Title
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Journal
Surgery, 168(4)

ISSN
0039-6060

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Publication Date
2020-10-01

DOI
10.1016/j.surg.2020.04.052

Peer reviewed

HHS Public Access

Author manuscript

Surgery. Author manuscript; available in PMC 2022 January 12.

Published in final edited form as:

Surgery. 2020 October ; 168(4): 601–609. doi:10.1016/j.surg.2020.04.052.

Cost-effectiveness of Consensus Guideline Based Management of Pancreatic Cysts: The Sensitivity and Specificity Required for Guidelines to be Cost-Effective

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Abstract

Background: Pancreatic cyst detection has outpaced our ability to stratify low-grade cysts from those at higher risk for pancreatic cancer, raising a concern for overtreatment.

Methods: We developed a Markov decision model to determine the cost-effectiveness of guideline-based management for asymptomatic pancreatic cysts. Incremental costs per quality adjusted life year (QALY) gained and survival were calculated for current management guidelines. A sensitivity analysis estimated the impact on cost-effectiveness and mortality if overtreatment of low-grade cysts is avoided, and the sensitivity and specificity thresholds required of cyst stratification methods to improve costs.

Results: "Surveillance" employing current management guidelines had an incremental cost-effectiveness ratio (ICER) of $171,143/QALY compared to no surveillance or surgical treatment, ("Do Nothing"). The ICER for surveillance decreases to $80,707/QALY if surgical overtreatment of low-grade cysts was avoided. Assuming a societal willingness-to-pay of $100K/QALY, diagnostic specificity for high-risk cysts must be >67% for Surveillance to be preferred over Surgery and Do Nothing. Changes in sensitivity alone cannot make Surveillance cost-effective. Most importantly, survival in Surveillance is worse than Do Nothing for three years after cyst

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Portions of this work were presented at the American College of Surgeons Clinical Congress, Boston, MA 10/23/18 and the Academic Surgical Congress, Jacksonville, FL 01/31/18

Disclosures/Conflicts: None declared

diagnosis, even though long-term survival is improved. The disadvantage is eliminated when overtreatment of low-grade cysts is avoided.

Conclusions: Current management of pancreatic cysts is not cost-effective and may increase mortality due to overtreatment of low-grade cysts. Risk stratification specificity for high-risk cysts must be greater than 67% to make Surveillance cost-effective.

TOC Statement- 20191248

This cost-effectiveness analysis shows that current management guidelines for IPMN are not cost-effective and calculates the sensitivity/specificity needed for guidelines to be cost effective. The importance of this report is to highlight the potential overtreatment of IPMN and provide goals for future guidelines and diagnostics tests to achieve cost-effectiveness and improve survival.

Keywords

Pancreatic cysts; cost-effectiveness; pancreas cancer; risk stratification

Introduction:

Up to 3 million incidental pancreatic cysts are diagnosed each year in the United States, a more than 3-fold increase over two decades, as abdominal CT and MRI are more readily utilized, imaging protocols improve, and the population ages[1–3]. During the past decade, there has been a sharp rise in the surgical treatment of pancreatic cysts due in part to these incidental findings (Figure 1). In 2014, 31% of pancreatic resections in the US were performed to remove cysts (approximately 5000 operations), up from just over 10% in 2001[4]. Importantly, this has not led to a decrease in the absolute number of invasive cancers detected, suggesting overdiagnosis and overtreatment. Unfortunately, current diagnostics cannot accurately stratify low-grade dysplasia (LGD) from high-grade dysplasia or invasive cancers (HGD/IC). The resulting clinical uncertainty further contributes to overdiagnosis and overtreatment of incidental pancreatic cysts.

Pancreatic cystic neoplasms (PCNs) comprise 90% of pancreatic cysts[5]. PCNs are broadly classified as mucinous cysts – most commonly intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasms (MCN) – or non-mucinous serous cystadenomas (SCN). Most of the remaining pancreatic cysts are inflammatory pseudocysts, that develop in the setting of pancreatitis or trauma. A subset of PCNs with obvious high-risk malignant features, so called “High Risk Stigmata” (main pancreatic duct involvement, solid mass, jaundice), are resected with confidence as HGD/IC is present in the majority of these lesions[5,6]. However, benign cysts (SCN, pseudocysts) are often difficult to distinguish from cysts with malignant potential (branch duct (BD)-IPMN, MCN), based on imaging alone[7–9]. To improve the accuracy of clinical decision-making, in 2006 the International Association of Pancreatology introduced consensus guidelines that included clinical, radiographic and endoscopic features. Improvements in the guidelines in 2012 and 2017 have resulted in a high sensitivity to identify potential cancers, however with poor specificity leading to high rates of resection of low grade cysts[10,11]. Additionally, in practice surgeons and patients choose to surgically remove cysts even more liberally than suggested by the guidelines, thereby increasing the potential for overtreatment with the attendant surgical morbidity, mortality, and health care costs[12].

Both pancreatic cancer and pancreatic surgery are associated with high rates of morbidity and mortality. The question then arises as to whether the harms of treating pancreatic cysts outweigh the benefits. In the current study, we evaluate the cost effectiveness and survival impact of current management guidelines to address this important question Further, we determine the potential cost and survival benefits of improving diagnostic accuracy to minimize missed cancers, while avoiding overtreatment of low-grade or benign pancreatic cysts.

Methods:

We developed a Markov decision-analytic model to evaluate the cost-effectiveness and outcomes of three management strategies for incidental PCN without obvious high risk features associated with malignancy, for whom the management has the most uncertainty, and the risk of overtreatment is greatest. Management strategies included I) Immediate surgery for all patients ("Surgery"), II) No surgical resection or imaging surveillance ("Do Nothing"), and III) Surveillance and resection based on the revised 2017 International Association of Pancreatology Consensus Guidelines for management of IPMN ("Surveillance"), the most widely followed guidelines utilized among pancreas surgeons[6,13]. We model three possible management strategies to evaluate their long-term impact.

Decision Model

We built a Markov decision-analytic model to compare three strategies for management of PCN for a hypothetical cohort of 60 year-old asymptomatic patients with a new diagnosis of 2.5 cm solitary PCN on cross-sectional imaging (sFigure 1). This cohort was chosen to represent the clinically challenging management case and is representative of the median size of resected IPMN in a recent large multisite study[12]. Three management strategies were compared: I) Upfront surgery for all patients ("Surgery"), II) No surgical resection or imaging surveillance ("Do Nothing"), and III) Surveillance and resection based on 2017 International Association of Pancreatology Consensus Guidelines for management of IPMN ("Surveillance")[6,13]. Comparison to an upfront surgery for the basecase was chosen because some groups recommend surgery to all patients with pancreatic cysts, and more than 20% of cyst resections are completed immediately following diagnosis for reasons outside of management guidelines[12,14–17]. Far fewer patients who undergo surveillance proceed to surgery[18–20]. Model development, inputs, and reporting were guided by CHEERs and the Second Panel on Cost-Effectiveness in Health and Medicine[21–23]. TreeAge decision analysis software was used (TreeAge Pro 2018 R1.0, TreeAge software, Inc. Williamstown, MA). Model outputs include "effectiveness" measured in quality-adjusted life years (QALYs) and "cost" measured in dollars. QALYs are attributed to each treatment strategy as the sum of the utility of each disease state in the model over the time period spent in a given disease state. Cost is the lifetime estimate of US dollars spent for all treatments per patient for a given strategy. Strategies are compared by the incremental cost effectiveness ratio

(ICER), which measures the difference in cost per QALY between two strategies. In terms of cost-effectiveness, the preferred strategy is one that maximizes QALYs at the lowest cost.

Inputs and Transition Probabilities

The presence of LGD, HGD and IC at initial resection, rates of cancer development and progression, and related mortality was based on the literature, published models, and a large multi-institutional Pancreas Cyst NIH U01 cohort comprised of patients from UCSF, MD Anderson Cancer Center, and the University of Utah (Table 1)[6,11,18,19,24–51]. Each baseline disease state (LGD, HGD or IC) was modeled with a likelihood to progress to invasive cancer based on radiographically surveilled natural history cohorts. Relative incidence of PCN with LGD, HGD, and IC, as well as disease progression were modeled using estimates of health and disease states for IPMN, the most common and most clinically relevant PCN. The US life table morbidity and mortality rates were incorporated into the model to account for age-specific annual mortality from other causes[52].

Costs and Utilities

Procedure and inpatient hospital services costs, including those for surgical complications, were based on the 2018 Medicare Physician-fee-schedule and included direct and indirect medical costs (Table 2)[53]. Annual care costs were estimated from the literature. All costs were adjusted to 2018 dollars[54–56]. Utilities were estimated based on published disease related disutilities[57,58]. A discount rate of 3% was used for costs and utilities in the model.

Sensitivity Analysis

Probabilistic and deterministic sensitivity analyses were conducted to determine which variables were most influential to the model and to determine threshold values at which the preferred strategy switched. Ranges for the sensitivity analysis were modeled using triangular distributions.

Model for Improved Cyst Stratification—To evaluate the benefit of improved stratification of HGD/IC from LGD, we modeled three new “Optimized Surveillance” strategies that adjust the Surveillance strategy as follows: I) “Optimized Sensitivity”, models 100% diagnostic sensitivity, in which all lesions containing HGD/IC are resected immediately in surveillance, at current specificity, II) “Optimized Specificity”, models 100% diagnostic specificity, in which cysts containing only LGD were spared upfront resection and put into surveillance, at current sensitivity and III) “Ideal Surveillance”, models 100% diagnostic accuracy (100% specificity and 100% sensitivity), in which all cysts containing HGD/IC were resected upfront and all cysts containing only LGD were surveilled. Primary focus was given to the Optimized Specificity strategy to reflect the potential cost, morbidity, and mortality benefits that could be incurred from preventing overtreatment of LGD.

The values for sensitivity (probability that all HGD/IC is identified and resected immediately) and specificity (probability that LGD is NOT resected) for a cyst diagnostic algorithm or assay were varied to determine the threshold values for sensitivity and specificity required based on cost-effectiveness measures of the Surveillance strategy. Finally, improvement of survival outcomes for these thresholds were modeled.

Results:

Cost-Effectiveness for Guideline-based Surveillance of Pancreatic Cysts

Figure 2a plots the costs versus effectiveness for possible management strategies for a 60-year-old with an incidental PCN. The Do Nothing strategy was least effective at 10.17 QALYs, but also the least costly at $126776. Compared to this strategy, the Surgery strategy added 1.07 QALYs and an incremental cost of $156,455, resulting in an ICER of $146,903/QALY, above a $100,000 cost-effectiveness plane. The Surveillance strategy was less efficient as the ICER was $171,143 and fell above the cost curve formed between the other strategies. As a result, it is not considered a preferred strategy.

For the base case, estimated overall survival for Do Nothing was greater than Surveillance at 1-year (99% vs 97%) but decreased after year 3 (figure 2b, 3a). Surveillance led to an overall survival advantage over Surgery, including lower cancer mortality and disease-specific mortality (cancer mortality plus surgical mortality) at 5-years (7.6% vs 8.7%, figure 3b) and at 10-years (13.8% vs 15.6%, figure 3c), but not at 20-years (21.3% vs 17.9%, figure 3d) as the survival curves cross at 14.7 years. Finally, lifetime rates of cancer death were 25.1% in the Surveillance group, compared to 32.5% in Do Nothing and 18.7% in the Surgery groups.

Sensitivity analysis

In a probabilistic sensitivity analysis, only 12.6% of patients undergoing Surveillance and 17.1% of Surgery patients are expected to achieve an ICER less than a WTP of $100K compared to Do Nothing (eFigure 2a). In contrast, if resection of LGD is avoided, 63% of patients would achieve an ICER <$100K (eFigure 2b).

In a tornado analysis, the most influential variables determining the incremental costs and effectiveness were specificity, age, prevalence of HGD, surgical mortality, rate and utility of surgical morbidity, and rate of progression of LGD in surveillance (eFigure 3). Based on an $100K WTP, each of these non-modifiable variables are predicted to influence the preferred strategy when comparing the Surgery and Surveillance groups (eFigure 3a). However, only specificity is able to decrease the ICER of Surveillance below the $100K WTP compared to Do Nothing (eFigure 3b). Improving specificity and sensitivity were considered separately below.

Potential Savings of Improved Risk Stratification of Pancreatic Cysts

The cost-effectiveness of PCN management was also calculated for the three Optimized Surveillance strategies to determine the impact of diagnostic uncertainty and the resulting overtreatment of LGD. Optimized Sensitivity resulted in an ICER of $159,997 compared to Do Nothing, comparable to Surveillance based on current diagnostics. In contrast the ICER for both Optimized Specificity ($80,707/QALY) and Ideal Surveillance ($78,519/QALY) compared to Do Nothing were below $100K, and resulted in a discount of $90,436/QALY and $92,624/QALY, respectively, compared to the ICER of Surveillance under the current diagnostic capabilities (Figure 4a).

Avoiding upfront resection of LGD in Surveillance (Optimized Specificity) also eliminated the early survival disadvantage compared Do Nothing and led to maximum benefit over all other strategies at 7 years (figure 4b). Optimizing specificity also improved cancer and disease related mortality compared to Surgery or current surveillance at 5 (6.1%) and 10 years (12.8%). This is in large part due to a 75% reduction of surgical mortality for Optimized Specificity compared to Surveillance at 5 years, and a 64% reduction at 10 years. Lifetime rate of cancer death improved to 22.8%.

Threshold targets for Sensitivity and Specificity for diagnostic testing of Pancreatic Cysts

Given impact of diagnostic sensitivity and specificity on cost-effectiveness and survival, threshold values at which Surveillance would be cost-effective were determined. A two-way sensitivity analysis showed that Do Nothing is the preferred strategy except when the sensitivity and specificity are both above 88% (figure 5a). To determine values for sensitivity and specificity required to change the preferred strategy individually, each was plotted over all range of possible values (0 to 1). Sensitivity above 83% favors Surveillance over Surgery for all, however, the ICER for Surveillance compared to Do Nothing remained >$100K for all possible values of sensitivity. As a result, changes in sensitivity alone cannot make Surveillance cost-effective (figure 5b). In contrast, Surveillance is favored over Surgery at a specificity >52% and Surgery is *dominated* (ICER becomes negative as the strategy is less expensive and more effective) at a specificity above 89% (figure 5c–d). Further, Surveillance is cost-effective compared to Do Nothing at specificity >67%, but it is not strictly dominant over Do Nothing at any value.

Discussion:

The number of adults diagnosed with pancreatic cysts has increased dramatically over the past two decades due to increased utilization of axial imaging and improved resolution to detect small cysts[2,25]. Although the majority of incidentally detected cysts are benign and asymptomatic, the rate of pancreatic resections for cysts has mirrored the increase in cyst detection over the same period (figure 1). Current consensus guidelines are intended to be highly sensitive for the detection of HGD/invasive cancer. However, due to low specificity of consensus guidelines and clinical practice that favors aggressive resection, 40–78% of resected cysts contain either no dysplasia or only low-grade dysplasia on final pathology[11,12,59]. Based on the low probability that benign cysts will become malignant, the long time to progression, and the short and long-term risks of pancreatic resection, surgical treatment is an unfavorable choice for most of these patients. As a result, people with pancreatic cysts are at risk for overdiagnosis and subsequent overtreatment.

Increased pancreatic cyst detection alone poses a significant cost burden to the healthcare system given the high cost of pancreatic resections and the high rate of complications associated with pancreatectomy[53]. The potential burden is amplified by the low specificity to identify and resect high-grade or invasive cysts in current practice[11,12,51]. Three prior studies evaluated the cost-effectiveness of IPMN management. Huang et al and Das et al found that surgery for all patients was prohibitively expensive, however, surveillance based on stratification with the 2006 International Consensus Guidelines was preferred in patients younger than 78 years, who are fit for surgery[39,40]. Weinberg et al took a patient centered approach and concluded that the management strategy should consider patient values for overall survival vs quality-adjusted survival, as well as cyst characteristics found in consensus guidelines[41]. These studies are significantly limited by consideration of BD-IPMN in the pancreatic head only and outdated guidelines. Additionally, they do not address metrics to improve costs.

Herein, we utilized a Markov decision-analytic model to show that management of pancreatic cysts by the updated 2017 International Association of Pancreatology Consensus Guidelines is not cost-effective and results in a 1-year mortality increase of approximately 2.5%. We show that patients are at early risk for increased mortality with the current approach to pancreatic cysts. In order to determine the best path forward to improve management strategies, we calculated the difference in incremental costs for optimal management and show that the most robust savings are generated by improving diagnostic *specificity* to identify high-grade or invasive cysts. We also sought to determine the targets for sensitivity and specificity that future diagnostics and/or management guidelines require to be cost-effective and improve survival. Our analysis showed that target specificity should be 67%, about fifty percent higher than the current guidelines[10–12]. In practice, surgeons have lower specificity (i.e. resect more low-grade lesions) than even the current guidelines suggest, so the problem is likely even more significant than our model shows[12]. To our knowledge, this is the first study to prescribe explicit goals for future clinical guidelines or diagnostics.

We found that the cost of Surveillance or Surgery for a newly diagnosed incidental pancreatic cyst is high, $171,143 and $146,903, respectively, and Surveillance based on consensus guidelines is the least cost-effective strategy. Additionally, a sensitivity analysis enabled us to determine which potentially actionable variables in cyst detection, risk stratification and treatment could improve cost-effectiveness and patient outcomes. With a focus on sensitivity and specificity, we found that optimizing sensitivity (maximizing detection of all high-risk patients (HGD/IC)) as many of the incremental improvements to consensus guidelines have aimed to do, only marginally improved Surveillance. Conversely, we show that identifying high-risk patients at the current rate but optimizing specificity (avoiding resection of LGD) bends the cost curve well below 100K-WTP and improves survival (figure 4B). In addition, compared to current Surveillance, there is a direct savings of $90,436/QALY made possible by avoiding resection of low-grade cysts. These data suggest that improving specificity to prevent resection of LGD, thereby preventing overtreatment, should be an important focus for the management of pancreatic cysts.

The impact of low specificity on driving overtreatment for pancreatic cysts was reinforced by sensitivity analysis. We identified specificity as the only variable that could be adjusted to change the preferred strategy. Given considerable effort in the field to create diagnostic assays or management nomograms to stratify risk groups, we considered specificity a modifiable variable and calculated that a 52% and 67% specificity are required for Surveillance to be favored over Surgery and Do Nothing, respectively. Current surgical consensus guidelines achieve only 22–38% specificity[11,51], however, there is no superior alternative. The American Gastroenterological Association guidelines, which evaluate many of the same clinical characteristics with a more stringent criteria for resection shows higher specificity, 64% in a pooled analysis, but the sensitivity is only 35–62%[60–62]. As a result, these guidelines similarly are not cost effective in our model. More recent investigational efforts have shown promise to improve stratification for HGD/IC, but these assays are not yet utilized widely in practice[63,64]. When considering cost-effectiveness, it is misguided to emphasize sensitivity over specificity due to the uncertainty in cyst biology. Assay developers and consensus committees should aim for a minimum benchmark of 67% specificity for future diagnostics.

The practical goal for specificity should be even higher. Despite the finding that Do Nothing is preferred below a specificity of 67%, few would "Do Nothing" when considering the attendant risk of pancreatic cancer. The comparison of Surveillance to Surgery for all then, can define the diagnostic targets. One area of controversy in the balance of an aggressive surgical approach to avoid missed cancers versus overtreatment of LGD is how to quantitatively compare the undue morbidity and mortality of over-resection versus the mortality disadvantage of a missed cancer given our poor understanding of cyst biology and progression. While we show that 52% specificity is the minimum value at which Surgery is no longer *cost-effective* for each QALY gained considering a $100K-WTP, society could choose to pay more for each added segment of life, and the aggressive approach would still be accepted. This is argued by Cho et al, who report that although we have a high rate of misdiagnosis of pancreatic cysts, the true costs are minimized when other potentially harmful diagnoses result or when cancer risk is valued over surgical risks[65]. We show that above 89% specificity, Surveillance has absolute dominance over Surgery. Put simply, at 89% specificity the benefits of avoiding overtreatment objectively outweigh the low risk of missing potential cancers. Most importantly, physicians can ensure patients that their shared choice is unlikely to cause undue harm. An 89% specificity is the target new diagnostic tests should reach to change practice.

Aggressive surgical resection for incidentally detected pancreatic cysts will prevent some cancers from developing, however, at what cost? Table 3 illustrates that the current focus on identifying and removing all potential cancers leads to a substantial improvement in life expectancy made by Surveillance compared to No Treatment, however, to achieve this, 2037 low-grade cysts would be removed. Pivoting the focus of patient selection to specificity would greatly decrease the number operations on low-grade disease. Additionally, improved specificity would decrease new cases of diabetes related to pancreatectomy, decrease cancer and surgical mortality and prolong the life expectancy over current Surveillance. Incidental detection of pancreatic cysts on abdominal imaging is unlikely to slow down as technology and access advances, so it is incumbent on practitioners to follow the lead of other screen detected cancers and understand the benefits and risks of aggressive treatment[66]. Surgeons should employ thoughtful patient selection and patient centered decision making to avoid resection of low grade or benign tumors, particularly older patients or those with low risk tumors, who may not benefit from aggressive treatment.

There are several limitations in this study. Prior cost-effectiveness analyses argue that surgical decisions should be tailored to the age of the patient[39]. We similarly found that Surgery is prohibitively expensive over Surveillance for patients over 82 years. In our model, Surveillance is not cost-effective at any age compared to Do Nothing based on a $100K WTP, so perhaps this is an inappropriate threshold for this disease or its treatment. This conclusion could change if a different WTP threshold was chosen for the overall cohort, or for certain groups. For instance, if WTP is based on age, a more liberal 150K WTP may be used to conclude that patients over 69.7 years can be followed without surveillance or surgery, or a lower 50K WTP could be used to conclude all patients under 50.9 years should undergo surgery regardless of risk (eTable). Further, analytic model outputs are only as strong as the assumptions they are built on. We aimed to build a model that is widely generalizable to patients with a new diagnosis of pancreatic cysts, particularly cysts that may be considered mucinous and thus at risk for malignancy. However, long-term or high-level data for pancreatic cyst progression is limited and typical comes from level II retrospective or non-controlled sources. There are few natural history studies of IPMN, rather most series represent surgical data and may overinflate the risk. For example, while we argue that low-grade cysts do not require resection, we accept that high-grade cysts are likely to become malignant, however, even high-grade cysts may have low malignant potential. If this were the case, the findings we present are strengthened, highlighting the critical need for a better understanding of the natural history of pancreatic cysts and biological basis to stratify risk.

Conclusions:

Increased detection of pancreatic cysts poses a considerable burden on the healthcare system given the complexity of pancreatic surgery, as well as, current inability to stratify risk. Because of these factors, and the morbidity and mortality associated with intervention, overtreatment is a concern. Our analysis shows that current management guidelines are not cost-effective and may lead to undue early mortality. However, improved diagnostic specificity above 67% could substantially improve cost-effectiveness and survival for surveillance management strategies of pancreatic cysts. Future research should investigate the natural history of pancreatic cysts so that disease outcomes can be better predicted. Additionally, future management guidelines should emphasize specificity for high grade or malignant pancreatic cysts to improve risk stratification and prevent overtreatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to acknowledge the Molecular Characterization of Screen Detected Lesions National Cancer Institute U01 (NIH CA196403-01 and CA2000468) who supported the design and development of this work.

Funding:

This work was supported by the National Institutes of Health, National Cancer Institute U01 collaborative grants (CA196403-01 and CA2000468)

Abbreviations:

CT	computerized tomography

MRI	magnetic resonance imaging
PCN	Pancreatic cystic neoplasm
IPMN	Intraductal papillary mucinous neoplasm
MCN	mucinous cystic neoplasm
LGD	low-grade dysplasia
HGD	high-grade dysplasia
IC	invasive cancer
SCN	serous cystadenomas
ICER	incremental cost-effectiveness ratio
QALY	quality adjusted life years

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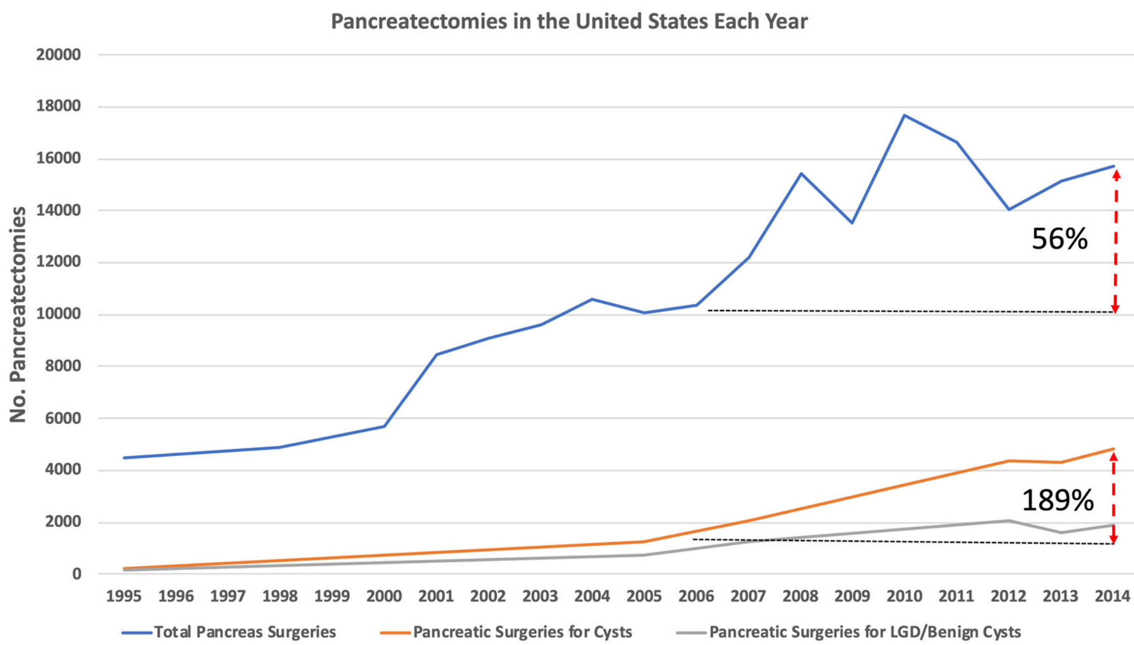
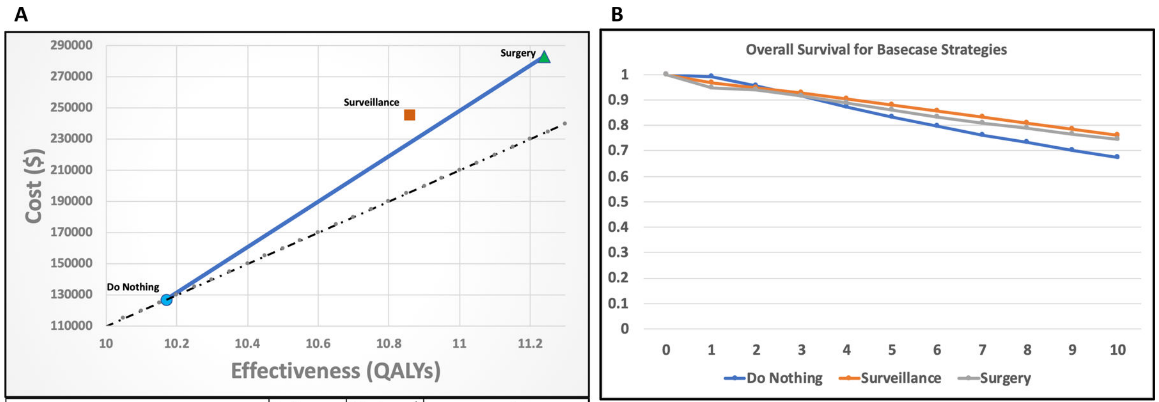


Figure 1: Pancreatic resections in the United States over time.

The total number of pancreatic resections (blue line), resections primarily for pancreatic cysts (orange line), and resections for low grade or benign pancreatic cysts have steadily increased over twenty years. Since the publication of the Sendai criteria for IPMN in 2006, the total number of pancreatectomies has increase by 56% or 28,000 per year, while the number of pancreatectomies for pancreatic cysts has increased by 189% or 15,000 resections per year over the same period. Data are taken from the National Inpatient Sample (NIS) and published sources (HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. https://hcupnet.ahrq.gov/).



Strategy	Cost[a]	Effectiveness[b]	Incremental cost/effectiveness
Do Nothing	126776	10.17	-
Surveillance	244800	10.86	171143*
Surgery	283231	11.24	146903
a- Average discounted lifetime cost in 2018 dollars			
b- Discounted quality adjucted life years (QALYs)			
c- Compared to common baseline, do nothing			
*Extended dominance			

Figure 2: Cost-effectiveness and Survival for Base-case Management Strategies for Pancreatic Cysts.

(A) Cost-effectiveness of the base-case strategies. Solid line represents the effectiveness frontier and indicates that Surgery (triangle) and Do Nothing (circle) strategies have extended dominance over Surveillance (square). Dotted black line indicates the $100K societal willingness-to-pay (WTP). (B) Overall survival for baseline strategy options to treat pancreatic cysts.

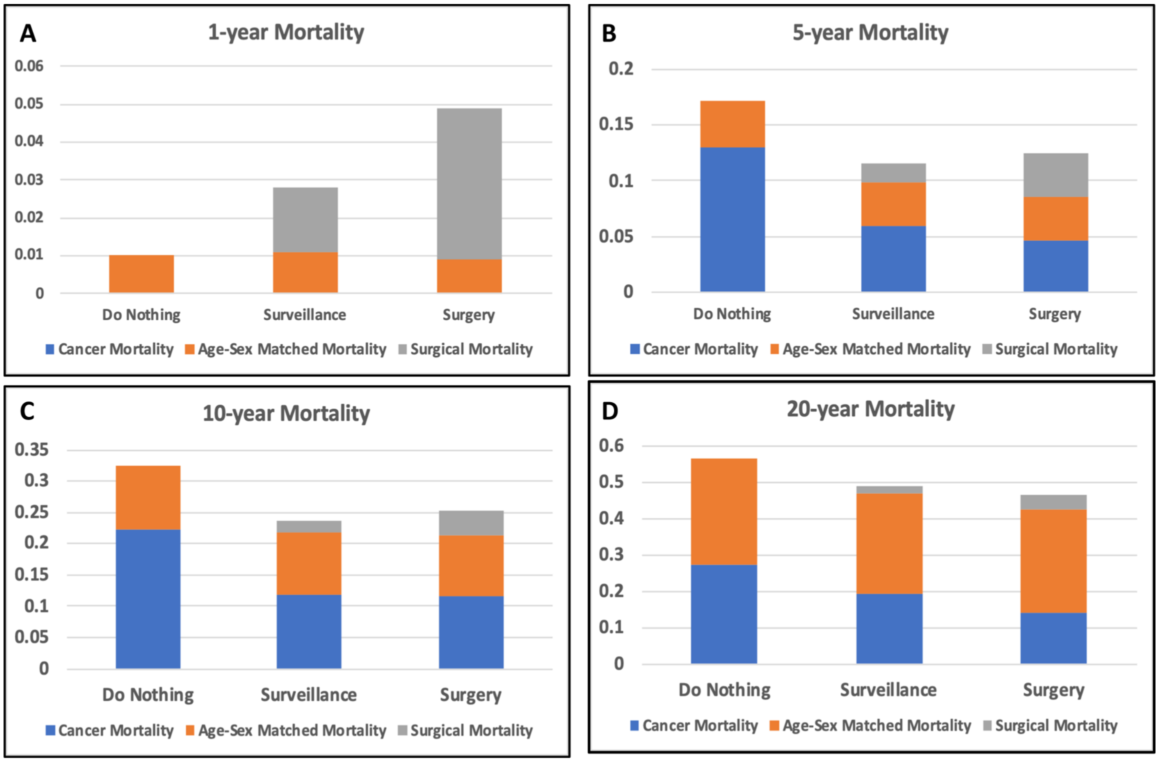
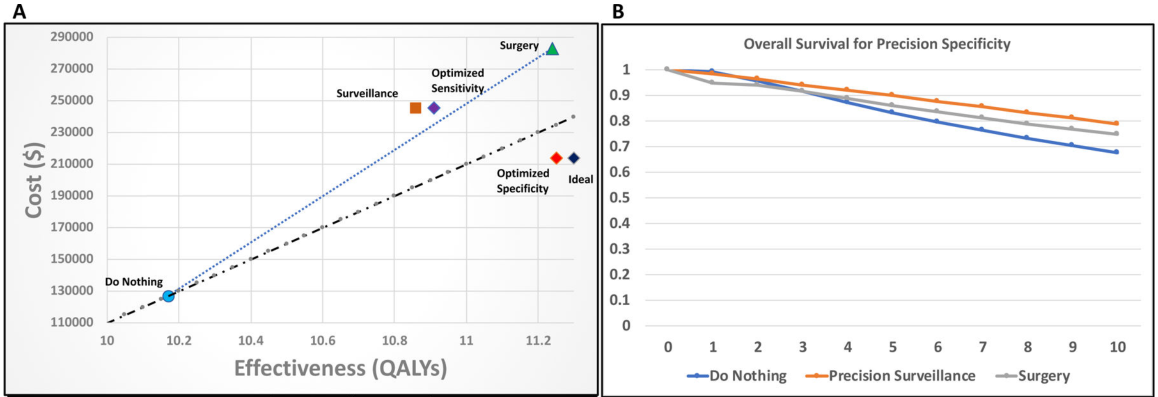


Figure 3. Survival and cause of death estimates for patients with pancreatic cysts treated with difference management strategies.

(A-D) 1-, 5-, 10-, and 20- year mortality estimates by cause of death. Disease-specific mortality incudes cancer deaths and surgical death.



Strategy	Cost[a]	Effectiveness[b]	Incremental cost/effectiveness[c]
Optimized Sensitivity	245421	10.91	159957
Optimized Specificity	212639	11.2	80707
Ideal	214444	11.25	78519

Figure 4. Cost-effectiveness and survival for guideline-based surveillance with improved risk stratification.

(A) Potential cost-effectiveness for improved Surveillance strategies for pancreatic cysts. Purple, Red, and Dark Blue triangles represent 100% sensitivity, 100% specificity, and 100% sensitivity and specificity, respectively. Dotted black line indicates the $100K WTP. Note that only Optimized Specificity and Ideal Surveillance fall below the $100K WTP. (B) Overall survival when specificity for diagnosing HGD/IC is 100% (Optimized Specificity).

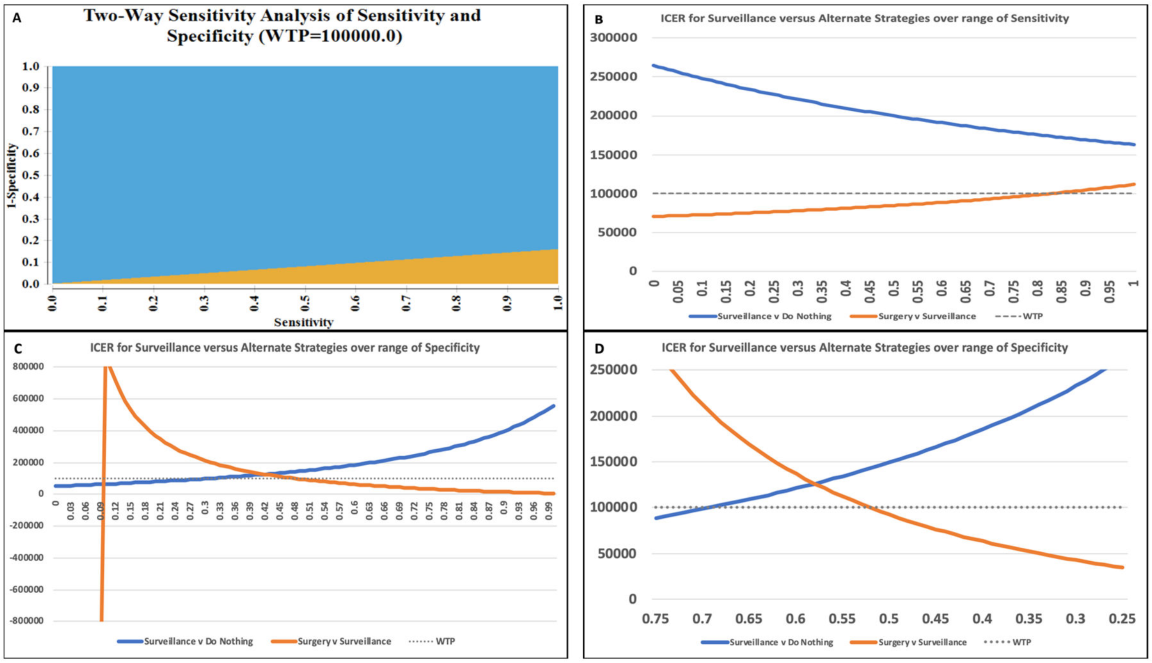


Figure 5. 1-Way and 2-way Sensitivity Analysis for Sensitivity and Specificity.

Sensitivity analyses for sensitivity and specificity for diagnostic testing for pancreatic cysts were conducted to determine the minimum levels required for Surveillance to be the dominant strategy based on $100K WTP. (A) 2-way sensitivity analysis varies sensitivity and specificity simultaneously at current sensitivity, specificity would have to be 67% or above for Surveillance to be cost-effective. (B) 1-way sensitivity analysis of diagnostic sensitivity shows that Surveillance is cost-effective over Surgery when sensitivity is at least 83%, however, Surveillance is not cost-effective over Do Nothing for any value when only sensitivity is improved. (C-D) 1-way sensitivity analysis of diagnostic specificity confirms that Surveillance dominates Surgery when specificity is greater than 89% (C). In a closer view, minimum specificity required for Surveillance to be cost-effective over Surgery and Do Nothing is 52% and 67%, respectively (D).

Table 1:

Model probability estimates

Variable	Base Case	Range[3]	References
Age	60	40–90	
Low-grade Cysts	85%	50–100%	6,26–28,30
Present with surgical indication[1]	42%	10–65%	12,51
Develop surgical indication (annually)	2%	0–4%	20,24,67
Annual Progression to High Grade	2.9%	0.5–20%	19,67
Annual Progression to disseminated cancer (no surgery)	3%/5yr	1–13%/5y	20,24,25,50,67
Annual Progression to disseminated cancer (after surgery)	2.8%/5yr	1–7%/5y	29–31,48,49
High-grade Cysts	8.85%	0–20%	6,26–29
Present with surgical indication[1]	90%	75–95%	11,12,25
Develop surgical indication (annually)	38.60%	20–50%	18,19,48,50,67
Annual Progression to Invasive Cancer	30%	5–65%	19
Annual Progression to disseminated cancer (no surgery)	45.5%/5yr	25–65/5yr	24,25,33,50
Annual Progression to disseminated cancer (after surgery)	15%/5yr	5–30/5yr	24,25,35,50
Invasive Cysts	6.15%	0–15%	6,26–29
Present with surgical indication[1]	92%	80–100%	12
Develop surgical indication (annually)	38.60%	20–50%	18,19,48,50,67
Annual Progression to disseminated cancer (no surgery)	29%	15–50%	29,30,35
Annual Progression to disseminated cancer (after surgery)	53%/5yr	35–70%	30–33,35,43
Present with a surgical indication (all comers)	43%	35–50%	12
Long term Surgical complication (DM, exocrine insufficiency)[2]	31.80%	20–50%	34,39,42,43,46
Surgical Mortality[2]	2.00%	1–10%	37,38,68,69
Temporary complication[2]	30.80%	20–50%	35,36,42,43
Mortality for disseminated pancreatic cancer	90%/yr	73–99%/yr	48,49

[1]indication for surgery calculated by # with HRS + # with WF/dysplasia on cytology

[2]Surgical mortality, Long term and temporary complications calculated by aggregate rate of DM or exocrine pancreatic insufficiency for pancreaticoduodenectomy and distal pancreatectomy

[3]Ranges calculated using a triangular distribution

Table 2:

Cost and utility estimates

Variable		Base Case	Range	References
Annual Diabetes care		$16,750	$9600–25000	56
Annual Health care		$7,150	$500–17500	56
End of life care *		$45,052	$10000–80000	45,53
Metastatic treatment of cancer		$63,533	$30000–112500	55
MRI		$3,471	$2830–4431	53
Pancreatectomy		$109,528	$76000–147000	53
Complication		$30,885	$17000–37000	53
Surgery disutility		−2.5%	−1.5 to −3.5%	39,57
Surgical complication disutility		−2.5%	−1.5 to −3.5%	39,57
Diabetes utility		88%	78–98%	58
Metastatic cancer utility		69%	59–79%	57
ASM utility		100%	90–100%	
Annual Discount Rate		3%	1–5%	22

*Adjusted to 2018 dollars

Table 3:

Patients at risk for overtreatment of incidentally detected pancreatic cysts

	No Treatment	Current Surveillance Strategy	Optimized Specificity Strategy	Difference if Specificity Improved
Pancreatic Cysts 1.0cm or larger	103402[a]	103402[a]	103402[a]	0
Pancreatic Cysts 2.5cm or larger	14550[a]	14550[a]	14550[a]	0
Surgeries for low-grade cysts in US per year	0	2037	186	−1851
Low grade cysts undergoing surveillance at 5 years	12368	4593	8668	4075
New Diabetes at 5 years	284	1876	1463	−414
Surgery-related deaths at 5 years	0	368	218	−151
Cancer Deaths at 5 years	1892	858	786	−73
Life expectancy	77.3 years	79.9 years	80.7 years	0.8 years

[a]Approximate population values