Published in final edited form as:

J Surg Res. 2012 May 15; 174(2): 222–230. doi:10.1016/j.jss.2011.08.022.

A Decision Model of Therapy for Potentially Resectable Pancreatic Cancer

Jacob P. VanHouten¹, Rebekah R. White, M.D.², and Gretchen Purcell Jackson, M.D., Ph.D.³

¹Vanderbilt University Medical Center, Nashville, TN

²Duke University Medical Center, Durham, NC

³Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN

Abstract

Background—Optimal treatment for potentially resectable pancreatic cancer is controversial. Resection is considered the only curative treatment, but neoadjuvant chemoradiotherapy may offer significant advantages.

Materials and Methods—We developed a decision model for potentially resectable pancreatic cancer. Initial therapeutic choices were surgery, neoadjuvant chemoradiotherapy, or no treatment; subsequent decisions offered a second intervention if not prohibited by complications or death. Payoffs were calculated as the median expected survival. We gathered evidence for this model through a comprehensive MEDLINE® search. One-way sensitivity analyses were performed.

Results—Neoadjuvant chemoradiation is favored over initial surgery, with expected values of 18.6 and 17.7 months, respectively. The decision is sensitive to the probabilities of treatment mortality and tumor resectability. Threshold probabilities are 7.0% mortality of neoadjuvant chemoradiotherapy, 69.2% resectability on imaging and 73.7% resectability at exploration after neoadjuvant therapy, 92.2% resectability at initial resection, and 9.9% surgical mortality following chemoradiotherapy. The decision is sensitive to the utility of time spent in chemoradiotherapy, with surgery favored for utilities less than 0.3 and −0.8, for uncomplicated and complicated chemoradiotherapy, respectively.

Conclusions—The ideal treatment for potentially resectable pancreatic cancer remains controversial, but recent evidence supports a slight benefit for neoadjuvant therapy. Our model shows that the decision is sensitive to the probability of tumor resectability and chemoradiation mortality, but not to rates of other treatment complications. With minimal benefit of one treatment over another based on survival alone, patient preferences will likely play an important role in determining best treatment.

Keywords

pancreatic cancer; neoadjuvant therapy; surgery; chemotherapy; radiation therapy; chemoradiation; decision model; decision analysis; sensitivity analysis; survival

Correspondence to: Gretchen Purcell Jackson, M.D., Ph.D. Monroe Carell Jr. Children's Hospital at Vanderbilt 2200 Children's Way, Suite 7100 Nashville, TN 37232-9780 gretchen.jackson@vanderbilt.edu Telephone: (615) 936-1050 Fax: (615) 936-1046.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Surgical resection is necessary to cure pancreatic cancer. However, surgical therapy alone is associated with 5-year survival rates of approximately 10%^{1–3}. The majority of patients with resected pancreatic cancer will ultimately have recurrence, with distant metastatic disease. High rates of margin positive (i.e., R1 or R2) resection and local recurrence in many series suggest that—even as a local therapy—surgical resection alone is not very effective⁴.

Over the last two decades, four randomized trials of surgical resection followed by postoperative adjuvant therapy (i.e., chemotherapy and/or chemoradiation) for pancreatic cancer have been completed. These trials have demonstrated a modest survival benefit in favor of adjuvant therapy with median overall survival of patients randomized to the “best” arms ranging from 17 to 22 months^{1, 3, 5, 6}. However, adjuvant therapy is not received by at least 25% of patients following pancreatic resection due to complications or slow recovery^{4, 7}, and even with modern imaging, not all patients taken to the operating room with radiographically resectable tumors are found to be resectable^{8–10}.

The disappointing results of the standard “surgery first” approaches have fueled interest in neoadjuvant (i.e., preoperative) therapy. The theoretical benefits of neoadjuvant therapy in resectable pancreatic cancer include: a) early treatment of distant micrometastatic disease in all patients; b) delivery of chemotherapy and radiation to a primary tumor with an intact blood supply, potentially improving negative margin (R0) resection rates; and c) the identification of patients who harbor occult metastatic disease. In several single institution and a few multicenter studies of neoadjuvant chemoradiation, between 15 to 45% of patients were found to have unresectable disease after neoadjuvant therapy, either on repeat imaging, staging laparoscopy, or exploratory laparotomy^{3, 6–8, 11–34}. These patients were spared a morbid surgical procedure that offered them no meaningful survival benefit. The 55 to 85% of patients who successfully completed neoadjuvant therapy followed by resection experienced median survivals of between two and three years, a difference that may be attributable to patient selection.

For patients with borderline resectable or locally advanced disease, initial chemoradiation therapy—with either “neoadjuvant” or “palliative” intent—is widely accepted. However, for patients with radiographically resectable disease, the optimal timing of multimodality therapy is highly controversial, and the evidence is evolving. The value of each approach depends not only on the survival rates of the patients who are fortunate enough to complete treatment, but also on the complications and outcomes of those patients who are not able to receive all components due to complications or tumor progression. It is challenging for clinicians to combine the variable and sometimes conflicting evidence from numerous small trials and translate that data into meaningful clinical recommendations.

Decision analysis offers techniques for formally modeling clinical decisions, incorporating the available evidence, and analyzing the factors that influence relevant outcomes. A decision model explicitly represents the choices (e.g., therapeutic options), the uncertainties (e.g., the probability of death or a complication after an intervention), and the values for specific outcomes (e.g., the expected survival after a certain course of treatment) and allows the calculation of an expected value for each choice. Sensitivity analysis allows one to explore how the values of individual choices are affected by uncertainties in the model, such as how the probability of a tumor being resectable changes the values of surgical versus medical treatment options³⁵. We sought to apply decision analytic techniques to explore the therapeutic choices for potentially resectable pancreatic cancer and to help clinicians translate the most recent evidence into informed clinical recommendations.

MATERIALS AND METHODS

Decision Model

We constructed a decision model to evaluate the initial treatment options for potentially resectable pancreatic cancer. We represented the choices of primary resection, neoadjuvant chemotherapy and radiation, or no treatment. The decision model is shown in Figure 1. In developing this model, we assumed that patients who experience major complications after primary surgical resection do not receive adjuvant therapy, that patients who are found to be resectable on imaging after neoadjuvant therapy undergo surgical exploration, and that patients who are found to have unresectable disease receive additional palliative therapy. Complications were defined as either a Grade 3 or 4 hematologic toxicity or as any complication that postponed or prevented recuperation or surgery.

For the neoadjuvant therapy choice, uncertainties include the probability that tumor is resectable on imaging after neoadjuvant therapy (pResectablePostCRT), the probability that tumor is resectable at subsequent surgery (pResectableAtSurgeryPostCRT), the probability of surgical complications after neoadjuvant therapy (pSurgicalComplicationPostCRT), the probability of surgical mortality after neoadjuvant therapy (pSurgicalMortalityPostCRT), the probability of chemoradiotherapy complications (pNeoCRTComplication), and the probability of chemoradiotherapy-related death (pNeoCRTMortality). For the initial surgery choice, uncertainties are the probability of adjuvant chemoradiotherapy complications (pAdjCRTComplication), the probability that the tumor is resectable at surgery (pResectableSurgFirst), the probability of a surgical complication (pSurgicalComplicationSurgFirst), and the probability of a surgical death (pSurgicalMortalitySurgFirst).

The model incorporates utilities for each of the following health states: receiving neoadjuvant chemotherapy and radiation without complications (uChemoRad), receiving neoadjuvant therapy with complications (uComplicatedChemoRad), undergoing surgical resection without complications (uSurgery), undergoing surgical resection with complications (uComplicatedSurgery), recovery after uncomplicated surgery (uRecovery), and slow recovery after complicated surgery (uSlowRecovery).

The expected value or payoff of each choice is calculated as a sum of the median survival in months, with each month being weighted by an appropriate utility to represent time spent in specific health states. For example, patients who receive neoadjuvant therapy without complications and then undergo resection with complications have a median survival of 27.2 months; the expected value of this outcome is calculated as follows: (2 months * uChemoRad) + (2 months * uComplicatedSurgery) + (4 months * uSlowRecovery) + 19.2 months. Because the post-treatment clinical courses are highly variable for this disease, we assumed that after completion of therapy, patients return to a state of perfect health. This approach provides an optimistic view of the effects of each treatment, while allowing some adjustments for the time spent in treatment and recovery.

For this analysis, all utilities were set to 1, which represents a state of perfect health. Thus, this study expresses expected value in terms of survival alone, without considering patient preferences or quality of life during treatment or recovery. The model does, however, explicitly represent the utilities for different health states to allow these parameters to be included in the future and to facilitate sensitivity analyses to determine whether their measurement is important.

One assumption made in creating this model is that the probability of chemoradiotherapy-related deaths is the same for both adjuvant and neoadjuvant therapies. It is difficult from

the literature to calculate a death rate attributable to adjuvant therapy due to censoring of data, but using the mortality rate for neoadjuvant therapy serves as a variable that can be modified as evidence becomes available.

Evidence Table

To gather evidence for the variables in this model, the Ovid MEDLINE® database (1950 to Present and In-Process & Other Non-Indexed Citations) was searched for papers containing the terms “pancreatic” or “pancreas” in addition to “cancer,” “neoplasms” or “tumor” and “resectable”, as well as any of the following: “surgery,” chemotherapy,” drug therapy,” “neoadjuvant” or “chemoradiotherapy.” English-language original research articles and reviews that focused on neoadjuvant therapy and patient outcomes were considered. Papers that appeared on cursory evaluation to contain relevant data pertaining were retained for further investigation, and additional papers were identified from the references lists and expert consultation.

Data were taken from papers that examined the outcomes of neoadjuvant chemoradiation therapy on potentially resectable pancreatic cancers and included adult patients older than 18 years of age. We excluded papers that did not contain primary data regarding at least one of the following: the probability of resectability initially and after neoadjuvant therapy, the probability of complications of neoadjuvant therapy, the probability of surgical complications, the probability of surgical mortality, or median survival time. Information regarding adjuvant therapy was taken from these articles when appropriate, and these data were added to data from several randomized controlled trials including this treatment modality. The probabilities used in the decision model were calculated by averaging the probabilities from individual studies with a weight determined by the number of participants in a particular study divided by the total number of participants from all the examined studies.

Analyses

The decision tree was built and analyzed using TreeAge Pro Healthcare (TreeAge Software, Inc., Williamstown, MA). Univariate sensitivity analyses were performed on all probabilities and utilities. Probabilities were varied over the range of 0 to 1, except where prohibited by coherence with other probabilities. Utilities were varied from -1 to 1, a range which includes values for health states that are considered worse than death (utility < 0). Previous work has shown that some individuals consider the health states associated with pancreatic cancer therapy as significantly worse than death, and these preferences can affect treatment decisions^{36, 37}. For this analysis, we used -1 as the minimal utility value and a maximal utility value of 1, representing perfect health.

RESULTS

Evidence for the Decision Model

Over 163 articles were returned from the MEDLINE search. Twenty-four relevant papers were used in estimating uncertainties, and ten were used in estimating survival. The evidence tables for the probabilities of resectability and complications are shown in Table 1 and Table 2. Using weighted averages, the probability of complications from neoadjuvant therapy was 27.4%, and the probability of death from neoadjuvant therapy was 2.0%. On average, 75.3% of patients who completed neoadjuvant therapy were found resectable on subsequent imaging, and 80.2% of all patients who underwent surgical exploration were found to be resectable. The average rates of surgical complications and mortality for this treatment were 31.4% and 3.6%, respectively.

Using weighted averages, the probability of complications from adjuvant therapy was 45.8%. On average, 84.6% of patients undergoing surgery first were found to be resectable. The average probabilities of surgical complications and mortality for initial resection were 41.9% and 1.7%, respectively.

The evidence table for the median survival time for the modalities of treatment is presented in Table 3. The average median survival for patients who receive no treatment was 6.8 months, which is relatively close to the value of 8 months published by Baxter *et al*³⁸. The average median survival for patients who were treated with neoadjuvant therapy but not resection was 7.6 months. Patients who had resection alone had an average median survival of 19.8 months, while patients who received surgery followed by postoperative chemoradiation had an average median survival of 19.9 months. Finally, patients who underwent neoadjuvant therapy and resection had the longest median survival of 27.2 months.

Expected Value and Sensitivity Analyses

Based on survival alone with utilities for all health states set to 1, neoadjuvant chemoradiation is slightly favored over initial surgery for the treatment of potentially resectable pancreatic cancer, with expected values of 18.6 months and 17.7 months, respectively.

One-way sensitivity analyses were performed to determine how the uncertainties in the model affect these expected values. The decision is sensitive to the probabilities of mortality from neoadjuvant therapy and tumor resectability. Initial surgery is preferred when the mortality rate due to neoadjuvant chemoradiation exceeds 7.0%. Neoadjuvant therapy is favored when the resectability on imaging after chemoradiation is greater than 69.2%, when resectability at surgical exploration after chemoradiation is greater than 73.7%, or when the probability of resection after initial surgery is less than 92.2%. The decision was also sensitive to the probability of surgical mortality, with neoadjuvant therapy preferred when this value is less than 9.9% after chemoradiotherapy.

For healthcare decision analyses, utilities of 0 and 1 represent the values associated with the health states of death and perfect health, respectively. Utilities for the time spent in treatment or recovery generally fall in between the anchors of 0 and 1, although they can be considered worse than death. In this analysis, the decision was sensitive to the utility of time spent in chemoradiotherapy. Initial surgery is favored over neoadjuvant therapy when the utility for uncomplicated chemoradiotherapy is less than 0.3 or the utility for complicated chemoradiotherapy is less than -0.8.

DISCUSSION

The optimal initial treatment for potentially resectable pancreatic cancer remains controversial. This decision model, which incorporates the most recent evidence for treatment modalities, shows only a slight expected survival advantage of neoadjuvant therapy over initial surgical resection. However, the neoadjuvant approach does offer patients a “test of time,” which may identify the patients with aggressive and perhaps already disseminated tumors who can avoid a major operative procedure that would not benefit them. Concerns that preoperative chemoradiation may increase postoperative complications have not been substantiated. As has previously been reported, the morbidity and mortality after pancreaticoduodenectomy do not appear to be increased by neoadjuvant therapy, and the pancreatic leak rate may be lower²⁰.

Our research has several limitations. The decision tree is a simplified representation of a disease process with a highly variable clinical course. We assume that patients return to perfect health after treatment for the remainder of survival. In reality, few patients may return to their baseline health status, and most experience ongoing complications of the disease or treatment until death. There are few studies that evaluate the quality of life between treatment and eventual death for pancreatic cancer. Modeling this series of transitions through health states is a complex process that will likely require a Markov model, and it is the subject of future research. Our model offers a framework for incorporating preferences for the health states associated with treatment and recovery from treatment of pancreatic cancer.

The data for the neoadjuvant approach in the model were derived from a heterogeneous assortment of retrospective and non-randomized prospective studies. Different radiation doses, fields, and schedules, and different chemosensitizing agents were used, which may be associated with different response and complication rates. Institutions also utilize slightly different staging protocols (e.g., staging laparoscopy, endoscopic ultrasound), different definitions for radiographic resectability, and sometimes different criteria for surgical resectability. These studies also span a period time over which the ability of imaging to detect unresectable disease has improved⁸. The intentional or unintentional inclusion of patients with unresectable disease into studies of neoadjuvant therapy for resectable disease introduces obvious bias against this approach. For the initial surgery approach, there were more randomized controlled trials from which to derive data. While these multicenter studies may be somewhat more uniform, they are also less likely to provide detailed data on complication rates associated with adjuvant therapy. We therefore made the simplifying assumption that rate of chemoradiotherapy complications is the same between adjuvant and neoadjuvant modalities. While this may not be entirely correct, we believe that the probability of a complication from neoadjuvant chemoradiotherapy is likely a conservative estimator of the probability of a complication from adjuvant therapy, which may be difficult to calculate due to reporting bias.

We also intentionally simplified the model by focusing on chemoradiation therapy rather than chemotherapy alone. We excluded data from a few recent studies focused on neoadjuvant chemotherapy²⁹ and adjuvant chemotherapy¹. We also made the simplifying assumption that patients found to be unresectable, whether at initial surgery or following neoadjuvant therapy, had similarly dismal survival. This assumption may or may not be true. However, since the survival benefits associated with palliative therapy are small at best, the inclusion of different palliative treatment modalities into the current model would be unlikely to affect the results. As more and better data become available, branches can be added to the tree to incorporate evidence about the efficacy of chemotherapy alone in the adjuvant, neoadjuvant, and palliative settings.

In conclusion, we present a decision model that evaluates the initial treatment for potentially resectable pancreatic cancer and incorporates the most recent evidence for the efficacy of the therapeutic options. Our analysis provides some support for a slight survival advantage to initial neoadjuvant therapy. More importantly, the decision model and the associated evidence tables represent a framework for incorporating both evolving evidence in this field and information about the quality of life after or patient preferences for treatment.

Acknowledgments

We would like to acknowledge the Medical Scientist Training Program Grant (NIH T32 GM007347) and the Vanderbilt Biomedical Informatics Training Program Grant (NLM T15LM 007450) for funding this research.

References

1. 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(3):267–77. [PubMed: 17227978]
2. Ueno H, Kosuge T, Matsuyama Y, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. *Br J Cancer*. 2009; 101(6):908–15. [PubMed: 19690548]
3. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg*. 1999; 230(6):776–82. discussion 782–4. [PubMed: 10615932]
4. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg*. 2000; 4(6):567–79. [PubMed: 11307091]
5. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004; 350(12):1200–10. [PubMed: 15028824]
6. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA*. 2008; 299(9):1019–26. [PubMed: 18319412]
7. Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol*. 1997; 15(3):928–37. [PubMed: 9060530]
8. White R, Winston C, Gonen M, et al. Current utility of staging laparoscopy for pancreatic and peripancreatic neoplasms. *J Am Coll Surg*. 2008; 206(3):445–50. [PubMed: 18308214]
9. Tamm EP, Loyer EM, Faria S, et al. Staging of pancreatic cancer with multidetector CT in the setting of preoperative chemoradiation therapy. *Abdom Imaging*. 2006; 31(5):568–74. [PubMed: 16465578]
10. Valls C, Andia E, Sanchez A, et al. Dual-phase helical CT of pancreatic adenocarcinoma: assessment of resectability before surgery. *AJR Am J Roentgenol*. 2002; 178(4):821–6. [PubMed: 11906855]
11. Yeung RS, Weese JL, Hoffman JP, et al. Neoadjuvant chemoradiation in pancreatic and duodenal carcinoma. A Phase II Study. *Cancer*. 1993; 72(7):2124–33. [PubMed: 8374871]
12. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. *Ann Surg*. 1995; 221(6):721–31. discussion 731–3. [PubMed: 7794076]
13. Staley CA, Lee JE, Cleary KR, et al. Preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for adenocarcinoma of the pancreatic head. *Am J Surg*. 1996; 171(1):118–24. discussion 124–5. [PubMed: 8554125]
14. Hoffman JP, Lipsitz S, Pisansky T, et al. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. *J Clin Oncol*. 1998; 16(1):317–23. [PubMed: 9440759]
15. White RR, Hurwitz HI, Morse MA, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. *Ann Surg Oncol*. 2001; 8(10):758–65. [PubMed: 11776488]
16. Pisters PW, Wolff RA, Janjan NA, et al. Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol*. 2002; 20(10):2537–44. [PubMed: 12011133]
17. Moutardier V, Giovannini M, Lelong B, et al. A phase II single institutional experience with preoperative radiochemotherapy in pancreatic adenocarcinoma. *Eur J Surg Oncol*. 2002; 28(5): 531–9. [PubMed: 12217307]
18. Magnin V, Moutardier V, Giovannini MH, et al. Neoadjuvant preoperative chemoradiation in patients with pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2003; 55(5):1300–4. [PubMed: 12654441]

19. Pipas JM, Barth RJ Jr, Zaki B, et al. Docetaxel/Gemcitabine followed by gemcitabine and external beam radiotherapy in patients with pancreatic adenocarcinoma. *Ann Surg Oncol.* 2005; 12(12): 995–1004. [PubMed: 16252135]
20. Cheng TY, Sheth K, White RR, et al. Effect of neoadjuvant chemoradiation on operative mortality and morbidity for pancreaticoduodenectomy. *Ann Surg Oncol.* 2006; 13(1):66–74. [PubMed: 16372154]
21. White RR, Tyler DS. Neoadjuvant therapy for pancreatic cancer: the Duke experience. *Surg Oncol Clin N Am.* 2004; 13(4):675–84. ix–x. [PubMed: 15350941]
22. Talamonti MS, Small W Jr, Mulcahy MF, et al. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. *Ann Surg Oncol.* 2006; 13(2):150–8. [PubMed: 16418882]
23. Macchia G, Valentini V, Mattiucci GC, et al. Preoperative chemoradiation and intra-operative radiotherapy for pancreatic carcinoma. *Tumori.* 2007; 93(1):53–60. [PubMed: 17455872]
24. Palmer DH, Stocken DD, Hewitt H, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. *Ann Surg Oncol.* 2007; 14(7):2088–96. [PubMed: 17453298]
25. Greer SE, Pipas JM, Sutton JE, et al. Effect of neoadjuvant therapy on local recurrence after resection of pancreatic adenocarcinoma. *J Am Coll Surg.* 2008; 206(3):451–7. [PubMed: 18308215]
26. Heinrich S, Pestalozzi BC, Schafer M, et al. Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008; 26(15):2526–31. [PubMed: 18487569]
27. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008; 26(21):3496–502. [PubMed: 18640930]
28. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg.* 2008; 206(5):833–46. discussion 846–8. [PubMed: 18471707]
29. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008; 26(21):3487–95. [PubMed: 18640929]
30. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet.* 2001; 358(9293):1576–85. [PubMed: 11716884]
31. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg.* 2006; 244(1):10–5. [PubMed: 16794383]
32. de Castro SM, Houwert JT, Lagarde SM, et al. Evaluation of POSSUM for patients undergoing pancreatoduodenectomy. *World J Surg.* 2009; 33(7):1481–7. [PubMed: 19384458]
33. Fischer M, Matsuo K, Gonen M, et al. Relationship between intraoperative fluid administration and perioperative outcome after pancreaticoduodenectomy: results of a prospective randomized trial of acute normovolemic hemodilution compared with standard intraoperative management. *Ann Surg.* 2006; 252(6):952–8. [PubMed: 21107104]
34. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med.* 2007; 356(2):129–37. [PubMed: 20071702]
35. Sox, HC. Medical decision making. Butterworths; Boston: 1988.
36. Purcell GP, White RR, Tyler DS. Preferences affect treatment decisions for pancreatic cancer. *Journal of the American College of Surgeons.* 2002; 195(3):S54.
37. Purcell GP, Martin GR, Tyler DS. Measuring utilities for temporary health states using the treatment of pancreatic cancer. *Journal of the American College of Surgeons.* 2003; 197(3):S72.
38. Baxter NN, Whitson BA, Tuttle TM. Trends in the treatment and outcome of pancreatic cancer in the United States. *Ann Surg Oncol.* 2007; 14(4):1320–6. [PubMed: 17225980]

Figure 1. Decision Model. This figure shows a decision tree for the treatment of potentially resectable pancreatic cancer. The options of initial resection, neoadjuvant therapy, and no treatment are represented along with the uncertainties associated with each choice.

Figure 2.

Sensitivity Analyses. This figure shows the results of sensitivity analyses on the probabilities in the pancreatic cancer decision model. The decision is sensitive to (a) the probability of tumor resectability on imaging after neoadjuvant chemoradiotherapy, (b) the probability of tumor resectability at surgery after neoadjuvant therapy, (c) the probability of death from neoadjuvant chemoradiotherapy, (d) the probability of death from surgery after neoadjuvant therapy and (e) the probability of tumor resectability at initial surgery.

Figure 3. Sensitivity Analyses. This figure shows the sensitivity analyses on the utilities in the pancreatic cancer decision model. The decision was sensitive to (a) the utility of time spend in uncomplicated chemoradiotherapy and (b) the utility of time spent in chemoradiotherapy with complications.

Weighted probabilities of outcomes from studies of potentially resectable pancreatic cancer using neoadjuvant therapy.

Table 1

Study	Patients	pNeoCRT Complication	pNeoCRT Mortality	Patients completing CRT	pResectable PostCRT	pResectableAt SurgeryPostCRT	Patients resected	pSurgical Complication PostCRT	pSurgical MortalityPostCRT
Yeung et al., 1993	26	11.5%	3.8%	25	72.0%	55.6%	10	60.0%	10.0%
Staley et al., 1996	39	15.4%	-	-	-	-	-	-	2.6%
Spitz et al., 1997	91	14.6%	0.0%	91	73.6%	77.6%	52	24.4%	0.0%
Hoffman et al., 1998	53	43.5%	3.2%	53	77.4%	58.5%	24	12.5%	4.2%
White et al., 2001	53	49.3%	3.8%	50	62.0%	83.9%	26	39.3%	7.1%
Pisters et al., 2002	35	8.6%	0.0%	35	85.7%	74.1%	20	55.0%	0.0%
Moutardier et al., 2002	19	5.3%	0.0%	19	84.2%	93.8%	15	33.3%	0.0%
Magnin et al., 2003	32	6.3%	3.1%	32	59.4%	-	19	-	5.3%
Cheng et al., 2006	79	-	-	79	-	-	79	65.8%	3.8%
Talamonti et al., 2006	20	5.0%	0.0%	20	100%	85%	17	17.6%	0.0%
Palmer et al., 2007	50	38.0%	2.0%	46	-	-	27	-	-
Greer, et al., 2008	28	-	-	28	-	-	28	-	14.3%
Heinrich, et al., 2008	28	35.7%	0.0%	28	92.9%	96.2%	25	4.0%	4.0%
Evans et al., 2008	86	53.5%	0.0%	85	87.1%	87.7%	64	14.1%	1.6%
Katz et al., 2008	160	18.1%	3.8%	125	65.6%	83.5%	66	16.7%	3.0%
Weighted Totals	-	27.4%	2.0%	-	75.3%	80.2%	-	31.4%	3.6%

Table 2
Weighted probabilities of outcomes from studies of potentially resectable pancreatic cancer treated with initial resection.

Study	Patients	pAdjCRT	Complication	pResectable	SurgFirst	Patients resected	pSurgicalComplication	SurgFirst	pSurgicalMortality	SurgFirst
Spitz et al., 1997	51	10.5%	82.4%	-	25	21.1%	0.0%			
Klinkenbijnl et al., 1999	81	1.2%	-	-	-	-	-			
Neoptolemos et al., 2001	413	17.9%	-	-	-	22.5%	-			
Cameron et al., 2006	1000	-	-	-	-	41.0%	1.0%			
Cheng et al., 2006	67	-	-	-	67	77.6%	4.5%			
Regine et al., 2008	451	70.5%	-	-	-	-	-			
White et al., 2008	1405	-	86.1%	-	891	-	-			
de Castro et al., 2009	652	-	-	-	652	50.9%	1.4%			
Fischer et al., 2010	209	-	77.5%	-	130	48.5%	0.0%			
van der Gaag et al., 2010	196	-	-	-	196	42.3%	6.6%			
Weighted Totals	-	45.8%	84.6%	-	-	41.9%	1.7%			

Table 3

Averages of median survival times for differing treatment modalities for resectable pancreatic cancer.

Study	Average Median Survival Time in months (no. of patients)				
	No Resection	Surgery Alone	Surgery and Adjuvant Therapy	Neoadjuvant Therapy, No Resection	Neoadjuvant Therapy and Resection
Yeung et al., 1993	-	-	-	8 (13)	29 (12)
Staley et al., 1996	-	-	-	-	19 (39)
Spitz et al., 1997	7.2 (48)	-	22 (19)	-	19.2 (41)
Hoffman et al., 1998	5.4(12)	-	-	8.3 (17)	15.7 (24)
Klinkenbijn et al., 1999	-	19.0 (103)	24.5 (104)	-	-
Pisters et al., 2002	-	-	-	7.0(15)	25.0(20)
Moutardier et al., 2002	-	-	-	-	30.0 (15)
Magnin et al., 2003	-	-	-	-	30 (19)
White et al., 2004	-	-	-	-	39.0(51)
Talamonti et al., 2006	-	-	-	-	26.0 (17)
Oettle et al., 2007	-	20.2(175)	-	-	-
Greer et al., 2008	-	21.0 (19)	-	-	-
Heinrich et al., 2008	-	-	-	-	19.1 (21)
Evans et al., 2008	-	-	-	7.1 (22)	34.0 (64)
Regine et al., 2008	-	-	18.7(451)	-	-
Weighted Totals (months)	6.8	19.8	19.9	7.6	27.2