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ORIGINAL RESEARCH

Cost Effectiveness of Metal Stents in Relieving Obstructive Jaundice in Patients with Pancreatic Cancer

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Abstract
Background ASGE and ESGE guidelines recommend endoscopic metal stent placement for pancreatic carcinoma patients with biliary obstruction, and whose estimated life expectancy is greater than 6 months. Because median overall survival (OS) of metastatic pancreatic adenocarcinoma until recently has been less than 6 months, plastic biliary stents were preferentially placed rather than metal due to the greater upfront cost of the latter. Recent advances in the treatment of metastatic pancreatic cancer have extended median OS beyond the 6-month range. Given this improvement in OS, we performed a cost-effectiveness analysis of initial metal biliary versus plastic stent placement in metastatic pancreatic cancer patients with biliary obstruction.
Methods A Markov model was developed to predict lifetime costs, quality-adjusted life years (QALYs), and cost effectiveness of metal compared with plastic stents. Adult patients entered the model with locally advanced cancer and underwent endoscopic retrograde cholangiopancreatography (ERCP) with placement of metal or plastic stents. A targeted literature search was conducted to identify published sources, which were used to estimate clinical, cost, utility, and event rate inputs to the model. Results were estimated from the third-party payer perspective in 2012 US dollars per QALY. One-way and probabilistic sensitivity analyses were conducted to assess the impact on model outcomes resulting from uncertainty among inputs.
Results Our analysis found that initial placement of metal stents was more cost effective than plastic biliary stents with lower overall costs due to lower restenting rates while at the same time associated with a better quality of life. Based on model projections, placement of metal stents could save approximately $1450 per patient over a lifetime, while simultaneously improving quality of life. These findings were robust in sensitivity analyses.
Conclusions Placement of metal biliary stents at initial onset of obstructive jaundice in adult patients with metastatic pancreatic carcinoma with an expected OS greater than 6 months was found to be a more cost-effective strategy than plastic stents. These results reinforce guidelines' suggestions for metal stent placement.

Keywords Pancreatic cancer · Obstructive jaundice · Endoscopic retrograde cholangiopancreatography · Biliary stents

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Introduction

Pancreatic adenocarcinoma (PC) comprises approximately 3% of all cancers while accounting for a disproportionate 7% of all cancer mortality. There are approximately 49,000 individuals in the USA diagnosed annually, and upwards of approximately 40,500 PC-related mortalities [2]. The economic impact of this burden is compounded by the high cost of PC treatment, estimated at over $65,000 per patient [19].

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Pancreatic adenocarcinoma is highly lethal with a 5-year overall survival (OS) rate for all stages combined of only 8% [2]. One of the problems is that approximately 50% of pancreatic cancer patients are diagnosed with stage IV disease, for which 1- and 5-year survival is 15 and 2%, respectively. Research estimates the survival of those diagnosed with locally advanced PC at approximately 16 months [6, 8]. Recent advances in chemotherapy have extended this survival and prognosis, with newer neoadjuvant chemotherapy regimens improving resectability rates. For example, the four-chemotherapeutic agent combination therapy FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), and gemcitabine and [nab-]paclitaxel.

New clinical and health care system considerations result from the improved survival of patients with PC. For example, locally advanced PC patients often present with obstructive jaundice. Either plastic or metal stents can be placed to provide relief, though metal stents are typically more expensive. American Society of Gastrointestinal Endoscopy (ASGE) and European Society of Gastrointestinal Endoscopy (ESGE) recommendations call for plastic stents to be used in patients with a life expectancy of less than 6 months, and metal biliary stents in patients with a greater than 6-month life expectancy. One rationale for these guidelines is the higher occlusion rates of plastic stents, causing them to occlude and need replacement more frequently than metal stents. Prophylactic exchanging of plastic stents prevents such occlusions and increases jaundice prevention. As systemic therapy options for pancreatic cancer continue to improve and prolong survival, this implies that pancreatic cancer patients (e.g., FOLFIRINOX; [8, 23]), may be more likely to need replacement of plastic biliary stents, thereby favoring placement upfront of metal rather than plastic stents.

Cost-effectiveness analysis (CEA) is useful for evaluation of whether the added cost of metal stents would now be justified, given improvements in median OS for locally advanced and metastatic pancreatic cancer. A previous analysis [3] used older data, warranting an updated analysis. We conducted a CEA from a payer perspective to assess the potential benefits of initial placement of metal versus plastic stents in patients with locally advanced or metastatic pancreatic cancer presenting with biliary obstruction.

Methods

Overview

We developed a Markov cohort model that projects, from the payer perspective, the cost effectiveness of using metal versus plastic stents in adult patients in the USA with nonresectable, locally advanced (stage III/IV) PC. Decision analytic models, of which Markov models are one type, allow for combining information from a variety of sources and comparison of outcomes not directly observed within clinical trials. Markov models allow for inclusion of risks that vary with duration of exposure (e.g., the probability of stent occlusion). Clinical, cost, and quality-of-life inputs were estimated using data from a targeted search of published literature, publically available databases, and expert opinion. For each initial stent placement (i.e., metal or plastic stent), we projected total costs, life years (LYs), and quality-adjusted life years (QALYs). QALYs represent both the length of survival and the quality of life during the lifetime of a patient. These model outcomes were used to calculate the incremental cost-effectiveness ratio (ICER) as cost/LY and cost/QALY of metal versus plastic stents. The ICER represents the economic value of a medical intervention, by quantifying the additional costs for each unit of clinical benefit (e.g., LY or QALY) for one treatment compared to an alternative. The following stent-related outcomes were also calculated: proportion of patients requiring a subsequent stent; median duration of initial stent patency; and average number of stents per patient. Because of potential uncertainty in model inputs, all parameters were varied in sensitivity analysis and the impact of key parameters were assessed in threshold analyses.

Model Structure

Figure 1 shows the model structure and the patients' progression through the various health states. Patients entered the model with locally advanced PC and initially had either metal or plastic biliary stents placed to relieve obstructive jaundice. The model simulated all patients for their lifetime, and during each monthly cycle patients faced risks of clinically relevant complications, such as stent migration, stent occlusion, or death (Table 1).

At initial and subsequent ERCP, patients faced risks of ERCP and stent placement complications. Patients also were at risk of progressive disease at any point from locally advanced to metastatic disease; this risk was independent of model events such as stent placement complications, stent migration, or stent occlusion. All migrated or occluded biliary stents (i.e., whether metal or plastic) were replaced; plastic stents could be replaced with either another plastic or a metal stent. All plastic stents were exchanged prophylactically every 3 months, at which time the plastic stents could be replaced by either another plastic or a metal stent. Metal stents are not typically exchanged prophylactically, and as such, we modeled metal stents' replacement occurring solely due to occlusion or migration. Discounting was not applied due to the short duration of PC survival. The model was developed using TreeAge Pro 2012 (TreeAge Software, Inc., Williamstown, Massachusetts).

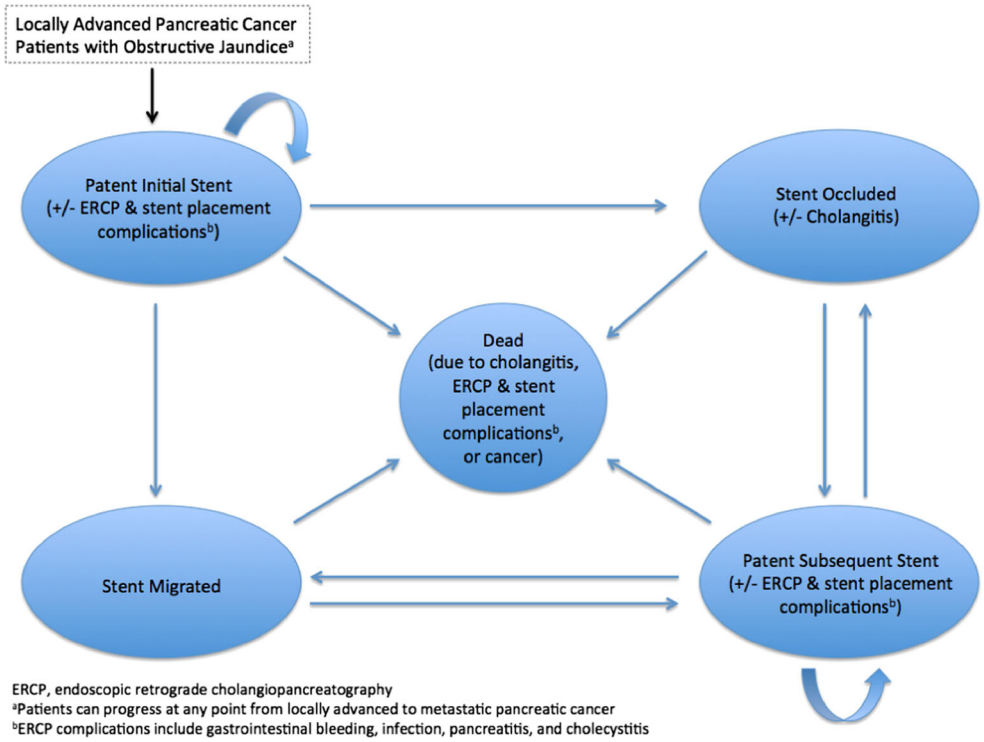

Fig. 1 Model schematic

Model Inputs

Clinical parameters used in the model are shown in Table 1. Survival estimates for patients with locally advanced and metastatic PC were calculated based on a trial of metastatic cancer patients treated with FOLFIRINOX [8], and were supplemented with results from clinical trials of patients with locally advanced cancer [6]. Mortality due to complications (i.e., ERCP and stent placement complications and cholangitis) were derived from published literature and applied at each occurrence of ERCP [1, 4, 11, 21, 24]. Transitional probability from locally advanced to metastatic PC was estimated from observed progression-free and overall survival rates. [18]. The following ERCP and stent placement-related complications were considered in the model: pancreatitis; gastrointestinal bleeding; cholecystitis; and cholangitis. Rates of such events differed for patients with metal versus plastic biliary stents, and were estimated from a targeted search of published literature [1, 4, 11, 24].

Costs were reported in 2012 US dollars, and estimated from a payer perspective using data from publicly available sources and published literature (Table 2). All patients accrued the cost of an initial ERCP procedure, and costs for placement of plastic and metal stents were equivalent. Adverse event costs were based on the published literature and estimated per episode. Depending on the nature of the adverse event, the patient may require a repeat ERCP. Patients with plastic stents were also assumed to have prophylactic stent exchanges every 3 months; metal stents were assumed to not be exchanged prophylactically. Throughout their lifetime, patients also incurred underlying locally advanced and metastatic PC-related direct medical costs to reflect chemotherapy treatment and supportive care. These costs took into account patient survival time, and were based on previously published SEER-Medicare estimates [17, 19].

The impact of disease and treatment on patients was incorporated in the model with utility weights. Utility weights are used to measure health-related quality of life and vary from 0 to 1. Lower values represent poor quality of life; 0 represents death, and 1 represents perfect health. Weights used in the model can be found in Table 2. A utility weight of 0.61 was applied for patients with locally advanced and metastatic PC [13]. The quality-of-life decrement associated with the ERCP procedure was assumed to last for 3 days (expert opinion), reducing the utility weight to 0.18 for patients undergoing ERCP during that 3-day period. ERCP and stent placement-related adverse events were assumed to resolve over a period of 2 weeks based on expert opinion, and therefore caused a 2-week 0.04 decrease [14].

Analyses

In the base case, initial placement of metal stents was compared to that of plastic stents over patients' lifetimes. To understand the impact of parameter uncertainty on model outcomes, one-way and probabilistic sensitivity analyses (PSA) were conducted. In one-way sensitivity analyses, all inputs were varied individually with ranges representative of

Table 1 Model clinical parameters

Parameter	Estimate	Sensitivity analysis range	Source
Pancreatic cancer mortality			
Locally advanced (median survival)	16.9 months	9–18 months	Conroy et al. [8], Buxbaum et al. [6]
Metastatic (median survival)	11.1 months	7.6–18 months	Conroy et al. [8]
Pancreatic cancer progression rate[a]	4.8%	2.4–9.7%	Loehrer et al. [18]
ERCP complication rate[b]			
Cholecystitis			
Plastic stent	0.0%	0–5.8%	Yoon et al. [24]
Metal stent	2.0%	0–5.8%	Gómez-Oliva et al. [11]
GI bleeding			
Plastic stent	5.4%	0–7%	Yoon et al. [24]
Metal stent	0.5%	0–7%	Gómez-Oliva et al. [11]
Pancreatitis			
Plastic stent	8.9%	0–9%	Yoon et al. [24]
Metal stent	2.5%	0–9%	Gómez-Oliva et al. [11]
ERCP complication mortality rate[b,c]	1.0%	0–2%	Adams et al. [1], Bakhru et al. [4], Gómez-Oliva et al. [11], Yoon et al. [24]
Stent migration rate			
Plastic stent	1.4%	0–10%	Bakhru et al. [4]
Metal stent	1.4%	0–2.3%	Bakhru et al. [4]
Stent occlusion rate			
Plastic stent	69.6%	32.9–69.6%	Yoon et al. [24]
Metal stent	55.4%	20.9–55.4%	Yoon et al. [24]
Cholangitis			
Plastic stent	21.4%	0–64%	Adams et al. [1]
Metal stent	7.0%	0–38%	Adams et al. [1]
Cholangitis mortality[d]	14.0%	0–28%	Pola et al. [21]
Subsequent stent choice for adult patients after initial plastic stents[e]			
Following prophylactic exchange			
Plastic stent	40%	n/a	Expert opinion
Metal stent	60%	n/a	Expert opinion
Following occlusion or migration			
Plastic stent	30%	n/a	Expert opinion
Metal stent	70%	n/a	Expert opinion
Prophylactic plastic stent exchange	Every 3 months	n/a	Khashab et al. [16]

ERCP endoscopic retrograde cholangiopancreatography, *GI* gastrointestinal, *n/a* not applicable

[a] Monthly rate of progression from locally advanced to metastatic cancer

[b] ERCP complications include procedure and stent placement related

[c] Mortality rate applies to cholecystitis, GI bleeding, and pancreatitis

[d] Rate includes mortality due to cancer

[e] Patients with metal stents will have subsequent metal stent placed only after occlusion or migration

plausible clinical values and informed by the literature and expert opinion (Tables 1 and 2). In PSA, all parameters were varied simultaneously for 1000 model iterations. Costs were assumed to follow a gamma distribution, utility weights a uniform distribution, and clinical parameters a normal distribution. Typically, in these types of economic evaluations, the results of one-way sensitivity analyses are depicted in a tornado diagram, which highlights the parameters that have the greatest impact on results. However, in this analysis the base case finding was that metal stents dominated plastic stents, which therefore resulted in a negative ICER. It is methodologically incorrect to report the results of negative ratios, so we instead identified the parameters with the greatest impact and conducted threshold analyses to determine at what values the results of dominance no longer appear.

Results

In the base case, the model projected that newly diagnosed locally advanced pancreatic carcinoma patients with initial placement of metal stents saved $1453 in total costs over a lifetime ($304,151 vs. $305,605) when compared with patients with initial plastic stent placement. Model results also

Table 2 Model cost and utility estimates

Parameter	Estimate[a]	Sensitivity analysis range	Unit	Source
Costs				
Pancreatic cancer				
Locally advanced	$12,338	$9509–$14,609	Month (initial 3 months)	Krzyzanowska et al. [17]
	$2348	$1809–$2780	Month (length of time depends on survival)	
	$7611	$5866–$9012	Month (final 3 months)	
Metastatic	$27,076	$20,867–$32,060	Month	O'Neil et al. [19]
ERCP Procedure (initial)				
Metal stent	$6757	$5207–$8000	Event	Boston Scientific Corp. [5]
Plastic stent	$6757	$5207–$8000	Event	
ERCP procedure (subsequent)[b]				
Metal stent	$3635	$2801–$4304	Event	Boston Scientific Corp. [5]
Plastic stent	$3635	$2801–$4304	Event	
ERCP complications				
Cholecystitis	$4549	$3506–$5387	Event	Riall et al. [22]
GI bleeding	$3975	$3063–$4706	Event	Perry et al. [20], HCUP NIS [12]
Pancreatitis[c]	$12,353	$9521–$14,627	Hospitalization	Fagenholz et al. [10]
Cholangitis	$9723	$7494–$11,513	Event	Chen et al. [7]
Utilities				
Pancreatic cancer	0.61		Month	Heiberg et al. [13]
ERCP procedure	0.18		Event[d]	Jeurnink et al. [15]
ERCP complications	–0.04		Event[e]	Howard et al. [14]
Cholangitis	–0.04		Event[e]	Howard et al. [14]

[a] In 2012 dollars

[c] Migrated and occluded stents assumed to incur equivalent costs as subsequent ERCP procedure costs

[d] Mean length of stay reported was 5.9 days

[e] Utility decreased to 0.18 for 3 days

[f] Utility decreased by 0.04 for 2 weeks

Table 3 Base-case results

	Cost	Quality-adjusted life months	ICER ($/QALY)	Stents (no. per patient)	Patients requiring 2nd stent (%)	Median patency of 1st stent (months)
Metal stents	$304,151	12.27	Plastic stents dominated[a] by metal stents	1.37	28.0	10
Plastic stents	$305,605	11.96		2.82	88.5	3
Δ	($1453)[b]	0.32		1.45	60.5	7

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *Δ* difference between plastic and metal biliary stents

[a] Dominated refers to a treatment being both less costly and producing greater quality of life for the population and time horizon modeled

[b] Cost saving

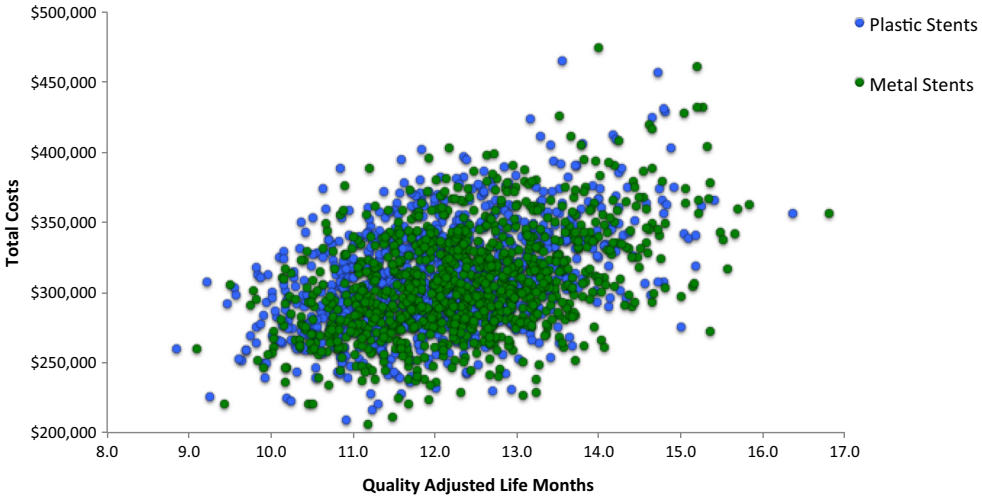

Fig. 2 Probabilistic sensitivity analysis: cost-effectiveness scatter plot. *Blue dots* represent costs and quality-adjusted life months for patients receiving plastic stents when all parameters are varied simultaneously for 1000 model iterations; *green dots* represent results for patients receiving metal stents

found that initial use of metal stents resulted in 0.3 months greater quality-adjusted life months (12.3 vs. 12.0 months) (Table 3).

Initial use of metal biliary stents reduced the number of patients requiring a subsequent stent by 61% (28 vs. 89%), and resulted in half the number of stents placed per patient over a patient's lifetime (1.4 vs. 2.8). The median length of initial stent patency was 10 months for patients with metal stents, compared to only 3 months for those with upfront plastic stent placement (Table 3).

In one-way sensitivity analyses, the finding of increased QALYs when using metal stents remained, when varying any of the 64 model parameters. In 58 (91% of all parameters) of these iterations, metal biliary stent placement also resulted in cost savings compared with initial plastic stent placement. In the remaining 6 iterations (reduced plastic stent cost, decreased likelihood of pancreatitis among plastic stent patients; increased survival among PC patients, and increased mortality associated with stent placement complications; all relative to the base case analysis), initial metal stent placement resulted in ICERs of <$200,000/QALY, implying that regardless of the analysis considered, metal stents provided at least acceptable value for money. Notably, many analyses suggest cost savings.

In probabilistic sensitivity analysis, initial placement of metal biliary stents resulted in greater quality-adjusted life than plastic stents in all iterations. In 76.5% of the iterations, metal stents also reduced costs. In 22.0% of iterations, the ICER was below $100,000/QALY, and in the remaining 1.5%, the ICER ranged from $100,000–$240,000/QALY (Fig. 2).

Threshold analyses were conducted to assess the values at which changing the following parameters resulted in metal biliary stents no longer dominating plastic stents: ERCP complication mortality rate; cholangitis mortality rate; metastatic PC survival; and plastic stent occlusion rate. In such analyses, we found that plastic stents were no longer dominated when median overall survival (OS) for patients with plastic stents was reduced relative to patients with metal stents, as that caused the treatment costs to decrease to the point where plastic stents were less expensive. This occurred under the following conditions:

- ERCP complication mortality increased from 1 to 1.5%,
- Cholangitis mortality increased from 14 to 19%,
- Median metastatic OS increased from 11.1 to 12.7 months
- Plastic stent occlusion rate increased from ~2.5 to 4.5%.

Discussion

Currently, both metal and plastic biliary stents are placed in locally advanced and metastatic pancreatic cancer patients presenting with obstructive jaundice. The choice of stent may be determined by expected survival and clinician preference. Historically, plastic stents had a role in relieving jaundice in this patient population due to short OS times and poor prognosis; however, the development of more efficacious treatments has prolonged expected survival, and with the development of newer molecularly targeted agents is expected to continue to improve. In light of recent advances and the increasing prevalence of 'value-based' purchasing and care delivery, an examination of the cost effectiveness of these treatments is warranted.

This analysis—to the best of our knowledge is the first to use survival data reflective of more modern chemotherapy regimens currently in use, e.g., FOLFIRINOX and gemcitabine/nab-paclitaxel—shows that use of metal biliary stents provides benefits in extending patency time and reducing rates of stent occlusion. Our model found that metal stent placement may also potentially lower costs compared to

plastic stents, when used to relieve obstructive jaundice in patients with locally advanced and metastatic PC. These results indicate that use of metal stents is likely more cost effective.

Results of this analysis should be considered in light of some limitations. The most significant source of uncertainty was in parameter estimation. When identifying potential model inputs in the literature, values across studies varied by patient population, type of biliary stent used, health status, and care delivery setting (e.g., inpatient, outpatient, and geography). To select inputs most applicable to the model's patient population, clinical opinion was incorporated in choosing sources, and estimates were varied in sensitivity analyses. Model inputs were based on a targeted literature search tested by clinical opinion, as opposed to a full meta-analysis. To the extent that not all published literature was considered in generating estimates, selection biases could arise. To address uncertainty in the model, all inputs in the model were varied, and the impact of uncertainty on results was assessed. Results were most sensitive to the length of metastatic cancer survival and complication mortality. However, the low amount of variation throughout the sensitivity analyses indicated that conclusions are robust despite data limitations. Additionally, costs were estimated from US sources, and to the extent that these differ among settings or costs significantly changed since 2012, results could be impacted. Finally, univariate sensitivity analysis suggests that longer patient base survival further strengthens the cost savings for metal stents. Put differently, as advancement in treatments in the future will continue to positively impact on OS while still requiring treatments for obstructive jaundice, the argument favoring metal biliary stents is further enhanced.

Structural changes underway in the healthcare system such as accountable care organizations and bundled payments have begun to make hospitals share with payers some of the financial risk of providing healthcare [9]. Thus, for these organizations, the suggested savings with metal stent placement will also be meaningful. Depending on these organizations' degree of risk sharing, their cost savings may be as low as $1453 (payer perspective), as may be the case for those organizations that have integrated the insurance and provision of healthcare.

Due to limited patency and risks of complications, an important consideration when deciding on what type of biliary stent to place in a particular patient is their expected overall survival: given the terminal nature of locally advanced and metastatic pancreatic cancer, clinicians and patients alike prefer to minimize the number of clinical encounters required. The use of metal stents better accomplishes this aim of minimizing additional office visits by reducing stent replacements and their related complications.

Cost-effectiveness analysis can highlight opportunities to improve efficiency in the health care system by identifying interventions that improve health at a reasonable cost. However, cost effectiveness is one of several factors to be considered in allocating resources. Other factors, such as patient preference, tolerability, equity, and affordability should also be included in the decision-making process. However, in those rare cases where one product both improves health outcomes and reduces costs, it becomes clear that the cost saving and benefit-enhancing intervention should be strongly considered.

Conclusions

Results of this analysis demonstrate that placement of metal rather than plastic biliary stents at onset of obstructive jaundice in patients with locally advanced pancreatic carcinoma reduces the need for stent replacement, may improve overall and quality-adjusted survival, and could be cost saving for payers and hospitals. These are important considerations for providers and policy makers.

Compliance with Ethical Standards

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Conflict of Interest Authors MC and LM are current and former employees of Boston Scientific Corporation, respectively. Authors MC and LM also own stock in the Company. Authors AA, TB, and JO are employees of a consultancy funded by Boston Scientific Corporation for the purposes of this study. All other authors declare that they have no conflict of interest.

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