Asymptomatic pancreatic cystic neoplasm: a cost-effectiveness analysis of different strategies of management

Ananya Das, MD, Saowanee Ngamruengphong, MD, Shweta Nagendra, MD, Amitabh Chak, MD

Scottsdale, Arizona, USA

Background: Optimal management of asymptomatic pancreatic cystic neoplasm is not known.

Objective: In a decision analysis, the cost-effectiveness of different strategies for managing solitary, asymptomatic pancreatic cystic neoplasm were compared.

Intervention: Three strategies were examined in a Markov model with a third-party-payer perspective. In strategy I, the natural history of the lesion was followed without any specific intervention. In strategy II, an aggressive surgical approach was considered in that all patients were considered for resection. In strategy III, an initial EUS-guided FNA with cyst fluid analysis was performed for risk stratification, and patients with mucinous cysts were considered for resection. Transitional probabilities, discounted cost, and utility values to estimate quality-adjusted life years were obtained from published information. An operability risk score based on patient age, comorbidity, and size and location of the cyst was developed to estimate the probability of surgical resection.

Results: In the baseline analysis, strategy III yielded the highest quality-adjusted life years with an acceptable incremental cost-effectiveness ratio. In a Monte Carlo analysis, the relative risk of patients developing unresectable pancreatic cancer was decreased in strategy III compared to the other strategies. Although threshold analyses identified few important parameters influencing the conclusion of the analysis, operability risk score was the critical determinant of the optimal management strategy.

Limitations: Indirect costs were not considered in this analysis.

Conclusion: For asymptomatic patients with incidental solitary pancreatic cystic neoplasm, a blanket policy of surgical resection for all patients cannot be justified. A strategy based on risk stratification of malignant potential by EUS-guided FNA and cyst fluid analysis is the most cost-effective strategy. (Gastrointest Endosc 2009;70:690-9.)

Pancreatic cystic neoplasms (PCNs) are increasingly encountered in clinical gastroenterology practice. The prevalence of these lesions is unclear. An autopsy study of 300 consecutive patients reported cystic lesions in 73 patients, or 24.3%, and approximately 20% of these lesions were neoplastic cysts.[1] However, in other clinical studies, the prevalence of PCN among patients undergoing abdominal imaging with CT or magnetic resonance imaging (MRI) was reported to be approximately 1% to 2%.[2] Although the true prevalence may not be known, it is clear that PCNs are increasingly diagnosed due to the more liberal use of imaging tests and refinements in radiological techniques. Comparing recent surgical series to those from 2 decades ago, it is evident that more and more patients identified with PCN are asymptomatic. Cystic lesions are often detected as incidental findings on abdominal imaging studies performed for unrelated indications.

Over 90% of incidental PCNs can be categorized as serous cystic neoplasm (SCN), intraductal papillary neoplasm (IPMN), or mucinous cystic neoplasm (MCN).[3-6] IPMNs can be further classified as main duct type, mixed type, and branch type, depending on the involvement of the main duct or side branches of the main duct of the pancreas. Main-duct IPMNs are generally associated with a markedly dilated pancreatic duct and are easily identified at endoscopy by the presence of mucin in a characteristic

Abbreviations: ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; ICER, incremental cost-effectiveness ratio; IPMN, intraductal papillary neoplasm; MCN, mucinous cystic neoplasm; MRI, magnetic resonance imaging; NNT, number needed to treat; PCN, pancreatic cystic neoplasm; SCN, serous cystic neoplasm; QALY, quality-adjusted life years.

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''fish mouth'' ampulla. With the exception of SCNs, all other cystic neoplasms are considered to have a variable malignant potential.[7] It is known that branch-type IPMNs, which present as cystic lesions, have less malignant potential compared to the main-duct-type IPMN.[8-10] Most SCNs, and IPMNs with main duct involvement have typical imaging features and can be readily distinguished from other types of pancreatic cystic lesions; on the other hand, although side branch IPMN and MCN are quite distinctive histopathological entities, it is often impossible to definitively distinguish one from another by imaging studies.

Given the concern of progression to malignancy, a recent consensus guideline recommends that all patients with MCN and IPMN, even if asymptomatic, should be considered for surgical resection.[11] However, with the increasing prevalence of incidental, asymptomatic PCN, and given that most of these lesions are detected in elderly patients with comorbid diseases, the benefits of prophylactic surgery, if any, in an asymptomatic patient might be outweighed by the surgical risks. In routine clinical practice, many of these asymptomatic cystic lesions are followed expectantly by noninvasive imaging studies such as CT scan or MRI and often by more invasive tests such as EUS.

There are no controlled trials on the optimal management of patients with asymptomatic, incidental PCNs. Data on the rate of progression of PCNs to malignancy are also quite limited. In the absence of a clinical trial, the purpose of this economic analysis was to compare different hypothetical management strategies to determine the most appropriate and cost-effective management of these patients. The goal was also to identify factors that are important in influencing clinical decisions, so further investigations to define these factors can be performed.

Capsule Summary

What is already known on this topic

- With the increasing prevalence of incidental pancreatic cystic neoplasms, given that most lesions are detected in elderly patients with comorbidities, any benefit of prophylactic surgery in an asymptomatic patient might be outweighed by the surgical risks.

What this study adds to our knowledge

- Based on results of a cost-effectiveness analysis, a blanket policy of surgical resection in asymptomatic patients with incidental solitary pancreatic cystic neoplasm was not justified. Risk stratification of malignant potential based on EUS-guided FNA results and cyst fluid analysis appeared to be the most cost-effective strategy.

METHODS

Decision analysis model

By using decision analysis software (TreeAge Pro, TreeAge Software, Inc, Williamstown, Mass), we built a hybrid model of a linear decision tree terminating in a Markov model to compare different strategies of management in a hypothetical cohort of asymptomatic patients detected to have a solitary cystic lesion in the pancreas on cross-sectional imaging of the abdomen done for unrelated indications.[12] In the Markov model, the natural history of patients with PCN was modeled by using various health and disease states, and, in addition to cancer-related mortality, the U.S. life table mortality rates were incorporated into the model to account for age- and sex-specific annual mortality from all other causes.[13] The time horizon of the model was the lifetime of the cohorts. The analysis was conducted according to the recommendations of the Panel on Cost-effectiveness in Health and Medicine for conducting and reporting a reference case analysis with a third-party-payer perspective.[14] The details of the decision model, strategies compared, outcome parameters, and, importantly, assumptions have been made available as an Appendix to this manuscript (available online at www.giejournal.org).

Baseline scenario. The baseline scenario considered a 65-year-old person who had an American Society of Anesthesiologists (ASA) score of III with a 3-cm, incidentally found, cystic lesion in the tail of the pancreas.

Strategies compared

Three strategies were compared in the model. In strategy I, after patient data were entered into the model, a conservative ''wait and watch'' policy was followed. In this model, serous (nonmucinous) cystic neoplasms were typically identifiable on cross-sectional imaging[15] and were considered to have a benign course requiring no imaging surveillance. On the other hand, the malignant potential of MCN was taken into account in the Markov model as described in the supplement.

In strategy II, an aggressive surgical approach was used, in that all patients were considered for resection if, without further diagnostic evaluation, they were thought to be operative candidates. Patients who underwent surgical resection were considered to be cured and were not required to undergo further surveillance.

To incorporate the multiple interrelated factors involved in determining the surgical candidacy of these patients, a surgical risk scoring system was developed by using a modified Delphi approach.[16] The scoring system has 4 components, including patient age (<65, 65-79, and ≥ 80 years), surgical risk in terms of ASA score,[17] size of the cystic lesion (≤ 3 cm, 4-5 cm, and >5 cm), and location of the cystic lesion (tail, body, or head of the pancreas).

In strategy III, all patients initially underwent an EUS-guided FNA for cytology and cyst fluid carcinogenic antigen (CEA) estimation. Based on the published

TABLE 1. Important clinical estimates used in the model

Variables	Baseline estimate (range)	Reference no.
Accuracy of imaging in differentiating serous and mucinous cystic neoplasm/branch-type IPMN		
Cross-sectional imaging	0.7 (0.5-1.0)	8, 15
EUS-guided FNA and cyst fluid analysis (carcinoembryonic antigen and cytology)	0.8 (0.5-1.0)	7, 18-21
Proportion of nonmucinous cystic lesions	0.3 (0.1-0.6)	8, 3, 22
Proportion of mucinous cystic lesion/branch-type IPMN at presentation		8, 23-31
Benign	0.65 (0-1.0)	
Borderline	0.20 (0-1.0)	
Malignant	0.15 (0-1.0)	
Annual probability of benign mucinous cystic lesion/branch-type IPMN transitioning from asymptomatic to symptomatic state		27, 32-35, Assumption
Cysts $\leq$3 cm	0.02 (0-0.05)	
Cysts $>$3 cm	0.1 (0.01-0.15)	
Annual probability of benign mucinous cystic lesion/branch-type IPMN transitioning from benign to malignant state		32-35, Assumption
Cysts $\leq$3 cm	0.025 (0-0.5)	
Cysts $>$3 cm	0.05 (0-0.5)	
Annual probability of malignant cysts transitioning from asymptomatic to symptomatic state	0.25 (0-1.0)	Assumption
Perioperative mortality	0.03 (0.01-0.15)	36, 37
Annual mortality from invasive malignant cysts	0.1 (0-0.5)	38, 39
Patient preferences (utilities) for health states		40-42
Normal	1.0 ($\pm$ 25%)	
Incidental cystic lesion	1.0 ($\pm$ 25%)	
Symptomatic cystic lesion	0.95 ($\pm$ 25%)	
Postoperative state	0.95 ($\pm$ 25%)	
Early cancer	0.9 ($\pm$ 25%)	
Late cancer	0.5 ($\pm$ 25%)	

IPMN, Intraductal papillary neoplasm.

performance characteristics of EUS-guided FNA, cyst fluid cytology, and CEA estimation, the diagnosis for many of these patients was mucinous cystic lesion (MCN or branch-type IPMN), and, depending on their surgical risk scores, they would undergo surgical resection as in strategy II. Those with a diagnosis of nonmucinous cysts would be followed in the model but without any further intervention.

Clinical probabilities and utilities

Clinical probabilities, including transitional probabilities between different health states and performance characteristics of cross-sectional imaging studies, and EUS-guided FNA with cyst fluid analysis were derived from published information (Table 1).[3,7,8,15,18-42] When specific published information was not available, expert opinion was obtained by consensus. Quality-adjusted life years (QALY) were estimated by adjusting the life expectancy of each health state by a weight or utility, which reflects patient preferences for that health state.[12] Utility values were obtained from published information.

Cost estimates

Costs, not charges, were considered in this analysis, and a third-party-payer perspective was taken (Table 2).[14,38,43-46] Only direct costs were considered, and all costs were adjusted to 2007 U.S. dollars.

Sensitivity analysis

We tested the robustness of the model by performing sensitivity analysis with the important clinical probabilities and cost estimates. Given that the natural history of incidental pancreatic cystic lesions is not well described, 1-way and multiple-way sensitivity analyses were performed by using clinical variables such as the probability of borderline and malignant cystic lesions at presentation in patients with incidental pancreatic cysts and rates of progression from benign to borderline and malignant

TABLE 2. Important cost estimates

Variables	Baseline (range)	Reference no.
Cost of EUS-guided FNA including cytology and carcinoembryonic antigen estimation	$1350 (± 25%)	38, 43-45
Cost of cross-sectional imaging (CT or MRCP)	$1000 (± 25%)	
Cost of pancreatic surgery	$40,000 (± 25%)	
Annual cost of palliative care	$10,000 (± 25%)	
Discount rate	3% (0%-7%)	14, 46

TABLE 3. Results of baseline analysis

Strategy	Cost per patient	Effectiveness (QALY)	Incremental cost-effectiveness ratio ($/QALY)*
II	$13,200	9.66	-
I	$18,883	10.34	$9474
III	$23,337	10.73	$11,394

QALY, Quality-adjusted life years.
*Compared with strategy II.

states in patients undergoing conservative follow-up. In a hypothetical cohort of 1000 patients with incidentally diagnosed solitary pancreatic cystic lesions, a second-order Monte Carlo simulation was performed, by using a triangular distribution for a probabilistic sensitivity analysis.[46,47]

Outcomes compared and statistical methods

The primary outcomes compared among the 3 strategies were incremental cost-effectiveness ratio (ICER) and net health benefit.[48,49] For analysis of the results of the Monte Carlo analysis, relative risk with 95% confidence intervals (CI) and number needed to treat (NNT) were calculated.

RESULTS

Baseline analysis

In the baseline analysis for a 3-cm incidental cystic lesion in the tail of the pancreas in a 65-year-old patient with an ASA score of III, strategy II was least costly at $13,200 per patient but also yielded the lowest QALY, 9.66. Strategy I was intermediate, being more expensive than strategy II but yielding higher QALY at an ICER of $8442 per QALY gained. Strategy III yielded the highest QALY but was also the most expensive strategy. The ICERs of strategy III, compared to those of strategy I and strategy II, were $9474 and $11,394, respectively, per QALY gained and were acceptable by current standards of health care intervention (Table 3).

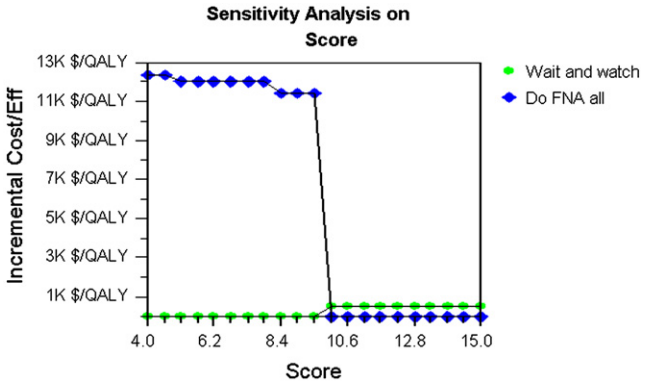

Figure 1. Result of a 1-way sensitivity analysis of operability risk score (*x*-axis) and corresponding incremental cost-effectiveness ratio (*y*-axis). Between the maximum and minimum risk scores, the choice of the optimal strategy in terms of cost-effectiveness was strategy II most of the time, except when the risk score was above 9, when the yield in effectiveness in terms of quality-adjusted life years was higher with strategy I. The line with *filled diamonds* represents strategy III and the one with *filled circles* strategy I. *K,* 1000; *QALY,* quality-adjusted life years.

Sensitivity analyses

Seemingly important variables such as cost of EUS-guided FNA, interval of surveillance by imaging, annual probability of development of symptoms in patients with incidental cystic lesions, annual probability of malignant transformation of benign cystic lesions, and perioperative mortality related to resection of pancreatic cystic lesions did not significantly impact the overall conclusions of the baseline analysis, within the range of estimates used in this analysis.

In 1-way sensitivity analyses, the most important parameter that determined the choice of optimal management strategy was operability risk score. Even with the lowest risk score, strategy II was never the favored strategy in terms of QALY gained. Between the maximum and minimum risk score, the choice of the optimal strategy in terms of cost-effectiveness was strategy III most of the time; however, when the risk score was above 9, the yield in effectiveness in terms of QALY was higher with strategy I (Fig. 1).

The conclusions of the model were sensitive to several other clinically important model parameters. For example, if the threshold value for the probability of an incidental mucinous cystic lesion being benign at entry into the model was 77%, then strategy III was more cost-effective. Above this threshold value, strategy I was more cost-effective (Fig. 2). Similarly, if the probability of a pancreatic cystic lesion being of a mucinous nature (MCN and

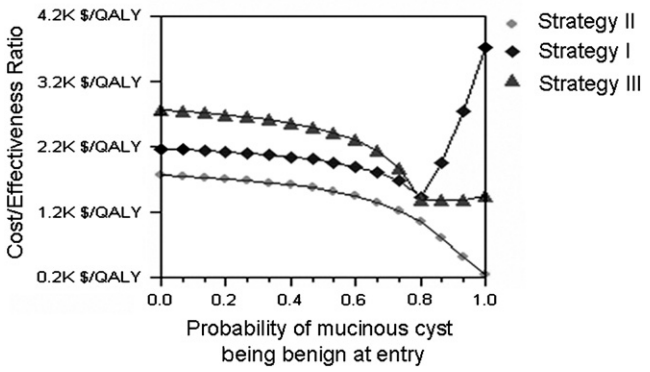

Figure 2. Result of a 1-way sensitivity analysis with the *x*-axis showing the probability of a mucinous cystic lesion being benign at entry into the model and the *y*-axis showing the corresponding incremental cost-effectiveness ratio. Strategy III is consistently more cost-effective except when the probability of a mucinous cystic lesion being benign exceeds 77%, when strategy I becomes more cost-effective. *K,* 1000; *QALY,* quality-adjusted life years.

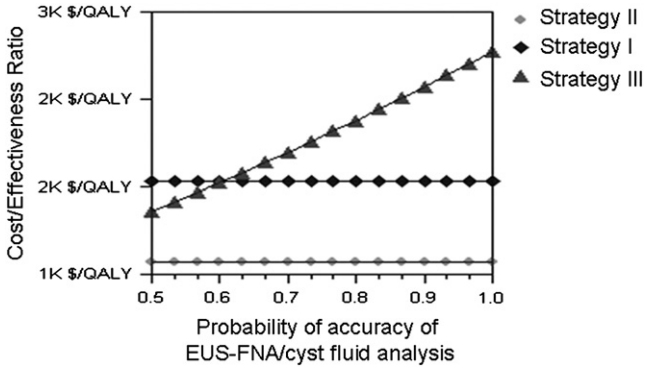

Figure 3. Result of 1-way sensitivity analysis with the *x*-axis showing the overall accuracy of EUS-guided FNA with cyst fluid analysis in differentiating mucinous from nonmucinous cystic lesions and the *y*-axis showing the corresponding incremental cost-effectiveness ratio. Again, strategy III is more cost-effective unless the accuracy of EUS-guided FNA drops below 60%. *K,* 1000; *QALY,* quality-adjusted life years.

side-branch-type IPMN) was less than 27%, then strategy I was more cost-effective than strategy III. Interestingly, if the accuracy of cross-sectional imaging in differentiating mucinous from nonmucinous cysts exceeded 81%, then strategy I, based on a conservative wait and watch approach, would be the favored strategy. Similarly, if the accuracy of EUS-guided FNA and cyst fluid analysis in differentiating neoplastic from nonneoplastic cysts was lower than 60%, then also, strategy I became the favored strategy (Fig. 3).

Figure 4 shows the preference of different strategies in a 4-way sensitivity analysis to show the impact of changing estimates of patient age at entry and size and location of the lesion, along with ASA scores. It is to be noted that strategy II is not an optimal strategy under any assumptions, and the conservative wait and watch approach with strategy I increasingly becomes the preferred strategy with increasing patient age and ASA scores, particularly when the cysts are located in the head of the pancreas.

Monte Carlo analysis

A second-order Monte Carlo analysis was performed by using tracking variables with 1000 hypothetical patients with pancreatic cystic neoplasm. The number of unresectable malignant cystic tumors that were diagnosed under each strategy during the lifetime of this cohort was estimated at 23 and 11 for strategies I and III, respectively. In this model with baseline estimates, compared to the wait and watch strategy, the relative risk of developing unresectable pancreatic malignancy in the strategy based on initial EUS-guided FNA and cyst fluid analysis was 0.48 (95% CI, 0.23-0.98), and the NNT for preventing advanced cystic malignancy was 83 (95% CI, 43-1000).

The scatter plots of distribution of ICERs of strategy I against strategy III for the simulation trial in the hypothetical cohort show that in nearly a quarter of the simulation trials strategy III is clearly superior; conversely, in 48% of simulations, strategy I is clearly inferior (Fig. 5). Figure 6 shows that strategy III yields the highest INHB, and strategy II yields the lowest over a range of willingness to pay.

DISCUSSION

This economic analysis evaluated 3 possible management strategies to identify the most cost-effective management of solitary, asymptomatic pancreatic cystic lesions. The results of our model showed that a strategy based on surgery in all patients with PCN is the least expensive strategy but also the least effective in terms of yield in QALY gained. Although the strategy of selective surgery based on EUS-guided FNA and cyst fluid analysis was the most expensive, it was also the most cost-effective with an ICER below the acceptable upper limit of cost-effectiveness of $50,000 per QALY gained by a health care intervention.[14] The wait and watch strategy was more effective than surgery, with an intermediate associated cost. Overall, the results of this economic analysis suggest that a guideline of indiscriminate surgical resection for all PCN is not a cost-effective approach. For incidental, asymptomatic PCN, a risk-stratification strategy based on EUS-guided FNA and cyst fluid analysis appears to be the most cost-effective strategy in managing these lesions.

The clinical significance of asymptomatic, incidental PCN is related to its malignant potential. There are wide variations in published data with respect to the natural history and the malignant potential of PCN. An early clinicopathological study reported that more than 80% of MCNs were either malignant or had dysplastic changes.[23] Two more recent surgical series of MCN described invasive carcinoma in 47 (36%) of 130 patients and 16 (29%) of 56 patients.[25,26] For branch-duct IPMN, the reported frequency

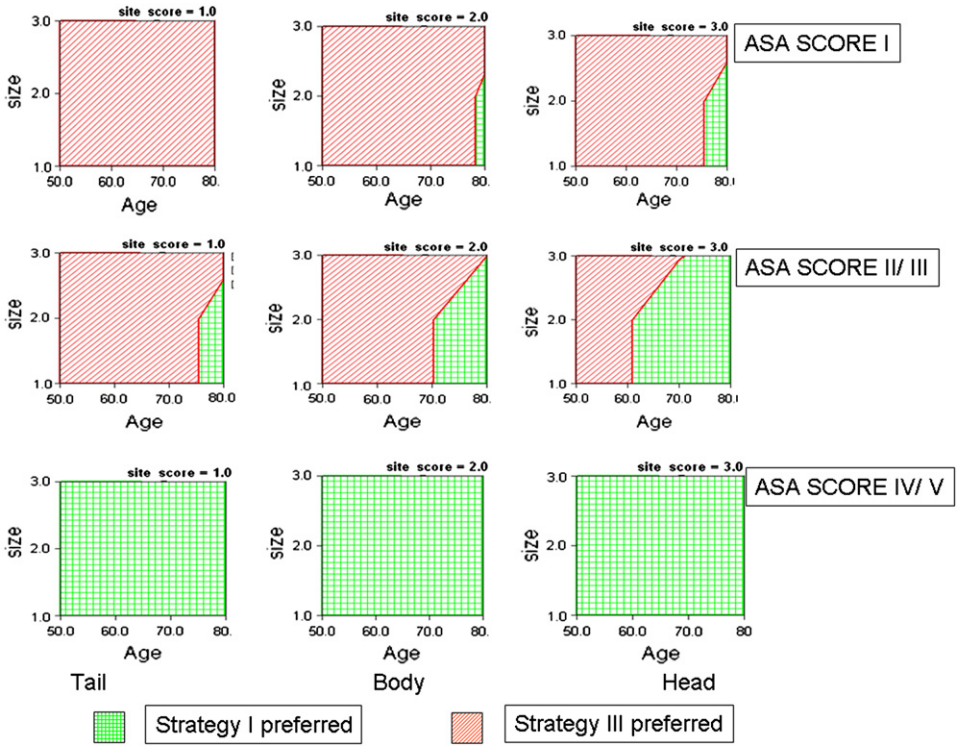

Figure 4. Preference of different strategies in a 4-way sensitivity analysis to show the impact of changing estimates of patient age at entry and size and location of the lesions along with the American Society of Anesthesiologists (ASA) scores. The *x*-axes represent increasing patient age. The *y*-axes represent a size of the lesion score (categorized in Supplementary Table 1) including lesion size of >5 cm, 4-5 cm, and ≤3 cm, scored as 1, 2, and 3, respectively. The right, middle, and left panel images are representative of cysts in the head, body, or tail of the pancreas, respectively. Along the vertical orientation, the upper, middle, and lower panels represent patients with ASA scores ranging from I to V, as labeled. Any point in the cross-patterned areas indicates that strategy I is preferred to other strategies in terms of cost-effectiveness; any point in the diagonal stripe patterned areas indicates that strategy III is the optimal strategy. Strategy I becomes increasingly the more preferred strategy with increasing patient age and ASA scores, particularly when the cysts are located in the head of the pancreas.

of malignancy lies anywhere between 6% and 46%, and invasive cancer has been reported to be present in 0% to 31% of all patients.[27-30] Surgical series from tertiary care institutions are subject to referral biases and may not include many asymptomatic patients in the population who were not referred for surgical evaluation. More recent studies suggest that most PCNs, particularly the smaller incidentally detected ones, have a much lower risk of malignancy and could be followed with observation, based on certain proposed criteria.[21,32-34,50] The decision on what strategy should be adopted to manage asymptomatic PCNs is sensitive to the proportion that are mucinous and what proportion of mucinous lesions are malignant or become malignant (Fig. 4).

The international consensus guidelines for management of IPMN and MCN, which do not specifically address management of incidental PCN, recommend surgical resection for all MCNs but recommend expectant management in asymptomatic patients with smaller (<30 mm), branch-type IPMNs without mural nodules.[11] Despite being distinct pathological entities with different potentials for developing invasive malignancy, MCN and branch-type IPMN are often clinically impossible to distinguish preoperatively. Justifications for aggressive surgical intervention for PCN include lack of definitive knowledge of the natural history of such lesions, concern for malignant transformation, and the limited ability to differentiate between benign and malignant lesions preoperatively. However, the substantial increase in detection of small, asymptomatic PCNs as incidental findings on cross-sectional abdominal imaging in patients who, more often than not, are elderly with significant comorbidities has led many clinicians to consider expectant management by serial imaging studies in lieu of surgical resection.[50] The health benefit and cost-effectiveness of such a strategy of expectant management have not been studied. The hypothetical analysis performed in this study found that in certain clinical scenarios expectant management is a very reasonable approach.

Clinical features such as the presence of symptoms, greater patient age, male sex, and morphological features such as larger lesion size, the presence of mural nodules, or segmental involvement of the main pancreatic duct in the case of branch-type IPMN are associated with higher potential for development of invasive malignancy.[11,31] Nonsurgical diagnostic efforts have focused primarily on analyzing tumor markers in cyst fluid aspirated by EUS-guided FNA. In a recent American Society for

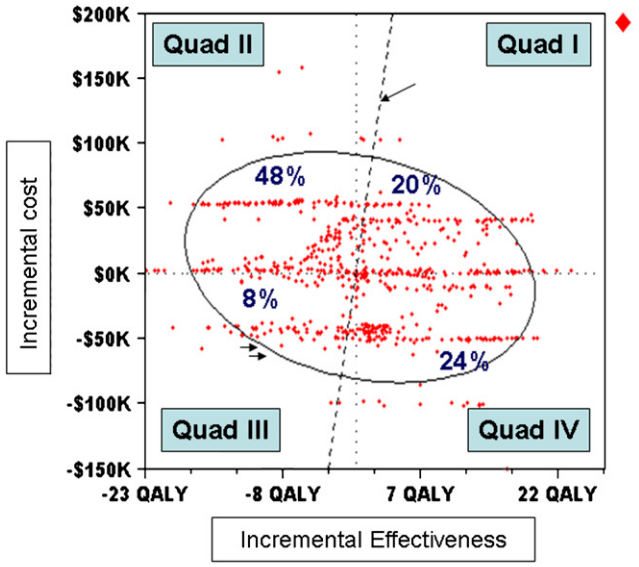

Figure 5. Scatter plots of the incremental cost-effectiveness ratio (ICER) of strategy I (wait and watch approach) against strategy III (EUS-guided FNA and cyst fluid analysis in all patients) for the simulation trial in the hypothetical cohort. The scatter plots include a single set of points representing pairs of incremental cost and cost-effectiveness values from the simulation results. The *x*-axis represents incremental cost-effectiveness in terms of quality-adjusted life years, and the *y*-axis represents incremental cost with the dotted lines denoting the zero planes in the graph. The threshold ICER (*willingness to pay*) line (marked with an *arrow*) in the graph intersects points having the specified ICER value, and the region below and right of the line includes cost-effective points. The scatter plot also has a 95% confidence ellipse (marked by *double arrow*). The scatter plots primarily show the proportion of simulation trials with ICER that will fall in quadrants marked as I to IV starting at the right upper quadrant and moving in a counterclockwise direction with quadrant IV being in the right lower corner. Any point in quadrant I shows that strategy III is more effective but more expensive compared to the baseline strategy; however, any point to the right of the *willingness to pay* line will be cost-effective. In quadrant II all points represent the ICER of strategy I, which is more expensive but less cost-effective and thus, clearly inferior to strategy III. In quadrant III, the comparator strategy III is less expensive but less cost-effective than the baseline and represents the area of indifference for the model. All points in quadrant IV represent less expensive but more cost-effective strategy III, which would be clearly superior compared to strategy I. The figures in brackets in each quadrant represent the proportion of simulation that resulted in an ICER that was mapped to a particular quadrant. *K,* 1000; *QALY,* quality-adjusted life years; *Quad,* quadrant.

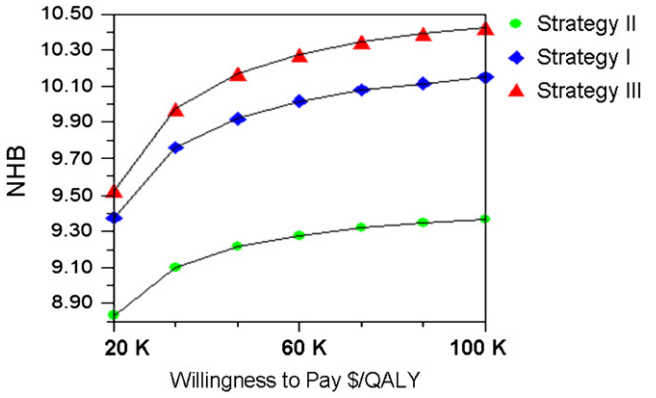

Figure 6. Average net health benefits (NHB) (*y*-axis) yielded under each strategy against *willingness to pay* (*x*-axis). Clearly, strategy III yields the highest NHB and strategy II the lowest over a range of *willingness to pay*. *K,* 1000; *QALY,* quality-adjusted life years.

Gastrointestinal Endoscopy guideline, based on observational studies, it was suggested that cytological analysis of cyst fluid obtained by EUS-guided FNA has high specificity for diagnosing malignant PCN.[20] A pooled analysis of 12 studies demonstrated that cyst fluid analysis is beneficial in the evaluation of PCN in asymptomatic patients and patients with an increased surgical risk.[18] In the recently published American College of Gastroenterology practice guidelines for the diagnosis and management of neoplastic pancreatic cysts, the authors recommend that for small, asymptomatic cysts the decision regarding surgery versus surveillance should be based on the determination of whether the cyst is mucinous or not. EUS-guided FNA and cyst fluid analysis for CEA seems to offer the best available discrimination between mucinous and nonmucinous cysts.[51] Although the diagnostic accuracy of EUS-guided FNA for distinguishing mucinous from nonmucinous PCN is only about 80% and clearly needs improvement, this economic analysis demonstrates that even at that current level of test characteristics this diagnostic test should play a clinical role in determining the optimal therapeutic strategy; indeed, it provides the clinician with an opportunity to opt for a reasonably cost-effective individualized approach in managing these patients instead of choosing between two radical options of either a wait and watch policy or one of across-the-board surgical resection.

Because little published data are available on the natural history of symptomatic pancreatic cystic lesions, in constructing the decision analysis model we had to make several assumptions (detailed in the Appendix) for certain clinical variables for modeling the natural history of these lesions. Sensitivity analyses were performed on these and other variables to assess their impact on the conclusions of the baseline analysis and also to determine threshold values of key variables where one strategy will be favored over the other strategies. Variables such as interval of imaging surveillance, annual probability of developing symptoms, annual probability of malignant transformation, and perioperative mortality did not have a significant impact on the overall conclusions. Consistent with our clinical experience, the most important variable in determining the optimal management strategy was the operability risk score, which in turn represents the important determinants of perioperative risk, patient age, and size and location of the cyst. It is important to note that even when the operability risk score is at the minimum, a blanket approach of surgical resection is not favored. Appropriately, when the surgical risk was prohibitively high, the expectant wait and watch strategy was more cost-effective.

Only 2 studies published earlier addressed the cost-effectiveness of different management strategies for PCN. In a retrospective study of 60 patients with PCN, Lim et al[52] suggested that a management algorithm based on clinical presentation, radiological findings, EUS-guided FNA, and CEA analysis of cyst fluid resulted in an estimated cost saving of $1403 per patient. In another study, in a simple decision tree, parameters that would support conservative treatment versus resection were evaluated, and resection was recommended only within a limited range of clinical variables, such as age of the patient and operative mortality.[53] Although both studies generally support our conclusions, neither study performed a formal economic analysis by using a Markov analysis or incorporated outcome parameters such as QALY and ICER.

It is important to note that our study is a hypothetical construct with inherent limitations. As with any decision analysis model, the conclusions are dependent on the validity of the data used. Because there are limited published data about asymptomatic PCN, several assumptions were made. When no data were available about clinical probabilities, expert opinion was used. These values were purposely biased in favor of the surgical strategy. For example, in the baseline analysis for estimates of perioperative mortality, we used the best figures from centers of excellence, which are much lower than those encountered in community practice[37]; all patients who underwent surgical resection were considered cured, although published data on long-term survival in these patients are less optimistic.[54] Further, a high utility value was used for quality of life in the postoperative state. Additionally, no follow-up expenses were accounted for in the strategy based on surgical resection. Despite these biases, the fact that the model did not favor strategy II, which is based on current guidelines of surgical resection of all PCN, supports the robustness of our conclusions. One important limitation when interpreting the results is that the surgical risk score developed for this analysis has not been validated clinically in formal prospective studies. Another limitation of this study is that it did not take into account all pancreatic cystic lesions. In particular, main-duct IPMNs including mixed type (both main-duct and branch-duct involvement) were not included because their management would likely involve a different diagnostic algorithm based on ERCP, which is considered the reference standard for diagnosis of main-duct-type IPMN and plays a crucial role in the evaluation of those patients.[8] Also, in this analysis we did not consider perioperative morbidity and complications related to EUS-guided FNA procedures; only direct costs were taken into account, and indirect costs related to management of PCN were not considered.

There are also several methodological strengths of this economic analysis. To minimize the inherent uncertainty of validity of input parameters in such an economic analysis, we performed a thorough search of all published information on PCN and used the most plausible range of estimates in our best-case and worst-case scenarios for sensitivity analyses. In addition, we used the powerful Monte Carlo simulation techniques to reflect the inherent uncertainties to simulated real-life clinical practice and to derive valid statistical measures of effectiveness such as relative risk and NNT.[55] We also used the concepts of incremental net health benefit and willingness to pay, which are considered more appropriate indices of cost-effectiveness compared to ICER for an economic analysis performed from a third-party-payer perspective.[56]

In summary, in this economic analysis we showed that for asymptomatic patients with incidental solitary PCN such as MCN and branch-type IPMN, a blanket policy of surgical resection for all patients cannot be justified on the basis of cost-effectiveness. A strategy based on stratification of risk of malignant potential by EUS-guided FNA examination and cyst fluid analysis is the most effective strategy in terms of yield of QALY gained within a broad range of clinical probabilities and cost estimates; the incremental cost incurred in this strategy is well within the currently accepted standards of health care interventions. In those patients in whom the surgical risk was prohibitively high, the expectant wait and watch strategy was more cost-effective. A randomized controlled trial with longitudinal follow-up for evaluating these management strategies for PCN is unlikely in the foreseeable future; however, prospective studies are urgently required to acquire quality data on key variables such as probability of incidental mucinous cystic lesions being benign at the time of diagnosis, accuracy of cross-sectional imaging and EUS-guided FNA and cyst fluid analysis in accurately differentiating mucinous from nonmucinous cystic lesions, and rates of progression of mucinous lesions to invasive cancer. Availability of such data will validate our decision analysis model and strengthen the practice guidelines to allow individualized patient management decisions based on appropriate risk stratification.

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Current affiliations: Division of Gastroenterology (A.D., S. Ngamruengphong), Mayo Clinic Arizona, Scottsdale, Arizona, Division of Gastroenterology (S. Nagendra, A.C.), University Hospitals Case Medical Center and Case Western Reserve University, Cleveland, Ohio, USA.

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Reprint requests: Ananya Das, MD, Division of Gastroenterology, Mayo Clinic Arizona, Scottsdale, AZ 85259.

If you would like to chat with an author of this article, you may contact him at Das.ananya@mayo.edu.

APPENDIX

Supplement with detailed description of the decision analysis model.

Data collection

Computer-assisted recursive literature searches of the MEDLINE, EMBASE, and Cochrane databases (January 1977 to October 2007) were performed by using predefined search criteria including the terms *pancreatic cystic neoplasm*, *serous*, *mucinous,* and *intraductal papillary mucinous tumor/neoplasm*. Abstracts from major gastroenterology meetings were also searched for relevant abstracts published from 1997 to 2007. Manual searches of the bibliography of selected publications were also performed.

Decision analysis model

By using decision analysis software, we built a hybrid model of a linear decision tree terminating in a Markov model to compare different strategies of management in a hypothetical cohort of asymptomatic patients with a solitary cystic lesion in the pancreas on cross-sectional imaging of the abdomen done for unrelated indications (Figs. 1S and 2S).[1] In the Markov model, the natural history of patients with PCN was modeled by using various health and disease states (such as healthy, asymptomatic PCN, symptomatic PCN, malignant PCN—resectable and unresectable, postoperative state, advanced pancreatic malignancy, and finally, death), each associated with a different set of costs and utilities. Each state was permitted transition to death (transitional probability dependent on age-specific mortality from U.S. life tables as well as state-specific mortality, such as perioperative mortality).[2] Each state could transition to the next state or stay in the same state, but certain transitions were not permitted, and the death state was considered an absorbing state (Fig. 2S).

At entry into the model, all members of the cohort had a solitary cystic lesion in the pancreas detected by abdominal CT and/or magnetic resonance imaging done for an unrelated indication; at the end of each cycle of the model, which was set at 1 year, cohort members were redistributed to different states depending on the estimated probabilities of transition among different health states. The time horizon of the model was the lifetime of the cohorts. The analysis was conducted according to the recommendations of the Panel on Cost-effectiveness in Health and Medicine for conducting and reporting a reference case analysis with a third-party-prayer perspective.[3]

Strategies compared

Three strategies were compared in the model. In strategy I, after entry into the model, the natural history of the lesion was followed without any specific intervention at entry. Based on available literature, it was estimated that up to 30% of these unselected cystic lesions were serous cystadenomas or other nonmucinous cystic lesions and represented a benign clinical course, mostly staying asymptomatic during follow-up with no risk of malignant transformation.[4] No imaging surveillance was performed in these patients. The model was constructed to allow misclassification of PCN by cross-sectional imaging by using published performance characteristics of CT in this setting.[4,5]

If the lesion was a neoplastic cystic lesion with a risk of malignant transformation (either a mucinous cystic lesion or branch-duct IPMN without main duct involvement), in strategy I, the patients entered the appropriate Markov model in which the natural history of such lesions was modeled in the following manner: most of the cysts would continue to be asymptomatic and benign and would require periodic surveillance with cross-sectional imaging such as CT scan; for baseline analysis the frequency of such surveillance was considered to be every 3 years; however, a small proportion would either harbor cancer or

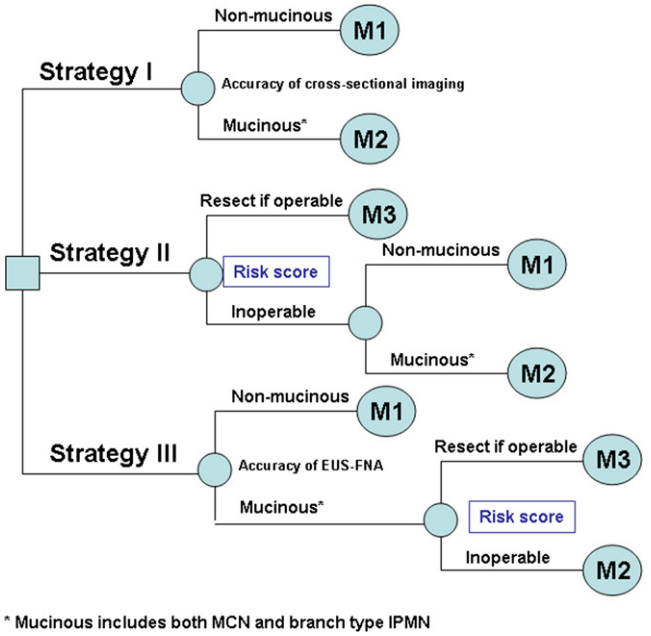

Figure 1S. Hybrid model of the linear decision tree terminating in Markov models. Three strategies are compared. In strategy I, a conservative wait and watch approach is followed without a specific intervention at entry. If the cysts were suspected to be nonmucinous cystic lesions, they were followed in the M1 Markov cycle. If they were suspected to be mucinous cystic lesions (mucinous cystic neoplasm [MCN] or branch type intraductal papillary neoplasm [IPMN]), they entered M2 Markov cycle. In strategy II, all patients at entry were evaluated for possible surgical resection and, if they are operable, they underwent surgery and entered the M3 Markov cycle. If they were deemed inoperable, they entered the M1 or M2 Markov cycle depending on the nature of the cystic lesions. In strategy III, all patients underwent a EUS-guided FNA along with cyst fluid analysis (carcinoembryonic antigen and cytology); if they were diagnosed with mucinous cystic lesions, they underwent resection based on their risk score; otherwise, they were followed in M2 Markov cycle. If they were thought to be nonmucinous cysts, they entered the M1 Markov cycle. In this decision tree, a *square node* means the decision node at entry, *filled circles* are chance nodes, and circles inset with ''M'' represent the Markov nodes.

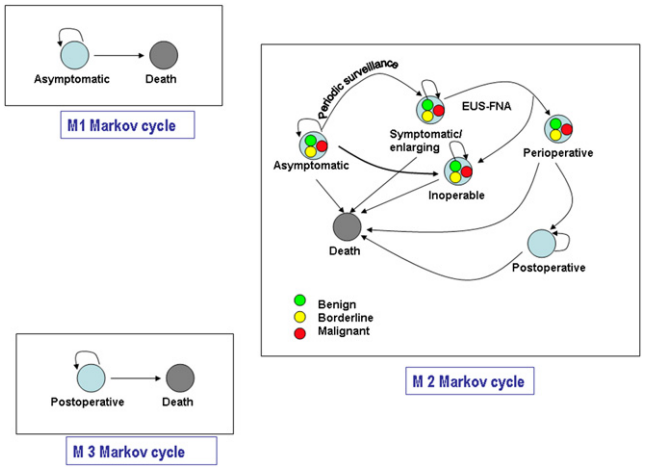

Figure 2S. Simplified model of different Markov cycles. In the M1 Markov cycle, the patient remains in an asymptomatic state or makes a transition to the dead state depending on the age-specific U.S. mortality. In the M2 Markov cycle, the patient enters the model in the asymptomatic state, undergoes periodic imaging surveillance, may stay in the same state (indicated by an inbound *arrowhead*), or may become symptomatic and/or show enlargement of the cyst on imaging. Such transition will trigger further evaluation with cross-sectional imaging and EUS-guided FNA, which may lead to increased surveillance with imaging or the consideration of surgery. If surgery is performed, the patient will transition through the perioperative state; if surgical resection is not feasible, they will be considered inoperable and continue to be in that state or may die in future cycles. Death is allowed from any state, but certain transitions are not allowed. A *single arrowhead* indicates transition from one state to another in the direction of the arrow head; *double arrowheads* indicate that transitions in both directions are allowed in the model. The *smaller colored circles* indicate that a cystic lesion could be benign, or harbor borderline or frankly malignant cells irrespective of symptomatic status.

would develop borderline malignancy or even overt malignancy. Any lesion that became symptomatic or showed significant growth on follow-up imaging studies with or without malignant transformation in the model would trigger further evaluation with cross-sectional imaging studies (CT abdomen) including EUS-guided FNA evaluation with cytology and cyst fluid analysis for carcinoembryonic antigen (CEA).

Because of persistent symptoms and/or as a result of EUS-guided FNA–based evaluation, some patients would undergo intense imaging surveillance such as CT scans done every 6 months to check stability of the size of cysts. A proportion these patients, either initially or later during intense surveillance, would be considered for surgery because of persistence of symptoms or diagnosis of malignancy. Depending on the operability of the lesion and the patient's surgical risk, a certain proportion of patients would undergo resection of the cystic lesion with its attendant postoperative mortality and morbidity but would be cured of the cystic lesion and would not require any further surveillance. Those patients who were symptomatic but did not undergo surgery would continue the natural history of the original lesion with attendant loss of utility in terms of reduced quality of life either due to a symptomatic state and/or unresectable malignancy. Costs associated with palliative care for unresectable pancreatic malignancy was built into the model.

In strategy II, an aggressive surgical approach was considered, in that all patients were considered for resection without further diagnostic evaluation if they were thought to be operative candidates. Patients who underwent surgical resection were considered to be cured and were not required to undergo any further surveillance. If, however, they were not operable, they would be followed up with an expectant approach but without further imaging surveillance.

To incorporate the multiple interrelated factors involved in determining the surgical candidacy of these

TABLE 1S. Components of operability score

Component	Score
American Society of Anesthesiologists (ASA) score	
I	0
II	1
III	2
IV/V	10
Age score (years)	
Age ≥80	3
Age 65-79	2
Age <65	1
Lesion location score	
Head of pancreas	3
Body of pancreas	2
Tail of pancreas	1
Lesion size score	
>5 cm	1
4-5 cm	2
≤3 cm	3

Total operability score: ASA score + age score + location score + size score. Minimum score 3; maximum score 19.

TABLE 2S. Probability of the patient undergoing surgery corresponding to the total operability score

Score	Probability (%)
<5	100
5-7	66
8-9	33
≥10	0

patients, a surgical risk scoring system was developed by using a modified Delphi approach.[6] After an initial score was developed by the authors, the scoring system was evaluated in 2 academic institutions by a total of 4 surgeons with an interest in pancreatic diseases. The surgeons were informed of the context of the scoring system and the basic approaches used for this decision analysis. The final scoring system incorporated the modifications suggested by the surgeons. The scoring system has 4 components, including age of the patient (<65, 65-79, and ≥ 80 years), surgical risk in terms of American Society of Anesthesiologists (ASA) score,[7] size of the cystic lesion (≤3 cm, 4-5 cm, and >5 cm), and location of the cystic lesion (tail, body, or head of the pancreas) (Table 1S).

The total operability score defined the probability of an individual patient for undergoing surgical resection (Table 2S) and also determined perioperative mortality in the patient. In our baseline analysis, a typical patient was considered to be in the age group of <65 years, with an ASA score of III and a 3-cm, cystic lesion located in the tail of the pancreas. The total score for such a patient would be 7, and the corresponding probability of this patient undergoing surgical resection was estimated at 66%.

In strategy III, all patients initially underwent an EUS-guided FNA for cytology and cyst fluid CEA estimation. Based on the published performance characteristics of EUS-guided FNA, cyst fluid cytology, and CEA estimation, many of these patients were diagnosed to have a mucinous cystic lesion (MCN or branch-type intraductal papillary neoplasm [IPMN]) and depending on their surgical risk score would undergo surgical resection as in strategy II. Those with a diagnosis of nonmucinous cyst would be followed in the model but without any further intervention. Both false-negative and false-positive diagnoses with EUS-guided FNA and cyst fluid CEA estimation were taken into account in the model; for example, in case of an incorrect diagnosis of a nonmucinous lesion (diagnosed as nonmucinous but actually a mucinous cyst), that particular patient would not undergo further imaging surveillance but would continue to have a small but definite possibility of having or developing malignancy, which would manifest during follow-up and eventually would incur cost and reduce QALY.

Clinical probabilities and utilities

Clinical probabilities, including probabilities of transition between different health states, and performance characteristics of cross-sectional imaging studies and EUS-guided FNA with cyst fluid analysis were derived from published information. When specific published information was not available, expert opinion was obtained by consensus (Table 3S).

Quality-adjusted life years (QALY) were estimated by adjusting the life expectancy of each health state by a weight or utility, which reflects patient preferences for that health state.[1] Utility values were obtained from published information.

Cost estimates

Cost, not charges, were considered in this analysis, and a third-party-payer perspective was taken (Table 4S). Only direct costs were considered, and all costs were adjusted to 2007 U.S. dollars. Costs were estimated based on the national average reimbursement allowed for each coded procedure by the Centers for Medicare and Medicaid Services during the fiscal year 2001. Inpatient medical, surgical, and diagnostic services were assigned current procedural terminology or diagnosis-related group codes to identify the health care resource utilization. Outpatient data were based on ambulatory payment classification and current procedural terminology.[8]

Sensitivity analysis

We tested the robustness of the model by performing sensitivity analysis with the important clinical probabilities and cost estimates. Given that the natural history of incidental pancreatic cystic lesions is not well described, 1-way and multiple-way sensitivity analyses were performed by using clinical variables such as the probability of borderline and malignant cystic lesion at presentation in patients with incidental pancreatic cysts and rates of progression from benign to borderline and malignant states in patients undergoing conservative follow up. In a hypothetical cohort of 1000 patients with incidentally diagnosed solitary pancreatic cystic lesion, a second-order Monte Carlo simulation was performed for a probabilistic sensitivity analysis. Monte Carlo simulation recalculates a model multiple times and incorporates uncertainties into an analysis in keeping with real-life situations.[9] In this method, sampling probability values from probability distributions (specifically, triangular distribution) of important variables (rather than from a single range defined by upper and lower bounds) places greater weight on likely combinations of parameter values, and simulation results quantify the total impact of uncertainty on the model in terms of the confidence that can be placed in the analysis results. By using tracker variables, the number of patients with unresectable malignant pancreatic cystic lesions was compared among different strategies.

Outcomes compared and statistical methods

The primary outcomes compared among the 3 strategies were incremental cost-effectiveness ratio (ICER), and net health benefit (NHB) incremental cost-effectiveness ratio was calculated as the difference in costs divided by the difference in outcome (life years) between the strategies (ICER = [cost strategy I - cost strategy II] / [effectiveness strategy I-effectiveness strategy II]). The ICER is a measure of the added cost for each additional life

TABLE 3S. Clinical estimates used in the model

Variables	Baseline estimate	Range	Reference no.
Accuracy of imaging in differentiating serous and mucinous cystic neoplasm/branch-type IPMN			
Cross-sectional imaging	0.7	0.5-1.0	8, 15
EUS-guided FNA and cyst fluid analysis (carcinoembryonic antigen and cytology)	0.8	0.5-1	7, 18-20
Proportion of nonmucinous cystic lesions	0.3	0.1-0.6	8, 3, 22
Proportion of mucinous cystic lesion/branch-type IPMN at presentation			8, 23-31
Benign	0.65	0-1	
Borderline	0.20	0-1	
Malignant	0.15	0-1	
Annual probability of benign mucinous cystic lesion/branch-type IPMN transitioning from asymptomatic to symptomatic state			27, 32-35, Assumption
Cysts $\leq$3 cm	0.02	0-0.05	
Cysts $>$3 cm	0.1	0.01-0.15	
Annual probability of benign mucinous cystic lesion/branch-type IPMN transitioning from benign to malignant state			32-35, Assumption
Cysts $\leq$3 cm	0.025	0.0-0.5	
Cysts $>$3 cm	0.05	0.0-0.5	
Annual probability of malignant cysts transitioning from asymptomatic to symptomatic state	0.25	0-1.0	Assumption
Annual probability of malignant cysts transitioning to advanced malignancy without treatment	0.25	0-1.0	Assumption
Perioperative mortality	0.03	0.01-.15	36, 37
Annual mortality from invasive malignant cysts	0.1	0-.5	38,39
Annual mortality from advanced pancreatic malignancy	0.9	0.25-1.0	40-42, Assumption
Patient preferences (utilities) for health states		$\pm$25%	40-42
Normal	1.0		
Incidental cystic lesion	1.0		
Symptomatic cystic lesion	0.95		
Postoperative state	0.95		
Early cancer	0.9		
Late cancer	0.5		

IPMN, Intraductal papillary neoplasm.

year gained by strategy II. Also, the net health benefit (NHB) of an alternative option, which is increasingly being used in economic evaluation of health care intervention, was calculated by using the formula NHB = E - C/WTP, where E represents effectiveness, C represents cost, and WTP is the willingness to pay (ie, the decision maker's threshold ICER).[10,11] The NHB is the health effect of the treatment minus the benefit that one would have obtained by investing the resources spent on a marginally effective treatment. Incremental net health benefit was calculated as the difference between two NHBs. NHB is often preferred to ICER as a measure of cost-effectiveness because of its direct interpretation as the average health gained per patient who undergoes the alternative

TABLE 4S. Cost estimates

Variables	Baseline	Range	Reference no.
Cost of EUS-guided FNA including cytology and carcinoembryonic antigen estimation	$1350	±25%	38, 43-45
Cost of cross-sectional imaging (CT or MRCP)	$1000	±25%	
Cost of pancreatic surgery	$40,000	±25%	
Annual cost of palliative care	$10,000	±25%	
Discount rate (%)	3	0-7	14, 46
Annual cost of care of advanced pancreatic malignancy	$50,000	±25%	38, 43-45
Annual cost of surveillance by imaging	$1000	±25%	38, 43-45

treatment adjusted for cost and willingness to pay. Also, unlike ICER, the NHB is a monotonic function of both health and cost. Higher values of NHB are always better. Health policy makers should favor a strategy for which the NHB takes the greatest positive value in relation to values of willingness to pay that seem reasonable with respect to known public policy. For analysis of the results of the Monte Carlo analysis, relative risk with 95% confidence intervals and number needed to treat were calculated.

Assumptions

Primarily because of a limited amount of published information or no published information, several assumptions were made in this model.

(1) It was assumed that an incidental solitary pancreatic cystic lesion would be categorized into one of 3 main types: nonmucinous cystic lesion including serous adenoma, mucinous cystic lesion, and branch-type IPMN. Main-duct or combined main-duct and branch-duct IPMN (mixed type) are quite distinctive histopathological entities with readily distinguishable imaging features and often require different clinical management. Other unrelated entities such as pseudocysts, simple cysts, and cystic neuroendocrine tumor as well as solid-pseudopapillary lesions were not considered in this model.

(2) In this model we considered solitary lesions only, and this limitation has been mentioned in the discussion part of the revised article. One objective was to keep the model as straightforward as possible. Multiple lesions, which are not uncommon, present more difficult management decisions, which are usually made on a case-by-case basis.

Multiple cystic lesions in the pancreas are commonly seen with side-branch or mixed-type IPMN (which is considered to be at a lower risk of malignancy compared to MCN or main-duct IPMN), and the presence of multiple lesions usually discourages surgical intervention (because of the need for extensive resection). When surgical intervention is chosen, it is usually based on symptoms related to a dominant lesion.

(3) Although there have been a handful of reports of malignant transformation of serous adenoma, in this model we considered them to have a benign natural history that did not mandate resection.[4,12]

(4) It was assumed that patients who would be selected for surgery and undergo surgery uneventfully would have complete resection of the cystic lesion, without any risk of recurrence. Although a recent report suggested that patients with pancreatic cystic lesions are at considerably high risk for developing pancreatic cancer in regions remote from cystic lesion, this was not considered in the model.[13]

(5) For cost and mortality estimates, it was assumed that all patients undergoing surgery would undergo laparotomy, and resection would be done with either a Whipple procedure for lesions in the head of the pancreas or a distal pancreatectomy for body/tail lesions. No emerging surgical techniques such as laparoscopic distal pancreatectomy were considered.

(6) With respect to EUS-guided FNA, it was assumed that EUS-guided FNA would be feasible in all patients. Only cytology and CEA estimation was considered for cyst fluid estimation for differentiating mucinous from nonmucinous cystic neoplasm. For simplicity, no complications related to EUS-guided FNA were considered in the model.[14,15] Complication rates related to EUS-guided FNA of pancreatic cysts are low, and complications are usually mild.[15]

Although there is emerging information that detailed molecular analysis of cyst fluid may be useful in predicting malignancy, such analyses were not considered in this model because of very limited information.[15,16]

Endoscopic treatment of neoplastic pancreatic cysts by ablation of cystic epithelium has been reported but was not considered in this model because the efficacy of such intervention has not been determined.[17]

Due to a lack of objective data, the potential adverse impact of patient anxiety with respect to the malignant potential of PCN on quality of life was not taken into account in this model.[18]

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