Cost-Effectiveness Decision Analyses Comparing Covered To Uncovered Self-Expandable Metal Stents To Elective Or On-Demand Polyethylene Stent Changes In Patients With Distal Malignant Biliary Obstruction.

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Acknowledgements

Firmly believing there is no truly independent effort, I am beholden to individuals of three groups for this accomplishment.

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ABSTRACT

INTRODUCTION: Endoscopic placement of stents is the preferred treatment for palliation of obstructive symptoms in non-operative candidates but significant differences in procedure and stent-related costs, patency of stents survival of patients exist. **AIM**: To determine the cost-effectiveness of two strategies using Polyethylene (PE) stents (PE with replacement on demand; PE with routine exchange every 3 months), as well as uncovered (U-SEMS) and covered self-expandable metal stent (C-SEMS) in the management of distal malignant biliary obstruction. **METHODS**: A Markov model comparing four different initial approaches was designed: 1) PE stent with replacement on demand (PE-D); 2) PE stent changed every 3 months (PE-Q3); 3) U-SEMS or 4) C-SEMS. Probabilities and parameters for distribution were abstracted from randomized controlled trials and imputed to a 12-month time horizon. Effectiveness was calculated as number of occlusion-free months. Procedural and complication-related costs were obtained from the Canadian Institute for Health Information and a Provincial perspective was adopted. A probabilistic cost-effectiveness analysis using Monte Carlo simulations was utilized to obtain a posterior joint distribution for costs and effectiveness. Average and incremental net health benefits, probabilities of cost-effectiveness and value of information were determined across a range of willingness to pay (Rc) values. **RESULTS**: PE-D has the lowest CE ratio, followed by C-SEMS at an incremental cost-effectiveness ratio (ICER) of 146.64/month of stent patency. C-SEMS has the lowest CE ratio under the following scenarios: probability of survival at 12 months greater than 83%, ERCP costs higher than $1,282.90, cost C-SEMS less than $1,485.60 and cost ratio between ERCP and C-SEMS greater than 0.4 . In the probabilistic analysis, PE-D is the strategy with the highest probability of cost-effectiveness for willingness to pay values lower than $150.60. However, C-SEMS is the most cost-effective strategy for all Rc values yielding positive mean net health benefit (NHB). The maximum probability of cost-effectiveness for C-SEMS is 64% and consequently, there is a 36% chance C-SEMS will provide lower amount of NHB than PE-D and U-SEMS. PE-Q3 was a dominated

strategy in our model. The uncertainty about the most CE strategy and the subsequent selection of suboptimal strategies in 36% of the time will lead to opportunity losses for the Canadian Health System ranging from $1.2 million to $3.0 million dollars/per month of stent patency over the next 5 to 20 years.

CONCLUSION: Conditional to the willingness to pay and current Canadian costs, PE-D and C-SEMS are the strategies with the highest probabilities of cost-effectiveness. However, a significant level of uncertainly remains and wrong decisions will occur given the existent information. Acquisition of further knowledge to decrease the uncertainty level may be indicated if it costs less than the opportunity losses.

INTRODUCTION:

La prothèse endoscopique est le traitement palliatif de choix chez les patients non opérables, souffrant de symptômes dus à une obstruction biliaire maligne. Cependant, il existe des différences importantes parmi les maintes stratégies de prise en charge, entre les coûts des différentes prothèses, ainsi que leurs durées de perméabilité.

BUT : De déterminer la coût-efficacité de deux stratégies utilisant une pose de prothèses en polyéthylène (PE) – avec un échange de prothèse au besoin (PE-D) ou aux 3 mois (PE-Q3), ou une pose de prothèses métallique expansible non couverte (U-SEMS) , ou couverte (C-SEMS) dans la prise en charge de patients avec une obstruction biliaire maligne distale.

MÉTHODES : Un modèle de type Markov comparant quatre approches initiales a été construit : 1) pose de prothèse en PE avec échange au besoin (PE-D), 2) même pose, mais avec échange aux 3 mois (PE-Q#), 3) pose de prothèse de type U-SEMS, ou 4) C-SEMS. Toutes les probabilités et paramètres de distribution ont été puisés d'études randomisés avec groupe contrôle et imputés sur une durée d'étude de 12 mois. L'efficacité fut calculée en nombre de mois écoulés sans occlusion de prothèse. Les coûts reliés aux gestes et aux complications furent obtenus du Canadian Institute for Health Information, en adoptant une perspective de payeur de tiers-parti. Une analyse de coût-efficacité de type utilisant des simulations de type Monte-Carlo a été complétée dans le but d'obtenir les estimations de distributions jointes postérieures pour les coûts et l'efficacité. Les « net health benefits » (NHB) moyens et marginaux ainsi que les probabilités de coût-efficacité et de valeur de l'information furent établis pour une fourchette de valeurs « willingness-to-pay » (Rc).

RESULTATS: L'approche PE-D a le rapport coût-efficacité le lus bas, suivi de celle utilisant une prothèse C-SEMS pour un rapport coût-efficacité marginale de $146.64 par mois de perméabilité de prothèse. La stratégie C-SEMS a le rapport coût-efficacité le plus bas en adoptant les scénarios suivants : probabilité de survie du patient de plus de 12 mois supérieure à 83%, les coûts de CPRE sont plus que $1,282.90, le coût d'une prothèse de type C-SEMS est moins que $1,485.60, et le rapport de coût CPRE - C / SEMS est plus que 0.4. Avec l'analyse probabilistique, l'approche PE-D est la stratégie

avec la plus grande probabilité d'être coût-efficace pour une valeur de « willingness-to-pay » inférieure à $150.60. Cependant, l'approche C-SEMS est la stratégie la plus coût-efficace pour toutes les valeurs Rc menant à un « net health benefit » moyen positif. La probabilité maximale de coût-efficacité pour la C-SEMS est de 64%, et conséquemment, il y a 36% de chances que celle-ci soit associée à un NHB inférieur que celui obtenu avec une approche PE-D et C-SEMS. La stratégie PE-Q3 fut dominée dans notre modèle. L'incertitude à propos de la stratégie la plus coût-efficace et le choix conséquent de stratégies sous-optimales 36% des fois mènent à des pertes d'opportunité pour le système canadien de santé variant entre $1,2 million et $3 millions de dollars par mois de prothèse perméable lors des prochaines 15 à 20 années.

CONCLUSION: En fonction de la « willingness-to-pay » et des coûts canadiens actuels, les approches PE-D et C-SEMS sont les stratégies associés avec les probabilités les plus grandes d'être coût-efficaces. Cependant, il demeure une incertitude appréciable et de mauvaises décisions seront prises basés sur les informations contemporaines. L'acquisition d'informations supplémentaires pour diminuer le niveau d'incertitude pourrait être indiquée si les coûts de celle-ci sont moins élevés que les coûts d'opportunité.

1 INTRODUCTION

1.1 Structure of the thesis

This thesis is divided into six chapters. The first chapter is a brief introduction to the pathophysiology, causes and clinical importance of biliary obstruction, available treatment options and an overview of the economic dilemma between the different endoscopic therapies used for palliation of obstruction in unresectable patients. Chapter 2 is dedicated to the literature review. First, a detailed discussion about the most common diseases causing malignant biliary obstruction is undertaken. A thorough examination of the curative and palliative treatments is provided, with emphasis on the endoscopic placement of plastic and metal stents and maneuvers which have been used to improve their efficacy. Second, an overview on the current knowledge in economic evaluations of biliary stents is provided. The background and stepping stone for this review are the studies by Arguedas and Yeoh [1, 2]. The chapter ends with an introduction to decision modelling and statistical methods used in cost-effectiveness analysis (CEA). It involves a description of decision and Markov modelling, notions about economic evaluations in health care interventions, and a comparison between deterministic and probabilistic CEA. Chapter 3 introduces the methods used to estimate the parameters entered in the decision model and the procedures utilized to handle uncertainty with emphasis to Bayesian approaches to CEA [3]. Chapter 4 contains the results for the CEA, presented from both deterministic and probabilistic perspectives. The output from the probabilistic analysis is also used for statistical inference and estimation of the expected amount of losses due to selection of wrong strategies. In Chaper 5, a discussion of the results is placed in context considering the existing economic evaluations in malignant biliary obstruction. A balance between the positive and negative aspects of the current investigation is given and the chapter finishes with the author's perspective of research in the area for the following years. In the last chapter, a summarized conclusion of the study is provided along with recommendations based on the results obtained in this investigation.

1.2 Biliary obstruction

Bile is an important vehicle of excretion of toxic substances and products of normal metabolism. If excretion is impaired, retention of bile salts and other normal bile constituents such as bilirubin and cholesterol occurs (cholesthasis). The reflux of bile in the systemic circulation and the decreased amount of bile salts reaching the intestine have systemic toxic effects and are associated with a wide spectrum of clinical manifestations such as jaundice, pruritus, malabsorption, hemodynamic and immunologic changes and renal dysfunction [4-6]. Bile exerts an important role in the digestion of lipids by promoting micellar formation and as an immunologic mediator by transporting immunoglobulin A into the intestine [7]. For instance, the decreased excretion of bile salts into the intestine to a level below those required for normal lipid digestion causes steatorrhea and fat-soluble vitamin malabsorption. Jaundice will result from the retention of bilirubin and the defective excretion of cholesterol may precipitate hematologic and skin abnormalities. These complications, which depend on the accumulation of bile in the vascular compartment and depletion in the small intestine, are more frequently seen in subacute conditions such as malignancies of the biliary and pancreatic systems as they usually evolve over an extended period of time. Obstruction of the biliary tree also promotes bile stasis and colonization of the bile by bacteria emanating from a physiologic duodenal-biliary reflux. Consequently the high-pressure zone in the biliary tree facilitates the introduction of contaminated bile into the systemic circulation and therefore increases the risk of an infectious process [8]. Lastly, obstruction of the orifices for the pancreatic and cystic duct can be simultaneously occluded and lead, rarely, to the development of pancreatitis and cholecystitis respectively. Reestablishment of the normal bile flow is necessary in order to prevent the short and long term complications associated with obstruction. Figure 1.1 illustrates the potential complications of biliary obstruction and its consequences.

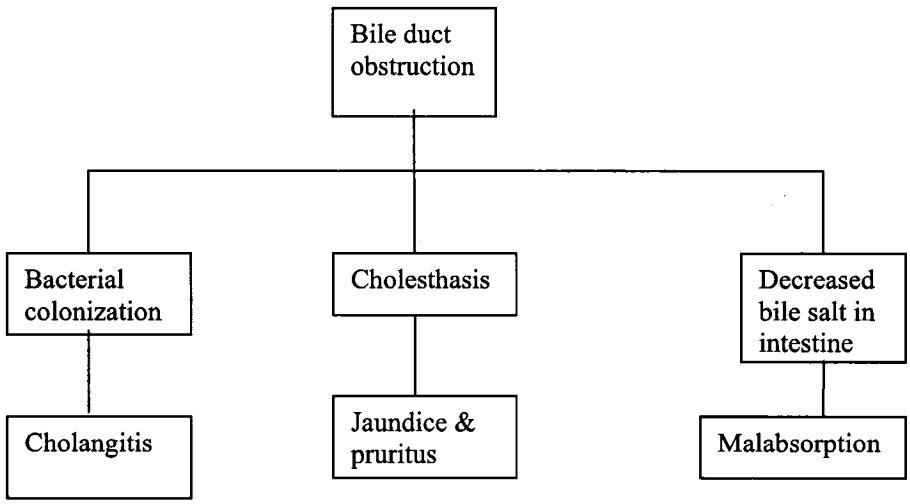

Figure 1.1 Schematic representation of complications of biliary obstruction.

The causes of cholesthasis can be broadly divided into intra and extra-hepatic. While intra-hepatic cholestasis includes processes affecting liver cells or the transport of bile into the biliary tree, extra-hepatic cholestasis refers to disorders in which the normal bile output exceeds the capacity of the biliary system to deliver bile into the intestine. Stones in the common bile duct (CBD), either due to migration from the gallbladder or much more uncommonly 'de novo' formation within the bile ducts (choledocolithiasis), are by far the most common extra-hepatic cause of biliary obstruction in western countries. This process is often acute and intermittent in nature and infrequently leads to complete bile flow obstruction. Therefore complications of cholestasis observed in subacute processes are not commonly seen in these benign scenarios and the need to intervene is driven by the acute symptoms and the presence of acute infection or biliary pancreatitis [9]. By comparison, malignant diseases have a more insidious onset and are usually diagnosed only after the tumor has invaded or obstructed the biliary tree. Because complete obstruction and the cholestatic symptoms tend to occur only at later stages of disease, these malignancies usually have a dismal prognosis when diagnosed at the symptomatic stage, which is unfortunately most often the case. The most common causes of malignant biliary obstruction are tumors originating from of the head of the pancreas, biliary system

and Ampulla of Vater and they tend to involve the biliary system at its most distal portion where the main bile duct approaches the duodenum. However, primary cancers of the liver and the biliary system as well as tumors from outside the gastrointestinal tract can also obstruct the bile ducts at more proximal locations. Regardless of etiology, location and duration of obstruction, the occurrence of cholestasis in association with extra-hepatic obstruction is conditional upon the impairment of bile flow into the intestine and its consequent accumulation of bile components in the blood (Figure 1.2) . In contrast, diseases involving isolated segments of the intrahepatic biliary tree or producing intermittent bile flow obstruction are unlikely to lead to cholestasis unless concomitant intrinsic and significant liver disease or involvement of the common bile duct exists.

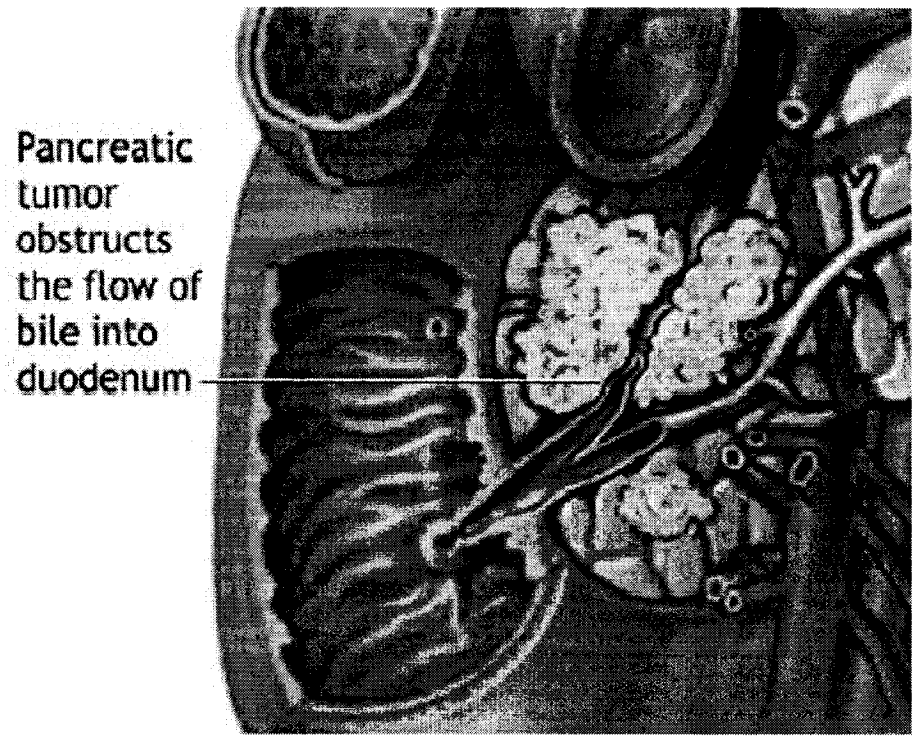

Figure 1.2 Distal biliary malignant obstruction.

1.3 Treatment

Management of patients with distal malignant biliary obstruction is a subject of substantial controversy and usually requires the involvement of a wide variety of specialists including gastroenterologists, radiologists, surgeons and oncologists. While a number of methods for palliation of obstruction exist, cure can only be achieved if surgical resection is performed at early stages of disease. Unfortunately, the natural history of pancreatic and biliary malignancies is such that they tend to become clinically apparent only when the disease is either widespread or has locally invaded vascular structures, precluding curative surgical procedures [10, 11]. In the majority of cases, patients are deemed not curable at the time of diagnosis or are not suitable to undergo a surgical curative procedure, and palliative treatment of the biliary obstruction is indicated. While re-establishment of the normal bile flow has no impact on survival [12], it has been shown to prevent complications related to the long-term obstruction and to improve quality of life in some patients [13-15].

Surgical, radiological and endoscopic approaches have been extensively utilized in the management of patients with non-resectable tumors causing distal malignant biliary obstruction. Although very effective in relieving obstruction and preventing reocclusion due to direct tumor invasion, surgical biliary bypass (e.g. hepatojejunostomy) is associated with a high rate of complications, a long hospital stay and consequently high costs [16-19]. Percutaneous insertion of plastic and metallic stents is also effective in the palliation of malignant obstruction, especially in the presence of dilated intra-hepatic radicals. Although still used preferentially in some centers highly specialized in radiological procedures, percutaneous transhepatic cholangiographic (PTC) carries a higher complication rate and 30-day mortality when compared to the endoscopic approach [20]. Insertion of plastic and metallic prostheses during endoscopic retrograde cholangiopancreatography (ERCP) is currently the procedure of choice for the management of distal biliary malignant obstructions, given its lower invasiveness and complication rates compared to other methods (Figure 1.3). Therefore, in centers where endoscopic expertise is available, PTC or combined endoscopic and radiological

approaches (rendez-vous technique) are reserved for endoscopic failures [21, 22].

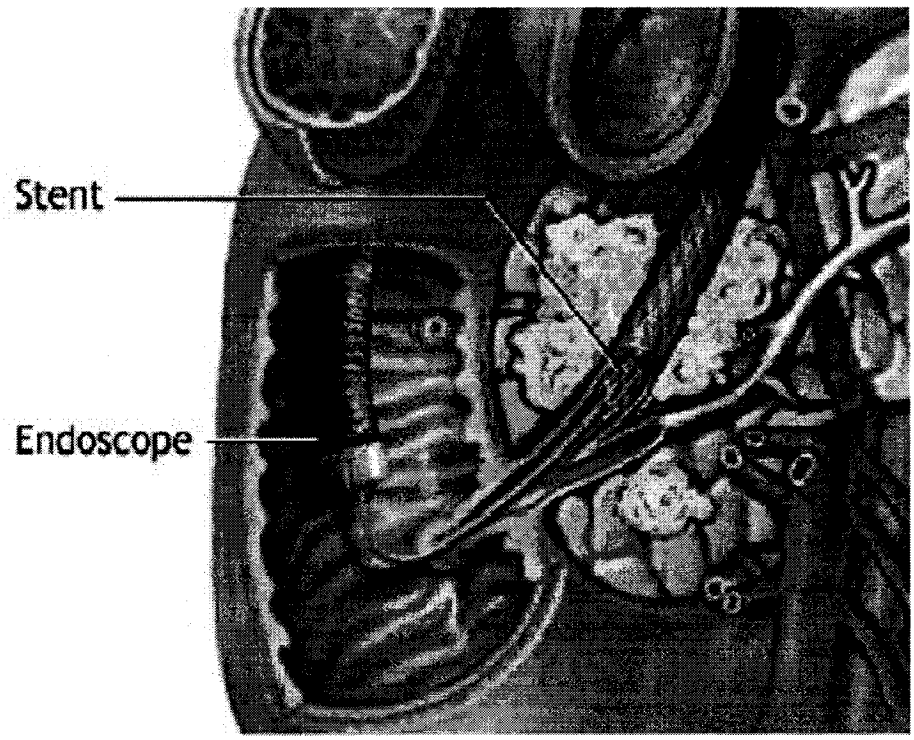

Figure 1.3 Endoscopic management of distal biliary malignant obstruction.

1.4 Research problems and objectives

Indications for palliative treatment and the choice of procedure to be utilized are well established. However the decision about the type of prosthesis to be inserted during ERCP is still subject to debate. A large number of endoprostheses are commercially available under different brand names that can be separated in two main categories: a) Plastic polyethylene (PE) stents, b) and self-expandable metal stents (SEMS), which can be either uncovered (U-SEMS) or covered (C-SEMS). All three stent types have been shown to be effective in the relief of obstruction and re-establishing patency of the biliary

tree but they differ in several aspects including physical characteristics, price, and average duration of patency [23-25].

The PE stent was the first method of endoscopic internal drainage to be utilized and became the treatment of choice for patients with unresectable malignant biliary obstruction [26] (Figure 1.4). PE stents have the advantage of being inexpensive and exchangeable should occlusion occur [26]. The main disadvantage is its duration of patency, which is frequently shorter than the patient's life expectancy [27, 28]. Because stent dysfunction occurs on average after 3-4 months and a significant proportion of patients survive beyond this period of time, stent exchange is needed in approximately 30 to 60% [19, 25]. Consequently, patients are at risk of experiencing recurrent jaundice due to stent obstruction and may require a repeated procedure and stent replacement [29]. Plastic stents get clogged by biliary sludge, a material which has no similarities with the sludge implicated in the pathogenesis of gallbladder stones. In contrast to gallbladder sludge, stent sludge is comprised primarily of protein, bilirubin, crystals and has almost no cholesterol within it [30]. The protein found in the obstructed stent is of unknown origin but it has been postulated to arise from bacterial products, given that stents perfused with sterile bile seem to not accumulate sludge [31]. Defects in the manufacturing of plastic biliary stents such as irregular inner surface and badly constructed side holes have been hypothesized to facilitate bacterial colonization and consequently may accelerate the time to occlusion [32, 33]. Bacteria are usually not present in the biliary tract of healthy individuals owing to their clearance by the constant flow of bile (800 – 1000 milliliters per day), and the presence of anatomical barriers (the sphincter of Oddi, and mucus produced by the biliary mucosa). When bacteria are allowed to reflux up the endoprosthesis, as the distal tip is positioned in the duodenal lumen, bacterial enzymes such as beta glucoronidases degrade bilirubin glucoronides and liberate glucuronic acid and bilirubinate which is precipitated into a bacterial glycocalyx. The bacteria themselves attach to the stent surface and multiply within the formed glycocalyx, subsequently forming a biofilm. This biofilm permits the bacteria to adhere firmly to the stent despite the shearing forces created by the bile flow. Continuous deposition of bacterial degradation products and growth of bacterial colonies eventually lead to complete occlusion of the stent [30, 34].

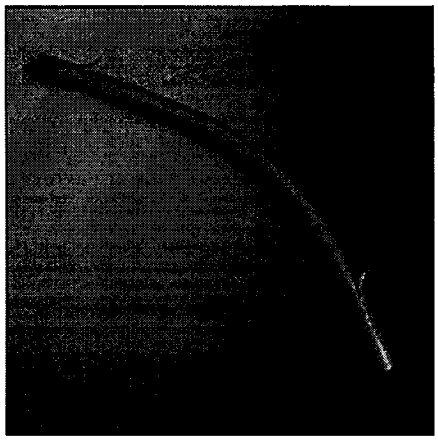

Figure 1.4 Polyethylene (PE) stent
(Cotton-Leung® Biliary Stent, Cook)

The problems associated with PE stent dysfunction were at least partially overcome with the advent of U-SEMS. Once fully deployed, U-SEMS reaches an internal diameter approximately 3 times bigger than PE stents, and is less likely to be clogged by bile plugs and biofilm [23]. Instead, U-SEMS are rather obstructed by tumor ingrowth and outgrowth which occurs on average 8-9 months after placement [35-37]. The lower obstruction rate of U-SEMS is advantageous since its median patency is not only longer than PE stents but also exceeds the average median survival time of patients with malignant biliary obstruction. The extended patency of U-SEMS is associated with several benefits including: 1) a better quality of life for patients not only because of avoidance of unnecessary procedures but also due to increased symptom-free period [13-15]; 2) improved survival because it could prevent life-threatening conditions such as acute cholangitis and procedure-related complications [38]; 3) lower costs because of avoidance of repeated ERCP.

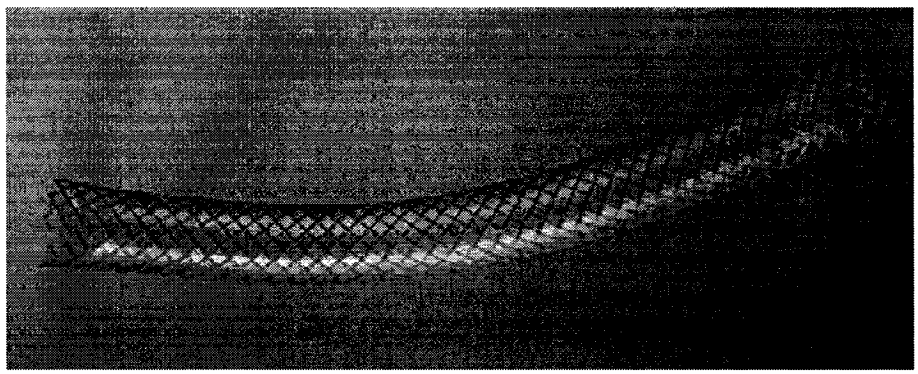

Figure 1.5 Covered SEMS (Wallstent® - Boston Scientific)

Covered SEMS (Figure 1.5) are currently available in the US and Canada. While both SEMS are built in a similar manner and achieve the same diameter when fully deployed, C-SEMS differs from the uncovered in that there is a Permalume membrane positioned over the alloy mesh. This property confers a theoretical advantage of prolonging patency by decreasing obstruction from tumor ingrowth. Initial experience with C-SEMS demonstrated improvement in the duration of stent patency but possibly also an unexpected greater complication rate attributed to migration, cholecystitis and pancreatitis [39, 40]. Regardless, the superior effectiveness of both SEMS is offset by significant higher up-front costs compared to PE stents. In addition, considering the overall poor life expectancy of patients with distal malignant biliary obstruction, a significant proportion of these patients can be successfully managed with a single PE stent because they will not survive long enough to benefit from SEMS. Use of a more expensive and efficient stent such as U-SEMS or C-SEMS would be advantageous in patients at high risk of developing stent obstruction as it would prevent additional costs and risks of complication associated with repetitive procedures. Undoubtedly, the risk of obstruction is associated with patient survival since:

$$\text{Risk} = 1 - e^{[-(\text{mean number of events/time})*(\text{length of observation})]} \quad [41]$$

Thus, for any given rate of stent patency, risk of stent occlusion rises monotonically with patients' survival. Therefore, patients with longer life expectancy are at higher risk of

experiencing an episode of PE stent occlusion and would be better managed with SEMS. In contrast, use of SEMS in patients at low-risk of experiencing an episode of stent occlusion would be undesirable since similar health benefits could be obtained at much lower cost with PE stents. Consequently, PE stent have been advocated for patients expected to survive less than 4-6 months [1, 2]. Nonetheless, the accurate prediction of a patient's survival is difficult and imprecise. Clinical parameters such as size of the tumor, presence of metastasis and baseline functional capacity have been associated with a shorter life expectancy in patients with malignant biliary obstruction, but survival cannot be predicted entirely based on these factors. In fact, survival is a function of many parameters and *a priori* estimation remains poor [42-44].

Although the literature demonstrates that SEMS have a longer duration of patency compared to PE stents, economic evaluations performed in clinical trials have been controversial as costs of each strategy vary significantly according to average patient survival [35, 45]. Insertion of a U-SEMS is associated with higher initial costs when compared to PE stents but it becomes more advantageous from the economic perspective as a patient's survival increases, because the average number of ERCP's in patients treated with U-SEMS is lower than in PE stents. However the exact time when U-SEMS becomes more cost-effective than PE is not fixed and varies according to local costs and practice [2]. The current standard approach for PE stent replacement at the time of occlusion has not been validated from an economic standpoint. The alternative approach of routine exchange of PE stents may indeed be more attractive if the additional risks and costs of a stent blockage surpass the costs attributed to the extra number of procedures. Moreover, there has been no economic evaluation performed with C-SEMS, which seems to have a longer patency than U-SEMS and PE stents. Finally, the cost-effectiveness analyses in the literature reflect the US relative costs and cannot be generalized to Canada.

Using a decision model, we propose a cost-effectiveness analyses to compare four different strategies in patients with distal malignant non-resectable biliary obstruction initially treated with one of the following types of stent: 1) Polyethylene (PE) stent with exchange on demand (PE-D); 2) PE stent with exchange every 3 months (PE-Q3); 3)

Uncovered SEMS (U-SEMS) and; 4) Covered SEMS (C-SEMS). The decision model is shown in Figure 1.6.

The objectives of this study are to: 1) obtain cost-effectiveness values for each one of the strategies in the model under different clinical scenarios in order to determine the most cost-effective strategy in comparison to its alternatives; 2) estimate the total resources utilized per year for each strategy as well as the resources saved by selecting the most cost-effective strategy; 3) determine parameters that are more likely to affect the result of the CEA. Delineate their magnitude of change that could potentially modify the end results of the decision analysis; 4) identify areas in the model where data are scarce and further studies needed.

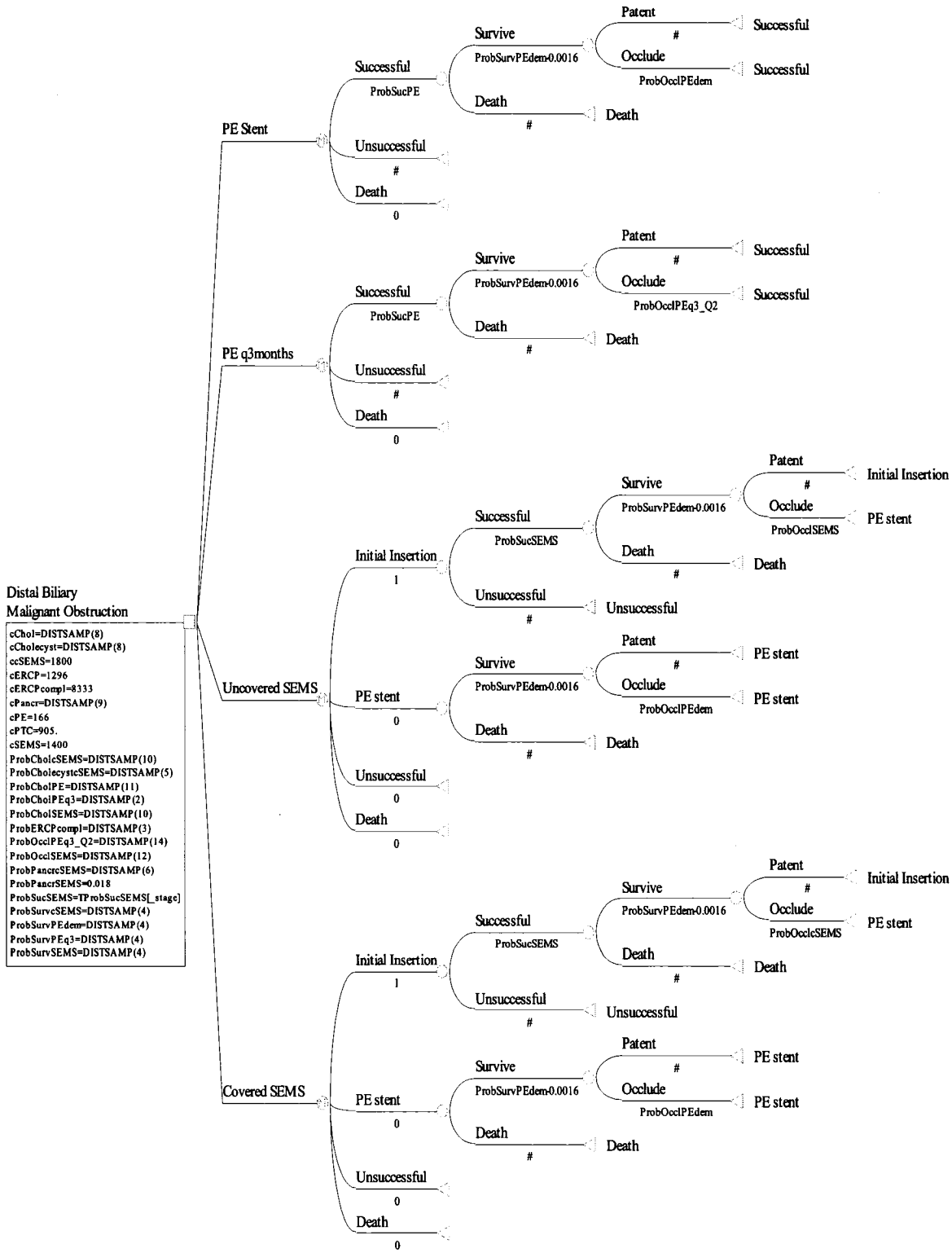

Figure 1.6 Cost-effectiveness decision tree

cChol: cost of of cholangitis; cCholecyst: cost of cholecystitis; ccSEMS: cost of covered SEMS; cERCP: cost of ERCP; cERCPcompl: cost of ERCP complication; cPancr: cost of pancreatitis; cPE: cost of PE stent; cPTC: cost of PTC; cSEMS: cost uncovered SEMS; ProbCholcSEMS: probability of cholangitis with covered SEMS; ProbCholecystcSEMS: 2-month probability of cholecystitis with covered SEMS; ProbCholPE: probability of cholangitis given obstruction of PE stent with replacement on demand; ProbCholPEq3: probability of cholangitis given obstruction of PE stent with routine exchange every 3 months; ProbCholSEMS: probability of cholangitis given obstruction of uncovered SEMS; ProbERCPcompl: probability of procedure-related ERCP complication (cholangitis, pancreatitis, hemorrhage, perforation and cardiorespiratory disorders); ProbOcclcSEMS: 2-month probability of occlusion of covered SEMS; ProbOcclPEdem: 2-month probability of occlusion of PE stent with replacement on demand; ProbOcclPEq3_Q2: 2-month probability of occlusion of PE stent with routine exchange every 3 months; ProbOcclSEMS: 2-month probability of occlusion of uncovered SEMS; ProbPancrcSEMS: probability of pancreatitis in patients with covered SEMS; ProbPancrSEMS: probability of pancreatitis in patients with uncovered SEMS; ProbSucPE: probability of successful insertion of a PE stent; ProbSucSEMS: probability of successful insertion of either uncovered or covered SEMS; ProbSurvPEdem: 2-month probability of survival

2 LITERATURE REVIEW

2.1 Epidemiology

Malignancies of the biliary and pancreatic systems are not unusual; together they are among the 10 most incident cancers in North America and Europe [46]. It is estimated that more than 31,000 new cases of pancreatic cancer will occur in the US in 2004 [46, 47]. While the incidence of pancreatic cancer has remained stable over the last 25 years, the epidemiology of cholangiocarcinoma has changed [11, 47, 48]. Incidence of intra-hepatic cholangiocarcinoma seems to be rising and the extra-hepatic to be dropping, but the reasons for such change in pattern are not known [47]. Because these cancers are usually diagnosed at advanced stages when the probability of cure is very low, the mortality rate is very high [11]. Consequently pancreatic cancer ranks as the 5th most lethal cancer in the US, and second as cause of digestive cancer-related death, only behind colon cancer [46]. The incidence of pancreatic and biliary malignancies increases with age and consequently these tumors are rarely seen before the age of 45. Epidemiological surveys have shown that median age of diagnosis is around 70 years. Exceptions are genetically predisposed individuals, and those with chronic pre-malignant conditions such as primary sclerosing cholangitis [47].

Pancreatic cancer is more common in males, blacks and Jewish people [49]. Diabetes, chronic pancreatitis, pernicious anemia, inherited disorders such as familial adenomatous polyposis, and high fat and meat intake are postulated as risk factors for pancreatic cancer [49]. A populational case-control study performed in Montréal showed that patients with pancreatic cancer were more likely to be smokers than controls but no association with either caffeine or alcohol intake was found [50]. Although rare and confined to clusters of families, genetic disorders such as hereditary pancreatitis and familial pancreatic cancer have also been linked to pancreatic cancer; individuals with these conditions appear to have a 40% lifetime risk of malignant transformation [51].

The majority of cases of cholangiocarcinoma have no underlying etiology. However,

a number of risk factors have been implicated in its development; most factors share long standing inflammation and chronic injury of the biliary epithelium. Primary sclerosing cholangitis is an uncommon disease, more commonly seen in middle aged males. It is characterized by stricturing, fibrosis and inflammation of the biliary tree, and is closely associated with inflammatory bowel disease, particularly ulcerative colitis. Approximately 10-20% of patients with primary sclerosing cholangitis will develop cholangiocarcinoma. The rare congenital fibropolycystic diseases of the biliary system are associated with increased risks of cholangiocarcinoma, particularly choledochal cysts and Caroli's disease. Choledochal cysts are associated with a 10% lifetime incidence of cholangiocarcinoma: there is a 1% per year risk which plateaus after 15-20 years [52]. In the Far East, other forms of chronic inflammation associated with cholangiocarcinoma include infestation with the liver flukes Clonorchis sinensis and Opisthorchis viverinni. Cholangiocarcinoma is also rarely seen in association with cirrhosis and has been weakly linked to hepatitis C infection [53, 54].

Among neoplasms involving the biliary tree, carcinoma of the gallbladder has the poorest prognosis with a 5-year survival ranging between 0% and 10% in most reported series [55]. Gallbladder cancer is the most incident malignant lesion of the biliary tract, and the fifth most common among malignant neoplasms of the digestive tract. It affects women two to six times more often than men, and the incidence increases with age [56]. Although its etiology is unknown, cholelithiasis is thought to be an important risk factor for gallbladder cancer [57, 58]. Other risks factors such as porcelain gallbladder, gallbladder polyps, anomalous pancreatobiliary junction and obesity have been suggested in epidemiological studies [58-60].

2.2 Natural history

Although not always present, obstruction of the distal common bile duct (CBD) occurs during the natural evolution of most of these tumors 0depending on their location and behavior [12]. The most common malignancy causing distal biliary malignant obstruction is pancreatic cancer followed by gallbladder cancer, malignant

lymphadenopathy and cholangiocarcinoma, the latter being relatively uncommon in western countries [49, 61, 62]. Carcinoma of the ampulla of Vater can also obstruct the distal CBD and although rarely seen in otherwise healthy individuals, it is particularly common in patients with familial adenomatous polyposis. In fact, it is a leading cause of death in this population [63]. The most common pancreatic malignancy causing obstruction of the biliary tree is adenocarcinoma of the head of the pancreas, accounting for more than 90% of cases [46]. Gallbladder cancer and cholangiocarcinoma involving the distal CBD may present in a similar manner but represent just a small fraction of all cases. The overall prognosis of malignancies that cause biliary obstruction is dismal. Except for extrinsic compressions caused by enlarged lymph nodes in the case of hematological malignancies such as non-Hodgkin's lymphomas and for ampullary tumors, the majority of patients found with unresectable disease have a median survival of 3-5 months [10, 64].

2.3 Diagnosis

While histological confirmation is not always feasible, the diagnosis and management of biliary and pancreatic malignancies commonly relies upon imaging study results. Advances in radiology over the last decades have permitted better visualization of the biliary and pancreatic systems and consequently avoided unnecessary surgical procedures. There is no ideal diagnostic procedure for the evaluation of these malignancies. Transabdominal ultrasound is the method of choice to differentiate obstructive jaundice from other forms of cholesthasis . It is inexpensive and non-invasive, and its sensitivity and specificity are excellent in the presence of jaundice [65]. Helical Computer Tomography (CT) is the single most useful test because it can not only visualize the entire gland, but also assesses the existence of metastatic disease. Newer generation CT scanners can provide highly detailed, tri-dimensional images. Endoscopy ultrasound (EUS) offers the advantage of detecting small lesions, lymph nodes and regional vascular invasion often not detectable by other modalities while allowing for

tissue sampling during the same procedure [12, 66-68]. In the majority of cases, the combination of these modalities is sufficient to make an accurate diagnosis and staging. More invasive diagnostic procedures such as diagnostic laparoscopy which was used in the past to exclude small peritoneal and liver metastases, is no longer indicated for staging of disease considered resectable by conventional radiology [69, 70]. The performance of diagnostic laparoscopy with ultrasound is not effective in preventing unnecessary laparotomy and is associated with additional hospital stay, patient discomfort and an increase in healthcare costs [71].

2.4 Management

2.4.1 Surgery

Patients with pancreatic cancer and no evidence of metastatic disease or local vascular invasion are offered curative surgical resection. Unfortunately these patients account for only 10 – 20% of all cases [11]. In addition, many elderly patients are not referred for consideration of surgery as they are judged unfit for operation due to advanced age or unrelated comorbidities. Despite an extensive pre-operative work-up, 11%-53% of patients are found to be unresectable at the time of laparotomy and the prospect for patients with cholangiocarcinoma and gallbladder cancer is much worse. Most patients thus end up receiving palliative treatment according to the symptomatology, which could involve either a surgical bypass or placement of a biliary stent [72]. The three most important conditions requiring treatment in patients with unresectable biliary and pancreatic cancers are cholestasis, pain, and gastrointestinal obstruction; these may be consequences of local tumor invasion into adjacent structures including the bile ducts, duodenum and neural celiac plexus [73].

Historically, surgical procedures were first used in the palliation of obstructive jaundice until less invasive techniques became available [74]. Except for underdeveloped countries where endoscopic and radiological expertise is not readily available, as well as

for patients with concomitant gastric outlet obstruction, surgical palliative techniques have been much less used in the management of obstructive jaundice; they have been replaced by percutaneous and endoscopic insertion of stents [75, 76]. Mortality 30 days after surgical palliation for pancreatic cancer and cholangiocarcinoma may be as high as 33% and the risk is even more pronounced in individuals either above 60 years of age or in those with metastatic disease [77]. Surgical biliary and gastrointestinal bypass is advocated for patients who also suffer from chronic pain, since celiac nerve block can also be performed at time of surgery [73]. Whether prophylactic gastrointestinal bypass should be offered to patients with malignant obstructive jaundice is unknown [78-80]. Recent studies have show that gastrojejunostomy in addition to biliary bypass may decrease the incidence of late gastric outlet obstruction without higher morbidity or mortality [73, 81].

Although less invasive procedures such as endoscopic stenting are available for the management of biliary obstructions, the need for repetitive re-interventions raises the question of surgery as a valid alternative. Three prospective randomised trials have compared open surgery and endoscopic stenting [16, 18, 19]. Smith and colleagues randomised 203 patients to 10-French (Fr) Amsterdam plastic stent or biliary bypass (choledocoduodenostomy and choledocojejunostomy). Patients who underwent stent placement had less procedure-related and major complication rates as well as a shorter hospital stay than the surgical group. Shepherd and Andersen conducted smaller studies that had shown similar results [16, 18]. While overall survival did not differ between treatments, they demonstrated that endoscopic stenting had a lower rate of short-term complication than surgical treatment. Although patients in the endoscopy group had more obstructions and needed more re-interventions, the total number of days in-hospital was higher in the surgical group. A meta-anaylsis perfomed with these three studies confirmed a higher likelihood of intervention in the stent group [82].

Although performed more than 10 years ago, before the advent of newer technologies for stents and less invasive surgical procedures, these studies suggest that endoscopic stents are effective and less costly than surgery. A recent single-center retrospective cost-analysis in the US also revealed a striking difference between endoscopic palliation and

surgery despite the need of repetitive interventions and readmissions in the endoscopic group [83]. However, surgical bypass remains an acceptable strategy in patients with unresectable disease at the time of laparotomy, and for those requiring concomitant gastrointestinal bypass and/or celiac nerve block for management of chronic pain [71]. Surgical bypass for palliation of malignant obstruction can be accomplished with an anastomosis between either the gallbladder or bile duct to the intestine. A retrospective, population-based, cohort study from Canada suggests that patients undergoing bypass utilizing the bile duct are less likely to have failures, and need less repetitive surgical or endoscopic reintervention. In contrast, bypass anastomosing bowel to the gallbladder were technically easier and could be performed laparoscopically [84]. The impact of minimally invasive surgical techniques will have in the management of these patients is still unknown and cost-effectiveness analysis alongside new randomised trials are needed [85].

2.4.2 Adjuvant therapy

While the cases of biliary obstruction due to lymphomas can be managed with stent insertion or surgical bypass, cure can be only achieved with remission of the underlying disease. Responsiveness to chemotherapy is the main predictor for outcome in these patients [86]. In contrast, cure of tumors of epithelial origin can only be achieved with surgical resection, even though adjuvant chemotherapy has been shown to improve 1 and 5-year survival after resection of pancreatic adenocarcinoma [87]. The role of chemotherapy in patients with unresectable disease is still limited. Studies have show that 5-Fluoracil (5-FU) based regiments are superior to observation or supportive treatment in patients with unresectable adenocarcinoma of the pancreas [87]. Unfortunately, the combination of other chemotherapeutic agents such as cisplatin with 5-FU is not better than 5-FU alone [88]. In fact, this combination is associated with an increased rate of systemic toxicity, which seems to be unrelated to the biliary obstruction and inability to excrete the drug metabolites [88]. An important breakthrough in the management of advanced pancreatic cancer occurred with gemcitabine and other citotoxic drugs as they are able to improve major symptoms such as pain and weight loss, clinical benefit

response, time to progression and survival. [89, 90].

The effect of chemotherapy in the management of malignant biliary obstruction is unknown. Because tumor invasion into the biliary tree is unlikely to be relieved by chemotherapy only, a procedure to palliate the obstruction is still necessary regardless of the administration and the response to adjuvant therapy. However, addition of a chemotherapeutic regimen in the treatment of patients with unresectable disease could result in an improvement in survival and consequently influence the choice of the palliative strategy. There are no studies evaluating the effect of chemotherapy on the patency of stents. While chemotherapeutic agents are unlikely to affect the mechanisms involved in plastic stent occlusion, reduction of the tumor mass could diminish the probability of tumor ingrowth and prolong patency of SEMS. It is unknown if it adjuvant chemotherapy can increase the risk of stent migration and malfunctioning as has been suggested for esophageal malignancies [91].

2.4.3 Palliative treatment

2.4.3.1 Non-Endoscopic palliation

Different non-operative methods to relieve distal biliary malignant obstruction exist. Percutaneous insertion of plastic stents and SEMS is an acceptable alternative for management of biliary malignant obstruction not successfully treated by an endoscopic approach. It is also commonly used for palliation of hilar tumors, in patients undergoing palliative brachytherapy and in obstructions complicated with a communicating liver abscess [92]. Percutaneous drainage had been the preferred palliative method in patients with malignant obstruction until several years ago. This procedure entails sterile catheterization of a peripheral biliary radical after percutaneous puncture. External drainage is accomplished by percutaneous transhepatic insertion of a catheter,manipulation of a guidewire, and insertion of a drainage catheter through the obstructing lesion that allows both internal and external bile flow. The technique has evolved over the years and nowadays insertion of an indwelling catheter without external

drainage is possible. When compared to endoscopic drainage, the percutaneous approach permits insertion of stents with larger diameters. The consequent benefit of a longer stent patency represented a significant advantage over the prosthesis inserted by ERCP which was limited by the size of the accessory channel of duodenoscopes. Also, percutaneous drainage appeared to be as effective as biliary bypass, and still had some inherent advantages. Bornman et al. found the overall survival to be similar in both surgical and percutaneous groups, and indeed percutaneous drainage was associated with a lower procedure-related complication and 30-day mortality rate [17]. The disadvantages of external biliary drainage are the risk of spontaneous catheter dislodgment, inflammation and pain around the puncture site, leak of ascitic fluid and bile around the catheter, and loss of fluid and electrolytes [93]. The complication rate for transhepatic biliary drainage can be substantial and varies with the patient status prior to procedure and diagnosis. The presence of coagulopathy, cholangitis, stone, malignant obstruction and intra-hepatic lesions are associated with high complication rates [94].

The advent of self-expandable metal endoprostheses, larger size accessory channels in duodenoscopes and the complication rate observed with percutaneous drainage have changed the standard of practice. Speer and colleagues conducted a prospective randomised study comparing percutaneous and endoscopic drainage [95]. While overall survival was not different between both arms, 30-day mortality both by intention-to-treat and per-protocol analysis was significant lower in the endoscopy group and justified the early termination of the study. The authors found that complications associated with the percutaneous procedure accounted for the difference in mortality and that endoscopic insertion of a stent was safer and more likely to succeed [95]. A collection of published series done by Coene et al. supports the superiority of an endoscopic *versus* a percutaneous approach with regards to early complication, 30-day mortality and successful drainage [96]. However, a recent RCT showed that patients undergoing percutaneous drainage had a longer survival than those in the endoscopy group, which conflicts with results from trials performed 2 decades ago [97]. The authors argued that advances in radiological techniques have led to a reduction in complication rates, and that the results from 'old' studies do not reflect current practice. Yet, closer assessment of the study design and results is warranted. First, the study selected not only patients with

unresectable distal biliary obstruction but also subjects with more proximal obstruction including hilar tumors. These inclusion criteria could explain the low success rate of PE stent insertion by endoscopy (58%) which in turn accounted for the suboptimal efficacy observed in this group. Second, the authors used SEMS in the percutaneous group and PE stents in the endoscopic drainage group, which confounds the comparison between both arms and compromises the internal validity of the study. The longer survival observed in the percutaneous group and the similar likelihood of readmission and stent occlusion in both strategies is not only a function of the insertion technique but also of the type of stent used and whether it was used in the palliation of intra-or extra-hepatic tumors. In addition, Pinol et al. conducted a "piggy-bag" economic evaluation and reported no difference between both treatments. However it is not clear why the author included the costs of the stents and hospital stay but not the procedures themselves. Percutaneous and endoscopic drainage are distinct procedures and utilize different amount of resources. While percutaneous drainage is a two-step procedure, endoscopic placement of stents is routinely done on an outpatient basis and does not require a follow-up intervention unless signs of stent dysfunction occur. In addition, the cost of a PE stent used in this study from Spain was much higher than the average costs reported in other European and North American trials. Thus, despite the apparent advantages of the percutaneous over the endoscopic approach in the management of distal biliary obstruction, there is sufficient evidence in the literature to advocate the use of endoscopy as first-line therapy [96].

Stents inserted by either percutaneous or endoscopic techniques have similar physical characteristics and should experience the same survival. However, in order to maintain the homogeneity of the patient population and minimize the chance of bias, only studies evaluating the use of PE, uncovered and covered SEMS inserted by endoscopic technique and in the treatment of patients with distal biliary obstruction were selected for this review.

2.4.3.2 Plastic endoprosthesis

Endoscopic placement of plastic biliary stents were first described by Soehendra and Reynders-Frederix as an alternative to choledocoduodenostomy in high-risk and inoperable cancer patients [26]. Plastic stents have several inherent advantages that are suitable in the management of patients with malignant biliary obstruction. First they are relatively cheap compared to metal stent and surgical bypass, are relatively easy to insert, and can be removed if necessary. Insertion of biliary stents requires a prior cholangiogram in order to delineate the level, extent and degree of obstruction. This can be accomplished during ERCP or, preferably, by a pre-ERCP magnetic resonance cholangiopancreatography (MRCP), or CT-cholangiogram, which can prevent forceful injection of contrast and contamination of the proximal biliary system. Once the anatomy is defined, selective cannulation and passage of a guidewire through the obstruction is needed. Although not necessary for introduction of a single plastic stent or SEMS, sphincterotomy may be performed because it may facilitate insertion of the stent, permits immediate subsequent access to the biliary tree and allows tissue sampling with brushing and biopsy forceps. However, a recent RCT suggested that sphincterotomy before plastic stent insertion did not affect the efficacy of the stents, and more complications were observed in the sphincterotomy group [98].

A large variety of biliary plastic stents are available with internal diameters ranging from 5 to 11.5 French (Fr) gauge with lengths varying from 5 to 15 centimeters (cm). Straight plastic stents with flaps in both extremities and side-holes are the most common type of stent used. The presence of flaps minimizes the risk of stent migration which is less likely to occur in pigtail stents due to their physical characteristic that allow greater anchoring inside the CBD and duodenum. Although no study has compared the occlusion and migration rate between straight and pigtail stents, animal studies suggest that straight stents may provide better bile drainage than pigtail stents [99, 100]. When compared to pigtail stents of equivalent diameters in either normal or dilated common bile duct, straight stents demonstrated a greater bile flow rate which indeed may decrease the risk of bile stasis, consequent biofilm formation [99] and subsequent stent clogging.

Nevertheless, plastic stents exhibit a shorter patency duration compared to other palliative modalities, and therefore are more likely to occlude during the life of a patient with malignant obstruction. Compared with SEMS or surgical biliary bypass, plastic stents are less effective and expensive. Understanding the mechanisms involved in the occlusion has motivated studies aiming to improve the patency of these stents. The following measures have been evaluated in different clinical studies:

1. *Size of internal diameter.* Rodkiewicz et al. have shown that bile, flow in a rigid tube behaves like a Newtonian fluid and the flow is thus laminar under physiological conditions [101]. The flow of bile through a stent is directly proportional to the internal diameter and the difference in pressure across the stent and inversely proportional to the viscosity of the fluid and the length of the stent ($Q = \pi.D^4.\Delta P/ 128.n.L$; where D is the internal diameter, P is the pressure across the stent, n is the viscosity of the fluid and L the length of the stent). Therefore, at least under physiological conditions, larger internal diameters should improve the laminar flow and decrease the chance of stent clogging. The calculated flow capacity for an 11.5Fr stent is 270% and 520% greater than a 10 and 8Fr stent, respectively. Although flow capacity in 8, 10 and 11.5Fr stents are much above the daily bile production, this may not be applicable to 'real life' conditions such as biliary obstruction. In this scenario, not only the amount to be drained (retained bile above the obstruction) and the viscosity of bile are greater than normal, but the presence of stones and debris can also disrupt the pattern of flow seen under physiological conditions. Thus, the bile flow rate can be markedly reduced to a point that a small caliber stent has no safety margin of spare flow capacity.

The hypothesis that increments in internal diameter of biliary stents improve patency rates was investigated in four non-randomized retrospective studies - two comparing 10Fr to 7Fr and 8.5Fr stents [20, 102] and two comparing 10Fr to 11.5Fr stents [42, 103]. Speer and colleagues reviewed the Middlesex Hospital experience with 8Fr and 10Fr PE stents in subjects with distal and hilar tumors. A total of 28 patients had 8Fr stents inserted on 38 occasions,

and 51 patients had 10Fr stents inserted on 61. The authors noticed that survival of the stent and incidence of cholangitis within two weeks of the procedure was more likely to occur in patients who had 8Fr stents. However, the comparison of 8Fr pigtail to 10Fr straight stents may have impaired the validity of the study, since straight stents are known to have greater bile flow rate [99]. Moreover, an unknown number of patients in both groups underwent stent replacement because of failure to relieve jaundice; indeed,stents inserted after an occlusion have not the same survival and are likely to occlude earlier on [104]. The inclusion of all stents in the survival analysis is not only a source of bias but also a possible confounder if the number of stent replacements was not balanced between groups. Therefore it is unclear if the difference in effectiveness observed between the 8Fr and 10Fr stents is indeed accurate. A study comparing 7Fr to 10Fr plastic stents showed opposite results [102]. Complications within 14 days of the procedure and duration of patency of the prostheses were not statistically different between groups in this retrospective analysis [102]. Pereira-Lima and colleagues studied 108 consecutive patients with unresectable pancreatic cancer who underwent 10Fr or 11.5Fr plastic stent insertion [42]. A total of 21 patients were excluded from the analysis for reasons such as procedure failure, unavailability of hard data and insertion of SEMS. Although the authors observed that time to clogging in 10Fr and 11.5Fr stents were not statistically significant different, the results ought to be interpreted with some reservation. Patient characteristics were not stratified according to the treatment received, and it is not clear if the groups were similar. Confounding is a potential threat to the validity of the study. Also, the survival of the stents was not adjusted for other factors that could have affected the rate of stent clogging. Lastly, the authors did not provide details about the subjects who were excluded from the study. Should the reason for exclusion be associated with the outcome of interest, selection bias may have occurred. However, similar results were obtained in a study performed by Kadakia and Starnes that supports the hypothesis that no significant difference exists between 10Fr and 11.5Fr

plastic stents [103]. These studies have supported the current practice of inserting 10Fr stents in the management of malignant biliary obstruction. In the absence of prospective evaluations of different sizes of plastic stents, retrospective studies suggest that 10Fr and 11.5Fr plastic stents are equally effective in providing drainage inpatients with malignant obstruction. However, it remains unclear if 10Fr stents are indeed superior to 7Fr or 8Fr stents.

2. *Presence of side-holes.* Side holes located at both extremities of PE stents are expected to permit bile drainage into the stent in case the cephalad orifice becomes occluded or abuts against the bile duct wall. However, in vitro studies suggested that side holes can also accelerate sludge formation presumably because of turbulence of the bile flow stream generated by its rough surface orifice [33]. Coene and colleagues performed an 'in vitro' and a pilot clinical study with plastic stents of different designs and materials. First, bile from post-operative patients was removed from T-tubes, pooled and run in a closed circuit that contained the stent. The 'in vitro' analysis revealed that presence of side holes significantly increased the amount of sludge irrespective of the type of plastic material used [33]. This finding was subsequently tested in 40 patients with distal biliary malignant obstruction. PE stents with and without side holes were inserted in a total of 40 patients and removed for analysis after 2 months. Although all stents were patent on eye examination at removal, a quantitative sludge analysis demonstrated that stents without side holes had a significant lower amount of sludge that was distributed along the entire inner surface; in contrast, sludge accumulation was greatest at the rims of the side holes [31, 33]. A series of studies comparing plastic stents with and without side holes have been done, most of which have compared PE and Teflon Tannenbaum (TT) stents. These stents differ not only with regards to the presence of side holes but also in the stent materials which display different coefficients of friction [105-108]. There has been only one RCT comparing stents of similar material with and without side holes [109]. Sung et al. randomized 70 individuals with benign and malignant

biliary obstruction to receive 10Fr PE stents with *versus* without side holes. These patients were followed prospectively. Stents were replaced if symptoms or laboratory evidence of obstruction arose. The number of stents found to be occluded, the median time to occlusion and the amount of sludge within the stents were similar in both groups [109]. These findings suggest that once colonization of bacteria into the inner surface of the stent occurs, adhesion is perpetuated regardless of the presence of side holes. In addition, the absence of side holes could make stents more prone to migration, although this difference was not statistically significant. In spite of encouraging efficacy studies demonstrating that patency could be improved by omitting side holes, the effectiveness of both types of stent seems to be similar. Therefore, the use of stents without side holes cannot be substantiated.

3. *Modification of stent surface.* In addition to PE, other polymers such as Teflon, Hydrophilic-coated Polyurethane (HCP) and Double Layer stent (DLS) have been investigated. These materials have been shown 'in vitro' to have a lower coefficient of friction. Consequently, they reduce bacterial adhesion and biofilm formation leading to prolonged stent patency. Teflon stents are commercially available as Teflon Tannenbaum (TT) and differ from PE stents in the material itself and the absence of side holes. Therefore trials comparing PE and TT stents evaluate the effect of 2 independent parameters which, at least 'in vitro', are known to influence the patency of plastic stents [105-107, 110]. Unfortunately, all RCTs comparing Teflon to PE stents have not substantiated the superior effectiveness of Teflon stents observed in the original study by Binmoller and colleagues [111]. There has been only one RCT comparing PE and Teflon stents with similar design; as discussed above, it showed no difference in duration of patency[112]. HCP stents have the same design as the conventional PE stents but the outer hydrophilic layer has an ultrasmooth surface which greatly reduces bacterial colonization 'in vitro' [113]. Like the Teflon stents, HCP stents have not demonstrated to be superior to PE stents despite promising 'in vitro' results [114]. DLS stents are constructed without side holes and consist of 3 layers. The inner layer is

made of smoothed Teflon, which results in a flatter surface and prevents bacterial adhesion. The middle layer is made of stainless steel and provides not only elasticity but also helps to bond the inner to the outer layer. The outer layer is made of a polyamide elastomer that gives sufficient stiffness to the stent to withstand the pressure from a stricture bile duct. The only RCT comparing PE to DLS revealed that patients who received DLS instead of PE stents were more likely to have a patent stent at time of death. The mean time to occlusion was shorter and the proportion of patients with stent occlusion was higher in the PE group [115].

4. Position of the stent. Although the biliary tract does not harbor any microorganisms, transient incursions of bacteria into the biliary tree can occur in healthy individuals [116]. Therefore, placement of the distal end of the stent above the sphincter of Oddi (inside-stent approach) was postulated to preserve the mechanical barrier, decrease the likelihood of duodenal reflux and bacterial contamination of the stent, and consequently prolong the patency of stents. In Western countries where pancreatic cancer accounts for the majority of cases, this strategy would be feasible in one-third of all malignant obstructions if a clearance length of 2 cm between the stricture and the sphincter of Oddi is needed and in approximately 45% of patients if a minimum clearance of 1 cm is required [117]. Pedersen and colleagues compared the patency of straight PE stents placed above and across the Sphincter of Oddi [118]. Median survival of stents and the proportion of stents exchanged were not significantly different. However, the causes of stent dysfunction were different between the 2 groups. Occlusion was the reason of most dysfunctions seen in patients with stents inserted by the conventional approach while stent migration accounted for most cases of dysfunction in patients with stents placed above the Sphincter of Oddi. The results suggest that a significant improvement in stent effectiveness can be achieved if stent migration could be avoided in patients with stents inserted above the Sphincter of Oddi. However, the observed high rate of stent dysfunction due

to migration and associated complications speaks in favor the use of the conventional placement technique.

5. *Administration of choleretic agents and/or antibiotics.* A variety of agents have been shown "in vitro" to interfere with the mechanism of stent clogging [119]. The earliest report was on the use of aspirin to reduce mucin secretion and doxycycline to inhibit bacterial colonization, an important process in the initial step of stent occlusion [120]. Although the amount of sludge was significantly lower in both treatment groups after 2 months from the initial insertion, this interval was not sufficient to document differences in occlusion rate, which was indeed affected by the high drop-out rate (50%). Libby et al. demonstrated that ciprofloxacin significantly reduced bacterial adherence to PE both 'in vitro' and in an animal model [121, 122]. The results of RCT have been controversial. Five studies evaluating the role of antibiotics either alone, with ursodeoxycholic acid (UDCA), or with a choleretic agent (Rowachol) failed to demonstrate any advantage over placebo or UDCA alone [123-127]. However, in a similar study, plastic stents of patients allocated to receive norfloxacin and UDCA experienced a longer survival compared to correspondent untreated controls [128]. Although the study by Gosh et al. commenced antibiotics and UDCA only 2 weeks after stenting (when biofilm formation was probably present), most other studies showed that antibiotics either alone or in combination do not improve survival of plastic stents. A recent meta-analysis including 182 patients from 4 RCT also suggested that adjuvant therapy has no effect on the patency of plastic stents. Aside from costs and patient compliance, long-term administration of antibiotics raises concern about bacterial resistance, change of bowel flora and antibiotic-associated diarrhea. Coating plastic stent with bactericidal agents could prevent the untoward effects of oral antibiotics and at the same time inhibit formation of bacterial biofilm. Indeed Leung and colleagues studied the 'in vitro' effect of silver coating in polyurethane stents and concluded that such a strategy reduced the number of bacterial colonies by 10 to 100 times

compared to untreated controls [129]. No corresponding human studies have been performed to date.

Bile salts also have potent antibacterial activity that contributes to bile sterility [130]. Hydrophobic bile salts such as deoxycholic and taurodeoxycholic acid are the strongest known inhibitors of bacterial adhesion to stent material, and could reduce bacterial adhesion on plastic 100 to 1000-fold [131]. However, their cytopathic effects and the associated gastrointestinal side effects make them more poorly tolerated than the hydrophilic bile acids such as UDCA, which have little effect on bacterial adherence. This explains why the former have never been evaluated as adjuvant therapy in clinical studies.

In summary, RCTs comparing different plastic stent materials (PE, TT and polyurethane), designs (with and without side holes) and adjuvant therapies have failed to demonstrate significant difference in terms of patency.

2.4.3.3 Self-expandable metal stents

The idea of inserting an expandable stent has been applied to strictures of the biliary tree as in blood vessels[132]. Self-expandable metal stents (SEMS) are braided in the form a tubular mesh from surgical grade steel alloy. The elastic properties of the material allow the stent to adopt different configurations according to the site and intensity of force applied. SEMS are delivered into the bile duct while completely constrained by a sheath, allowing its insertion as a small-circumference delivery system. As the constraining sheath is progressively retracted from its more distal end, the intrinsic expansile forces of the stent make it regain its original configuration. After the sheath is completely withdrawn, the end result is an expanded stent which accommodates the shape of normal (if the diameter of the bile duct is smaller than the maximal stent diameter) and strictured bile duct by maintaining constant radial pressure against its wall. Since its first use in patients with biliary malignancies, a multitude of SEMS types have been released. SEMS differ in regards to the type of delivery system, structural

composition, design, length and diameter (Table 2.1) and all achieve a much larger internal diameter and longer patency rate compared to the plastic stents.

Features / Name	Delivery system (F)	Metal and design	Deployed length (cm)	Deployed diameter (mm)
Wallstent	7.5	Steel wire mesh	4, 6, 8	8
			4.2, 6.8, 8	10
Spiral Z-stent	8.5	Stainless steel, open wire mesh	5.7, 7.5	10
Za stent	8.5	Nitinol, open wire mesh	4, 6, 8	10
Memotherm	7.5	Nitinol mesh	4, 6, 8, 10	8, 10
Diamond Ultraflex	9.25	Open wire nitinol mesh	4, 6, 8	10

Table 2.1. SEMS for palliation of malignant biliary obstruction

Five RCT have clearly shown that survival of uncovered SEMS is longer than plastic stents [35, 36, 45, 133, 134]. Davids et al. randomized 105 patients with unresectable malignant extrahepatic biliary obstruction to either a metal (n = 49) or PE stent (n = 56). Mean duration of patency for uncovered SEMS was significantly longer than for PE stent, although patients' survival did not differ between groups. An economic evaluation performed along side this study revealed that initial insertion of an uncovered SEMS resulted on average in a 28% reduction in ERCP which offset the high upfront cost of the stent. Given the differences in costs of stents and the average number of ERCP required, the authors calculated an incremental cost-effectiveness ratio (ICER) of $1760/ERCP prevented. Therefore, the investigators considered placement of an uncovered SEMS more economical when ERCP-related costs exceeded $1760 when all other values remained constant [35]. The Wallstent Study Group multicenter trial is the largest comparative study to date, but was published in abstract form only. The study included

163 patients with either a hilar (n = 48) or common duct (n = 115) malignant obstruction who were randomly assigned to placement of either a 10–11.5 Fr plastic stent or a Wallstent®. Details regarding initial stent placement and timing were not included. Of note, 30% of all patients previously had had an initial plastic stent placed and were returning for stent replacement. Although the number of patients who developed stent occlusion before death or at the last follow-up was equal for both groups, median time to obstruction was shorter with plastic stents than SEMS. The 30-day mortality rate did not differ between groups [133]. Knyrim et al. prospectively randomly assigned 62 patients with malignant common bile duct obstruction to endoscopic insertion of either an SEMS or PE stent. An initial attempt was made to place the stents endoscopically. A combined percutaneous-endoscopic approach was performed because endoscopic insertion failed in 7 patients (22%) in the SEMS group and 5 patients (16%) in the plastic-stent group. During the first 30 days after stent insertion, 1 patient with a plastic stent experienced stent migration and no patient in either group developed stent occlusion. Longer follow-up (>30 days) was available for 27 patients in the SEMS group and 28 patients in the plastic-stent group. Stent occlusion was more common in the PE than SEMS group but not significantly different between both strategies. The re-intervention rate for managing stent occlusion was significantly greater in the plastic-stent group compared with the SEMS group. The cost of retreatment due to stent failure was significantly greater in the plastic-stent group compared with the SEMS group ($3658 ± $940 vs. $1283 ± $606; $P <$ 0.028). However, there was no significant difference in overall costs (for the stent and hospitalization) [36]. Prat et al. evaluated 101 patients with malignant distal biliary strictures. Patients were randomly assigned to placement of either a 11.5 PE stent to be exchanged on evidence of dysfunction, a PE stent to be replaced every 3 months, or an uncovered Wallstent®. The group of patients randomly assigned to routine PE stent changes or uncovered Wallstent® insertion had a significantly longer asymptomatic interval and shorter hospitalization compared with the group undergoing stent exchange on demand. Although those undergoing routine PE stent exchange were more likely to be symptom-free than those treated with on-demand replacement, they required a higher number of ERCP which significantly impacted on the results of the cost analysis also performed. An overall cost advantage was seen for uncovered SEMS versus prophylactic

or on-demand PE stent exchange. However, if all patients with survival < 3 months received a PE stent, the estimated cost was lower for PE with replacement on demand versus the Wallstent®. The calculated difference in costs for patients surviving < 6 months was similar for each group. The investigators concluded that placement of an SEMS is less expensive than placement of a plastic stent in patients surviving > 6 months [45]. Most recently, Kaassis et al. conducted a multicenter study comparing the efficacy and cost of Teflon Tannenbaum (TT) stents and uncovered Wallstent® in 118 patients with malignant extrahepatic biliary obstruction. Time to initial obstruction was longer for those in the SEMS group and number of occlusions was higher in the TT versus the SEMS group. For the subgroup in which stent occlusion occurred, the number of additional days of hospitalization, duration of antibiotic therapy, and number of ERCP were all significantly greater in those receiving a TT stent. There was no difference in duration of survival between groups [134]. Schmassmann et al. conducted a retrospective study involving 156 patients with unresectable malignant extrahepatic obstruction (72%) and intrahepatic or hilar obstruction (28%). They found that SEMS offered more prolonged stent patency than plastic stents and a decreased need for additional endoscopic procedures. In addition, this is the only endoscopic study to find a significant survival advantage for SEMS. However, better compliance in the SEMS group is thought to have led to the improved survival duration. A cost-analysis was performed and the ICER between plastic and uncovered SEMS was $2105/ERCP prevented. Therefore, the investigators concluded that placement of a Wallstent® was more economical when ERCP-related costs exceeded $2105/ERC based on their assigned values [38].

Although all studies used the uncovered Wallstent® SEMS, recent RCTs suggested all uncovered stents are equally effective [135, 136]. It is also clear that patients treated with uncovered SEMS are less likely to be hospitalized and require endoscopic re-intervention due to stent dysfunction; it certainly has an economical impact that is related to the local standards and costs. However, it remains unclear if use of an uncovered SEMS is associated with a longer patient survival. If present, it is not known if it represents a measurement of efficacy (e.g. prevention of occlusion-related cholangitis) or effectiveness (e.g. better patient compliance) of the metal stent per se. In addition to the study by Schmassmann et al., a meta-analysis of 184 patients from 3 out of the 5 RCTs

comparing plastic or Wallstent®, suggested that uncovered SEMS may also confer a survival advantage [38, 137].

More recently, covered SEMS have been introduced as an attempt to prevent tumor ingrowth and stent-induced biliary epithelial hyperplasia. Initial poorly controlled studies comparing uncovered to covered SEMS not only failed to demonstrate any benefit of covered SEMS but also suggested a higher rate of stent-related complications such as migration, cholecystitis and pancreatitis [39, 138]. To date one RCT comparing covered to uncovered SEMS has been performed [40]. Isayama et al. randomized 112 patients with unresectable distal biliary malignant obstruction to receive a covered polyurethane (n=57) or an uncovered polyurethane diamond stent (n=55). All patients underwent stricture dilation and subsequent drainage with nasobiliary or plastic drainage before insertion of the metal stent. Percutaneous insertion after unsuccessful endoscopic deployment was utilized in 12/57 (21%) and 9/55 (16.3%) of patients with covered and uncovered SEMS respectively. Stent occlusion, which was significantly different in between groups, occurred in 14% of patients in the covered group and 38% in the uncovered group at a mean follow-up of 304 and 166 days respectively. The patency duration of covered SEMS was superior to the uncovered but no difference in patient survival was noted. The study also documented a higher incidence of complications in the covered (4.8% of cholecystitis and 8.7% of pancreatitis) versus the uncovered group (no cholecystitis and 1.8% pancreatitis), although was not formally compared statistically. The authors concluded that covered diamond stents were superior to uncovered in preventing tumor ingrowth but carried a higher risk of complications not previously observed with uncovered SEMS.

2.5 Economical appraisal of endoscopic palliation

The medical decision of inserting a biliary plastic or a metal stent to manage complications related to distal biliary malignant obstruction is complex with multiple areas of uncertainty and trade-off. In the absence of standard recommendations, decisions are commonly made based on a physician's previous knowledge, personal preference or

in some cases an educated guessing. Unfortunately, comparison of all possible outcomes is difficult to process in the face of complex medical scenarios.

While stents are known to have no impact on the progression of the underlying disease, the amount of health benefit (symptom-free months) provided by SEMS is clearly higher than plastic stents but indeed at a higher upfront cost [35, 36, 40, 45, 133, 134]. Insertion of SEMS would be advantageous in patients who more likely to experience an episode of stent occlusion if a plastic stent had been initially inserted. Although duration of patency of stents is a function of several variables and is not easily predictable, studies suggest that median time to occlusion in plastic stents is approximately 4 months. Consequently, insertion of SEMS in patients surviving more than 4 months would prevent a repeated procedure, related complications and its associated costs. However, just a small proportion of patients survive long enough to benefit from a more effective and expensive stent. Identification of these patients is not straightforward. Factors which are associated with poorer survival have been identified but these linear models explain a fraction of the total variability in survival. Prat and colleagues looked at predictors of survival in a cohort of 105 newly diagnosed pancreatic cancer patients enrolled in a RCT aimed at comparing different stents for palliation of obstructive jaundice [43]. The mean follow-up was 166 days and the median survival 143 days. The survival curve revealed that 37.6%, 30.7% and 31.7% of patients survived less than 3, between 3-6 and more than 6 months respectively. The only variable that independently predicted survival in both univariate and multivariate analysis was tumor size. The median survivals for patients with tumors smaller and larger than 30 mm in length were 6.6 and 3.2 months respectively. When applied to the actual cohort, this cut-off identified 80.2% of patients who would survive more than 6 months [43]. Cubiella et al. performed a similar evaluation on 134 patients with unresectable pancreatic cancer. In this study only 61 patients (45%) had obstructive jaundice, which was managed surgically, radiologically or endoscopically. Survival analysis showed that 51%, 28% and 8% were alive by 3, 6 and 12 months. A multivariate analysis indicated that absence of metastases and preserved baseline performance status (Eastern Cooperative Oncology Group scale) were associated with a more prolonged survival [44]. In addition to survival, other factors such as impending duodenal obstruction, previous plastic stent

failure, and living in a remote geographic area are also taken into account. Previous plastic stent occlusion may be an indication for SEMS. Menon et al. showed that patients with early stent plastic stent occlusion will experience re-occlusion of subsequent plastic stents much earlier. Although average patency of SEMS in this selected population is also worse than in otherwise naïve patients, this strategy not only avoided repeated ERCP for plastic stent exchange but also was cost saving [104].

Whether plastic or metal stent is properly used, it is unlikely that patient outcomes will change. The consequences of a wrong selection will be either decreased quality of life (QOL) for patients undergoing repetitive and unnecessary procedures or increased health care expenses. Consequently, the debate between plastic and metal stents becomes an economical dilemma, especially where health care budgets are limited and if it is not possible to provide all beneficial health services to all people. Under these conditions, health resources ought to be spent in the most cost-effective way in order to produce the maximal amount of health benefits.

In addition to the cost analyses performed alongside RCTs, decision models suggest that SEMS are economic advantageous than plastic stents in palliating malignant extrahepatic biliary obstruction in patients whose life expectancy exceeds 6 months. Arguedas et al. used quality adjusted life months (QALM) as outcome measure to complete a cost-effectiveness model. They designed a model of the natural history of pancreatic carcinoma with malignant biliary obstruction, and compared 2 strategies: (1) initial plastic stent placement and (2) initial endoscopic SEMS placement. Following occlusion, a plastic stent was exchanged (group 1) or inserted through the SEMS (group 2). Initial insertion of a plastic stent resulted in a total cost of $13,879/patient and 1.799 quality-adjusted life-months compared with $13,466/patient and 1.832 quality-adjusted life-months for initial SEMS use. They determined that SEMS are financially beneficial as long as the SEMS occlusion rate is 1.65 times less than that for plastic stents and that initial placement a SEMS is the most cost-effective strategy, particularly in patients with a greater than 6 months expected survival [1]. However, not only patient survival and stent patency influence the cost-effectiveness of a particular strategy; the cost of ERCP exerts an important role in this decision process as it can be vary significantly according

to the standards of practice. Yeoh et al. compared the costs of 3 strategies for palliating malignant obstructive jaundice that involved initial placement of: (1) a plastic stent, with exchange for another plastic stent on occlusion; (2) SEMS, with coaxial plastic stent insertion on occlusion; and (3) plastic stent, with SEMS exchange on occlusion. When the cost of SEMS is high relative to an ERCP (cost ratio of SEMS-ERCP> 0.7), initial plastic stent insertion is favored (group 1). Conversely, when the cost of a SEMS is relatively small compared with that of an ERCP (cost ratio of SEMS-ERCP < 0.5), initial placement of a SEMS is favored (group 3). They also correlated cost with expected survival and found that initial insertion of a plastic stent was the preferred method if survival was less than 4 months [2].

2.6 Decision modeling in economic evaluations

2.6.1 Overview

Decision analytical models are widely used in economic evaluation of health care interventions with the objective of generating valuable information to assist health policy decision-makers in allocating scarce health care resources efficiently. The whole decision modeling process can be summarized in four stages: (i) a systematic review of the relevant data (including meta-analyses), (ii) estimation of all inputs into the model (including effectiveness, transition probabilities and costs), (iii) sensitivity analysis for data and model specifications, and (iv) evaluation of the model. It is also becoming recognized that economic evaluations should ideally be undertaken early in the development of new healthcare technologies when decision modeling may exert an important role. There are several types of economic evaluations; their description is beyond the scope of this thesis. CEA defines a framework for evaluating the health effects and costs of health interventions. Many of the techniques discussed later, such as decision analysis, can be used as components of a CEA. In addition, CEA adds two new concepts: estimation of costs, which requires estimating and valuing the resources used for interventions; and comparison of costs with health effects.

According to O'Brien et al., the source of information used by the investigators separates economic evaluations into either a prospective 'stochastic' analysis or a secondary 'deterministic' analysis of retrospective data [139]. While the former is characterized by accessibility of the original study data by the investigator (e.g. RCT), the latter uses effectiveness and costs data from different sources. In theory, economic evaluations alongside RCT could provide point estimates and determine the difference between one or more strategies with high internal validity. If an intervention is proven to have clinical efficacy, there may be considerable pressure for its adoption. However, RCTs are commonly criticized as vehicles for economic evaluations. A number of methodological and practical considerations have to be considered in order to ensure internal validity of the economic components and address issues of generalizability. For instance, given that sample size is driven by the estimated difference in outcome, the RCT may be statistically underpowered for economic studies. Moreover, if a treatment has been deemed to be safer and efficacious, further randomization is no longer acceptable due to break of clinical equipoise. Costs based on RCT cannot be directly applied to clinical practice which often reflects local prices and the methodological rigor of the study design. Protocol-driven care within a trial can lead to significantly higher levels of compliance, monitoring of safety and general care than occurs in practice.

Carrying out an economic evaluation alongside a RCT allows detailed information to be collected about the quantities of resources used by each study patient. A record can be kept for every patient of the actual staff present, time taken, consumables used, and inpatient stay etc.... Such information allows an estimate of the cost of treatment to be obtained per patient, producing a set of "patient specific" cost data. Availability of patient specific cost data not only allows the use of statistical inference as a basis for drawing conclusions about costs but reduces the extent to which the comparison between randomized groups is based on assumptions about resource use. In addition it allows the relation between costs and other factors such as patient characteristics and clinical outcomes to be investigated. Pragmatic RCT provides a suitable environment not only for assessing clinical effectiveness but also for comparing costs. Nevertheless, in the absence of direct comparisons, a decision analytic framework can be constructed by incorporating the best available data from a variety of sources.

Decision analysis can be defined as a systematic approach to decision making under conditions of uncertainty [140]. Models of various types are commonly used in a wide variety of areas as an attempt to represent the complexity of the real world decisions in a more simplistic and understandable manner. Decision modeling is used to estimate the cost-effectiveness of healthcare interventions in two situations: 1) When relevant clinical data is not available either because trials have not been performed or when the study itself is not feasible. In these scenarios, decision modeling can be used to synthesize the best available evidence. If RCT exist, modeling avoids overloading of trials with extra data collection. 2) If RCT have short follow-ups, statistical models are used to extrapolate beyond the trial results. In addition, modeling plays a major role in systematically characterizing the degree of uncertainty of parameters by using sensitivity and threshold analyses. This property permits the identification of certain parameters that are likely to make the new intervention more cost-effective than the current intervention. If data are not readily available, models can identify areas where further research is needed. However, statistical inferences can be drawn only when data are readily available and point estimates and parameters for the sampled population can be calculated. In the absence of data on a parameter of known importance, decision modeling is carried out using sensitivity analysis either individually or in combination with others parameters; results are reported over a range of values. However, this technique does not clarify the statistical issues associated with estimation of the parameters.

Economic evaluations ought to make clinically relevant comparisons that can be applied in "real world". Whilst a multitude of treatment options can be studied, the alternatives are commonly contrasted with the current treatment(s). This 'head-to-head' comparison allows the health care provider and the decision maker to grasp the shift in costs and benefits with implementation of the alternative treatment. In decision modeling, all types of study designs and even expert opinion can be used to estimate parameters when consistent sources of hard data do not exist. Careful attention ought to be paid to quality of the studies included in the estimation of the parameters. Non-randomized and retrospective studies have the advantage of a higher generalizability but they are often poorly controlled and may threaten the internal validity of the analysis. Although not an instrument of effectiveness, RCTs are the most reliable and common source of data

employed in all types of economic evaluations, including cost-effectiveness analysis. The advantages of an RCT are numerous, but in particular the methodology ensures that effect is attributable to the intervention alone and reduces the potential of biases. Guidelines to improve reporting of RCTs and meta-analyses have been published [141, 142], but small RCTs and meta-analyses of multiple small trials may still show a favorable result for a given therapy merely because of chance or incorrect estimation. Selection of poor quality studies can result in biased estimates and ultimately compromise the validity of the decision model. Consequently, there has been a progressive higher level of scrutiny of economic evaluations using decision modeling, considering that they are harder to peer-review, and because of their potential financial implications. Nevertheless, there will always be a need for decision modeling since not all answers can be obtained from well-controlled studies [143].

2.6.2 Markov model

A particular type of model frequently used in economic evaluations is the Markov model. In the past limited by the complex algebra, this model has become more accessible with the widespread use of personal computers and the advent of user-friendly decision-analysis software. Markov models are commonly used to represent random processes that can be characterized as involving transitions from one state to another over time (e.g evolution of chronic diseases). The health state under investigation is divided into distinct states and transition probabilities are assigned for movement between these states over a discrete time period called 'Markov cycle'. By attaching estimates of resource and health outcome consequences to the states and transitions in the model, and then running the model over a large number of cycles, it is possible to estimate long term cost and outcomes associated with a disease and a particular health care intervention.

The first step in the construction of a Markov model is the definition of the disease states. These states should be mutually exclusive since a given patient cannot be at two different stages of disease at the same time. Transitions are assumed to take place for each cycle of the model and the sum of the probabilities of moving to states must add to

one. One important limitation of the Markov model is that the probability of moving out of a state is not dependent on the states a patient may have experienced before. This 'memoryless' feature indeed divides the Markov models into 2 main categories according to the transition probabilities: 1) Markov chains where all transition probabilities are maintained constant over time; 2) Time-dependent Markov processes where transition probabilities vary over time. While the first has several logistical advantages, many assumptions make it too restrictive for application to health care. On the other hand, the time-dependent Markov models are more complex algebraically but offer flexibility with regards to modeling chronic health states [144].

Markov models can be interpreted using 2 different approaches. The first method is called Cohort simulation. This approach is simpler and hypothesizes an imaginary cohort of patients starting together in either the same or different disease states. At each cycle of the model the appropriate transition probabilities are applied and the distribution of patients in each state of the Markov model is adjusted. Running the analysis over many cycles builds up a long term distribution profile of patients. The proportion of patients from the initial cohort that has moved to different stages is then determined. The second method of evaluation is the Markov Chain Monte Carlo (MCMC) simulation. Rather than following an entire cohort of patients simultaneously, in this method individual patients are entered and followed through the decision analytic model. The difference between methods resides in the principle that a given patient can only be at one stage at a time and therefore may or may not transit between states in any given cycle. Paths followed by different patients will vary due to random variation. While the cohort method attaches cost and effectiveness to the cumulative proportion of patients according to their stage, the MCMC sums the individual costs and effectiveness values of each individual patient and averages them over the number of simulations. Consequently the cohort method, gives an exact solution for any given length cycle and yields a precise result. In contrast, the MCMC simulation never gives the same result on any 2 occasions because it accounts for the random nature of the simulation. The absolute difference between the 2 methods is likely to be minimal. The advantage of the MCMC approach is the inherent uncertainty of the probabilistic method (first-order simulation) and estimation of the existence variance in the model [144]. Equally important is the allowance of the parameters to vary

over a given range with a distribution (second-order simulation), in addition to the uncertainty due to the way individuals travel through the model. Although covariance may exist between certain parameters of the model, the probabilistic sensitivity analysis performed in the present study assumed independence among all variables in the model.

2.7 Cost-effectiveness analysis

2.7.1 Conventional methods

Economic evaluations performed using decision analytic modeling can generate valuable information for decision makers. However, the utility of the results depends on the quality of the data input into the model and the statistical methods used. Most of the literature in the field has focused on 2 main topics: 1) The most appropriate procedure to parameterize cost-effectiveness models, 2) The statistical method to make inference given the data observed. From the perspective of the health care provider needing to decide which treatment to apply to a certain population, the mean cost and the mean effectiveness over the entire population are the parameters of interest. Inferences for anything other than means do not address the relevant questions to be answered on behalf of health care providers. The initial approach of health economists is to measure cost-effectiveness with incremental cost-effectiveness ratio (ICER) and in order to compare 2 or more strategies a decision-maker's willingness-to-pay coefficient or ceiling cost-effectiveness ratio (Rc) is stipulated. Therefore a treatment is found to be more CE relative to another should either ICER < Rc while difference in effectiveness is greater than zero or ICER > Rc while difference in effectiveness is lower than zero. Otherwise, the intervention is considered not to be CE and resources should be allocated to more worthwhile interventions. However, estimates of cost-effectiveness of health care interventions are subject to uncertainty which shall be taken into account during the decision making process.

The traditional approach of handling uncertainty due to sampling variation would be to estimate confidence intervals (CI) for the ICER and compare the interval to Rc.

Although this method does not appear contentious, it does present a number of problems because one-dimension CI can not entirely interpret a two-dimensional cost-effective equation. First, ratios pose a particular problem for standard methods of calculating CI when the denominator is a potential small value. Ratios become very unstable in such circumstances and small variations in the denominator can significantly change the result of the analysis, which would ultimately affect health care decisions. Second, a negative ratio can have opposite meanings from a decision-making perspective. Negative ratios due to negative costs are completely different from the ones due to negative effectiveness and occupy distinct locations in the cost-effective plane.

2.7.2 Net health benefit

A number of approaches to produce meaningful CI sets for ICER are available [145]. Nonetheless, dissatisfaction with these statistical methods together with problems in definitions has led some authors to suggest alternative target parameters [145]. To circumvent this problem, a solution has been suggested given the Rc for the decision-making is known. The approach involves using the Rc to rescale either the effect or the cost difference in order to provide a net health benefit (NHB) statistic in the respective parameter. Thus,

$$NHB = E_1 - C_1/Rc \quad (1)$$

$$INHB = \Delta E - \Delta C/Rc \quad (2)$$

where, ΔE stands for difference in effectiveness, ΔC for difference in costs and INHB for incremental NHB. The incremental NHB (INHB) has several advantages over the ICER. First, INHB is measured in units of health effectiveness adjusted for cost. Second, INHB has none of the ambiguities of ICER with respect to negative or positive values. Third, INHB is a monotone function and higher values are always better. Fourth, because INHB is a linear function, the distribution of INHB will approach normality even if the underlying distributions of cost and effectiveness are not normal. However, in comparison to ICER, INHB has a major drawback. NHB relies on predefined values of

Rc, whereas in fact Rc is not known. Different parties to health care decision – hospital, HMO, governments, individuals – may have different thresholds that can lead to numerous decisions.

Similarly to CI attached to ICER, cost-effectiveness acceptability curves (CEAC) aim to represent uncertainty concerning the cost-effectiveness of health care interventions [146]. CEAC is a schematic representation of the probability of cost-effectiveness for each of the strategies at different values of Rc. A correspondence between the joint distribution in the incremental cost and effectiveness plane and the CEAC exists. The CEAC is derived from the joint density of incremental costs (ΔC) and incremental effects (ΔE) for the intervention of interest, and represents the proportion of the density where the intervention is cost-effective for a range of values of Rc. In other words, the probability of cost-effectiveness of a given strategy is given by the percentage of iterations yielding the highest amount of NB among all alternatives. In the incremental cost-effectiveness (ICE) plane, it represents the proportion of iterations of a given strategy falling to the right of the Rc. However, when more than 2 alternatives are being evaluated simultaneously, significant overlap between iterations may exist and the probability of cost-effectiveness of each strategy might not be obvious in the ICE plane. CEAC does not substitute but is complementary to the ICE plane as it does not provide the relationship of dominance between alternatives.

It is important to emphasize that probability of cost-effectiveness and maximum expected benefits are different concepts. Probability of cost-effectiveness refers to the proportion of iterations yielding the highest value of NB, while expected benefit represents the mean of the distribution for NB. Although probability of cost-effectiveness and expected amount of NB conditional to Rc will frequently coincide, mismatch is likely to occur in the presence of a skewed posterior distribution for INB. Therefore, the strategy with the highest probability of cost-effectiveness is not necessarily the optimal for a given Rc [147]. The natural way of interpreting the acceptability curves are the probability that an intervention is cost-effective, as it directly addresses the issue of interest for decision-makers. Although Bayesian analysis is the only possible way of making probability statements given the data, a frequentist interpretation of acceptability

curves is possible by considering that, conditional to Rc, the curve indicates the p values on the net benefit statistic.

3 METHODS

3.1 Construction of the model

3.1.1 Design of the decision tree

In the design of a decision tree, there are basic guidelines to be considered. First, time flows from left to right, in which each successive set of branches represents the outcomes of an event or decision. Second, a variety of nodes exist and every single branch in the tree will be followed by a node at its right-end side. A decision node (square) is used to indicate a choice of facing the decision maker, which will be made based on the strict interpretation of the value of each alternative. A chance node (circle) is used to represent an uncertain event with multiple possible outcomes. Branches emanating from chance nodes are possible outcomes of a single event that are mutually exclusive. Consequently the sum of probabilities attached to all branches to the right of a chance node adds to one. Finally, a terminal node (triangle) denotes a final outcome or the end of a path in the model. All the right-most nodes in a tree must be terminal nodes which are assigned values or payoffs.

A Markov node also exists and the branches emanating from it enumerate the number of Markov states. Initial probabilities are commonly used during the evaluation of Markov models but all subsequent movements utilize transitional probabilities, which are specified at the branches to the right of the Markov states. Further details on principles of Markov modeling is provided in section 3.1.2. As illustrated in Figure 1.4, each branch emanating either from a Markov node or from chance nodes has effectiveness and costs attached to it, that are named Markov state information and transitional values respectively. Markov state information is separated into initial, incremental and final effectiveness and costs. Initial and final inputs accounted for values entered either prior or at the end of the model respectively. Consequently, values attached at these levels would be accrued only once, independently of the number of Markov cycles.

In the model we constructed, procedure, stent and complication-related costs, which are expected to be present regardless of the destination path within the strategy, were entered at the initial level. In contrary, incremental effectiveness and costs values would be summed to the model for all individuals passing through the branch and at all cycles. Incremental values of effectiveness and costs were not used in our particular model since they varied according to the patency status. Therefore, the correspondent values were inserted at the appropriate terminal node. For instance, the costs of an extra ERCP would only be added for patients who had a blocked stent. This value was consequently attached to the terminal node "occlusion'. Nevertheless, patients from both nodes "occlusion" and "patent" cycled back into same branch.

3.1.2 Case scenario

Clinically and economically relevant strategies which are routinely used to manage patients with distal malignant biliary obstruction were selected for comparison. While previous cost-effective studies evaluated different scenarios such as the initial insertion of plastic versus U-SEMS versus a plastic followed by U-SEMS, we included two other potential alternatives in our decision model [1, 2]. Except for the "piggy-back" analysis alongside the original studies, there have been no economic evaluations done on either plastic stents routinely exchanged every 3 months or covered SEMS, [40, 45]. Moreover, studies were conducted in Europe and Asia where the standards of practice and medical costs may be distinct from Canada.

A decision tree was then built up to simulate a "real life" scenario (DATA Treeage Pro 2004, TreeAge Software, Inc). Six health states were chosen based on prior clinical knowledge on the natural course of the disease: 1) Successful; 2) Unsuccessful; 3) Survive; 4) Death; 5) Patent; 6) Obstruction. The basic model structure assumed a cohort of patients with jaundice due to unresectable distal biliary malignancy obstruction. Criteria for unresectability of such tumors have been described elsewhere [148]. Patients eligible for endoscopic treatment were assigned to one of the 4 strategies under investigation: a) Initial placement of a PE stent with replacement on demand (PE-D); b)

Initial placement of a PE stent with routine replacement every 3 months (PE-Q3); c) Initial placement of an uncovered SEMS (U-SEMS); d) Initial placement of a covered SEMS (c-SEMS) (See Figure 1.4). The parameters were divided into three categories: a) proportions; b) costs and; c) months of stent patency. In the base-case scenario, probabilities of patient survival for each strategy were assumed to be the same across all interventions and were obtained from survival data from both metal and plastic stent studies. We will discuss inferences on each of these parameters and describe how uncertainty was handled. At the outset we note that, without access to primary data, we will have to assume the parameters were independent.

3.1.3 Inferences about proportions

Inferences on the probabilities of survival for patients, successful insertion and occlusion of stent, cholangitis, cholecystitis, pancreatitis and ERCP-related complications were obtained from the literature. A MEDLINE search using the National Library of Medicine database (http://www.pubmed.com) was performed with the following keywords: biliary obstruction, malignancy, stent, endoscopy, prospective, randomized controlled trial. The diagnosis was not limited to pancreatic cancer but comprised all malignancies that involved either the common bile or common hepatic duct and excluded involvement of the bifurcation and intrahepatic radicals. Also, for the base-case scenario, previous palliation with surgical biliary bypass but not endoscopic stenting was an exclusion criterion. All peer-reviewed RCTs published in English, irrespective of the publication date were considered. Studies published in abstract form were excluded. A total of 27 RCTs that aimed to evaluate patency of plastic and metal stents with or without adjuvant therapy were selected. Adjuvant therapy, defined as any intervention that could potentially prolong the patency of stents, consisted of oral medications.

Once strategies were defined, construction of the tree was undertaken by adding main chance nodes to the right of each strategy. These nodes represent the probabilities of survival of patients and successful insertion and occlusion of the stent. The time horizon of the model was 12 months but probabilities were calculated for 2-month

intervals and integrated into a Markov model. Once a full 2-month cycle was completed, an individual patient could be located in one of the four following terminal states:

- Unsuccessful initial stent insertion. This probability was attributed exclusively to for the first stent inserted. However, given the absence of hard data in the literature for rates of successful stent exchange or insertion of plastic stent through a SEMS, if stent obstruction occurred and replacement of the stent was needed, the success rate for exchange was considered to be 100%. Probabilities of insertion were similar for both strategies using plastic and both using metal stents. Rates of successful initial stent insertion were calculated by dividing the number of successful stent placements by the total number of attempts. Studies that either did not provide detailed information or randomized patients post stent insertion (i.e. studies evaluating adjuvant therapy) were not included in the final calculation.
- Death was accounted for those who had a successful stent insertion at time zero and were followed over time. Probability of death captured not only the risk attributable to the underlying disease but also to ERCP-related mortality. Survival probabilities were entered for each 2-month interval for the entire time horizon. The probability of dying was not constant throughout the model although it was assumed to be the same for all strategies under the base-case scenario. Patient and stent survival probabilities for all 2 month-periods were obtained directly from Kaplan-Meier (KM) curves whenever available. Consequently, studies which did not display KM curves were disregarded. Table 1 demonstrates the references for all probabilities obtained in the study. Once data for all studies were abstracted, the point estimates for the decision tree were calculated. If the point estimate used for the tree was derived from a single study, a distribution approximation using the absolute numbers was used. Whenever more than one source of data was available, an average of the individual rates was calculated and weighted according to the number of patients enrolled in each study. Uncertainty around the point estimates was handled by inserting a distribution shape for each parameter. A Beta distribution for the likelihood data was chosen according to the number of

"successes" and 'failures" observed for all 3 parameters. Advantages of the beta distribution family such as finite interval ($0 < X < 1$) and absence of zero, make it suitable for several scenarios including economic models [149]. The beta distribution can be mathematically described as follows:

$$f(X) = \kappa X^{m-1}(1-X)^{n-1} \quad \text{where} \quad \kappa = \Gamma(n+m)/\Gamma(n)\Gamma(m)$$

and n and m are positive integers, and $\Gamma(n)$ is Euler's gamma function.

- For patients who survived during the 2-month cycle, possible outcomes remain. The stent inserted could either remain patent or obstruct. While unsuccessful insertion and death were considered final (absorbing) states, patients reaching the terminal nodes 'patent' and 'occlusion' were cycled back into the decision at the level of stent insertion. These patients would return to the survival and stent occlusion chance nodes and the Markov model would continue for a total of 6 cycles or 12 month time horizon.

The references from which data were obtained, and types and parameters of distribution used for proportions in the decision tree are summarized in Table 3.1.

Item	Parameters	Confidence Interval (CI)	Distribution	Reference
Probability of Cholangitis of C-SEMS	$(\alpha; \beta) = (12; 37)$	(0.13; 0.36)	Beta distribution	[35]
Probability of Cholecystitis of C-SEMS	$(\alpha; \beta) = (2; 40)$	$(10^{-3}; 0.11)$	Beta distribution	[40]
Probability of Cholangitis of PE-D	$(\alpha; \beta) = (23; 33)$	(0.28; 0.53)	Beta distribution	[35]
Probability of Cholangitis of PE-Q3	$(\alpha; \beta) = (23; 33)$	(0.28; 0.53)	Beta distribution	[35]
Probability of Cholangitis of U-SEMS	$(\alpha; \beta) = (12; 37)$	(0.13; 0.36)	Beta distribution	[35]
Probability of ERCP complication	$(\alpha; \beta) = (189; 988)$	(0.13; 0.18)	Beta distribution	[150]

Probability of occlusion of C-SEMS	(α; β) (10^{-6}; 57) (1.71; 55.29) (1.65; 53.63) (4.29; 49.34) (10^{-6}; 49.34) (2.96; 46.38)	 (10^{-6}; 0.06), ($2*10^{-4}$; 0.07), (10^{-4}; 0.07), (0.17;0.15), (10^{-6}; 0.07), ($6*10^{-3}$; 0.12)	Beta distribution	[40]
Probability of occlusion of PE-D	(α; β) (66.41; 224.59) (61.21; 163.37) (38.12; 125.25) (14.74; 110.50) (2.57; 107.93) (4.16; 103.76)	 (0.18; 0.27) (0.21; 0.33) (0.16; 0.29) (0.06; 0.17) (10^{-3}; 0.05) ($7*10^{-3}$; 0.07)	Beta distribution	[35, 106, 110, 115, 126, 151]
Probability of occlusion of PE-Q3	(α; β) (2.04; 31.96) (3.83; 28.12) (5.34; 22.78) (2.05; 20.73) (1.65; 19.07) (1.52; 17.54)	 (10^{-3}; 0.13) (0.02; 0.23) (0.05; 0.33) ($2*10^{-3}$; 0.20) ($5*10^{-4}$; 0.19) (10^{-4}; 0.19)	Beta distribution	[45]
Probability of occlusion of U-SEMS	(α; β) (16.37; 423.63) (25.12; 398.50) (21.26; 377.23) (23.25; 353.98) (33.70; 320.27) (16.18; 304.09)	 (0.02; 0.05) (0.03; 0.08) (0.03; 0.07) (0.03; 0.08) (0.06; 0.12) (0.02; 0.07)	Beta distribution	[35, 36, 40, 134, 136, 151]
Probability of pancreatitis of C-SEMS	(α; β) = (5; 52)	(0.02; 0.16)	Beta distribution	[40]
Probability of pancreatitis of U-SEMS	(α; β) = (1; 54)	($7*10^{-5}$; 0.05)	Beta distribution	[40]
Probability of successful insertion PE stent	0.88			[19, 35, 36, 97, 105-107, 110, 112, 114, 115, 152, 153]
Probability of successful insertion SEMS	0.927			[35, 36, 40, 135, 136]
Probability of Survival	(α; β)		Beta	[15, 16,

	(482.71; 130.29) (388.51; 94.19) (326.25; 62.26) (278.83; 47.41) (261.85; 16.97) (252.74; 9.11)	(0.75; 081) (0.76; 0.83) (0.81; 0.88) (0.81; 0.89) (0.91; 0.96) (0.94; 0.98)	distribution	35, 40, 43, 45, 106, 107, 110, 112, 123, 124, 126, 128, 135, 151]

Table 3.1 Parameters, distributions and sources of estimates in the decision model

3.1.4 Inferences about costs

The second variable for the CEA is cost, which in this study is measured in 2004 Canadian dollars. Several types of costs comprise the total resource use to be considered in comparing health care interventions. However, numerous sources of costs are often very difficult to quantify as it involves direct, indirect, opportunity and intangible costs. Therefore, often, surrogate markers such as hospital charges, bed price, average hospital stay and reimbursement collection data such as from Medicare have to be used to estimate patient specific resource usage [154, 155]. In view of the difficulty of capturing all true costs, a decision on the types of costs and the perspective to be adopted has to be made *a priori*. The choice of the perspective assumes important role in the way health care resources are selected into the model and estimates are calculated. For instance, a patient's time from the societal perspective reflects a wage whereas a provincial perspective may value it at zero. In the latter case, costs were priced from the hospital perspective rather than the patient or health care provider involved in the financing of personal health services. The reason behind this selection is that most medical resource consumption decisions are divorced from the liability for their financial implications. Thus, an additional blood or imaging test ordered for a patient will not impose any additional burden on the insured patient as the highest cost component of the health care system is the hospital care. Also, results from another perspective such as societal may not be applicable to real life as it can put physicians in an untenable position. Indeed, to represent society's interest, interventions that could potentially harm a patient economically would have to be denied irrespective of the potential medical benefit; but this would be a violation of medical ethics by not representing patients' best interest.

It has long been recognized that, owing to imperfection in the health care market, market prices may not reflect opportunity costs. However, due to the perspective adopted in this study, adjustments of values were not made since actual charges may be more relevant than costs. Also, due to the short time horizon (12 months), no allowance for differential timing of costs was given. Thus, the unit of money spent at the beginning of the treatment was assumed to be worth the same at the end of the study. Once the perspective is chosen, the types of costs included in the analysis must be declared. Costs may be classified according to their behavior (fixed, variable or intangible) and source (direct medical or non-medical and indirect). Only "initial" or "induced" direct medical health care resources related to the strategies under evaluation, such as costs of procedures (including devices), stents and medical complications were considered in this analysis. Indirect or direct non-medical costs as well as costs 'averted" by the interventions under study were not considered. The following seven direct medical costs were attached to the decision model: a) Market price of PE stent; b) Market price of U-SEMS; c) Market price of C-SEMS; d) Cost of therapeutic ERCP at the Montreal General Hospital (MGH); without physician fees; e) Cost of percutaneous transhepatic cholangiogram (PTC) according to the Canadian Institute for Health Information (CIHI); f) Cost of cholangitis; pancreatitis and cholecystitis according to CIHI; g) Cost of ERCP-related complications. The values and source of costs are shown in Table 3.2.

The medical resources utilized in the diagnosis of complications which occurred in our model were abstracted from CIHI 2003-2004 (Canadian Institute for Health Information – http://www.cihi.ca). The cost data (Resource Intensity Weights (RIW)) are based on outputs (375,000 records) provided by hospitals from Ontario, Alberta and British Columbia. RIW is a relative resource allocation methodology for estimating hospital's direct (supplies, equipment etc...) and indirect (administration, plant maintenance, laundry, food, etc...) inpatient costs, which does not include the professional fees for the physicians. The RIW also excludes the atypical cases.

Item	Value (CDN$)	Distribution	Reference
Cholangitis	Range: 2020- 6850 Likeliest: 4165	triangular	CIHI 2004
Cholecystitis	Range: 2020- 6850 Likeliest: 4165	triangular	CIHI 2004
C-SEMS	Range: 1300 - 1800 Likeliest: 1650	triangular	Boston Scientific
ERCP	Range: 772-1281 Likeliest: 1050	triangular	CIHI 2003
ERCP complication	Range: 500 -1000 Likeliest: 639	triangular	CIHI 2004
Pancreatitis	Range: 2139-10218 Likeliest: 6764	triangular	CIHI 2004
PE stent	Range: 135 -170	rectangular	Wilson-Cook
PTC	905	-	CIHI 2003
U-SEMS	Range: 1200 - 1600 Likeliest:1400	triangular	Boston Scientific

Table 3.2 Costs used in base-case scenario and sources of the estimates.

PE-D: Polyethylene stent with replacement on demand; PE-Q3: Polyethylene stent routinely replaced every 3 months; U-SEMS: Uncovered self-expandable metal stent; C-SEMS: covered self-expandable metal stent; PTC: Percutaneous transhepatic cholangiogram

CIHI classifies the RIW per age group and per clinically relevant and statistically homogeneous Case Mix Groups (CMG) based on the patient's Most Responsible Diagnosis (MRD). Each CMG is divided in 4 complexity levels, being the least complex cases at level 1 and the most severe cases at level 4. In addition, age categories existed for each level of severity and the final costs resulted from a combination of 2 strata (18-70 years and older than 70 years) of age-specific costs. We selected the CMG and the age group which most likely represented the group of diagnosis needed for the model. Hence, values provided by CIHI represent an estimate of the mean cost of disease for a subpopulation of patients defined by the level of complexity/severity and age. Considering that unresectable distal malignant obstruction and its underlying causes are more commonly seen in elderly individuals who often have coexistent medical conditions, we arbitrarily selected 3 (range 1 – 4) as the complexity level which would best correlate to the population under investigation and used the costs associated to levels

1 to 4 as the limits for the distribution. Costs for stents and PTC were provided as a single value, and costs for ERCP were derived from a micro cost-analysis performed at the MGH using similar methodology to previously published work [156]. This analysis included all items which are regularly used for an ERCP such as space cost (cleaning, electricity, maintenance), salary of the professionals, consultation, equipment (purchasing price, maintenance, repair), drugs and administrative expenses (fax, telephone, reception); subsequently costs were attached to all items. Each cost was estimated according to the micro analysis method in which a unit price was obtained based on an average cost per use for each item.

Uncertainty around estimated values was handled entering a distribution. A distribution for costs was entered in the model but this is known not to have a normal shape [157]. Costs are bounded below by zero and a small percentage of patients exhibit extremely high values, these types of distributions tend to be skewed with a long tail to the right. Unfortunately, the median value in economic studies are not as important as the mean and consequently distributions other than normal have been claimed to be more appropriate. This intrinsically non-normal patient-level data leads to concerns about the use of methods based on normal distribution. Faced with such difficulties, it is attractive to consider simple non-parametric statistical methods that may be applied without regard to the shape of the population distribution. Therefore, in the absence of the actual data or parameters for the distribution, triangular and rectangular distributions were chosen for the model. By selecting these type of distributions, we assumed that all costs contained in the range of values had chances of being sampled in the probabilistic sensitivity analysis. Lower and upper bounds for the costs of stents/ procedures and diagnosis of diseases were obtained from the published literature and the CIHI categories of complexity (1 -4).

3.1.5 Inferences about stent patency

Total time of stent functioning measured in months was the unit of effectiveness in this analysis. The decision model was designed so that patients who successfully received a given stent were at risk of dying and having stent occlusion during each 2-month cycle.

Hence, taking into account the chances of surviving and requiring a new stent insertion, the model aimed to capture the average number of stent patency-months patients in each strategy would experience at the end of the 12 months. The measurement of interval time between insertion and occlusion of the stent was obtained from survival curves for stents in the selected RCTs. The ascertainment of stent occlusion was defined 'a priori' in each study and consisted of recurrence of jaundice or development of constitutional symptoms or acute cholangitis after initial laboratorial and clinical improvement with stent insertion. Although bile plugs and tumor ingrowth explain most cases of stent occlusion, our model assumption considered all potential causes of dysfunction regardless of the actual mechanism. This is due to the suboptimal accuracy of the clinical and laboratory tests used to select individuals with stent blockage. The modest sensitivity of these methods of ascertainment, which may result in failures to appropriately diagnose an episode of stent obstruction in a timely manner, occurs because bile drainage may still happen alongside an obstruct stent and therefore not lead to significant clinical or laboratory changes. In contrast, conditions such as metastatic involvement of the liver due to progression of the underlying malignancy may result in abnormal findings suggestive of stent obstruction but indeed in the presence of a fully working prosthesis. Diagnostic misclassification, under and overestimation of stent obstruction will ultimately lead to an inadequate use of the resources. Some patients with stent obstruction that would benefit of stent exchange are not captured by the periodic assessments, while others are referred for a repeated procedure and an unnecessary stent exchange; but this is what occurs in real-life. Therefore, stent patency and re-intervention are not always correlated but for effectiveness purposes, whenever a repeated procedure was necessary, a stent was considered to have failed and stent exchange is assumed to have been undertaken. Hence, this effectiveness model aimed to capture any event which might subsequently lead to another intervention and its associated costs.

In the decision model, patients who were alive at the end of a cycle, and did not experience stent obstruction during this time, were granted 2 months of stent patency (effectiveness measurement). For patients who were alive at the end of the cycle but indeed required an additional procedure for stent exchange, a total of 1 month of stent patency was given. This value of effectiveness comes from the uncertainty surrounding

the time when the occlusion may have occurred within the 2-month cycles. Although the proportion of patients in the occlusion node at the end of each cycle is known, it is just an estimate of the cumulative probability of having a stent occluded. This rate does not give any information on the probability of obstruction over time (hazard function). Consequently, we used the midpoint of the interval between 0 and 2 as our best guess for the actual unknown time of occlusion in each cycle [158]. The same rationale is valid for patients who died. The probabilities of survival are also entered for periods of 2 months and an unknown percentage of these patients died with a patent stent. The mean value is again the best estimator of the unknown amount of time an individual patient spent with a patent stent before expiration.

3.2 Analysis

In order to assess the cost-effectiveness of each strategy and compare the results with alternative interventions, different statistical methods were used. Since the mean value for the cost and effectiveness is the parameter of interest for decision-makers, a deterministic CEA was performed and the sensitivity analysis used to evaluate the model under different assumptions. ICER is the parameter of interested as it determines the amount of extra resource needed to obtain one additional unit of effectiveness once the next more costly and effective strategy is selected. Thus, the ICER for the strategies are summarized as follows:

$$ICER_{C\text{-}SEMS} = C_{C\text{-}SEMS} - C_{PE\text{-}D} / E_{C\text{-}SEMS} - E_{PE\text{-}D}$$

$$ICER_{U\text{-}SEMS} = C_{U\text{-}SEMS} - C_{C\text{-}SEMS} / E_{U\text{-}SEMS} - E_{C\text{-}SEMS}$$

$$ICER_{PE\text{-}Q3} = C_{PE\text{-}Q3} - C_{C\text{-}SEMS} / E_{PE\text{-}Q3} - E_{C\text{-}SEMS}$$

where C=cost and E=effectiveness, PE-D is the reference for C-SEMS and U-SEMS and PE-Q3 are dominated strategies. Selection of variables and values for sensitivity analysis was done based on prior clinical information. Ranges of values for the sensitivity analysis were extracted from the raw data utilized for calculation of point estimates (e.g. probabilities of stent occlusion and survival of patients) and from estimates available in

databases (e.g. CIHI). The following variables were evaluated by the one-way sensitivity analysis: 1) Life expectancy: because PE stents occlude on average after 3 months, patients with short life expectancy are unlikely to benefit of more effective and expensive stents such as SEMS; 2) Cost of ERCP: given its high variability across different institutions and countries and because it explains a significant fraction of the total cost of the treatment, the cost of ERCP was also analyzed in the sensitivity analysis; 3) Ratio ERCP/SEMS: costs of ERCP are susceptible to significant variations depending on local costs and practice standards. Therefore, in order to make the results of this analysis more generalizable, a cost ratio between ERCP and U-SEMS (REuS) or ERCP and C-SEMS (REcS) was entered in the decision model and varied in the sensitivity analysis; 4) Cost of U-SEMS and C-SEMS.

A probabilistic approach was subsequently done by entering distributions for the variables in the model. Each distribution represents the uncertainty about a specific parameter given the data available and the best judgment in the absence of data. Using a Monte Carlo Markov Chain (MCMC) simulation with 10,000 iterations, random sampling from the distribution of each variable permitted the software to accumulate a set of computed values across repeated sampling. This entails making random draws of the uncertain parameters from their probability distribution, running the model for each simulated set of parameters and collecting the outputs from each run. These are then a random sample from the induced probability distribution of model outputs. Outputs from the model include mean costs and mean effectiveness. In comparing the cost-effectiveness of two treatments, uncertainty about incremental mean costs and effectiveness can be displayed in the ICE plane as a scatterplot of the Monte Carlo output sample. The results obtained from MCMC simulation provided expected values for each strategy and allowed performance of statistical inference using a variety of methods such as ICER and INHB. The results of the probabilistic CEA permit decision makers to select the strategy genuinely most cost-effective with a certain level of confidence.

Once the probability of cost-effectiveness for each strategy according to Rc values has been displayed, determination of the difference between strategies and statistical inferences using the standard approach of estimating a confidence interval for a

parameter (INHB) were used. However, despite the advantages, statistical implications of hypothesis testing and the implications of a non-significant cost-effective result on decision making remains present. It turns out that, conditional to Rc, economically superior treatments can be chosen according to the relation of CI and the upper or lower limit of an area of clinical equivalence. However, when mutually exclusive strategies are being compared and a decision cannot be deferred, selection of the most advantageous strategy should be based on the mean amount of NB irrespective of the level of uncertainty that exists [159]. Indeed, failure to choose the strategy yielding the highest amount of NB will result in unnecessary costs. Statistical inference is important because it provides an estimate of the existent level of uncertainty, and also gives an estimate of the impact of the costs of making the wrong decision (loss function). The expected cost of uncertainty is determined by the probability that a treatment decision will be wrong given the available data. This is also referred as Expected Value of Perfect Information (EVPI), since perfect information eliminates the chance of making wrong decisions. Consequently, EVPI is also the maximum price decision makers want to pay to obtain such information. EVPI for a strategy j is calculated as follows:

$$\text{EVPI} = \text{Expected } \max_j \text{NB} - \max_j \text{Expected NB} \quad [159]$$

If costs of additional research to answer the uncertainty are less than EVPI for the population who can potentially benefit of it, acquisition of further information is considered cost-effective and may be pursued. In contrast, if performance of studies to address the research questions costs more than the maximum loss attributable to a wrong decision, performance of further research is deemed not to be cost-effective.

4 RESULTS

4.1 Overview

The results for this CEA are presented from both deterministic and probabilistic approaches. In both methods, we defined the optimal strategies for the base model and try to identify variables more likely to influence the model. The main objective in presenting both methodologies is not only to demonstrate the benefits and limitations of each, but also to obtain results which can be applied to clinical practice.

4.2 Deterministic cost-effectiveness analysis

4.2.1 Cost and benefits of programs

Table 4 shows the mean values for costs, effectiveness and incremental values for all 4 strategies which allowed the calculation of ACER and ICER. C-SEMS have the lowest ACER followed by U-SEMS, PE-D and PE-Q3, and these values represent the average costs for the production of one unit of output (e.g. month of stent patency). However, when mutually exclusive strategies are being evaluated, the deterministic rule is to eliminate dominated programs and calculate ICER. Considering the mean estimates from the parameters in the decision tree, PE-D is the most cost-effective intervention, followed by C-SEMS at an ICER of $146.64 per month of stent patency, and the other two strategies are considered dominated because of their lower effectiveness at higher costs (Table 4.1).

Output / Strategy	Cost	Effectiveness	ACER ($/month stent patency)	ICER ($/month stent patency)
PE-D	2,881.00	5.19	554.58	
C-SEMS	2,976.90	5.84	508.99	146.64
U-SEMS	3,127.80	5.71	547.16	Dominated
PE-Q3	4,467.20	5.39	828.56	Dominated

Table 4.1 Cost and effectiveness values obtained through the deterministic approach

PE-D: PE stent exchanged on demand, PE-Q3: PE stent exchanged routinely every 3 months, U-SEMS: Uncovered self-expandable metal stent, C-SEMS: Covered self-expandable metal stent. SD: standard deviation

Figure 4.1 shows the relative position of all strategies in the cost-effectiveness plane according to their mean values of cost and effectiveness. An imaginary line connecting these two strategies in the cost-effective plane delineates a "cost-effectiveness frontier" (CE frontier) where strategies located to the rightmost of this line are deemed cost-effective while the ones to the left side would be disregarded as being either more costly, less effective or both. Under this scenario, PE-Q3 and U-SEMS are considered dominated strategies and should not be funded given the existence of more cost-effective strategies.

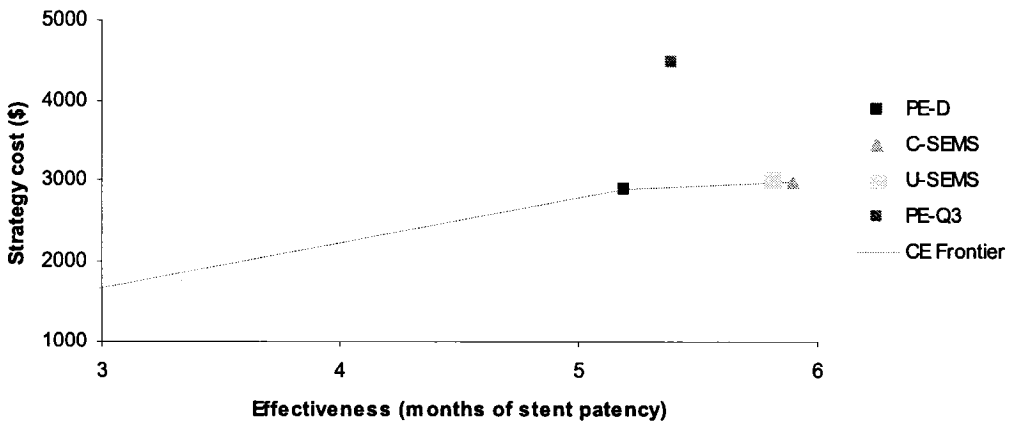

Figure 4.1. Cost-effectiveness plane using the deterministic approach

4.2.2 Sensitivity analysis

In order to check the robustness of the model and how final results are affected by isolated variations of parameters in the model, one-way sensitivity analysis was performed.

- Life expectancy: One-way sensitivity analysis suggests that C-SEMS is the optimal strategy if probability of survival at 12 months is greater than 83%. Moreover, U-SEMS is also preferred to PE-D above this level of survival expectancy suggesting that more efficient stents should be used in patients expected to live longer and consequently at a higher risk of experiencing an episode of stent obstruction (Figure 4.2)

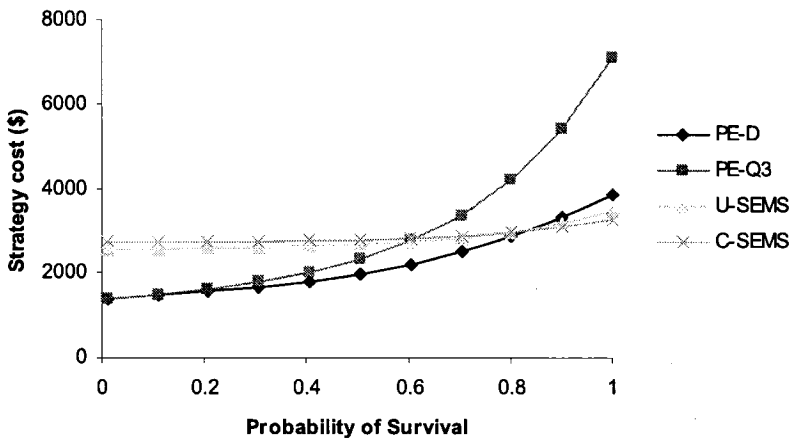

Figure 4.2. One-way sensitivity analysis on expected probability of patient survival.

- Cost of ERCP: Figure 4.3 shows the estimated value (EV) of each strategy as price of the ERCP changes. Because it implies a routine ERCP every 3 months, PE-Q3 is always the most expensive alternative except when ERCP costs are unrealistically low. In contrary, at low ERCP values U-

SEMS and C-SEMS have a higher upfront cost which is mainly driven by the price of the stent. However, the EV for metal stents increase at a lower rate than PE stent strategies, as they have a longer patency rate and on average, patients require a lower number of ERCPs than those treated with PE stents. The graph also shows a threshold value for ERCP cost of $1281.90, where C-SEMS becomes more expensive than PE-D.

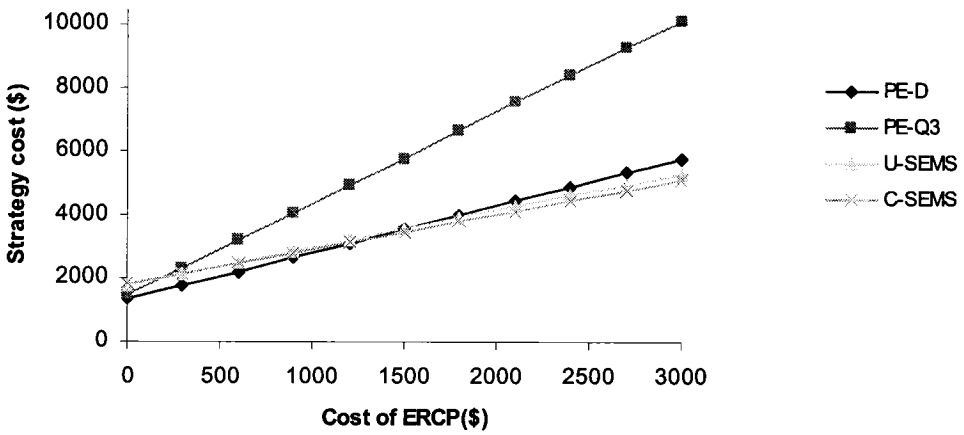

Figure 4.3. One-way sensitivity analysis on the cost of ERCP

- Ratio ERCP/SEMS: The results indicated that U-SEMS overcomes PE-D when REuS $\geq$ 0.5 or RcSE $\geq$ 0.4 and these ratios can then be directly applied to real cost data. For instance, given the REuS and REcS calculated and assuming U-SEMS and C-SEMS cost are $1400 and $1800 respectively, U-SEMS would be the optimal strategy if local costs for ERCP is greater than $700. Since ERCP costs have a much larger impact on the total costs of strategies utilizing PE stents because of the higher average number of procedures needed in these strategies, insertion of a metal stent becomes preferable as costs of ERCP increases, assuming costs for U-SEMS and C-SEMS remain constant. This result can be also appreciated in the one-way sensitivity analysis for ERCP costs.

- Cost of U-SEMS and C-SEMS: Figure 4.4 shows that a reduction of $131.70 or more on the mean cost of U-SEMS (threshold U-SEMS price $1268.30) would make this alternative the most cost-effective if all the other parameters of the model remained constant. Similarly, a drop in the mean price of C-SEMS from $1800.00 to $1485.60 would make this alternative more costly than PE-D (Figure 4.5).

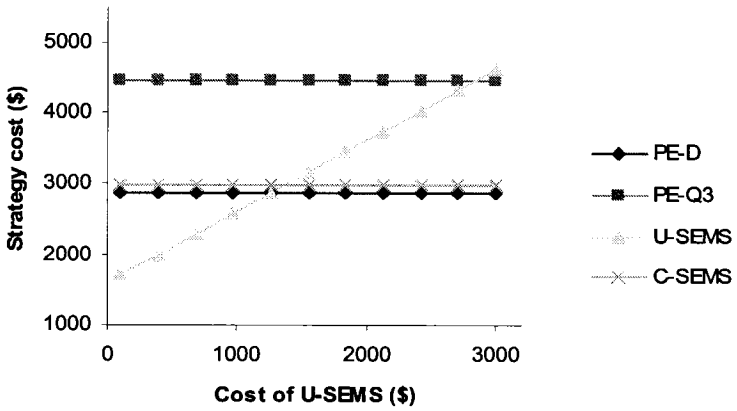

Figure 4.4. One-way sensitivity analysis on cost of U-SEMS

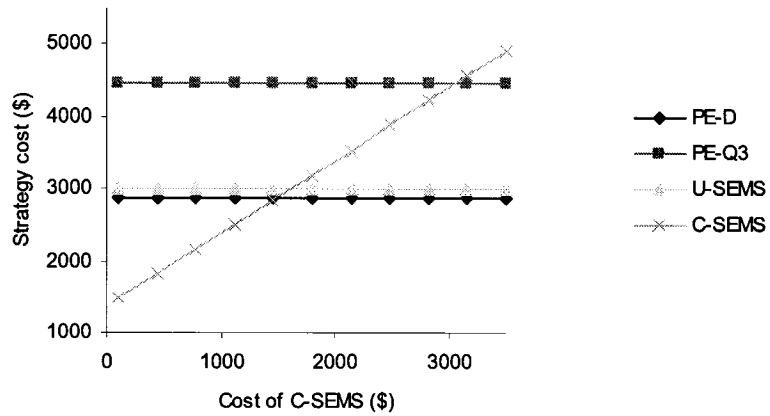

Figure 4.5. One-way sensitivity analysis on cost of C-SEMS

4.3 Probabilistic cost-effectiveness analysis

4.3.1 Cost and benefits of programs

The mean cost of each strategy per patient and the 95% CI was also obtained using MCMC with 10,000 iterations (Table 4.2). Although up-front costs of PE stents are much lower than U-SEMS and C-SEMS, the final costs of each strategy are also a function of costs attributable to the number of ERCPs and complications associated with each intervention. MCMC demonstrates that the number of patency-free months obtained with C-SEMS (mean= 5.89 months, SD= 0.19) and U-SEMS (mean= 5.81 months, SD= 0.18) was superior to both PE-D (mean= 5.19 months, SD= 0.18) and PE-Q3 (mean= 5.39 months, SD= 0.18). Consequently, patients managed with metal stents have a lower average number of procedures than patients treated with PE stents. The estimated number of ERCPs over a 12-month time horizon in patients treated with PE-D (mean=1.49, SD=0.03) or PE-Q3 (mean=2.89, SD=0.06) was superior to U-SEMS (mean=1.18, SD=0.02) and C-SEMS (mean=1.09, SD=0.03). In addition, the higher number of procedures and the lower patency duration observed in the strategies involving PE stent contributed to an increased number of expected overall complications (e.g. stent and ERCP-related cholangitis, pancreatitis, cholecystitis, bleeding, perforation) in both PE-D (mean=0.42, SD=0.03) or PE-Q3 (mean=0.52, SD=0.03) when compared to U-SEMS (mean=0.24, SD=0.01) and C-SEMS (mean=0.20, SD=0.02). (Table 4.2).

Output / *Strategy*	Estimated value [$, (CI)]	Patency-free time [months, (CI)]	ERCP [number/patient, (CI)]	Complications [number/patient, (CI)]
PE-D	2,884.07 (2,479.59; 3,288.54)	5.19 (4.83; 5.54)	1.49 (1.43; 1.54)	0.42 (0.36; 0.47)
PE-Q3	4,472,20 (3,999.53; 4,944.46)	5.39 (5.03; 5.74)	2.89 (2.77; 3.00)	0.52 (0.46; 0.57)
U-SEMS	3,012,39 (2,729.80; 3,294.97)	5.81 (5.45; 6.16)	1.18 (1.14; 1.21)	0.24 (0.22; 0.25)
C-SEMS	2,980.47 (2,653.82; 3,307.11)	5.89 (5.51; 6.26)	1.09 (1.03; 1.14)	0.20 (0.16; 0.23)

Table 4.2 Estimated outputs for PE-D, PE-Q3, U-SEMS and C-SEMS using MCMC

4.3.2 Monte Carlo simulation

Despite its simplicity and widespread use, deterministic approach to CEA does not recognize the existence of uncertainty in the model as the inferences are derived from single point estimates for each parameter. While inputs in the model are systematically varied over a range of values in deterministic sensitivity analysis, probabilistic sensitivity analysis accounts for the relative plausibility of the unknown parameters. Posterior marginal and joint distributions for cost and effectiveness can be formed by performing repetitive probabilistic sampling (MCMC), which allows inferences on incremental cost-effectiveness to be made.

Similarly to the deterministic analysis, a "CE frontier" is constructed to demonstrate strategies which are likely to be considered "cost-effective" given the existing alternatives. Figure 4.6 displays the scatterplot cost-effectiveness graph for all strategies after 10,000 iterations using MCMC simulation. PE-Q3 remained a dominated strategy as all individual replications fall into a more expensive area than the remaining interventions and indeed provided no more effectiveness. Initially regarded as most cost-effective alternatives, PE-D and C-SEMS strategies have their iterations split by the "CE frontier" line and therefore have a certain probability of being cost-effective given the alternatives available. Perhaps the most dramatic discrepancy in results between probabilistic and deterministic methods affects U-SEMS. Although considered a dominated strategy by the deterministic method, U-SEMS cannot be disregarded as a possible cost-effective strategy in face of the existing alternatives as a significant fraction of the replications observed lie on the cost-effective side of the "CE frontier" and there exists significant overlap with the iterations from C-SEMS.

Table 4.3 shows the cost, effectiveness, ratios and confidence intervals for all 4 strategies obtained with the MCMC simulation. The mean values are similar to those obtained in the deterministic approach and shown in Table 4.1. The trivial differences observed can be explained by the probabilistic and random variability existing with the MCMC. Using the ratio-based decision rule, PE-D is the most cost-effective strategy as it is the least expensive and produces on average less units of effectiveness than the next most expensive alternative (C-SEMS). An extra unit of effectiveness (month of stent patency) can be obtained at an increment cost of $110.49 by choosing C-SEMS. Nevertheless, statistical inferences on ICER values is difficult to make given the large, uninformative distributions of these ratios.

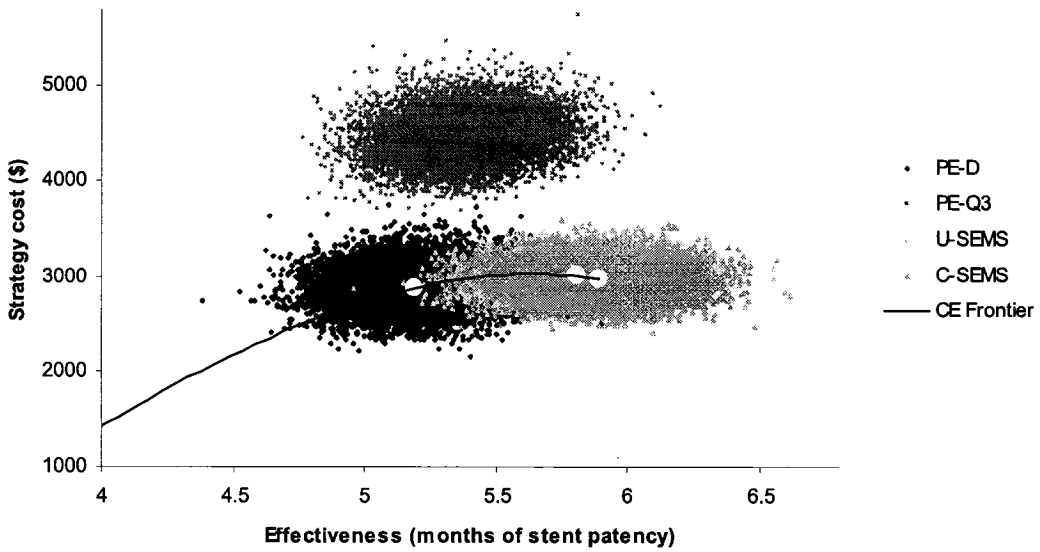

Figure 4.6. Cost-effectiveness plane after MCMC (10,000 iterations).

Output / Strategy	Cost ($, [CI])	Effectiveness (months, [CI])	ACER ($/month stent patency, [CI])	ICER ($/month stent patency, [CI])
PE-D	2,884.07 (2,479.59; 3,288.54)	5.19 (4.83; 5.54)	556.4 (472.12; 640, 67)	
C-SEMS	2,980.47 (2,653.82; 3,307.11)	5.89 (5.51; 6.26)	506.2 (442.30; 570.09)	110.49 (-7,365.91; 7,586.89)
U-SEMS	3,012,39 (2,729.80; 3,294.97)	5.81 (5.45; 6.16)	519.3 (462.85; 575.74)	-910.54 (-177,104.70; 175,283.60)
PE-Q3	4,472,20 (3,999.53; 4,944.46)	5.39 (5.03; 5.74)	830.1 (734.25; 925.94)	-7,212.33 (-301,021.10; 286,596.50)

Table 4.3. Cost and effectiveness values obtained through the probabilistic approach

PE-D: PE stent exchanged on demand, PE-Q3: PE stent exchanged routinely every 3 months, U-SEMS: Uncovered self-expandable metal stent, C-SEMS: Covered self-expandable metal stent. CI: confidence interval. ACER: average cost-effectiveness ratio; ICER: incremental cost-effectiveness ratio

The cost-effectiveness for individual strategies can also be demonstrated according to the decision makers' willingness to pay for one unit of effectiveness. Figure 4.7 shows the average amount of NHB provided by each strategy according to Rc. The mean NHB obtained from each strategy tend to increase and approximate as Rc grows, and plateau when the Rc for each month of stent patency is set beyond acceptable levels. The value of the NHB which provides zero NHB (intersects x axis) correspond to the average cost-effectiveness ratio for a given strategy as shown in Table 4.3. Except for PE-Q3, the remaining strategies have equivalent average cost-effectiveness ratios, with C-SEMS having the lowest value. As Rc increases, NHB sweeps out the CE frontier which is identical to the frontier produced by the incremental cost-effectiveness ratio (Figure 4.8). In comparison to this analysis, the determination of NHB demonstrates that C-SEMS will

line the CE frontier for all WTP values associated to a positive NHB (Figure 4.7). Although not explicity shown in Figure 4.7, C-SEMS will only yield less mean NHB than PE-D for low Rc values, which provide a negative mean NHB. For instance, if the policy maker is willing to pay only CDN$10 for the palliation of a patient with distal malignant biliary obstruction, the mean NHB for PE-D (-283.21) will be higher than C-SEMS (-292.15). However, for all WTP values that yield a positive mean NHB, C-SEMS is the preferred strategy because it provides a higher amount of effectiveness adjusted its costs.

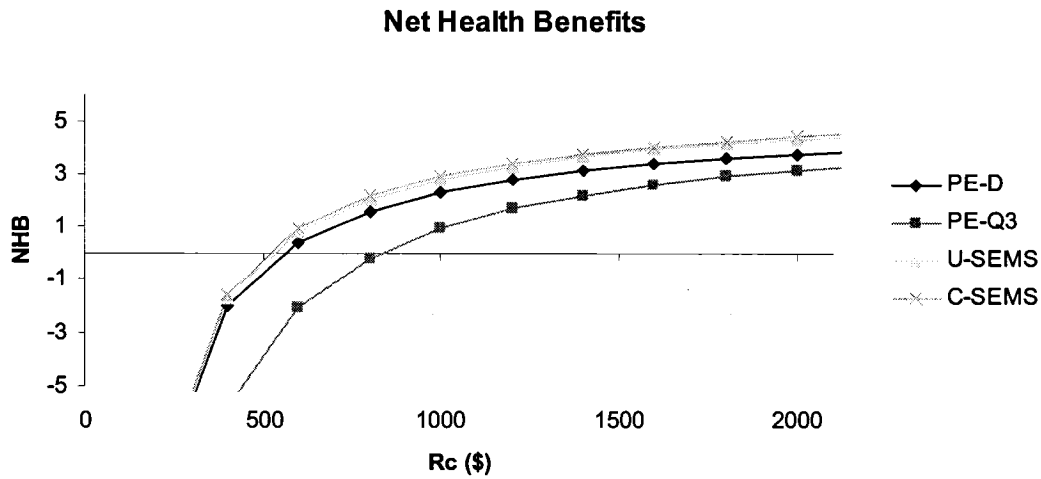

Figure 4.7. Mean net health benefit for each strategy according to willingness to pay.

4.3.3 Probability of cost-effectiveness

Calculation of incremental cost-effectiveness based on mean values shows PE-D to be the most cost-effective, followed by C-SEMS if the decision maker is willing to pay a minimum of $110.49 for an extra month of patency (Table 4.3). U-SEMS and PE-Q3 are considered dominated programs. However, the limits of the CI for the ICER is so wide that prevents comparisons between strategies and consequently the sequence of strategies according to cost-effectiveness remains undetermined. The joint posterior distribution for incremental costs and effectiveness also indicated these results are not necessarily consistent under all assumptions (Figure 4.8). PE-D does not appear in the graph as it is

the reference category for calculation of the incremental costs and effectiveness relative to C-SEMS. Thus, PE-D served as the reference strategy for C-SEMS, while C-SEMS was for the remaining 2 strategies. Although a considerable proportion of iterations for incremental costs and effectiveness for C-SEMS fall into the NE quadrant of the cost-effective plane, the probability it can fall in any of the remaining 3 quadrants is not remote. ICER for C-SEMS indicates that its cost-effectiveness can vary from dominated (more costly and less effective) to dominant (less costly and more effective) according to Rc. Along the same line, incremental values between U-SEMS and C-SEMS occupy all quadrants of the ICER plane. A considerable proportion of these iterations fall in the SE or northeast (NE) quadrants indicating that it is not necessary a dominated strategy as proposed by the deterministic analysis. When compared to C-SEMS, ICER for PE-Q3 indicates this strategy to be dominated (less effective and more costly) as most iterations fall in the northwest (NW) quadrant of the ICE plane. PE-Q3 would become cost-effective only under unacceptably high Rc values, when a proportion of the iterations located in the NE quadrant would fall to the right of Rc.

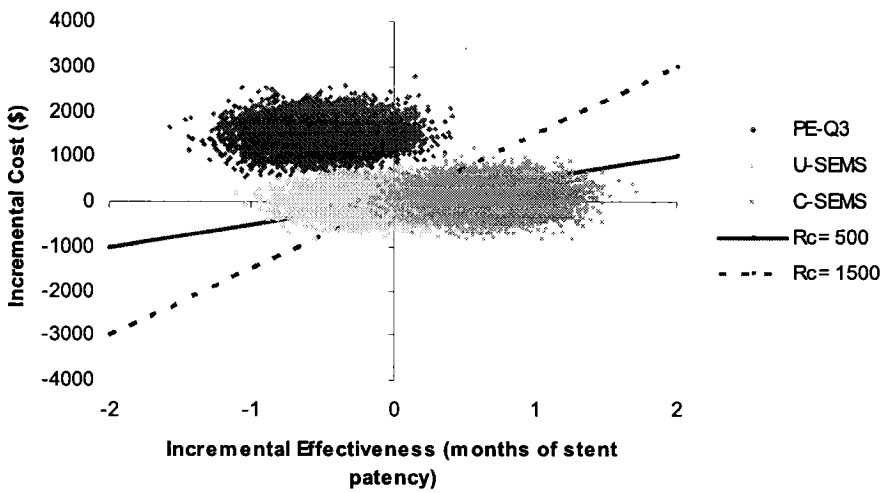

Figure 4.8. Scatterplot of the incremental cost-effectiveness plane.

The diagonal dashed lines indicate the pair of incremental cost and effectiveness values when health provider is willing to pay $500 and $1,500 per month of stent patency. The proportion of iterations falling to the right of the Rc represent the probability of cost-effectiveness conditional to the decision maker's willingness to pay. Another method to illustrate the probability of cost-effectiveness (proportion of iterations from each strategy falling to the right of the Rc) is through CEAC.

Figure 4.9 illustrates the CEAC for all strategies. The probability of cost-effectiveness of each strategy is displayed according to the WTP value. The graph demonstrates that the probability of cost-effectiveness (the percentage of iterations for each strategy which provides the highest NHB value) changes according to Rc. Nevertheless, the amount of NHB provided by each strategy will always increase as the willingness to pay raises (Figure 4.7). When the decision maker's willingness to pay for each month of stent patency approaches zero, the least expensive alternative (PE-D) has the highest probability among all strategies of being cost-effective (54.6%). However, looking at Figure 4.7 we can see that this is not realistic since the mean NHB at low Rc values is negative. PE-D will only give positive NHB at Rc values above $556.40 (Figure 4.7). For instance, on average patients with distal malignant biliary obstruction who receive palliation with PE-D consume $556.40 dollars/month of stent patency. Rc values lower than that will be not sufficient for the management of this condition and therefore can not be accepted from the clinical perspective. As Rc increases and for all values yielding positive mean NHB, PE-D becomes less likely to be cost-effective while U-SEMS and C-SEMS have their probability increased. At Rc values above $1000 the proportion of iterations for each strategy falling to the right side of the Rc remains constant.

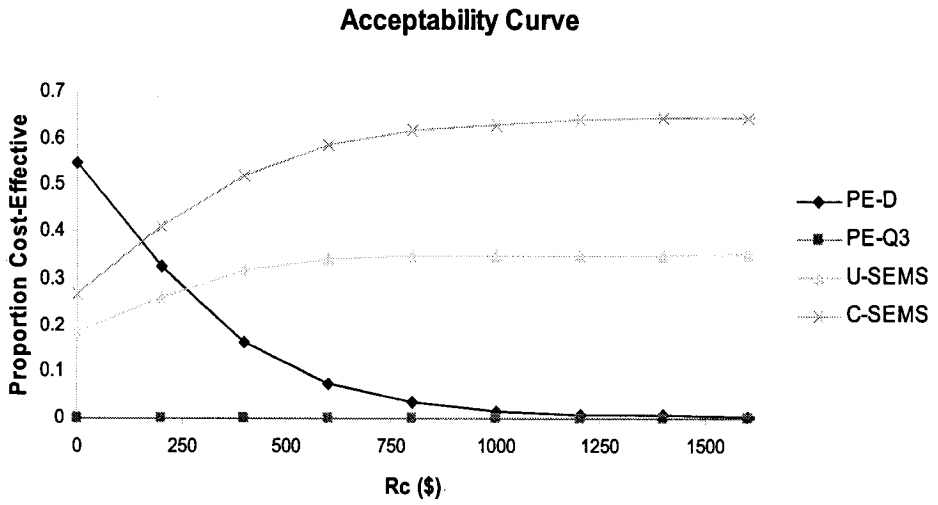

Figure 4.9 Cost-effectiveness acceptability curves

The CEAC for PE-Q3 cuts the Y axis at zero and asymptotes toward zero because none of the density involves cost-saving and none of the joint density involves incremental health gain, therefore this strategy is preferentially located in the NW quadrant of the incremental cost-effectiveness plane and entirely situated to the left of the Rc as shown in Figure 4.8. At exorbitant Rc values such as $ 700,000/month of stent patency, there is a trivial chance PE-Q3 will become cost-effective and this is represented by a small number of iterations in the NE quadrant of the ICE plane (Figure 4.8). The PE-D curve does not cross the Y axis at zero because some of the joint density involves cost-savings (54.6%), but at the same time it asymptotes toward zero; this indicates that none of the density involves incremental health gains and consequently the observations will fall either in the NW or SW quadrants of the incremental cost-effectiveness plane. The U-SEMS joint density also involves cost-saving and therefore it crosses the Y axis at 18.6%. Some of the density also involves health gains (35%) and therefore the distribution under the incremental cost-effectiveness plane occupies all quadrants, but mostly the SW region (less costly and less effective). Finally, C-SEMS also involves some cost-savings and health gains as the CEAC crosses Y at 26.7% and asymptotes to 63.1%. Like for U-

SEMS, the curve for C-SEMS occupies all 4 quadrants of the plane but most of C-SEMS iterations will be situated in the NW quadrant (more costly and more effective).

If the shadow price for a single month of stent patency in patients with distal malignant obstruction were known, it would be possible to choose between all treatment options and not just identify those which form the "CE frontier" (Figure 4.10). Unfortunately, the Rc is unknown and therefore, conditional upon knowing the Rc, there is only 1 option out of the 4 alternatives which is more cost-effective. The CE frontier is a mapping of the CEAC which identifies the most cost-effective strategies over a range of Rc. In Figure 4.10, PE-D is the strategy with the highest probability of being cost-effective if the Rc is lower than $ 150.60. For Rc values above $150.60, C-SEMS becomes the most likely cost-effective alternative. The coordinate shown in the graph represents the scenario where PE-D ends and C-SEMS starts delineating the CE frontier. Because probability of cost-effectiveness and maximum expected NB do not always coincide, the Rc value at which C-SEMS produces higher amount of NB compared to PE-D was calculated and found to be $136.60. It implies that between Rc values of $136.60 and $150.60, PE-D is more likely to be chosen as optimal therapy because it bears the CE frontier, but in fact C-SEMS is the strategy which yields the maximum amount of NB and therefore should be preferred. Nevertheless, the probability of cost-effectiveness has to be interpreted in context with the amount of NHB provided by each strategy. For all Rc values providing a positive mean NHB (Table 4.3), C-SEMS is the strategy exhibiting the highest probability of cost-effectiveness, followed by U-SEMS. In contrast, PE-D and PE-Q3 have trivial probabilities of cost-effectiveness for Rc providing positive mean NHB.

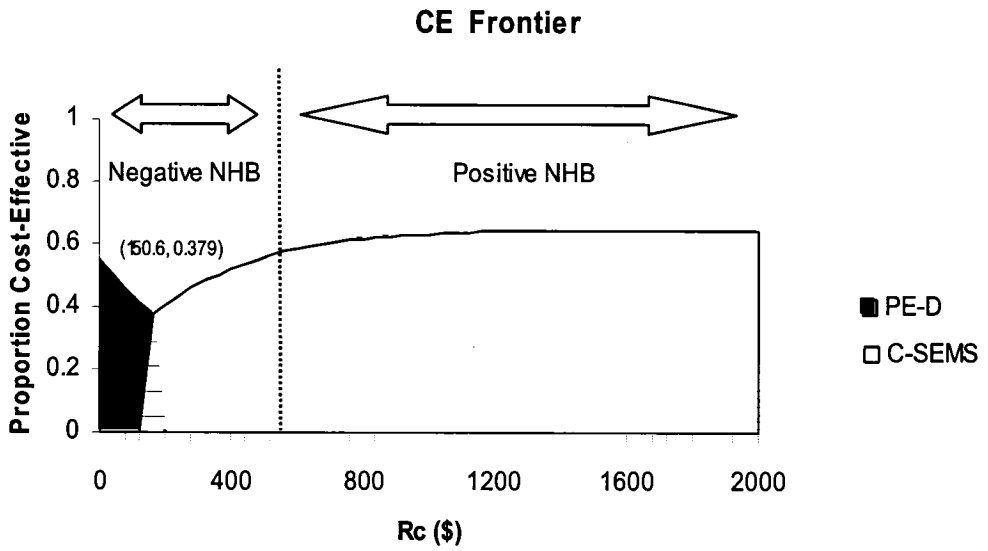

Figure 4.10 Cost-effective frontier.

4.3.4 Sensitivity analysis

In addition to obtaining the probabilities of cost-effectiveness and absolute outputs for each outcome given the existent uncertainties of the model, the output from the probabilistic sensitivity analysis was used to estimate parameter influence. The outputs for the 10,000 iterations obtained for the parameters in the decision model were regressed against the average cost-effectiveness ratio for PE-D and C-SEMS. The coefficients and the 95% CI for the multivariate linear regression model for PE-D are shown in Table 6. None of parameters used in the model for calculation of the cost-effectiveness ratios of PE-D and C-SEMS have a substantial effect on the respective average cost-effective ratio.

Variables	Coefficient	95% CI
(Intercept)	566.6	(490.08; 643.12)
Probability ERCP complication	-61.29	(-140.87; 18.29)
Probability of survival	7.756	(-68.17; 83.67)
Cost of ERCP	-0.0083	(-0.0165; -0.0001)
Cost of cholangitis and cholecystitis	0.00052	(-0.0003; 0.0013)
Cost of pancreatitis	$-4.2*10^{-05}$	(-0.0005; 0.00045)
Probability of cholangitis	4.74	(-8.4; 17.88)
Probability of PE-D stent occlusion	-4.7	(-50.88; 41.48)
Effectiveness (occlusion)	0.46	(-2.38; 3.3)
Effectiveness (death)	0.26	(-2.56; 3.08)
Cost PE stent	-0.048	(-0.132; 0.036)
Cost ERCP complication	0.0051	(-0.0029; 0.013)

Table 4.4 Regression of MCMC outputs on CER for PE-D strategy

4.3.5 Statistical inference

Probabilistic sampling and construction of a posterior distribution for costs and effectiveness permits statistical inferences to be made with a certain level of confidence. However, the parameter of interest in CEA is not the marginal, but the joint distribution for costs and effectiveness with ICER's being the most commonly used parameters in CEA. The insertion of CI's around costs and effectiveness values is feasible but often yields non-normal distributions for the ICER because the fraction ($\Delta C/\Delta E$) becomes unstable in the presence of small values in the denominator. Consequently, the distribution is often uninformative due to its large standard deviation (SD). Table 4.3 shows the means and CI for cost, effectiveness and cost-effectiveness ratios in all strategies. Although the marginal distributions for costs, effectiveness and the joint distribution for average cost-effectiveness ratio appear normally distributed, the small incremental values in effectiveness which form the denominators for ICER yield an imprecise posterior distribution with a very large SD. Therefore, the results from the joint posterior distribution for ICER do not allow statistical inference to be made. Incremental net health benefit (INHB) is an alternative measure as it estimates the difference between the amounts of health benefit gained and lost by choosing an alternative at a range of

values for Rc. The advantages of INHB over ICER are discussed in section 2.6. Inserting a CI around the INHB and evaluating its relationship to an area of clinical equivalence would permit inferences on cost-effectiveness between strategies to be made more accurately. Initial results from both deterministic and probabilistic approach indicate that PE-Q3 is unlikely to be a cost-effective strategy in this CEA model because, on average, it is more expensive and provides a lower amount of effectiveness than the competitive alternatives (Table 4.3). Therefore, INHB for PE-D, U-SEMS and C-SEMS were calculated across a range of plausible values of Rc. Figure 4.11 shows the mean values and 95% CI for the INHB between C-SEMS and PE-D. C-SEMS is preferred over PE-D for Rc greater than $110.49 because it yields, on average, a higher amount of health benefit. This corresponds to the minimum extra amount of money needed to obtain an extra unit of effectiveness. However, the level of uncertainty is substantial for low Rc values and only at Rc greater than $750,00 there is statistical evidence that INHB for C-SEMS is superior to PE-D.

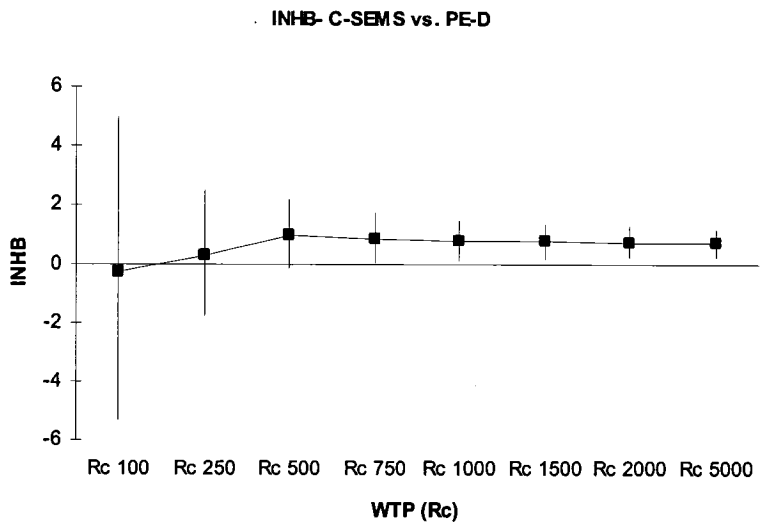

Figure 4.11. Incremental net health benefit between C-SEMS and PE-D

Figure 4.12 shows the INHB between U-SEMS and C-SEMS. For a wide range of Rc values, U-SEMS is less optimal than C-SEMS as it provides less amount of health

benefit. In contrast to the ICER between C-SEMS and PE-D, the Rc value where the INHB is zero does not match to the point estimate shown in Table 4.3 and demonstrates the instability of the ratio in the presence of wide distribution (CI [-177,104.70; 175,283.60]). The difference tends to decrease as Rc increases but results remain indeterminate even at unlikely extreme values for Rc.

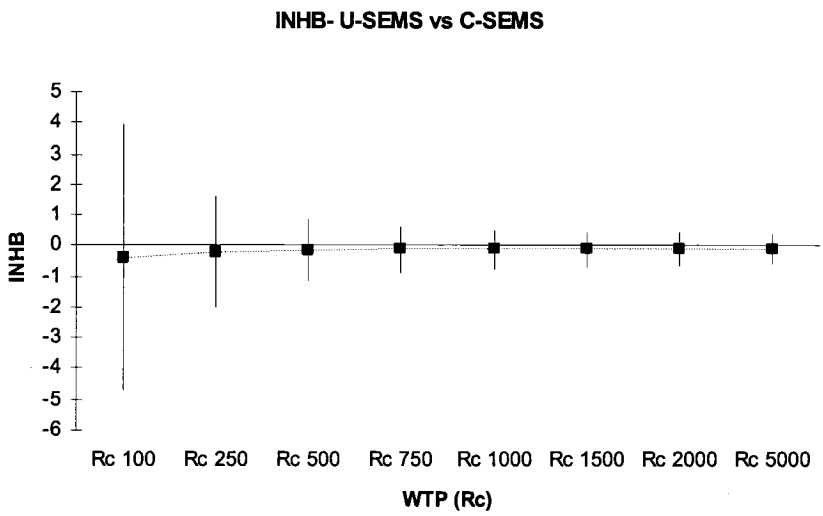

Figure 4.12. Incremental net health benefit between U-SEMS and C-SEMS

In comparison to the ICER, the INHB provided meaningful point estimates between strategies and more informative uncertainty values which can assist decision makers in the selection of the most appropriate intervention and decide if additional information needs to be obtained.

4.4 Value of Information

The application of NHB measurements and performance of a probabilistic analysis provided the following answers: 1) strategies more likely to be cost-effective conditional to Rc values, which permitted delineation of a CE frontier; 2) determination of the

expected NB conditional to Rc and consequently selection of the strategy providing the highest amount of NHB; 3) estimation of uncertainty levels between individual strategies through insertion of CI's at INHB and comparing all strategies together by constructing CEAC curves. While the first two results are essential for selection of the strategy to be funded, uncertainty measurement gives an estimation of the chance of choosing strategies less cost-effective and therefore spending unnecessary resources. Such information allows decision makers to calculate the opportunity costs and provides the rationale for pursuing acquisition of more information.

Because the expected NHB yielded by all strategies tends to improve as the Rc increases, the absolute differences in between strategies will consequently decrease. As shown in Equation 1, as the willingness to pay increases, the fraction (cost/Rc) becomes smaller and the NHB for each strategy becomes a function of the effectiveness. Consequently, the difference in effectiveness between strategies will progressively decrease (Figure 4.7). Figure 4.13 shows that higher values of Rc are associated with smaller EVPI (measured in units of effectiveness). EVPI represents the difference between the maximum benefit a patient could gain from all four strategies and the expected benefit yielded by the most cost-effective strategy. However, the EVPI is a function of the Rc, and the higher the value a decision maker is willing to pay for a given treatment, the higher will be the opportunity cost if a wrong decision is made (measured in monetary units). The EVPI for a single patient with unresectable distal biliary malignant obstruction is shown in Figure 4.14. The initial peak in EVPI corresponds to the point in the CEAC where the probability of cost-effectiveness is the lowest. At that point, the probability of a wrong decision is the highest and consequently the opportunity costs increases. Once the CE frontier plateaus and the probability of uncertainty remain constant, the slope of EVPI becomes proportional to the Rc as demonstrated in Figure 4.15.

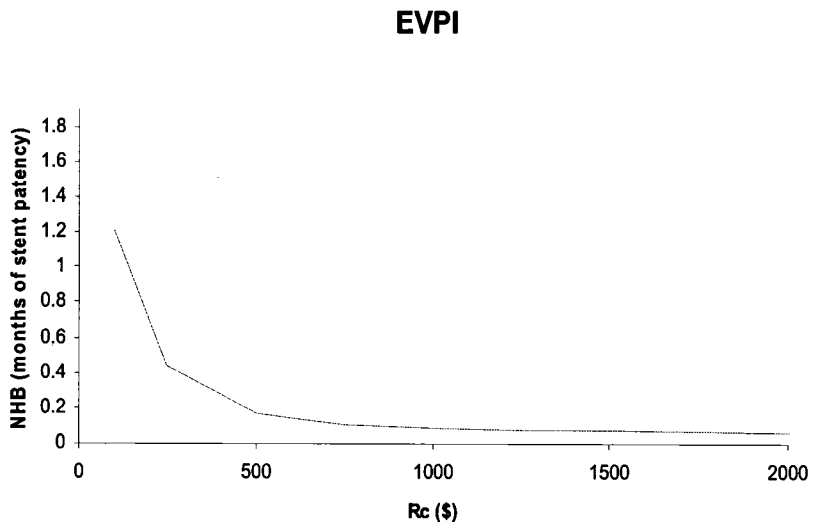

Figure 4.13 EVPI for a single patient measured in units of effectiveness.

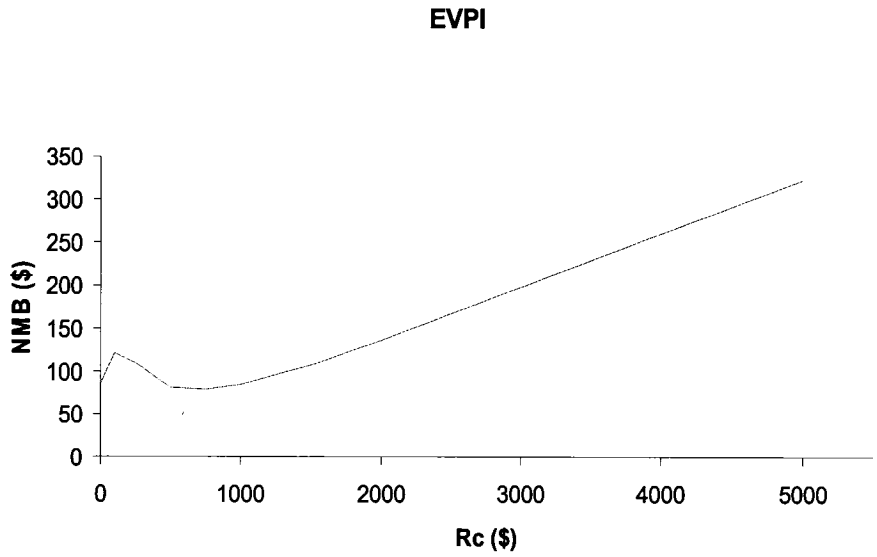

Figure 4.14 EVPI for an individual patient with distal biliary malignant obstruction

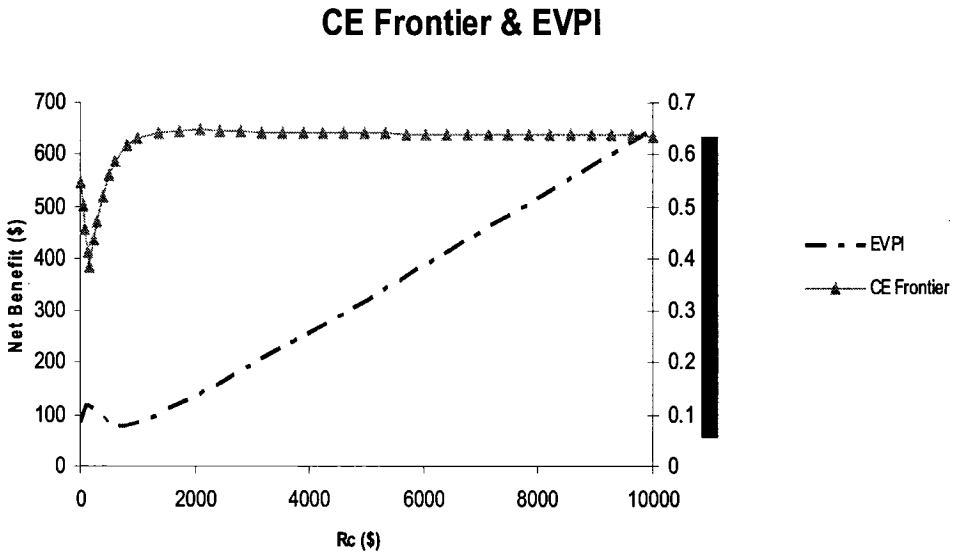

Figure 4.15 Relation in between the CE frontier and the EVPI

In addition, information generated by research is cumulative and has "public good" characteristics. Once available, it can be used to inform treatment decisions for all eligible patients. EVPI for a given population can be calculated once the incidence of distal biliary malignant obstruction and the effective lifetime of stent-related technology are estimated. Figure 4.16 illustrates the populational EVPI for Canada and North America assuming an annual incidence of 3000 and 30000 cases of malignant obstructive jaundice respectively. The estimated value for EVPI of a population also accounts for the expected life time of the technology (stent) under evaluation; such values were calculated for 5, 10 and 20 year cohorts of patients with distal biliary obstruction.

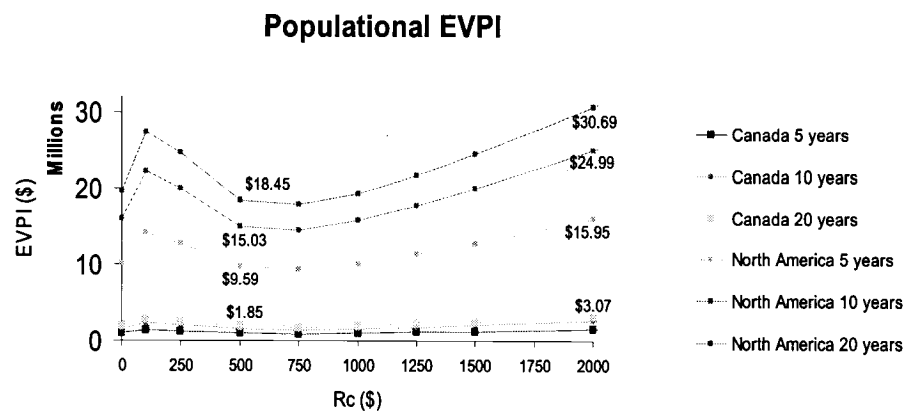

Figure 4.16 EVPI for Canadian and North American population.

EVPI for the population of Canada and North America is an estimate of the amount of additional resources utilized over the following years because of wrong decisions. For instance, if the technologies under evaluation remain valid for the next 20 years and the incidence of distal biliary obstruction remains constant over this period, Canada will have spent an additional $1.85 million per month of stent patency because of selection of suboptimal strategies if the Rc is $500. If we consider that C-SEMS yields on average 5.89 months of stent patency (CI [5.51; 6.26]), the total opportunity losses will approximate $10.89 millions (CI [10.19; 11.58]). Accordingly, this value also represents the maximum amount decision makers should spend in the acquisition of further information. Indeed, conditional to Rc value of $500, additional research to answer the existent uncertainty may be cost-effective if it costs less than $10.89 millions. Otherwise, the amount of monetary losses due to selection of a less cost-effective strategy does not justify funding additional research in the field.

5 Discussion

5.1 Overview

Unresectable distal biliary obstruction is a highly fatal condition not uncommonly seen in North America. Over the last 2 decades, improvements in endoscopic technology and the advent of biliary endoprosthesis has permitted delivery of effective methods of palliation using less invasive techniques at lower costs. Different types of biliary stents are currently available and numerous studies have validated their efficacy. Although palliation can be successfully achieved with any one of the existent surgical, radiological or endoscopic techniques available, a rationale approach to managing this condition is lacking. Given the scope of the problem, it is surprising that only few studies have been published as significant savings can be obtained using an evidence-based approach. This is in sharp contrast to other new technologies such as drug-eluding coronary stents where much more research and cost-effectiveness data have been generated [160, 161]. In the absence of solid recommendations, it is not unusual to see mixed opinions and strategies being implemented by physicians practicing in a same geographic area. Hopefully the results presented in this dissertation will assist the implementation of a policy for the use of biliary stents in distal malignant biliary obstruction and remove the subjective assessment criteria currently used by many physicians.

The current study evaluated three different technologies and four strategies in the management of distal biliary malignant obstruction. In addition to PE stent with replacement on demand (PE-D) and uncovered self-expandable metal stent (U-SEMS) that have been investigated in two previous economic evaluations, PE with routine exchange every three months and the newest technology of C-SEMS, were also investigated. As part of this assessment, several epidemiologic and health economic aspects of distal biliary malignancies were analyzed. Although no prospective randomized control trials comparing all 4 strategies have been performed, data from the available literature were amalgamated and incorporated into a decision model which attempted to summarize all possible outcomes experienced by an individual undergoing

palliation with an endoscopically placed endoprosthesis. The results of these analyses should be seen as an effort, using best available evidence, to estimate the cost-effectiveness of and suggest factors influencing on strategy selection. The literature used to calculate the point estimates used in the decision model were multiple and included the majority of published RCTs to date. Most of these studies compared different technologies of plastic stent and metal stent in distal biliary malignant obstruction; however there has been no investigation to date addressing the role of no intervention as a possible treatment option for this population of patients.

PE with replacement on demand and routinely exchanged every 3 months are strategies not infrequently used by gastroenterologists in Canada. In our experience, at least 70% of initial insertions for distal biliary malignant obstruction are with PE stents, and a significant proportion of patients undergo routine replacement every 3-4 months. Seldom physicians choose a SEMS before failure of one or two plastic stents. The reasons behind this decision are many and vary among physicians. First, there is no consensus about the proper timing for insertion of a biliary endoprosthesis. While some physicians opt to decompress the biliary system only if cholestatic symptoms occur, some opt to provide palliation at the very beginning even before radiological staging and tissue diagnosis is obtained. Under the latter condition, it is seems reasonable to insert a plastic stent since SEMS are difficult to be removed, repositioned and can affect the surgical procedure should the tumor is deemed resectable. Although initial ERCP and stent insertion have the advantages to permit tissue sampling and provide immediate resolution of the jaundice, it will result in performance of unnecessary procedures as a significant fraction of these patients are candidates for surgical resection. Moreover, because staging of these malignancies can be done promptly with non-invasive radiological studies, many centers across the United States and Canada tend to reserve ERCP and stent placement only for those with unresectable disease.

Despite of its economical drawbacks, plastic stents may continue to be used either on demand or with routine replacement until we obtain further knowledge on the best way of palliating patients with malignant obstructive jaundice. However, our decision model assumes patients to be unresectable either due to advanced disease or high risk for the operative procedure and consequently the results can not account for interventions

previously performed. Second, insertion of an endoprosthesis is a palliative treatment for terminal patients and it is widely felt that survival remains unchanged regardless of the type of the stent inserted. Because there is no true net gain other than the potential economical savings, physicians tend to be risk-avert and adopt conventional methods of palliation. Third, the potential economic benefits observed with SEMS are conditional to the number of procedures saved during the remaining period of life. However, the inability to predict a patients' life expectancy adds to physicians' propensity to choose the cheapest approach. In addition, time preference could at least partially explain the reasons why PE is chosen more frequently than SEMS. Instead of paying a high up-front price for a stent (SEMS) and enjoy advantages in the future, this economical principle states to be more intuitive to obtain the benefits immediately at much lower price (PE stent) and run into risks, uncertainties and additional costs in the future. Procedural costs may not be relevant to physicians (who are the decision makers at an individual operative level). Procedures tend to not require additional consumption of significant amount of heavy resources as equipment and personnel are already available. The most expensive tool needed for ERCP (the duodenoscope) is re-usable and has a long-lasting life (5-7 years). Consequently, the costs of procedures become diluted within the other routine endoscopic procedures. Thus, even if costs attached to the insertion of a PE stent are higher than the ones for SEMS, the majority of these are not readily "apparent" to many of the physicians making decisions at an individual patient perspective. Moreover, insertion of a cheaper stent (PE) may be financially advantageous for physicians (decision-makers) performing procedures in community settings as it raises the volume of procedures performed and the reimbursement. In contrast, insertion of SEMS could be a more attractive alternative from the Ministry of Health perspective which would consider all resource utilization. Fourth, SEMS is designed in such a manner that it is difficult to be removed or repositioned once it is fully deployed. Therefore, not necessarily all physicians feel comfortable with this technology and may prefer using plastic stents which carry a lower risk of untoward events.

Two previous CEAs performed in the U.S. suggested PE stent to be more cost-effective than U-SEMS if patients survived less than 4-6 months [1, 2]. The investigators also assessed the relationship between U-SEMS and local ERCP cost as a method of

generalizing the results across different practice settings. The results from these 2 studies have influenced the way gastroenterologists select the type of stent in patients with malignant biliary obstruction. Although some of these parameters are objective and easily translated into daily practice (e.g. cost of stent), others are very difficult to estimate as they are governed by a large number of factors. When displayed in such away, results seem to be sensible and answer the research question, but seldom can they in fact be directly applied to patient care. For instance, it seems counterintuitive to determine the cost-effectiveness of interventions conditional on a parameter that can be only measured '*a posteriori*', once a decision has already been made. Indeed, life expectancy is a function of multiple variables and consequently difficult to predict. Although independent predictors of survival have been identified, it is important to emphasize that these parameters explain a small fraction of the total survival function. For instance, patients with metastatic disease, poor baseline physical capacity and tumor size greater than 3 cm are more likely to have a shorter survival than patients without such findings. However, the presence of these factors only increases the odds of observing the outcome but does not exclude an alternative possibility.

In fact, most decisions in clinical practice are based on "educated guesses". The absence of guidelines for use of biliary stents in malignant obstruction introduces a significant component of subjectivity to the decision process of selecting the most appropriate stent for the management of a given patient with a distal biliary obstruction. The lack of a systematic approach will necessarily result in suboptimal medical choices as physicians' decisions are not comprehensive enough in order to account for the existence of all possible outcomes in complex problems [140].

5.2 Strengths and limitations of the study

Apart from the cost-effectiveness, our study presents outcome measurements of complications and number of procedures related to each strategy used in the management of patients with unresectable distal biliary malignant obstruction undergoing palliation with endoscopically placed endoprostheses. Each result is discussed with its limitations and interpretations.

5.2.1 Strengths

Analytical methods assist the decisions to adopt or reimburse a technology based on current evidence. It can also inform whether more evidence needs to be acquired given the objectives and constraints of the provision of health care. In contrast to epidemiological studies, health policy decisions require the distribution of all parameters of interest due to sources of error, both random and systematic. This information is often not utilized by health researchers who base their inferences only on random errors, reporting point estimates and confidence intervals. Thus, epidemiological methods overemphasize issues of precision but fail to analyze the potential underlying uncertainty. The dominant rule of thumb of maintenance of the '*status quo*' until an alternative statistically significant better alternative is available cannot be supported in health economics. In the latter perspective, a decision must be made given the current knowledge and regardless of the quality of information available. The correct decision should be derived from the expected net health benefit attributable to different management options instead of waiting until an alternative strategy passes some statistical test. Unfortunately, this answer cannot be obtained from more traditional approaches such as deterministic CEAs, which are based on single point estimates. In contrast, the probabilistic analysis takes into account the posterior joint distribution of costs and effectiveness and provides the probability that each strategy is cost-effective conditional to the data used in the model.

The probabilistic approach to CEA becomes particularly advantageous as the number of therapeutic strategies increases and the probability of selecting the most cost-effective strategy is reduced. In the current analysis, the advent of a more expensive and efficacious technology (C-SEMS) added more uncertainty to the problem of deciding between a plastic stent insertion or U-SEMS alternative. In practice, the presumed superior patency rate of C-SEMS in comparison to U-SEMS has pushed physicians to adopt this new technology despite absence of economic evaluations and reports of higher rates of complications such as migration, cholecystitis and pancreatitis [40]. In many countries, decisions to adopt, reimburse or issue guidance on health technologies are

increasingly based on explicit cost-effectiveness analyses using a probabilistic decision analytical framework. A prime example is the National Institute for Clinical Excellence (NICE) in the UK, where recent guidance on the methods of technology appraisal reflects the importance of probabilistic analysis and value of information (http://www.nice.org.uk/) .

Point estimates for the current decision tree were abstracted from RCTs comparing one or more technologies under investigation. This *a priori* decision increases the internal validity of the results and the exclusion of poorly controlled studies decreased the chances of confounding. At the same time, costs attached to the model were derived from a national database (Canadian Institutes for Health Information) in order to preserve the external validity of the results and to avoid costs driven by the methodological rigor of RCT, with their decreased generalizability.

Although the main results of this analysis are presented in monetary units and months of stent patency, estimations of the average number of complications and performed ERCP's that were observed with each therapeutic approach are also outlined. This information permit results to be generalized to settings in which costs of ERCP and ERCP-related complications are markedly different from the ones used in the current analysis.

The current investigation compared results obtained using deterministic and probabilistic methods. The difference in the results underscores the importance of the methodologies used to estimate cost-effectiveness. The deterministic approach is based on the assumption that values obtained for the decision model are accurate estimates of the true unknown parameters. However, because the unit of cost-effectiveness is a ratio (ICER), the fraction becomes volatile and even minimal changes in the values of the denominator can have a significant impact in the final outcome measurement. In contrast, the probabilistic analysis constructs a posterior joint distribution of costs and effectiveness for all strategies using Monte Carlo simulations. Consequently, this method produces more robust results as it accounts for the underlying uncertainty of the parameters being evaluated in the model. Although it is unlikely that a single strategy is optimal for all scenarios, selection of the one with the highest probability of being cost-effective will indeed minimize the total amount of losses due to incorrect decisions. In

addition, the level of uncertainty in the model can be used to calculate the expected opportunity losses for a population and to estimate the maximum amount of resources decision makers should allocate for future research in the field.

5.2.2 Limitations

5.2.2.1 General study limitations

Endoscopic insertion is currently considered the preferred route for placing plastic and metal stents because it carries lower complication and mortality rates than the percutaneous approach [95]. However, this technique requires specific expertise and therefore the results of the decision tree are conditional on the patients' access to a facility that can provide this level of care. The decision model also did not account for minimally invasive surgical biliary techniques, which may be attractive in selected patients at high risk for both biliary and gastric outlet obstruction.

This study evaluated four methods of palliation commonly used but other therapeutic options exist and it is unknown how our results would compare to those. Yeoh et al. found that initial insertion of a plastic stent with replacement with a U-SEMS upon occlusion was the most cost-effective strategy for the base-case scenario [2]. This strategy seems to be relevant in cases of new-onset malignant obstruction for which resectability has not been yet evaluated. Although many centers across North America perform endoscopic insertion of biliary endoprostheses before staging, our experience suggests that a minority of patients require immediate palliation. Therefore, our study assumes that patients have been fully worked-up for resectability and deemed not to be candidates for surgery because of either advanced staging (unresectability) or high operative risk (inoperability).

5.2.2.2 Methodological issues

In spite of advantages over the deterministic method, the probabilistic approach has also some disadvantages. Perhaps the major one is the conditioning of results according to WTP values. Although it is possible to determine the threshold value which provides a positive mean net health benefit, WTP are not fixed and are influenced by factors such as monetary resources, source of payment (patient, insurance company, government), state of knowledge and severity of disease. In the current analysis, the probabilities of cost-effectiveness for the strategies in our model did not significantly change across a large range of WTP values yielding positive mean NHB.

Arbitrarily chosen distributions were chosen to account for uncertainty of parameters in the probabilistic model. However, the most appropriate type of distribution to be used for each parameter is unknown. For instance, in the absence of patient-level data, costs were assumed to follow a triangular distribution. If the distributions used in our model in fact does not match the underlying distribution of the true parameter, inaccuracies in estimations may have occurred during the MCMC simulations.

5.2.2.3 Bias

Bias could have occurred at different stages of the current analysis. In the methods, publication bias could have resulted from the exclusion of unpublished and non-randomized studies. In addition, studies with follow-up periods shorter than the time horizon of the CEA (12 months) were excluded from data abstraction, which is a potential source of selection bias. Selection bias could have also occurred at the time of patient enrollment for the RCTs. Some studies selected patients with previous manipulation of the biliary tree while others permitted only newly diagnosed patients, a difference which may confound the outcome. Indeed, patients with previous manipulation may experience stent clogging earlier on (confounding), and, as they have entered the study at a later stage of their disease, may also experience a shortened survival (lead time bias). Although studies were unblinded and the methods of measurement of the outcome (stent occlusion) and follow-up of patients differed between studies, no difference was

likely to have occurred among individuals within the same study and therefore ascertainment bias was unlikely.

5.3 Directions of future research

Over the last two decades, different technologies and therapeutic maneuvers to prolong patency of biliary stents have been tested. The development of U-SEMS was heralded as a solution to plastic stent occlusion but its widespread use was halted by its increase upfront costs. Yet stent obstruction continued to occur and the subsequent advent of C-SEMS aimed to further prolong stent patency by retarding the main mechanism of occlusion in SEMS, tumor in and outgrowth. Although the current economic evaluation suggests that initial insertion of a C-SEMS is the endoscopic therapy with the highest probability of cost-effectiveness, the conclusion is based on data from a single RCT. Despite its superior effectiveness, this study reported an unexpected higher rate of cholecystitis and pancreatitis with C-SEMS which deserve to be confirmed by further research. In contrast, the results obtained for the remaining strategies are more robust as they are derived from a multitude of prospective randomized trials comparing PE to U-SEMS. Undoubtedly, further studies with C-SEMS are needed to not only confirm the improvement in patency duration, but also to better determine the potential adverse events associated with this new technology.

The strategies assessed in this economic evaluation reflect current standard practice for the management of patients with unresectable distal biliary malignancies. While it is unlikely that percutaneous approach will replace the endoscopic insertion of biliary stents over the next few years, a significant progress is expected with the development of minimally invasive surgery. Laparoscopic biliary bypass is a procedure currently being performed in only few highly specialized centers, and its role in the management of malignant biliary obstruction remains to be determined. Newer metal stent technologies such as drug-eluding stents to prevent tumor ingrowth, and expandable plastic stents with a longer patency duration while cheaper than SEMS are being developed. In addition to new stent technologies, advances in adjuvant therapy for the underlying malignancies is likely to continue to occur. New chemotherapeutic agents, tri-dimensional radiotherapy

and locally implantable radio devices may significantly impact the natural history of the diseases causing malignant biliary obstruction. Although it is unlikely that cure will be achieved with chemo or radiation therapy, a marked improvement in survival may be obtained. The advent of new regimens that improve patient survival will, from an economic perspective, favor the insertion of longer lasting stents such as SEMS.

Survival of patients with unresectable distal biliary malignant obstruction remains the most important factor in the decision making process. However, the inability of physicians to predict the remaining life expectancy is a major obstacle to optimal cost-effective decisions. Although independent predictors of survival have been identified, these parameters themselves account for a small fraction of the total variation of the survival function. In order to be able to provide a more cost-effective treatment, a better understanding of factors that influence survival is needed. We anticipate that molecular makers for biliary malignancies may allow a better characterization of prognosis.

6 Conclusions

The present study shows that conditional to the willingness-to-pay (WTP), current Canadian costs and the existing data, initial insertion of C-SEMS is the strategy with the highest probability of cost-effectiveness in patients with distal malignant biliary obstruction. Although PE-D has the highest probability of being cost-effective at low WTP, these values are not realistic for the current standards of practice because they are lower than the average estimated cost of stent patency and yield a negative mean health benefit (NHB). C-SEMS is the optimal strategy for all values of WTP providing a positive NHB. Nevertheless, a substantial probability of making a wrong decision remains even when the strategy with the highest probability of cost-effectiveness is selected. In contrast to the results provided by the deterministic model, U-SEMS should not be disregarded as a potential cost-effective strategy; PE-Q3 is unlikely to be a cost-effective strategy as it remained a dominated strategy under most assumptions in both the deterministic and probabilistic models. Although the deterministic analysis delineated thresholds of patient and stent survival probabilities as well as cost ranges for ERCP that could alter the choice of strategy, many of these parameters cannot be accurately predicted and consequently are very difficult to be translated in clinical practice. Thus, in order to minimize opportunity losses, it is suggested that the program yielding the highest amount of health benefit be chosen, irrespective of the subjective assessment made at an individual level.

According to policy makers' willingness to pay, C-SEMS is the most cost-effective method of palliation for unresectable distal malignant obstruction and should be selected because, on average, it will provide highest amount of health net benefit than the other alternatives. Nevertheless, decision makers must be aware that all remaining strategies under evaluation with exception of PE-Q3 have a certain probability of being cost-effective. Even though C-SEMS has the highest probability of cost-effectiveness given all strategies, there will be a 35-40% probability that C-SEMS will provide less NHB than PE-D and U-SEMS. The resulting selection of a suboptimal strategy will lead to expenditure of extra amount of resources which will range from 1.85 to 3.0 millions of

Canadian dollars per month of stent patency over the next 5-20 years. Similarly to economic evaluations of other health technologies, this study provides evidence for development a policy for selection of stents in the management of distal biliary malignant obstruction.

7 Glossary

- **ampulla of Vater**: orifice formed by the junction of the common bile and pancreatic duct.
- **bayesian statistics**: a method of statistical inference that begins with the state of knowledge and augments with the incorporation of the study data to yield a final state of knowledge, described by a *posterior* distribution. This method does not use statistical significance tests (see frequentist and p value).
- **bias**: systematic error introduced by the investigator or study participants leading to deviation from the truth.
- **biliary system**: organs and ducts (bile ducts, gallbladder, and associated structures) that are involved in the production and transportation of bile into the intestine (see Figure ....)
- **benefit**: (1) positive consequence of system operation. (2) monetary value associated with positive consequence.
- **charge**: the price of the resource consumed
- **cholangiocarcinoma**: malignancy of the epithelial cells (lining) of the bile ducts
- **cost**: (1) monetary value of a production input. (2) negative consequence of system operation or monetary value associated with negative consequence.
- **cost effectiveness**: relationship between operating costs and benefits described as the result of cost-effectiveness analysis.
- **cost-effectiveness analysis**: method of comparing the relative costs and effectiveness of two or more different interventions.
- **direct cost**: are the economic values of specific medical treatment costs incurred within the health care sector (provider's time, equipment, supplies) and relevant non-medical costs (transportation).
- **effectiveness**: measure of the extent to which a specific intervention or procedure, when deployed in the field in routine circumstances, does what is intended to do for a specific population.

• **efficacy**: measure of the extent to which a specific intervention or procedure produce a beneficial result under ideal conditions.

• **efficiency**: the extent to which the resources used to provide a specific intervention or procedure of known efficacy or effectiveness are minimized.

• **ercp**: endoscopic retrograde cholangiopancreatography. Procedure which allows access to the biliary and pancreatic system through the small intestine.

• **frequentist**: statistical method based on the sampled data and dependent on repeated observations to make inference on frequency probability.

• **indirect cost**: include all other costs which cannot be counted as direct costs, such as human capital (earnings lost, psychological discomfort) and willingness to pay the economic value associated with preference of one health state over another.

• **opportunity cost**: the value of a resource in its next best use

• **p value**: the probability that a test statistic would be as extreme as or more extreme than observed if the null hypothesis were true (see also frequentist)

• **parameter**: model constant.

• **perspective**: refers to the scope of the costs being considered, the costs to society, a third party (e.g., an HMO or insurance company), health providers (physicians or hospital) or the patient.

• **quality of life (QOL)**: the degree to which persons perceive themselves able to function physically, emotionally and socially.

• **randomized controlled trial (RCT)**: epidemiologic experiment in which subjects in a sample are randomly allocated into study groups, to receive or not an experimental preventive or therapeutic intervention or procedure.

• **rate**: a measurement of frequency of occurrence of a phenomenon in a specified period of time.

• **risk**: the probability that an event will occur within a state period of time.

• **sensitivity analysis**: a method to determine the robustness of an assessment by examining the extent to which results are affected by change in the methods, values of variables or assumptions.

• **shadow price**: An economic term to denote the rate at which the optimal value changes with respect to a change in some right-hand side that represents a resource supply or demand requirement.

• **simulation**: process by which understanding of the behavior of a physical system is obtained by observing the behavior of a model representing the system.

• **time horizon**: the time to which all decision-making variables have meaning or the time beyond which the values of decision-making variables are ignored.

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