Published in final edited form as:
Gastroenterology. 2010 February ; 138(2): 531–540. doi:10.1053/j.gastro.2009.10.001.

Asymptomatic Pancreatic Cyst Neoplasms: Maximizing Survival and Quality of Life Using Markov-based Clinical Nomograms

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Abstract

Background—The natural history and management of pancreatic cysts, especially for branch duct intraductal papillary mucinous neoplasms (BD-IPMNs), remains uncertain. We developed evidence-based nomograms to assist with clinical decision-making.

Methods—We used decision analysis with Markov modeling to compare competing management strategies in a patient with a pancreatic head cyst radiographically suggestive of BD-IPMN, including: (1) initial pancreaticoduodenectomy (PD), (2) yearly non-invasive radiographic surveillance, (3) yearly invasive surveillance with endoscopic ultrasound (EUS), and (4) “do nothing.” We derived probability estimates systematic literature review. The primary outcomes were overall and quality-adjusted survival. We depicted the results in a series of nomograms accounting for age, co-morbidities, and cyst size.

Results—Initial PD was the dominant strategy to maximize overall survival for any cyst >2cm, regardless of age or comorbidities. In contrast, surveillance was the dominant strategy for any lesion <1cm. However, when measuring quality-adjusted survival, the “do nothing” approach maximized quality of life for all cysts <3cm in patients aged <75. Once age exceeded 85 years, non-invasive surveillance dominated. Initial PD did not maximize quality of life in any age group or cyst size.

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Authors’ Role in Manuscript: Brennan Spiegel and Benjamin Weinberg were involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis, and study supervision. James Farrell and James Tomlinson were involved in analysis and interpretation of data and critical revision of the manuscript for important intellectual content.

Disclaimer: The opinions and assertions contained herein are the sole views of the authors and are not to be construed as official or as reflecting the views of the Department of Veteran Affairs.

No conflicts of interest to disclose

Concousions—Management of pancreatic cysts can be guided using novel Markov-based clinical nomograms, and depends on age, cyst size, comorbidities, and whether patients value overall survival *vs*. quality-adjusted survival. For patients focused on overall survival, regardless of quality of life, surgery is optimal for lesions >2cm. For patients focused on quality-adjusted survival, a 3cm threshold is more appropriate for surgery except for the extreme elderly.

Keywords

Pancreatic Cyst; IPMN; Decision Analysis; Nomogram

INTRODUCTION

The prevalence of pancreatic cysts has increased dramatically – a likely consequence of increased use and improved quality of abdominal imaging, coupled with the aging of the population. The management of a single isolated pancreatic cyst in an asymptomatic patient represents a clinical conundrum. Whereas intraductal papillary mucinous neoplasms (IPMN) or mucinous cystic neoplasms (MCNs) are considered at increased risk for malignant transformation, other cysts, including serous adenomas or pseudocysts, have no known malignant potential.[1,2] Moreover, it is often difficult to prognosticate and predict the natural history of individual pancreatic cysts. This clinical uncertainty is distressing to patients and their providers who seek guidance in determining whether to do nothing, initiate invasive or non-invasive surveillance, or proceed directly to surgical resection – a seemingly draconian maneuver given the often times low pre-test likelihood for malignancy.[3,4] Yet many patients are at risk for subsequent malignancy; the clinical decision cannot be taken lightly.

In particular, the incidence of IPMNs has increased 5-fold in the last decade.[5,6] Both main duct (MD-IPMN) and branch duct (BD-IPMN) types are premalignant lesions, recognized histologically along a spectrum ranging from benign adenomas to invasive cancers.[7-9] The rate of malignant transformation of MD-IPMN is considerably higher than BD-IPMNs.[1,2,5,10-18] Because of the unpredictable and potentially less aggressive natural history of these BD-IPMN lesions, some argue in favor of surgical resection of advanced lesions, such as carcinoma in situ and invasive cancer, while continuing to survey patients with early lesions, such as adenomas.[2,19,20]

With current imaging techniques, including computerized tomographic (CT) scanning, magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) combined with pancreatic cyst fluid analysis, MD-IPMN and BD-IPMN can be diagnosed with an accuracy of 80%.[21,22] However, our ability to reliably predict the underlying histology or rate of malignant transformation remains imperfect.[10,13,21-26]

In light of the diagnostic and prognostic uncertainty, international guidelines were developed in 2006 in Sendai, Japan to guide the clinician in operative and non-operative management of presumed IPMNs. However, for BD-IPMN surgical resection should only be considered if the size exceeds 3cm, the main pancreatic duct exceeds 6mm, there are mural nodules, or if there are related foregut symptoms. If these criteria are not met, then surveillance should be undertaken.[12]

However, these guidelines are imperfect for a variety of reasons. As there is a paucity of prospective natural history data studying pancreatic cysts, these guidelines rely predominantly on data gleaned from retrospective surgical data which carries its own biases.[27-29] Similarly, the guidelines have not been able to account for evolutions in diagnostic technologies or our increased understanding of the natural history of pancreatic cysts. Moreover, the guidelines do not account for issues relating to operative mortality, patient age, functional status, or patient

preference. Given the lack of prospective randomized data and the uncertainty about how to evaluate and manage patients with pancreatic cysts, we sought to better define the optimal management strategy for pancreatic cysts which are believed to be BD-IPMN through a decision analysis using currently available data.[30]

METHODS

Model Overview

Using decision analysis software (DATA 4.0, TreeAge Software, Inc., Williamstown, MA), we evaluated a hypothetical cohort of patients ranging from 65 to 85 years old with a variety of asymptomatic pancreatic cysts ranging from 0.5cm to >3cm lesions in the head of the pancreas. This location was chosen as it is the most common location for branch duct IPMNs, and because it represents a significant surgical challenge.[5,10,19,31] Of note, our model does not apply to patients with symptoms that can be attributed to the pancreatic cyst. Decision-analysis is less applicable in symptomatic patients since competing non-invasive strategies are generally not recommended in the presence of attributable symptoms; guidelines recommend surgery over surveillance.

Although the base-case patient was considered to have likely BD-IPMN based on typical clinical features, we ensured that the patient was eligible to have other cystic lesions. This distinction acknowledges the clinical reality that the true cyst type is largely unknown with certainty at the time of diagnostic imaging; instead, physicians work with a range of pre-test likelihoods.[21,22] Diagnostic certainty can only be established after surgery, yet the clinical challenge is whether to perform surgery in the first place. We explicitly developed our model to mimic this common yet complex clinical scenario. Patients entered the model with the possibility that at the time of diagnosis they could have a malignant IPMN, benign branch duct IPMN, a benign non-mucinous cyst, or pancreatic cancer with cystic degeneration. They then entered one of four competing strategies: (1) immediate pancreaticoduodenectomy (PD) followed by surveillance; (2) noninvasive surveillance with either MRI or CT followed by PD if malignant features develop (*i.e.* cyst >3cm; main pancreatic duct >6mm; presence of mural nodules)[12]; (3) invasive surveillance with EUS coupled with fine needle aspiration (FNA) followed by a PD if malignant features develop; or (4) "do nothing," in which watchful waiting ensued without active surveillance, followed by PD only if cancer developed.

Using a Bayesian approach, the model incorporated the sensitivity and specificity of diagnostic testing along with the prevalence of underlying disease in the hypothetical cohort. In each strategy, if the type of lesion were not already malignant at baseline, then the patient assumed a probability of subsequent malignant transformation. The model accounted for false positive, false negative, true positive, and true negative diagnostic pathways. This created a range of clinical scenarios, including both appropriate and inappropriate PD or surveillance. This Bayesian approach was incorporated into all arms of the model except the "do nothing" approach, where active diagnostic surveillance was not employed. In this strategy, only the development of cancer led to definitive evaluation and potential surgical intervention. To test a variety of age ranges, we ran separate models to estimate outcomes in 65, 75, and 85-year-old base-case patients.

Competing Strategies

Our model included 4 competing strategies, described below. These strategies incorporated over 50 probability estimates governing relevant clinical probabilities in the management of IPMN, benign pancreatic cysts, and pancreatic cancer (Table 2). To derive these estimates, we performed a systematic search of MEDLINE from 1966 to July of 2007 using pre-specified phrases and key words, and limited our data abstractions of English-language. When data were

not available, we relied on expert consensus opinion to inform our base-case estimates, and conducted sensitivity analyses over a wide range of values. All Markov transition probabilities were expressed as annual probabilities.

"Noninvasive Surveillance" Strategy—Patients in this strategy entered into a Markov model with annual radiographic surveillance with either abdominal CT scan or MRI. The patients either developed malignant transformation of their lesion, or did not. In both instances, the images either revealed evidence of malignant features, or did not. This yielded four diagnostic pathways: (1) imaging demonstrated a true positive where a malignant process is appropriately identified; (2) a false negative where a malignant process is missed; (3) a false positive where a benign process is mistakenly identified as having worrisome features; or (4) a true negative where a benign process is appropriately identified as benign. Figure 1 depicts an example of one of the many different Markov states.

"Invasive Surveillance" Strategy—Patients in this strategy entered annual surveillance with repeated EUS examinations with or without fine needle aspiration (FNA). This arm was identical to the "noninvasive surveillance" strategy except in two regards: (1) the invasive strategy included a measureable yet low risk of complications from EUS-FNA, including mortality; and (2) EUS-FNA had a small yet measurable improvement in sensitivity and specificity for detecting malignant features compared to CT or MRI – a consequence of improved diagnostic accuracy from cyst fluid analysis and careful evaluation of cyst wall characteristics.

"Initial Pancreaticoduodenectomy (PD)" Strategy—In this strategy all patients progressed directly to PD regardless of presence *versus* absence of malignant features. The model accounted for perioperative morbidity and mortality from PD – a function of surgical experience and patient comorbidities. Patients found to have malignant IPMN or pancreatic cancer subsequently received adjuvant chemotherapy – itself associated with morbidity and mortality.

"Do Nothing" Strategy—In this strategy all patients had no further active surveillance or workup performed after identification of their lesion. Patients were re-evaluated only if cancer developed. Once cancer developed all patients were considered for PD. The percentage of those who were operable candidates was lower than in the surveillance arms because of the delay in diagnosis. Patients who were resectable then entered Markov cycles identical to the original "initial PD" strategy.

Conditional Probabilities

We assumed that patients could harbor any of several potential underlying diagnoses, including malignant IPMN, benign branch duct IPMN, a benign non-mucinous cyst, or pancreatic cancer with cystic degeneration. Because the risk of malignancy correlates with cyst size, we established a series of probabilities conditional on cyst size. Using logic nodes, in which probabilities are conditional on concurrently measured variables (in this case cyst size), we conditionally linked size-specific data (i.e. rate of malignant transformation, baseline risk of underlying prevalent malignancy, etc.) to cyst size (Table 1). In addition, we varied these parameters over a wide range in sensitivity analyses.

Outcomes

We performed a decision analysis to evaluate two outcomes: unadjusted life years (LY), which tracks overall survival, independent of quality of life and morbidity, and quality-adjusted life-years (QALYs), a standard metric in decision models that accounts for both quantity of life (i.e. overall survival), *and* quality of life, as measured by utilities. We did not incorporate costs

into the model as our objective was to focus solely on effectiveness, not cost-effectiveness. The purpose of our clinical nomograms, described below, is to assist patients and physicians with understanding how their decisions affect overall survival and quality of life – not the economic costs of competing decisions.

Utilities

To calculate QALYs, we incorporated a range of relevant health state utilities, or health related quality of life estimates, based on previously published health related quality of life data.[32, 33] The utilities related to those undergoing PD were based on four studies.[34-37] No studies evaluated utilities for the short and long-term complications of PD, as was required in our model. Therefore, we extrapolated utilities from related data from other surgeries and health states, and used sensivitity analysis to test these estimates over a wide range of values. We were unable to identify validated utilities for pancreatic cancer or malignant IPMN. Therefore, we extrapolated data from breast cancer studies to estimate utilities for undergoing chemotherapy, inoperable cancer, and recurrent cancer.[38] Because breast cancer is a potentially curable disease while malignant IPMN and pancreatic cancer carry worse survival rates, we lowered the respective utilities for each variable in our base-case model and performed sensitivity analysis over a wide range of estimates.

Sensitivity Analyses

Table 2 lists the base-case probability estimates with respective ranges. To test the influence of all variables on the model results, we performed a multivariable sensitivity analysis ("tornado analysis") to help identify the most influential variables. We then performed 1-way sensitivity analysis on all variables and 2-way sensitivity analyses on the most influential variables. We present the 1-way analyses stratified by 3 age groups: 65, 75, and 85 year old. We present the 2-way analyses visually as age-stratified "nomograms" to assist decision-makers with identifying strategies that optimize outcomes under varying clinical circumstances.

Monte Carlo Simulations

Whereas 1-way and 2-way analyses provide information regarding the robustness of a model, they are inadequate to fully simulate real-world conditions. To acknowledge the reality that each individual carries a unique composition of clinical probabilities, we conducted a probabilistic (Monte Carlo) simulation under the assumption that all variables were triangular in distribution. We evaluated a series of Monte Carlo simulations stratified by age and cyst size, using 1000 trials per simulation. We report the absolute number of patients (per 1000) for which each competing strategies maximizes outcomes.

RESULTS

Table 3 displays the results of the base-case analyses, stratified by pancreatic cyst size (1cm, 2cm, and 3c,) and age (65, 75, and 85 years). The model revealed that the optimal strategy is conditional upon several factors, including patient age, cyst size, and whether the patient values overall survival or quality-adjusted survival. In patients who value overall survival regardless of quality of life, surgical resection with initial PD was the dominant strategy for any cyst size ≥2cm, even after considering the perioperative risks and the possibility that the cyst is not malignant. However, in patients who seek to maximize quality-adjusted survival (not just overall survival), the "do nothing" strategy maximized QALYs across all age groups for any cyst <3cm. Notably, the absolute differences in quality-adjusted survival were small across all groups with cyst sizes <3cm. However, for cysts >3cm, surgical resection dominated in patients 65-75 years – both for overall survival, as above, and quality-adjusted survival. As the age of

the patient advanced to 85 years with cysts >3cm, surveillance then became the dominate strategy.

Sensitivity Analysis

Table 4 lists the results of the sensitivity analyses for 65, 75, and 85 year old patients with a <1cm suspected IPMN. The most influential variables were the annual rate of malignant transformation of a sub-centimeter IPMN, prevalence of underlying malignant IPMN at baseline, mortality related to untreated malignant IPMN, and surgical morality related to a PD. For example, if a 65 year old patient had a rate of malignant transformation exceeding 1% per year, a pre-test likelihood of underlying malignancy exceeding 4.5%, or a perioperative mortality rate below 6.4%, then surgery became the dominant strategy. Non-invasive and invasive surveillance were nearly equivocal. However, if the mortality rate for EUS-FNA exceeded 0.01%, despite its better sensitivity and specificity, it became inferior to CT/MRI.

Clinical Nomograms

Figure 2 **and Figure 3** demonstrate nomograms to assist decision-makers with selecting between competing strategies. The nomograms plot cyst size against perioperative mortality, itself a function of age and comorbidities. Figure 2 depicts the data using life years as the outcome of interest, and **Figure 3** depicts the data using QALYs as the outcome. Refer to the figure legends for further details regarding nomogram interpretation.

Monte Carlo Simulations

Table 5 displays the results of the Monte Carlo simulations stratified by patient age, cyst size, and patient preference for unadjusted survival *versus* quality adjusted survival. Each analysis lists the results for a hypothetical cohort of 1000 patients, and provides the absolute number of patients for which each competing strategy maximizes outcomes. The preferred strategy mirrors the findings in Table 3.

DISCUSSION

The optimal management of pancreatic cysts remains uncertain and challenging. To date, no randomized prospective trials have been carried out for this disease. It is critical for providers and patients to have evidence-based guidance when selecting between competing management strategies to optimize individualized care. Therefore, we conducted a comprehensive, evidence-based Markov model to help inform decision making in this uncertain area.

Our model has five key findings: First, for patients primarily focused on maximizing survival, regardless of quality of life, a 2cm size threshold appears optimal for proceeding to surgery – this is smaller than the 3cm threshold supported by the Sendai guidelines. Second, for patients focused on optimizing both quantity *and* quality of life, either the “do nothing” or surveillance strategy appear optimal for any patient with a <3cm lesion who is between 65-75 years of age. Moreover, if quality of life is the outcome of interest, then no lesion in a patient over 85 years of age should undergo resection. Third, the optimal strategy for any given patient varies depending on surgical morbidity, age, cyst size, and whether the patient values overall survival or quality-adjusted survival – factors balanced in our clinical nomograms. Fourth, our findings emphasize that future research should evaluate three key variables which are pivotal in the understanding of this disease process: annual rate of malignant transformation of a benign IPMN; prevalence of malignant IPMN in a cystic lesion presumed to be a BD-IPMN; and natural history of malignant IPMN which does not undergo treatment. Last, given the importance of quality of life in guiding decision-making, future research should better define and validate health utilities relevant to the management of pancreatic cysts.

The Sendai guidelines serve as the template for which most providers manage this disease.[12] Our model parallels these guidelines for cysts <1 cm and ≥3cm. However, despite these similarities, our model deviates from the guidelines. For lesions ≥2 cm we find that surgery is the dominant strategy for maximizing overall life expectancy (in contrast to quality-adjusted life expectancy). This suggestion of decreasing the size cutoff to ≥2cm is not a novel one, having been suggested by data from a recent retrospective study.[39] In addition, our model varies from the guidelines when accounting for quality of life – a factor not explicitly acknowledged by the Sendai document. We find that surgery remains the superior strategy for maximizing quality of life in patients who are 65 and 75 years of age with ≥3cm cysts, but conclude that patients >85 years old have improved quality of life when managed with surveillance. This is likely because the poor quality of life experienced postoperatively often outweighs the minimal benefit derived from surgical resection in this population.

Our nomograms are novel tools which may allow patients and providers to identify specific strategies that optimize outcomes while accounting for cyst size and predicted surgical risk. For instance, the nomograms indicate that a 65-year-old patient with an estimated 8% surgical mortality who has a 2cm presumed BD-IPMN in the head of pancreas should choose surgery to maximize overall survival. However, if the same patient were 85 year old, then the nomogram recommends surveillance in lieu of surgery. This is similar to the management of prostate cancer in the elderly, where “watchful waiting” is often more appropriate than radical prostatectomy.[5]

Our study has limitations. First, as with any decision model, it is difficult to accurately capture the complexities of everyday clinical decision-making. Second, our model does not examine combinations of both EUS-FNA and CT/MRI. Since invasive surveillance with EUS+FNA currently offers the greatest sensitivity and specificity for the detection of radiologically malignant features, it is not surprising that it always dominates over the non-invasive strategy with CT or MRI. Third, while our model finds the “do nothing” strategy maximizes quality of life for patients with cysts <3cm, this must be interpreted with caution. The dominance of “do nothing” only has minimal superiority over the surveillance strategies. Therefore, as many patients and physicians may not feel comfortable “doing nothing,” our data demonstrate that surveillance is a reasonable approach and still superior to initial surgery. Fourth, this model focuses on pancreatic cysts arising in the head of the pancreas; it does not apply to cysts arising in the body or tail, or to patients with multiple cysts or symptomatic cysts. As surgical management of isolated pancreatic body or tail cysts allows for less morbid surgery, initial surgical intervention might become the favored approach in these patients. Finally, our model is limited in its ability to accurately capture all factors that drive quality of life, including patient willingness to undergo surgery and fear of underlying malignancy. These factors are difficult to reliably capture in a computerized decision analysis. The usual approach to capturing this information in decision analysis, where tenable, is to account for quality of life decrements related to fear and concern. Our model does incorporate a wide range of utilities for both the outcomes and process of care engendered by the competing strategies. For example, we account for the quality of life decrement of watchful waiting, keeping in mind that not undergoing surgery also leaves some patients with quality of life decrements.

In summary, our model further validates many of the recommendations of the Sendai guidelines. However, it also deviates from the guidelines by suggesting that a 2cm threshold may be appropriate for surgery in patients who value overall survival regardless of quality of life. For patients focused on both quantity *and* quality of life, the 3cm threshold appears optimal. Additionally, the model provides novel insight into decisions based on quality of life and provides a nomogram for factoring patient specific surgical risks and cyst size into the decision making process.

Acknowledgments

Grant support: Dr. Spiegel is supported by a Veteran's Affairs Health Services Research and Development (HSR&D) Career Development Transition Award (RCD 03-179-2), and by the CURE Digestive Disease Research Center (NIH 2P30 DK 041301-17). Dr Farrell is supported by a NIH K12 Career Development Award.

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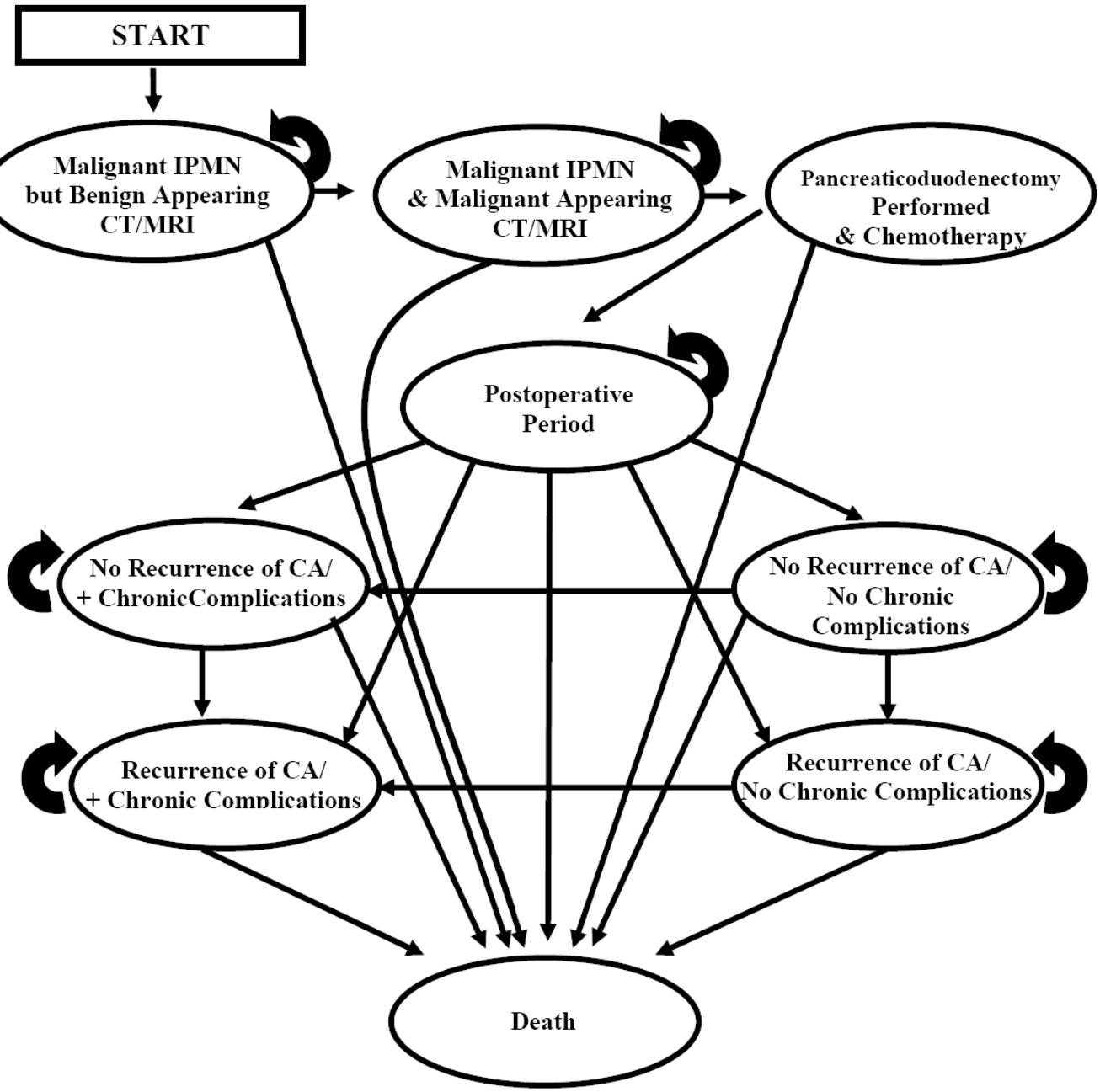
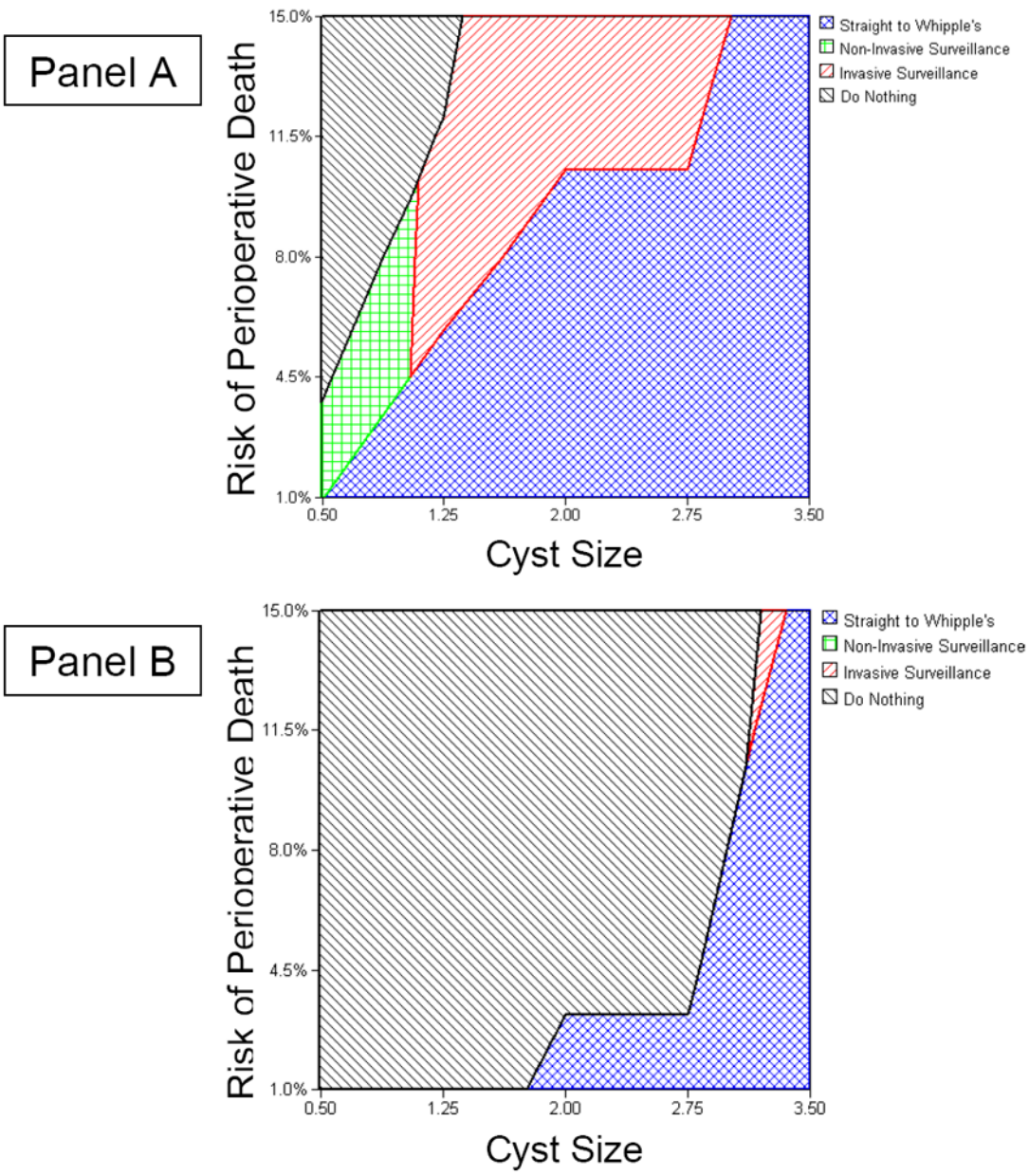


Figure 1.

Example Markov State Diagram. Patients in the model cycled between health states according to annual probability estimates. The model included a wide variety of possible movements across the competing strategies. As an example, the diagram below demonstrates the possible state paths for patients undergoing non-invasive surveillance in a patient with an underlying, unrecognized, malignant IPMN.

a.



b.

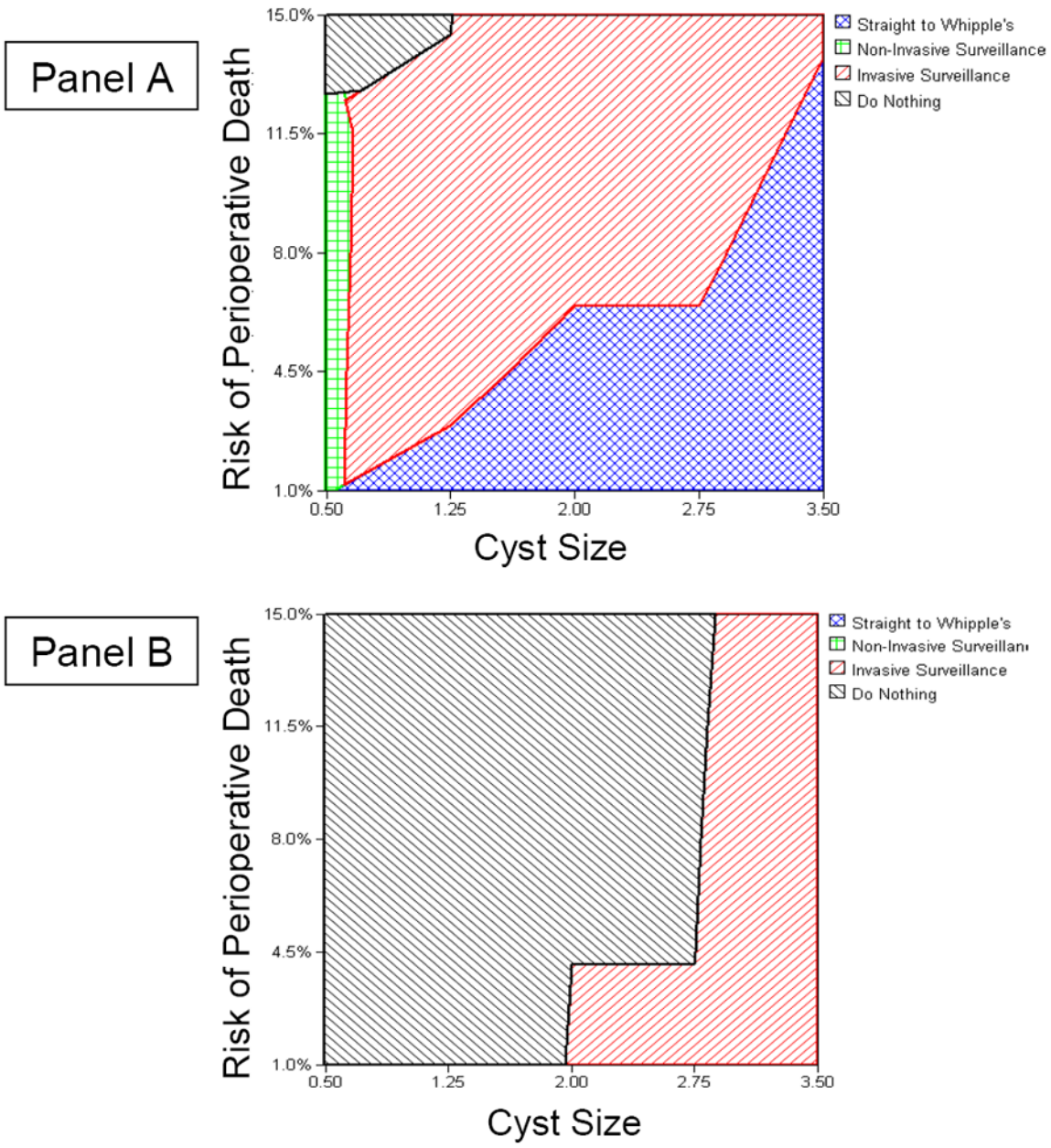


Figure 2.

Clinical Nomograms to Guide Decision-Making in a Hypothetical 65-Year-Old Patient with Suspected BD-IPMN (Figure 2a) and a Hypothetical 85-Year-Old Patient with Suspected BD-IPMN (Figure 2b).

Panel A. Nomogram for a patient focused primarily on maximizing overall survival, independent of quality of life. **Panel B**. Nomogram for a patient focused on maximizing quality-adjusted survival.

Figure 2a. For example, for a 65 year old patient with a 2cm cyst and an estimated 5% risk of perioperative mortality from a Whipple operation, surgery maximizes overall survival, yet

doing nothing maximizes quality-adjusted survival. However, if the cyst exceeds 3cm in size, then surgery is warranted in both instances (see text for details).

Figure 2b.For example, for an 85 year old patient with a 2cm cyst and an estimated 8% risk of perioperative mortality from a Whipple operation, surgery maximizes overall survival, yet doing nothing maximizes quality-adjusted survival. However, if perioperative mortality exceeded 13%, then surgery would never be warranted for this patient (see text for details).

Table 1

Probability Estimates for BD-IPMNs of Varying Sizes

	Size < 1	Size 1 to <2cm	Size 2 to <3cm	Size ≥ 3cm
% Benign Cysts [41]	9%	9%	9%	9%
% Benign BD-IPMN [2,12,15,27,31,39,40,42-47]	89%	86%	79%	70%
% Malignant BD -IPMN [2,12,15,27,31,39,40,42-47]	1%	3%	11%	20%
% Pancreatic CA*	1%	1%	1%	1%
Rate of Benign to Malignant Transformation per Year[43,48,49]	0.001%	1%	1.7%	3%

Table 2

Probability Estimates

Variable	Weighted Mean	Range in Literature	Range in Sensitivity Analysis	Source
Probability that a benign cyst grows	0.035	0.035	0 – 0.1	50
Probability of chronic complications after a pancreaticoduodenectomy	0.194	0.15-0.30	0.06-0.30	8,43,51
Probability of perioperative complications after a pancreaticoduodenectomy	0.412	0.2-0.68	0.3-0.6	2,8,27,44,46,51-57
Probability of death with a recurrent malignant IPMN following surgical resection	0.842	0.80 – 1.0	0.3 – 0.9	19,27,58,59
Probability of death with a recurrent pancreatic cancer following surgical resection	0.9	n/a	0.3 -0.9	57,60-64*
Probability of developing symptoms with a benign cyst	0.05	n/a	0.01-0.15	50*
Probability of developing symptoms with a benign IPMN	0.05	n/a	0.01-0.15	Expert opinion
Probability of developing symptoms with unrecognized malignant IPMN	0.95	n/a	0.8-1.0	Expert opinion
Probability of dying from adjuvant chemotherapy	0.002	0 – 0.01	0 – 0.01	65-68
Probability of dying from an EUS-FNA	0.0001	0 – 0.002	0 – 0.01	67,69-72
Probability of dying from a malignant IPMN without treatment	0.6	n/a	0.4 – 0.8	Expert opinion
Probability of dying from pancreatic cancer without treatment	0.9	n/a	0.8 -1.0	Expert opinion
Probability of dying from a pancreaticoduodenectomy	0.064	0 – 0.07	0.01 – 0.2	2-4,27,51,52,54,55,57,59,73-75
Probability that a malignant IPMN found in the “do nothing” strategy is operable	0.15	n/a	0 – 0.2	Expert opinion
Probability that a malignant IPMN will return post pancreaticoduodenectomy	0.17	0.11 –0.99	0 – 0.6	33, 32, 84, 10, 12, 14, 15, 20, 24, 25, 29
Probability that pancreatic cancer will return post pancreaticoduodenectomy	0.24	n/a	0 -0.6	Expert opinion
Probability that a pancreatic cancer found in the “do nothing” strategy is operable	0.1	n/a	0.01-0.3	Expert opinion
Probability that a CT of a benign IPMN will demonstrate a true negative result	0.99	0.72-0.92	0.5 -1.0	44,49,76*
Probability that a CT of a malignant IPMN will demonstrate a true positive result	0.8	0.72 -0.92	0.5 -1.0	44,49,76

Variable	Weighted Mean	Range in Literature	Range in Sensitivity Analysis	Source
Probability of a EUS-FNA of a benign IPMN demonstrating a true negative result	0.99	0.75-1.0	0.5 -1.0	14,17,44,48,49,77*
Probability that a EUS-FNA of a malignant IPMN will demonstrate a true positive result	0.86	0.75 – 1.0	0.5 – 1.0	14,17,44,48,49,77
Quality of life (utility) of chemotherapy for malignant IPMN or pancreatic cancer	0.62	n/a	0.4 – 0.9	38*
Quality of life (utility) of chronic complications from a pancreaticoduodenectomy	0.65	0.42 – 1.0	0.4 - 0.9	34-37
Quality of life (utility)of perioperative complications from a pancreaticoduodenectomy	0.50	0.42 – 1.0	0.4 - 0.9	34-37
Quality of life (utility) of developing inoperable malignant IPMN or pancreatic cancer	0.65	n/a	0.4 -0.9	38*
Quality of life (utility) of undergoing invasive surveillance	0.98	n/a	0.5 – 1.0	78*
Quality of life (utility) of undergoing noninvasive surveillance	0.98	n/a	0.5 – 1.0	78
Quality of life (utility) of having been cured of cancer without any complications	0.99	0.42 – 1.0	0.5 – 1.0	34-37
Quality of life (utility) of developing recurrent malignant IPMN or pancreatic cancer	0.68	0.42 – 1.0	0.4 – 0.8	38*
Quality of life (utility) of undergoing a pancreaticoduodenectomy with no complications	0.98	0.42 – 1.0	0.5 – 1.0	34-37,79

* Represents probabilities where a combination of available data and expert opinion were used to generate the specific probabilities

Table 3

Results of Base-Case Analyses. The table depicts a visual heuristic to help identify the optimal strategy by patient age, cyst size, and patient preference for unadjusted *vs.* quality adjusted survival. Shading demonstrates the degree of superiority over the competing strategies. Each number represents the length of discounted years that a patient will live, on average, with each individual strategy. For instance, if an 85 year old patient has a 3cm cyst, then a pancreaticoduodenectomy (Whipple) adds a modest 0.356 years over the other strategies. However, if quality of life is desired over unadjusted survival, then the invasive surveillance strategy is superior, although it provides a minimal benefit of 0.030 years of quality adjusted life compared to the next closest competitor.

		Life Years				Quality Adjusted Life Years			
Age	**Cyst Size (cm)**	**Do Nothing**	**Non-Invasive**	**Invasive**	**Whipple**	**Do Nothing**	**Non-Invasive**	**Invasive**	**Whipple**
65	1	12.713	12.760	12.763	12.733	12.546	12.180	12.196	11.449
	2	10.353	11.556	11.571	12.090	11.105	10.966	10.992	10.810
	3	9.713	10.099	10.129	**12.090**	9.361	9.497	9.534	**10.810**
75	1	8.786	8.810	8.813	8.615	8.677	8.469	8.480	7.646
	2	8.005	8.143	8.156	8.284	7.830	7.776	7.794	7.298
	3	4.883	4.960	4.968	4.969	6.814	6.941	6.968	7.298
85	1	5.256	5.265	5.267	5.084	5.195	5.092	5.098	4.387
	2	4.883	4.960	4.968	4.969	4.774	4.760	4.770	4.248
	3	4.449	4.598	4.613	4.969	4.278	4.366	4.381	4.248

Shading	Strength of Recommendation
	Strong superiority over other strategies (yields > 1 additional years of life)
	Modest superiority over other strategies (yields ≥ 0.3 additional years of life)
	Minimal superiority over other strategies (yields < 0.3 additional years of life)

Table 4

Sensitivity Analysis for a 65 year old with <1cm presumed Branch-Duct (BD) IPMN.

Variable	Base Case Estimate	65 year-old Threshold	75 year-old Threshold	85 year-old Threshold	Explanation
Annual probability of incident cancer in a <1cm BD-IMPN	0.1%	1%	2.0%	3%	If the annual rate of malignant transformation of a benign IPMN exceeds threshold then surgery is superior to surveillance
Baseline probability of prevalent cancer in a <1cm BD-IPMN	1%	4.5%	6.0%	7.5%	Once the prevalent rate of cancer exceeds threshold surgery is superior to surveillance
Annual death rate from untreated malignant IPMN	60%	65%	69%	73%	If the annual mortality rate for an untreated malignant IPMN exceeds threshold then surgery is superior to surveillance
Perioperative mortality with pancreaticoduodenectomy	6.4%	6%	3.8%	2.0%	When the mortality rate of a Pancreaticoduodenectomy is below threshold then a Pancreaticoduodenectomy is the superior strategy.
Peri-procedural mortality with EUS-FNA	0.01%	0.01%	0.01%	0.01%	If the mortality rate with EUS-FNA increases above threshold then noninvasive surveillance becomes the superior strategy over invasive surveillance.

Table 5

Results of Monte Carlo Simulations. The table provides a visual heuristic with a similar interpretation as Table 3. For each simulation there are 1000 hypothetical patients subjected to the competing strategies. The results provide the absolute number of patients that would optimally benefit from each competing strategy, stratified by patient age, cyst size, and patient preference for unadjusted *vs*. quality adjusted survival. Shading demonstrates the degree of superiority over the competing strategies. For instance, for 1000 patients who are 85 years of age with a 3cm cyst, Whipple is the optimal strategy for 823 patients, invasive surveillance is optimal for 162 patients, and "do nothing" is optimal for only 15 patients.

		Life Years				Quality Adjusted Life Years			
Age	**Cyst Size (cm)**	**Do Nothing**	**Non-Invasive**	**Invasive**	**Whipple**	**Do Nothing**	**Non-Invasive**	**Invasive**	**Whipple**
65	1	56	116	530	298	903	0	97	0
	2	0	0	110	890	767	52	179	2
	3	0	0	0	**1000**	0	0	0	**1000**
75	1	62	0	885	53	871	59	70	0
	2	0	0	548	552	819	0	181	0
	3	0	0	98	**902**	0	0	104	896
85	1	922	0	88	0	**1000**	0	0	0
	2	79	0	722	199	894	0	106	0
	3	15	0	162	823	12	460	528	0