion exceeds 94.5 % in the initial plastic stent group or if this same probability in the case of no complication decreases below 85.2 % in the metal stent group, an initial plastic stent insertion approach remains more expensive but becomes more effective than initial metal stenting. Across all other variations of assumption estimates (▶ **Table 1**), initial metal stent insertion always remains the dominant strategy.

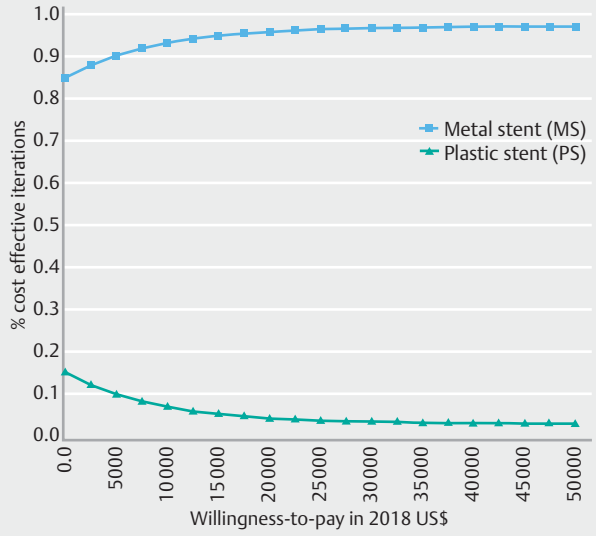
In our baseline scenario, the patients who suffer no complication after insertion are all considered ready for surgery if they remain alive until then. However, when assessing theoretical variability in this assumption, deterministic sensitivity analysis demonstrates that if the probability of being ready after no complication remains above 79.2 %, initial metal stents are still preferred because of the additional costs associated to an initial plastic stent insertion strategy.

▶ **Table 3** lists possible threshold values beyond our adopted variable ranges (that may or not be clinically plausible), identifying possible scenarios for when an initial metal stent choice becomes no longer dominant, with the relevant changes in cost and/or effectiveness results. Although initial metal stenting is no longer dominant, it is still the preferred strategy, considering a baseline a priori WTP set at US$50,000.

Probabilistic analysis confirms the robustness of the results across a broad range of assumptions with much more favourable cost-effective ratios provided by initial metal stent insertion. The cost-effectiveness acceptability curve (▶ **Fig. 2**) shows that whatever the value of WTP, there is a strong likelihood that an initial metal stent is the preferred strategy when compared to the plastic alternative. Indeed, even if the WTP were to be as low as US$ 1,000, there would still remain an 86 % probability favouring the initial metal stent approach. The cloud diagram further confirms the robustness of the findings with metal stents dominating plastic stents in 81 % of the 100,000 iterations modelled for (▶ **Fig. 3**).

Discussion

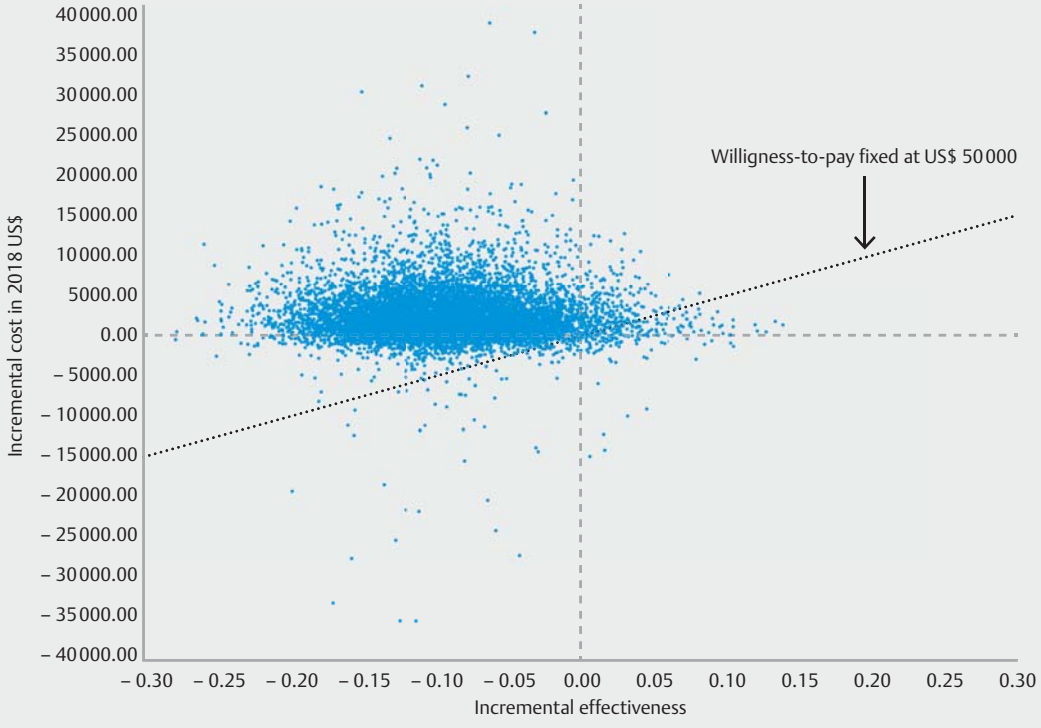
Self-expandable metal stents (SEMS) demonstrate longer patency duration and a lower rate of dysfunction than plastic stents; however, most studies have addressed the sole pallia-



▶ **Fig. 2** Cost-effectiveness acceptability curve.

tion of patients with malignant distal biliary obstruction [24, 25]. In contradistinction, there still exists controversy as to which initial stent technology should be chosen in patients with biliary obstruction undergoing chemotherapy pre-operatively for pancreatic cancer [26, 27]. Adding to the equipoise between initially using metal or plastic stents during neo-adjuvant chemotherapy is the suggestion that stent-related complications may in fact not impact significantly on resectability [14]. Even within the metal stent technology, the optimal choice of a covered vs uncovered prosthesis remains unclear [4, 28] although most societies now recommend a short fully covered self-expanding metal stent in cases of distal malignant biliary obstruction as a bridge to surgery while neoadjuvant therapy is administered [3, 29–31]. The controversy about the optimal stent approach is further compounded by the high up-front costs of metal versus plastic biliary stenting and the disparate results reported in the literature [12–17]. We therefore performed a cost-effectiveness analysis to address this important clinical question, which is especially timely given the increasing volumes in oncological pancreatic surgery [32].

Our analysis demonstrates that initial insertion of a metal stent is a dominant economic strategy that is not only cost-effective due to its lower overall attributable costs (US$ 9,304 vs. US$ 11,538) but is also associated with a higher probability of reaching the all-important clinical outcome of readiness for surgery (96 % vs. 85 %) and it does so 18 days earlier, an additional benefit that may further favor subsequent oncological outcomes for which we could not model. Strengths of the model include a broad sampling of available RCT and observational data, thus increasing generalizability of the results [12–17]. The choice of primary outcome of a patient being “ready for surgery” is the clinically most relevant endpoint, especially in the absence of reliable quality-of-life measurements applicable to the patient population in the preoperative period. We mod-



▶ **Fig. 3** Incremental cost-effectiveness scatter plot of initial plastic stent versus metal stent strategy. The point (0:0), represents the MS as the strategy of reference. The dots represent the PS strategies for the simulations of the Monte-Carlo iterations.

eled for the possible development of cholangitis as representative of procedure- or stent-related complications as it is the principal complication related to stent dysfunction requiring hospitalization with its subsequent very significant usual impact on costs and time-delay to being ready for surgery [26, 27]. Death was not considered due to the difficulty in assigning a cost to this health state and the realization that there is no reason to anticipate a difference in this outcome between adopted strategies based on existing comparative data.

Costs are based on representative updated national recent US information updated by the national consumer price index for 2018. As an assessment of validity, our estimation for hospitalization costs of cholangitis (reflecting procedure or stent-related complications) are in accordance with those of other groups [12]. The time horizon of 12 months (which did not exceed 10 months in the model) was chosen as it is specifically adapted to the clinical situation, based on the best available data carefully collected in recent controlled settings [17], though it is probably longer that what would be usually planned as a time period for receiving neoadjuvant therapy, even if the chemotherapeutic regimens vary in the literature [33]. The strategy of replacing a dysfunctional plastic by a metal stent reflects what was done in some studies [17] but perhaps even more importantly provides a conservative estimate of effectiveness, optimizing stent patency in the initial plastic group [4, 34].

Our final results remain robust after extensive one-way and probabilistic sensitivity analyses testing with essentially unaltered conclusions across a broad range of clinically plausible ranges for all input cost and effectiveness variables. Most interestingly, this analysis demonstrated that the use of metal stents remains a dominant strategy even when the WTP threshold is decreased from a usual baseline assumption of US$ 50,000 in such analyses [6, 19, 20] to a much lower level of US$1,000. It is estimated that the average WTP threshold value for middle to high income countries may range from US$ 2,307 to US$ 9,028 [35]. The conclusions, therefore, appear to be generalizable to many health care settings other than those in the US health care environment. Importantly, even though there exist disparate approaches to the optimal chemotherapeutic regimen favored among adult patients with borderline resectable pancreatic cancer, our point estimates and ranges, which capture most adopted regimens, coupled with the broad sensitivity analyses, allow us to capture such variation and provide results that remain robust even in the presence of lack of consensus opinion.

Limitations of this work include the variability of source data that the assumptions are based on, as well as not adopting possible alternate case-scenarios that would include replacing a plastic stent by another or solely cleaning a blocked metal stent. In all cases, the robustness of the sensitivity analyses is reassuring and make any different conclusions unlikely. The adopted unit of effectiveness represents a compromise in the absence of quality-of-life adjusted information in this specific patient population over the adopted time horizon. Chemotherapy-related complications were not modeled for as there is no a priori reason to believe that these would affect one stent group more than the other, thus not altering incremental effectiveness of cost estimates.

Conclusions

In conclusion, this study demonstrates the economic dominance of an approach of initial metal biliary stenting in patients undergoing preoperative neoadjuvant chemotherapy for borderline resectable pancreatic cancer when compared to initial plastic stent insertion. Such an approach results in greater effectiveness as measured by a higher probability of readiness for surgery at an earlier time and at decreased cost, over a broad range of assumptions.

Competing interests

Dr. Barkun is a consultant for Olympus Canada Inc. Dr. Yen-I Chen is a consultant for Boston Scientific.

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