

Asymptomatic Pancreatic Cystic Neoplasms: Maximizing Survival and Quality of Life Using Markov-Based Clinical Nomograms

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BACKGROUND & AIMS: The natural history and management of pancreatic cysts, especially for branch duct intraductal papillary mucinous neoplasms (BD-IPMNs), remain 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 the following: (1) initial pancreaticoduodenectomy (PD), (2) yearly noninvasive radiographic surveillance, (3) yearly invasive surveillance with endoscopic ultrasound, and (4) “do nothing.” We derived probability estimates from a systematic literature review. The primary outcomes were overall and quality-adjusted survival. We depicted the results in a series of nomograms accounting for age, comorbidities, and cyst size. **RESULTS:** Initial PD was the dominant strategy to maximize overall survival for any cyst greater than 2 cm, regardless of age or comorbidities. In contrast, surveillance was the dominant strategy for any lesion less than 1 cm. However, when measuring quality-adjusted survival, the do-nothing approach maximized quality of life for all cysts less than 3 cm in patients younger than age 75. Once age exceeded 85 years, noninvasive surveillance dominated. Initial PD did not maximize quality of life in any age group or cyst size. **CONCLUSIONS: 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 greater than 2 cm. For patients focused on quality-adjusted survival, a 3-cm threshold is more appropriate for surgery except for the extreme elderly.**

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. Although intraductal papillary mucinous neoplasms (IPMNs) or mucinous cystic

neoplasms are considered at increased risk for malignant transformation, other cysts, including serous adenomas or pseudocysts, have no known malignant potential.^{1,2} Moreover, it often is 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 noninvasive surveillance, or proceed directly to surgical resection—a seemingly draconian maneuver given the oftentimes low pretest 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 past 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 surgical and nonsur-

Abbreviations used in this paper: BD-IPMN, branch duct intraductal papillary mucinous neoplasms; CT, computerized tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasms; MD, main duct; MRI, magnetic resonance imaging; PD, pancreaticoduodenectomy.

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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 PD	0.194	0.15–0.30	0.06–0.30	8,43,51
Probability of perioperative complications after a PD	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 after surgical resection	0.842	0.80–1.0	0.3–0.9	19,27,58,59
Probability of death with a recurrent pancreatic cancer after surgical resection	0.9	N/A	0.3–0.9	57,60–64 ^a
Probability of developing symptoms with a benign cyst	0.05	N/A	0.01–0.15	50 ^a
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 PD	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 after PD	0.17	0.11–0.99	0–0.6	10,12,14,15,20,24,25,29,32,33
Probability that pancreatic cancer will return after PD	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 show a true-negative result	0.99	0.72–0.92	0.5–1.0	44,49,76 ^a
Probability that a CT of a malignant IPMN will show a true-positive result	0.8	0.72–0.92	0.5–1.0	44,49,76
Probability of a EUS-FNA of a benign IPMN showing a true-negative result	0.99	0.75–1.0	0.5–1.0	14,17,44,48,49,77 ^a
Probability that a EUS-FNA of a malignant IPMN will show 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 ^a
Quality of life (utility) of chronic complications from a PD	0.65	0.42–1.0	0.4–0.9	34–37
Quality of life (utility) of perioperative complications from a PD	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 ^a
Quality of life (utility) of undergoing invasive surveillance	0.98	N/A	0.5–1.0	78 ^a
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 ^a
Quality of life (utility) of undergoing a PD with no complications	0.98	0.42–1.0	0.5–1.0	34–37,79

^aRepresents probabilities in which a combination of available data and expert opinion was used to generate the specific probabilities.

Noninvasive surveillance strategy. Patients in the noninvasive surveillance 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 4 diagnostic pathways: (1) imaging showed a true positive in which a malignant process is identified appropriately, (2) a false

negative in which a malignant process is missed, (3) a false positive in which a benign process is identified mistakenly as having worrisome features, or (4) a true negative in which a benign process is identified appropriately as benign. Figure 1 depicts an example of one of the many different Markov states.

Invasive surveillance strategy. Patients in the invasive surveillance strategy entered annual surveillance with repeated EUS examinations with or without FNA.

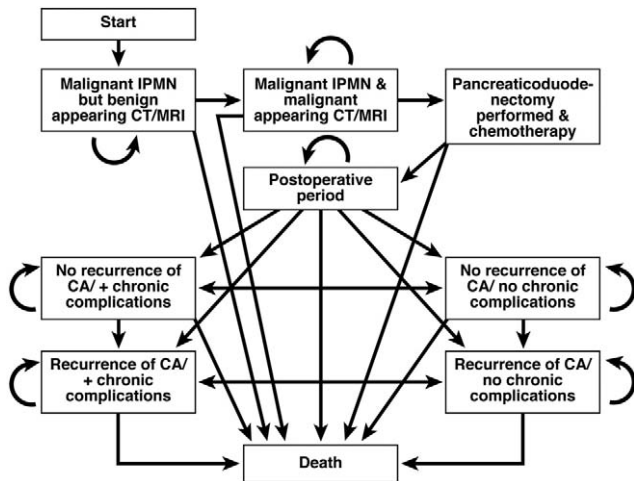


Figure 1. Example of a Markov state diagram. Patients in the model cycled between health states according to annual probability estimates. The model included a wide variety of possible movements across the competing strategies. As an example, the diagram shows the possible state paths for patients undergoing noninvasive surveillance in a patient with an underlying, unrecognized, malignant IPMN. CA, cancer.

This arm was identical to the noninvasive surveillance strategy except in 2 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 with CT or MRI, a consequence of improved diagnostic accuracy from cyst fluid analysis and careful evaluation of cyst wall characteristics.

Initial PD strategy. In the initial PD strategy all patients progressed directly to PD regardless of the presence vs 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, which is associated with morbidity and mortality.

Do nothing strategy. In the do nothing strategy all patients had no further active surveillance or work-up 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 patients who were surgical 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 BD-IPMN, a benign nonmucinous 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. By using logic nodes, in which probabilities are conditional on concurrently measured variables (in this case cyst size), we conditionally linked size-specific data (ie, rate of malignant transformation, baseline risk of underlying prevalent malignancy, and so forth) 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 2 outcomes: unadjusted life years, which tracks overall survival, independent of quality of life and morbidity; and quality-adjusted life-years, a standard metric in decision models that accounts for both quantity of life (ie, overall survival), and quality of life, as measured by utilities. We did not incorporate costs into the model because our objective was to focus solely on effectiveness, not cost effectiveness. The purpose of our clinical nomograms, described later, 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 quality-adjusted life-years, 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 4 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 sensitivity 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 whereas 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 (ie, *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 years 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

Although 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 strategy maximizes outcomes.

Results

Table 3 displays the results of the base-case analyses, stratified by pancreatic cyst size (1, 2, and 3 cm) and age (65, 75, and 85 y). The model revealed that the optimal strategy is conditional on 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 2 cm or greater, 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 quality-adjusted life-years across all age groups for any cyst less

than 3 cm. Notably, the absolute differences in quality-adjusted survival were small across all groups with cyst sizes less than 3 cm. However, for cysts greater than 3 cm, surgical resection dominated in patients 65–75 years old—both for overall survival, as described earlier, and quality-adjusted survival. As the age of the patient advanced to 85 years with cysts greater than 3 cm, surveillance then became the dominant strategy.

Sensitivity Analysis

Table 4 lists the results of the sensitivity analyses for 65-, 75-, and 85-year-old patients with a less than 1-cm suspected IPMN. The most influential variables were the annual rate of malignant transformation of a subcentimeter 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 pretest likelihood of underlying malignancy exceeding 4.5%, or a perioperative mortality rate below 6.4%, then surgery became the dominant strategy. Noninvasive 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 shows 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 2A depicts the data using life-years as the outcome of interest, and Figure 2B depicts the data using quality-adjusted

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Table 3. Results of Base-Case Analyses

Age, y	Cyst size, cm	Life-years				Quality-adjusted life-years			
		Do nothing	Noninvasive	Invasive	Whipple	Do nothing	Noninvasive	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

NOTE. 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 shows 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 3-cm 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 with the next closest competitor.

Shading Strength of recommendation
 ■ Strong superiority over other strategies (yields >1 additional year 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-, 75-, and 85-Year-Old Patient With a Presumed BD-IPMN of Less Than 1 cm

Variable	Base-case estimate	65-year-old threshold	75-year-old threshold	85-year-old threshold	Explanation
Annual probability of incident cancer in a <1-cm BD-IPMN	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 <1-cm 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 PD	6.4%	6%	3.8%	2.0%	When the mortality rate of a PD is below threshold, then a PD is the superior strategy.
Periprocedural 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.

life-years 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 vs 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. No randomized prospective trials have been performed 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 5 key findings. First, for patients primarily focused on maximizing survival, regardless of quality of life, a 2-cm size threshold appears optimal for proceeding to surgery; this is smaller than the 3-cm 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 appears optimal for any patient with a less than 3-cm lesion who is between 65 and 75 years of age. Moreover, if quality of life is the outcome of interest, then no lesion in a patient older than 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 3 key variables that 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 that 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 less than 1 cm and cysts 3 cm or greater. However, despite these similarities, our model deviates from the guidelines. For lesions 2 cm or greater 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 cut-off size to 2 cm or greater 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 between 65 and 75 years of age with 3-cm or larger cysts, but conclude that patients older than 85 years 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 that 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 2-cm presumed BD-IPMN in the head of pancreas should choose surgery to maximize overall survival. However, if the same patient were 85 years old, then the nomogram recommends surveillance

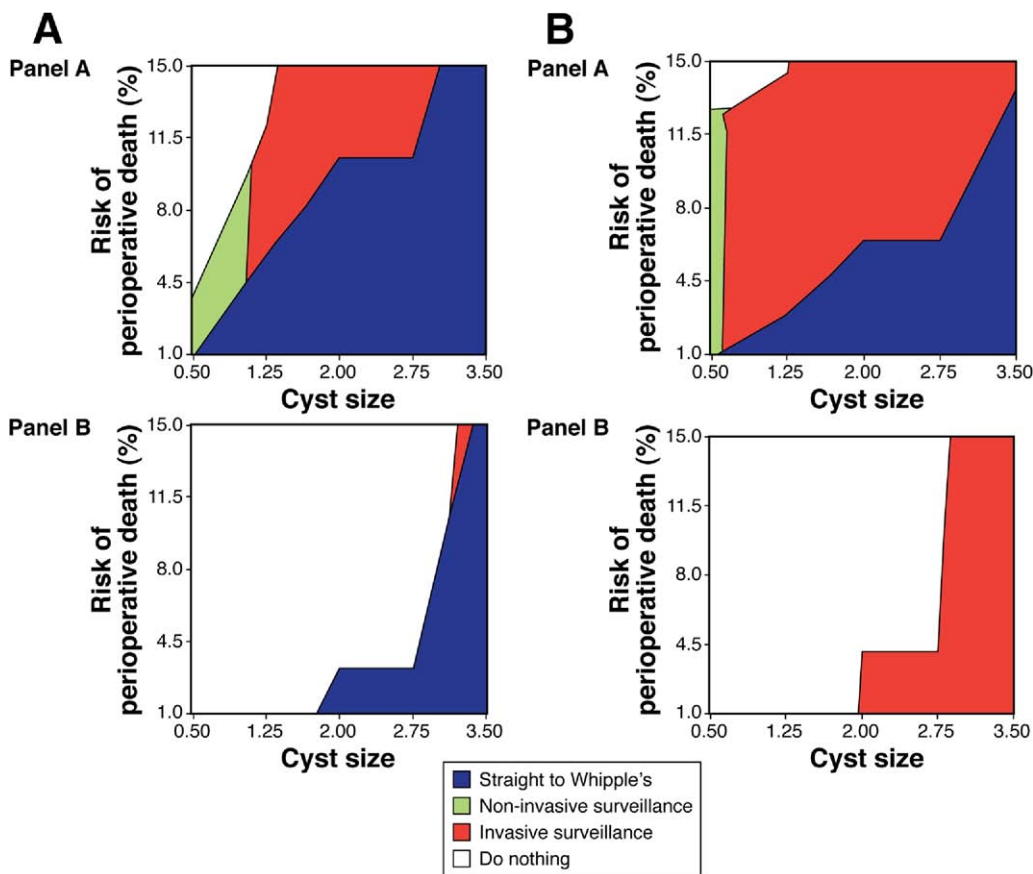


Figure 2. Clinical nomograms to guide decision making in a (A) hypothetical 65-year-old patient with suspected BD-IPMN and a (B) hypothetical 85-year-old patient with suspected BD-IPMN. (A) Nomogram for a patient focused primarily on maximizing overall survival, independent of quality of life. For example, for a 65-year-old patient with a 2-cm cyst and an estimated 5% risk of perioperative mortality from a Whipple surgery, surgery maximizes overall survival, yet doing nothing maximizes quality-adjusted survival. However, if the cyst exceeds 3 cm in size, then surgery is warranted in both instances (see text for details). (B) Nomogram for a patient focused on maximizing quality-adjusted survival. For example, for an 85-year-old patient with a 2-cm cyst and an estimated 8% risk of perioperative mortality from a Whipple surgery, 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).

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 had 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. Because 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 noninvasive strategy with CT or MRI. Third, although our model finds that the do nothing strategy maximizes quality of life for patients with cysts less than 3 cm, this must be interpreted with caution. The dominance of do nothing only has minimal superiority over the surveillance strategies. Therefore, because many patients and physicians may not be comfortable doing nothing, our data show that surveillance is a reasonable approach and still superior to initial surgery. Fourth, this model fo-




cused 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. Because 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 capture reliably 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.

Table 5. Results of Monte Carlo Simulations

Age, y	Cyst size, cm	Life-years				Quality-adjusted life-years			
		Do nothing	Noninvasive	Invasive	Whipple	Do nothing	Noninvasive	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

NOTE. 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 who would optimally benefit from each competing strategy, stratified by patient age, cyst size, and patient preference for unadjusted vs quality-adjusted survival. Shading shows the degree of superiority over the competing strategies. For instance, for 1000 patients who are 85 years of age with a 3-cm 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.

Shading Strength of recommendation

-  Strong superiority over other strategies (yields >1 additional year 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).

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 2-cm 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 3-cm threshold appears optimal. In addition, 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.

References

- Spinelli KS, Fromwiller TE, Daniel RA, et al. Cystic pancreatic neoplasms: observe or operate. *Ann Surg* 2004;239:651–657.
- Sohn TA, Yeo CJ, Cameron JL, et al. IPMN of the pancreas: an updated experience. *Ann Surg* 2004;239:788–797.
- Tran KT, Smeenk HG, van Eijck CH, et al. Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure: a prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors. *Ann Surg* 2004;240:738–745.
- Yeo CJ, Abrams RA, Grochow LB, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. *Ann Surg* 1997;225:621–633.
- Goh BK, Tan YM, Cheow PC, et al. Cystic lesions of the pancreas: an appraisal of an aggressive resectional policy adopted at a single institution during 15 years. *Am J Surg* 2006;192:148–154.
- Tang RS, Weinberg B, Dawson DW, et al. Evaluation of the guidelines for management of pancreatic branch-duct IPMN. *Clin Gastroenterol Hepatol* 2008;6:815–819.
- Kloppel GS, Longnecker E. Histological typing of tumors of the exocrine pancreas. In: World Health Organization: international histological classification of tumors. Berlin, Germany: Springer-Verlag, 1996.
- Seiler CA, Wagner M, Bachmann T, et al. Randomized clinical trial of pylorus-preserving duodenopancreatectomy versus classical Whipple resection-long term results. *Br J Surg* 2005;92:547–556.
- Irie H, Yoshimitsu K, Aibe H, et al. Natural history of pancreatic IPMT of branch duct type: follow-up study by MRCP. *J Comput Assist Tomogr* 2004;28:117–122.
- Kawamoto S, Horton KM, Lawler LP, et al. IPMN of the pancreas: can benign lesions be differentiated from malignant lesions with multidetector CT? *Radiographics* 2005;25:1451–1468.
- Terris B, Ponsot P, Paye F, et al. IPMT of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. *Am J Surg Pathol* 2000;24:1372–1377.
- Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of IPMN and mucinous cystic neoplasms of the pancreas. *Pancreatol* 2006;6:17–32.
- Yamaguchi K, Ogawa Y, Chijiwa K, et al. Mucin-hypersecreting tumors of the pancreas: assessing the grade of malignancy preoperatively. *Am J Surg* 1996;171:427–431.
- Kubo H, Chijiwa Y, Akahoshi K, et al. IPMT of the pancreas: differential diagnosis between benign and malignant tumors by endoscopic ultrasonography. *Am J Gastroenterol* 2001;96:1429–1434.
- Matsumoto T, Aramaki M, Yada K, et al. Optimal management of the branch duct type IPMN of the pancreas. *J Clin Gastroenterol* 2003;36:261–265.
- Kobari M, Egawa S, Shibuya K, et al. IPMT of the pancreas comprise 2 clinical subtypes: differences in clinical characteristics and surgical management. *Arch Surg* 1999;134:1131–1136.
- Doi R, Fujimoto K, Wada M, et al. Surgical management of IPMT of the pancreas. *Surgery* 2002;132:80–85.
- Kitagawa Y, Unger TA, Taylor S, et al. Mucus is a predictor of better prognosis and survival in patients with IPMT of the pancreas. *J Gastrointest Surg* 2003;7:12–18.
- Chari ST, Yadav D, Smyrk TC, et al. Study of recurrence after surgical resection of IPMN of the pancreas. *Gastroenterology* 2002;123:1500–1507.
- Yamaguchi T, Baba T, Ishihara T, et al. Long-term follow-up of IPMN of the pancreas with ultrasonography. *Clin Gastroenterol Hepatol* 2005;3:1136–1143.

21. Chaudhari VV, Raman SS, Vuong NL, et al. Pancreatic cystic lesions: discrimination accuracy based on clinical data and high resolution CT features. *J Comput Assist Tomogr* 2007;31:860–867.
22. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004;126:1330–1336.
23. Kawamoto S, Lawler LP, Horton KM, et al. MDCT of IPMN of the pancreas: evaluation of features predictive of invasive carcinoma. *AJR Am J Roentgenol* 2006;186:687–695.
24. Procacci C, Carbognin G, Biasiutti C, et al. IPMT of the pancreas: spectrum of CT and MR findings with pathologic correlation. *Eur Radiol* 2001;11:1939–1951.
25. Cellier C, Cuillierier E, Palazzo L, et al. IPMT of the pancreas: accuracy of preoperative computed tomography, ERCP and endoscopic ultrasonography, and long-term outcome in a large surgical series. *Gastrointest Endosc* 1998;47:42–49.
26. Sugiyama M, Atomi Y. IPMT of the pancreas: imaging studies and treatment strategies. *Ann Surg* 1998;228:685–691.
27. Rodriguez JR, Salvia R, Crippa S, et al. Branch-duct IPMN: observations in 145 patients who underwent resection. *Gastroenterology* 2007;133:72–79.
28. Raimondo M, Tachibana I, Urrutia R, et al. Invasive cancer and survival of IPMT of the pancreas. *Am J Gastroenterol* 2002;97:2553–2558.
29. Salvia R, Fernandez-del Castillo C, Bassi C, et al. Main-duct IPMN of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg* 2004;239:678–685.
30. Spiegel BM, Targownik LE, Kanwal F, et al. The quality of published health economic analyses in digestive diseases: a systematic review and quantitative appraisal. *Gastroenterology* 2004;127:403–411.
31. Suzuki Y, Atomi Y, Sugiyama M, et al. Cystic neoplasm of the pancreas: a Japanese multiinstitutional study of IPMT and mucinous cystic tumor. *Pancreas* 2004;28:241–246.
32. Schmier J, Elixhauser A, Halpern MT. Health-related quality of life evaluations of gastric and pancreatic cancer. *Hepatogastroenterology* 1999;46:1998–2004.
33. Park SM, Park MH, Won JH, et al. EuroQol and survival prediction in terminal cancer patients: a multicenter prospective study in hospice-palliative care units. *Support Care Cancer* 2006;14:329–333.
34. Behrman SW, Mulloy M. Total pancreatectomy for the treatment of chronic pancreatitis: indications, outcomes, and recommendations. *Am Surg* 2006;72:297–302.
35. McLeod RS, Taylor BR, O'Connor BI, et al. Quality of life, nutritional status, and gastrointestinal hormone profile following the Whipple procedure. *Am J Surg* 1995;169:179–185.
36. Billings BJ, Christein JD, Harnsen WS, et al. Quality-of-life after total pancreatectomy: is it really that bad on long-term follow-up? *J Gastrointest Surg* 2005;9:1059–1066.
37. Scheingraber S, Scheingraber T, Brauckhoff M, et al. Comparison between a general and a disease-specific health-related quality-of-life questionnaire in patients after pancreatic surgery. *J Hepatobiliary Pancreat Surg* 2005;12:290–297.
38. Lidgren M, Wilking N, Jonsson B, et al. Health related quality of life in different states of breast cancer. *Qual Life Res* 2007;16:1073–1081.
39. Jang JY, Kim SW, Lee SE, et al. Treatment guidelines for branch duct type IPMN of the pancreas: when can we operate or observe? *Ann Surg Oncol* 2008;15:199–205.
40. Hammel PP, Palazzo P. Frequency of lesions leading to erroneous diagnosis of IPMT of the pancreas. *Gastroenterology* 2007;132:A-761.
41. Schmidt CM, White PB, Waters JA, et al. IPMN: predictors of malignant and invasive pathology. *Ann Surg* 2007;246:644–651.
42. Jang JY, Kim SW, Ahn YJ, et al. Multicenter analysis of clinicopathologic features of IPMT of the pancreas: is it possible to predict the malignancy before surgery? *Ann Surg Oncol* 2005;12:124–132.
43. Tada M, Kawabe T, Arizumi M, et al. Pancreatic cancer in patients with pancreatic cystic lesions: a prospective study in 197 patients. *Clin Gastroenterol Hepatol* 2006;4:1265–1270.
44. Zamora C, Sahel J, Cantu DG, et al. IPMT of the pancreas: report of a case series and review of the literature. *Am J Gastroenterol* 2001;96:1441–1447.
45. Sugiyama M, Izumisato Y, Abe N, et al. Predictive factors for malignancy in IPMT of the pancreas. *Br J Surg* 2003;90:1244–1249.
46. Salvia R, Crippa S, Falconi M, et al. Branch-duct IPMN of the pancreas: to operate or not to operate? *Gut* 2007;56:1086–1090.
47. Pelaez-Luna M, Chari ST, Smyrk TC, et al. Do consensus indications for resection in branch duct IPMN predict malignancy? A study of 147 patients. *Am J Gastroenterol* 2007;102:1759–1764.
48. Levy P, Jouannaud V, O'Toole D, et al. Natural history of IPMT of the pancreas: actuarial risk of malignancy. *Clin Gastroenterol Hepatol* 2006;4:460–468.
49. Kobayashi G, Fujita N, Noda Y, et al. Mode of progression of IPMT of the pancreas: analysis of patients with follow-up by EUS. *J Gastroenterol* 2005;40:744–751.
50. Tseng JF, Warshaw AL, Sahani DV, et al. Serous cystadenoma of the pancreas: tumor growth rates and recommendations for treatment. *Ann Surg* 2005;242:413–419.
51. D'Angelica M, Brennan MF, Suriawinata AA, et al. IPMN of the pancreas: an analysis of clinicopathologic features and outcome. *Ann Surg* 2004;239:400–408.
52. Diener MK, Knaebel HP, Heukauffer C, et al. A systematic review and meta-analysis of pylorus-preserving versus classical pancreaticoduodenectomy for surgical treatment of periampullary and pancreatic carcinoma. *Ann Surg* 2007;245:187–200.
53. Wade TP, el-Ghazzawy AG, Virgo KS, et al. The Whipple resection for cancer in U.S. Department of Veterans Affairs Hospitals. *Ann Surg* 1995;221:241–248.
54. Imaizumi T, Hanyu F, Harada N, et al. Extended radical Whipple resection for cancer of the pancreatic head: operative procedure and results. *Dig Surg* 1998;15:299–307.
55. Schafer M, Mülhaupt B, Clavien PA. Evidence-based pancreatic head resection for pancreatic cancer and chronic pancreatitis. *Ann Surg* 2002;236:137–148.
56. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997;226:248–257.
57. Maire F, Hammel P, Terris B, et al. Prognosis of malignant IPMT of the pancreas after surgical resection. Comparison with pancreatic ductal adenocarcinoma. *Gut* 2002;51:717–722.
58. Wada K, Kozarek RA, Traverso LW. Outcomes following resection of invasive and noninvasive IPMN of the pancreas. *Am J Surg* 2005;189:632–636.
59. Lin PW, Lin YJ. Prospective randomized comparison between pylorus-preserving and standard pancreaticoduodenectomy. *Br J Surg* 1999;86:603–607.
60. Benassai G, Mastrorilli M, Quarto G, et al. Survival after pancreaticoduodenectomy for ductal adenocarcinoma of the head of the pancreas. *Chir Ital* 2000;52:263–270.
61. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. *Am J Surg* 1993;165:68–72.
62. Millikan KW, Deziel DJ, Silverstein JC, et al. Prognostic factors associated with resectable adenocarcinoma of the head of the pancreas. *Am Surg* 1999;65:618–623.

63. Tsao JI, Rossi RL, Lowell JA. Pylorus-preserving pancreatoduodenectomy. Is it an adequate cancer operation. *Arch Surg* 1994;129:405–412.
64. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. *Ann Surg* 1995;221:721–731.
65. Stocken DD, Buchler MW, Dervenis C, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. *Br J Cancer* 2005;92:1372–1381.
66. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007;297:267–277.
67. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001;358:1576–1585.
68. Glimelius B, Hoffman K, Sjoden PO, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996;7:593–600.
69. Eloubeidi MA, Gress FG, Savides TJ, et al. Acute pancreatitis after EUS-guided FNA of solid pancreatic masses: a pooled analysis from EUS centers in the United States. *Gastrointest Endosc* 2004;60:385–389.
70. Eloubeidi MA, Chen VK, Eltoun IA, et al. EUS guided fine needle aspiration biopsy of patients with suspected pancreatic cancer: diagnostic accuracy and acute and 30-day complications. *Am J Gastroenterol* 2003;98:2663–2668.
71. Bourmet B, Miguères I, Delacroix M, et al. Early morbidity of EUS: 13 years' experience at a referral center. *Endoscopy* 2006;38:349–354.
72. O'Toole D, Palazzo L, Arotcarena R, et al. Assessment of complications of EUS-guided fine-needle aspiration. *Gastrointest Endosc* 2001;53:470–474.
73. Cuillerier E, Cellier C, Palazzo L, et al. Outcome after surgical resection of IPMT and mucinous tumors of the pancreas. *Am J Gastroenterol* 2000;95:441–445.
74. Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. *Ann Surg* 1996;223:273–279.
75. White R, D'Angelica M, Katabi N, et al. Fate of the remnant pancreas after resection of noninvasive IPMN. *J Am Coll Surg* 2007;204:987–993.
76. Taouli B, Vilgrain V, Vullierme MP, et al. IPMT of the pancreas: helical CT with histopathologic correlation. *Radiology* 2000;217:757–764.
77. Soweid A, Azar C, Labban B. Endosonographic evaluation of IPMT of the pancreas. *JOP* 2004;5:258–265.
78. Mackenzie R, Hollingworth W, Dixon AK. Quality of life assessments in the evaluation of magnetic resonance imaging. *Qual Life Res* 1994;3:29–37.
79. Nguyen TC, Sohn TA, Cameron JL, et al. Standard vs. radical pancreaticoduodenectomy for periampullary adenocarcinoma: a prospective, randomized trial evaluating quality of life in pancreaticoduodenectomy survivors. *J Gastrointest Surg* 2003;7:1–8.

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Conflicts of interest

The authors disclose no conflicts.

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