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Neoadjuvant therapy versus upfront surgical strategies in resectable pancreatic cancer: A Markov decision analysis

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Abstract

Background: Neoadjuvant therapy is gaining acceptance as a valid treatment option for borderline resectable pancreatic cancer; however, its value for clearly resectable pancreatic cancer remains controversial. The aim of this study was to use a Markov decision analysis model, in the absence of adequately powered randomized trials, to compare the life expectancy (LE) and quality-adjusted life expectancy (QALE) of neoadjuvant therapy to conventional upfront surgical strategies in resectable pancreatic cancer patients.

Methods: A Markov decision model was created to compare two strategies: attempted pancreatic resection followed by adjuvant chemoradiotherapy and neoadjuvant chemoradiotherapy followed by restaging with, if appropriate, attempted pancreatic resection. Data obtained through a comprehensive systematic search in PUBMED of the literature from 2000 to 2015 were used to estimate the probabilities used in the model. Deterministic and probabilistic sensitivity analyses were performed.

Results: Of the 786 potentially eligible studies identified, 22 studies met the inclusion criteria and were used to extract the probabilities used in the model. Base case analyses of the model showed a higher LE (32.2 vs. 26.7 months) and QALE (25.5 vs. 20.8 quality-adjusted life months) for patients in the neoadjuvant therapy arm compared to upfront surgery. Probabilistic sensitivity analyses for LE and QALE revealed that neoadjuvant therapy is favorable in 59% and 60% of the cases respectively.

Conclusion(s): Although conceptual, these data suggest that neoadjuvant therapy offers substantial benefit in LE and QALE for resectable pancreatic cancer patients. These findings highlight the value of further prospective randomized trials comparing neoadjuvant therapy to conventional upfront surgical strategies.

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Keywords: Neoadjuvant therapy; Decision support techniques; Markov process; Pancreatic neoplasms; Surgical procedure

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Introduction

Pancreatic cancer represents the fourth leading cause of cancer-related death in the United States and remains an unsolved health care problem: its incidence is nearly equivalent to its annual death toll.¹ Complete surgical resection offers the only possibility for cure although the majority of operated patients develop recurrence.² Adjuvant therapy

has been shown to improve overall survival in resected pancreatic cancer patients and is currently accepted as standard of care.³

Unfortunately, up to 25–50% of patients who undergo pancreatic resection are unable to receive subsequent multimodal therapy as planned; postoperative complications, decreased performance status, comorbidities, or early recurrence may delay, shorten or prevent treatment delivery.⁴ Neoadjuvant therapy avoids these issues and has been demonstrated to be safe and effective in subsets of other cancers.⁵ Importantly, neoadjuvant therapy offers the time for patients with rapidly progressive disease who are destined to develop overt metastatic disease to “declare themselves” on re-staging scans prior to surgery and thus, avoid the morbidity and mortality of an operation. However, the latter could be interpreted by opponents of neoadjuvant therapy as loss of the “window” of resectability.^{6–9} Furthermore, advocates of neoadjuvant therapy have emphasized the potential added benefit of systemic therapy in an immune competent host prior to the stress imposed by major surgery.¹⁰ To what extent the emerging data on immune checkpoint blockade and manipulation of the adoptive immune system that is seen in other solid tumors will translate to pancreatic cancer is also unknown but would argue in favor of treatment in the preoperative rather than postoperative setting.^{11,12}

Neoadjuvant treatment is safe and effective in several other types of cancer and has increasingly been accepted as a valid treatment for borderline resectable pancreatic cancer; however, the current experience with neoadjuvant therapy in evidently resectable pancreatic cancer is fairly limited.^{13–15} The current study compares the life expectancy (LE) and quality-adjusted life expectancy (QALE) of resectable pancreatic cancer patients treated with neoadjuvant therapy to conventional upfront surgical strategies using a Markov decision analysis model.

Patients and methods

Model structure

We constructed a Markov cohort decision analysis model using TreeAge Pro 2015 (TreeAge Software Inc., Williamstown, MA) to evaluate the initial treatment options for resectable pancreatic cancer. In the model, two treatment strategies are represented: 1) attempted pancreatic resection followed by recovery and postoperative chemoradiotherapy; or 2) neoadjuvant chemotherapy or chemoradiotherapy followed by restaging and, if appropriate, attempted pancreatic resection. Patients that were not able to proceed to surgery were accounted for in the neoadjuvant therapy arm. The model did not allow patients who received neoadjuvant therapy and successfully underwent resection to receive additional adjuvant therapy. Therefore, the neoadjuvant therapy and surgery health state included survival data from some patients that proceeded to adjuvant

therapy. The Markov model included the following health states: untreated, recovering from surgery, postoperative major complications, no complication from chemotherapy or chemoradiotherapy, chemotherapy or chemoradiotherapy complication, chemotherapy or chemoradiotherapy alone, surgery alone, completed multimodal therapy and death. The cycle length in the model was three months. Patients cycled through the health states in the model, according to transition probabilities informed by the literature, until death.

Literature search

The probabilities and survival outcomes used in the model were derived from a systematic literature search of PUBMED from January 2000 until December 2015. The search strategy included the following search terms: ((“2000/01/01”[Date – Publication]: “2015/12/30”[Date – Publication])) and (“resectable”) and (“pancreas” or “pancreatic”) and (“neoplasm” or “neoplasms” or “cancer” or “cancers” or “adenocarcinoma”) and (“neoadjuvant” or “preoperative” or “adjuvant”). Inclusion or exclusion of studies was performed hierarchically based on review of the title, followed by review of the abstract, and, if warranted, review of the full text (S.W.L.de G). If the initial study was followed by a more comprehensive study or a study that included the original dataset, only the most recent and complete report or the study with the highest design in the evidence pyramid was included. These linked studies were identified based on authors, institutional affiliations, design, length of follow-up, and study populations.

The literature search was further narrowed down to English-language publications in humans age 18 years and older. This study only included publications on radiographically resectable pancreatic cancer patients with histologically or cytologically confirmed adenocarcinoma of the pancreas treated between 2000 and 2015. In this report, pancreatic cancer will refer to only pancreatic adenocarcinoma. Furthermore, studies on intraoperative radiation, irreversible electroporation or radiotherapy without chemotherapy were excluded, as were studies on immunotherapy or vaccine therapy. All other chemotherapy or chemoradiotherapy treatment regimens were included and no specific schemata were assumed.

Utilities

Utilities are numeric estimates of preference for a given health state or outcome, reflecting the associated health-related quality of life (QOL) on a scale from 1 (corresponding to perfect health) to 0 (equivalent to dead). All utilities were based on outcomes of the European Quality of Life Survey (EQ-5D). The following utilities obtained from the literature were used in the Markov model: 0.81 for living with stable pancreatic cancer, 0.81 for undergoing CRT, 0.53 for experiencing CRT complications, 0.59 for

recovering from pancreatic surgery, 0.48 for experiencing surgical complications.^{16–18}

Transition probabilities

To estimate pooled proportions and 95% confidence intervals for the probabilities in the model, we used random rather than fixed effect models in order to take into account the heterogeneity of the estimates.¹⁹ Data were analyzed using a previously published Microsoft Excel spreadsheet for random effects models.²⁰ The probability of transitioning to the death state in any given health state of the model was calculated from the median overall survival obtained from the published literature based on the assumption that survival is an exponential function that evenly decreases over time.²¹ The following equation was used to obtain the transition probability to death after 3 months from the median survival: $S(t) = e^{-3((-\ln(0.5))/\text{median survival in months})}$ ^{22,23}

Statistical analysis

The Markov decision analysis model was analyzed using TreeAge Pro 2015 (TreeAge Software Inc., Williamstown, MA). Deterministic sensitivity analyses were performed to assess the robustness of the decision analysis model for LE and QALE in response to changes in all parameters. Probabilities were varied between the highest and lowest value obtained from the published literature, while holding the other parameters fixed. In the absence of a minimal and maximal probability described in the literature, 95% confidence intervals obtained from the available data were used. In addition, two-way sensitivity analyses for LE and QALE were performed for resectability after neoadjuvant therapy and resectability during upfront surgery, since these variables play a critical role in surgical decision-making in the treatment of resectable pancreatic cancer patients. Probabilistic sensitivity analyses (PSA) using second-order Monte Carlo simulation were performed to assess the uncertainty in the LE and QALE. The PSA was performed by simultaneously drawing from beta distribution functions for each model parameter according to their means and standard deviations.

Results

Literature search

Of the 786 potentially eligible studies identified, 22 studies met the inclusion criteria (Supplementary Fig. 1 and Table 1). In total, probabilities from 871 and 789 patients treated with neoadjuvant therapy (Supplementary Table 2) and upfront surgical strategies (Supplementary Table 3), respectively, were included in the Markov decision analysis model (Fig. 1, schematic representation Markov model; Supplementary Figs. 2 and 3, Markov model as used in TreeAge). The weighted average transition

probabilities used for the base case, deterministic and probabilistic sensitivity analysis are shown in Table 1.

Base case analysis

The results of the base case analysis showed that the neoadjuvant therapy strategy resulted in a substantially higher LE (32.2 vs. 26.7 months) and QALE (25.5 vs. 20.8 quality-adjusted life months) compared to the upfront surgery strategy (Table 2).

Deterministic sensitivity analysis

Multiple one-way sensitivity analyses were carried out for all the variables entered in the model. The optimal strategy changed at lower resectability rates after neoadjuvant therapy, lower survival rates after neoadjuvant therapy alone, lower survival rates after neoadjuvant therapy followed by surgery and higher survival rates after upfront surgery followed by adjuvant therapy than used for the base case analysis. When the rate of resectability after neoadjuvant therapy was below 0.57 and 0.55, the optimal treatment strategy changed to upfront surgery in terms of LE and QALE, respectively. Similarly, the optimal treatment strategy changed to upfront surgery when the probability of living 3 months after neoadjuvant therapy fell below 0.919 for LE (corresponding to a median survival of 24.8 months) and 0.918 for QALE (corresponding with a median survival 24.4 months). Furthermore, when the probability of living 3 months after upfront surgery followed by adjuvant therapy exceeded 0.939 (corresponding with a median survival 33.3 months) and 0.940 (corresponding to a median overall survival of 33.8) for LE and QALE, an upfront surgery approach would be preferable on one-way sensitivity analysis. If the probability of living after neoadjuvant therapy alone dropped below 0.698 (corresponding to a median survival of 5.8 months) the optimal treatment strategy for LE would revert to upfront surgery. The optimal treatment strategy is otherwise robust in terms of LE and QALE across the range of probabilities tested for the other probabilities used in the model.

Two-way sensitivity analyses for LE and QALE with respect to the probability of being resectable after neoadjuvant therapy and during upfront surgery are shown in Figs. 2 and 3. As the rate of resectability after neoadjuvant therapy increases, the neoadjuvant therapy strategy remains optimal despite increasing probability of being resectable at upfront surgery.

Probabilistic sensitivity analysis

Incremental outcomes from the probabilistic sensitivity analysis, expressed as a difference in LE and QALE obtained between the two strategies, were obtained using a Monte Carlo simulation. The probability that the

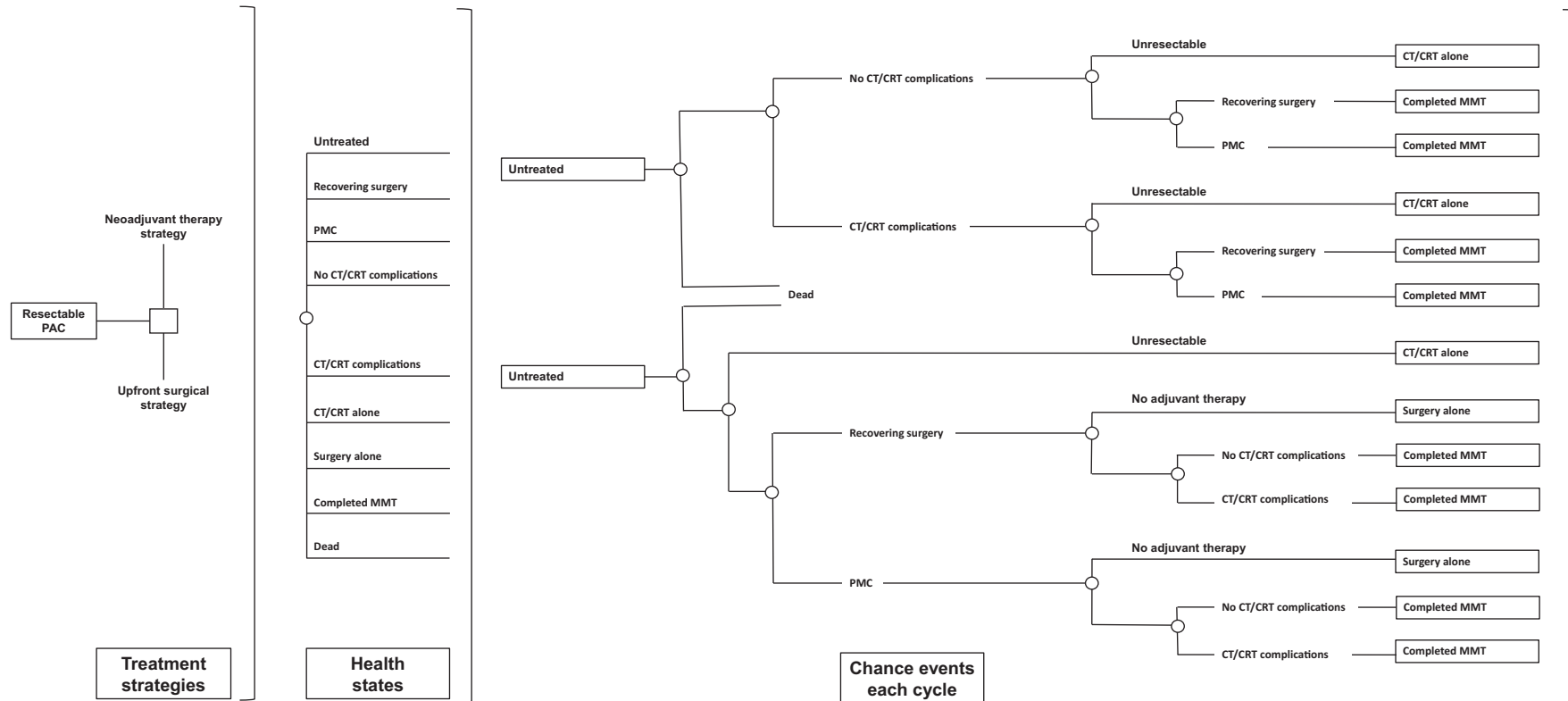


Figure 1. Schematic representation of the Markov decision analysis model. *Abbreviations:* CT, chemotherapy; CRT, chemoradiotherapy; PAC, pancreatic adenocarcinoma; MMT, multimodality therapy; PMC, postoperative major complications.

Table 1

Probability distributions and parameter estimates used in the base case analyses, deterministic and probabilistic sensitivity analyses. *Abbreviations:* ADJCT, adjuvant chemotherapy; ADJCRT, adjuvant chemoradiotherapy; NACT, neoadjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy; PMC, post-operative major complications; US, upfront surgery.

Variables	Deterministic sensitivity analysis		Probabilistic sensitivity analysis		Reference
	Base case	Range	Distribution	Parameters	
Probability NACT/NACRT complications	0.27	0.06–0.66	Beta	$\mu = 0.27; \sigma = 0.10$	26,34–38
Resectability after NACT/NACRT	0.81	0.50–0.97	Beta	$\mu = 0.81; \sigma = 0.03$	7,25–28,30,34–42
Surgical mortality after NACT/NACRT	0.02	0.00–0.04	Beta	$\mu = 0.02; \sigma = 0.01$	25,43
PMC after NACT/NACRT	0.25	0.06–0.56	Beta	$\mu = 0.25; \sigma = 0.05$	25–28,30,34,37,39,40
Probability living 3 months after NACT/NACRT alone	0.8034	0.6918–0.8306	Beta	$\mu = 0.8034; \sigma = 0.1048$	25–28,38,40,42
Probability living 3 months after NACT/NACRT and surgery	0.9349	0.9035–0.9547	Beta	$\mu = 0.9349; \sigma = 0.0476$	7,25–28,35,37,38,40–42,44
Resectability at US	0.92	0.65–1.00	Beta	$\mu = 0.92; \sigma = 0.14$	28
Surgical mortality during US	0.02	0.00–0.04	Beta	$\mu = 0.02; \sigma = 0.01$	25,43
PMC after US	0.43	0.17–0.52	Beta	$\mu = 0.43; \sigma = 0.06$	28,30,43
Probability receipt of ADJCT/ADJCRT after US	0.59	0.44–0.62	Beta	$\mu = 0.59; \sigma = 0.07$	28,30,43
Probability ADJCT/ADJCRT complications	0.54	0.31–0.68	Beta	$\mu = 0.54; \sigma = 0.08$	45–47
Probability living 3 months after US alone	0.8637	0.8522–0.8730	Beta	$\mu = 0.8637; \sigma = 0.0725$	28,29,43
Probability living 3 months after US and ADJCT/ADJCRT	0.9200	0.9013–0.9520	Beta	$\mu = 0.9200; \sigma = 0.0431$	28,29,43,45–49

Table 2

Results of base case analyses.

Strategy	Life expectancy (in months)	Gain in life expectancy	Quality adjusted life expectancy (in months)	Gain in quality adjusted life expectancy
Neoadjuvant therapy	32.2	5.5	25.5	4.7
Upfront surgery	26.7	–	20.8	–

neoadjuvant therapy strategy is optimal in terms of LE and QALE is 59% and 60%, respectively.

Discussion

The present treatment guidelines support the use of neoadjuvant therapy for patients with borderline resectable pancreatic cancer; however, the optimal treatment strategy for patients with resectable pancreatic cancer remains controversial.²⁴ Therefore, in the absence of conclusive results from randomized controlled trials, the present study used an evidence-based Markov decision analysis model to compare neoadjuvant therapy to upfront surgical strategies in resectable pancreatic cancer patients. In our analysis, neoadjuvant therapy offered a 5.5 month (32.2 vs. 26.7 months) and 4.7 quality-adjusted month (25.5 vs. 20.8 quality-adjusted life months) improvement in LE and QALE, respectively, compared to a surgery-first approach in resectable pancreatic cancer patients. On probabilistic sensitivity analyses, neoadjuvant therapy resulted in a higher LE and QALE in 59% and 60% of cases, which supports the strong consideration of a neoadjuvant therapy approach in resectable pancreatic cancer patients.

Currently, upfront resectable pancreatic cancer patients rarely receive neoadjuvant therapy outside of clinical trials or a handful of unique centers. However, published data from prospective and retrospective experiences with neoadjuvant therapy have shown favorable survival durations for patients with resectable pancreatic cancer who receive neoadjuvant therapy and go on to surgical resection, with median overall survivals ranging from 26 to 45 months.^{25–27} Such survival durations have not been reported, even from single institutions, with a surgery first approach with or without adjuvant therapy.^{28,29} Unfortunately, the first randomized control trial comparing neoadjuvant therapy to upfront surgery was unable to demonstrate a survival benefit for either treatment sequence due to poor accrual.³⁰ Given these logistical challenges for clinical trial enrollment, decision analysis may serve as an important interim source of information.³¹ Previous decision analysis models comparing neoadjuvant therapy to upfront surgical strategies included both borderline resectable and clearly resectable pancreatic cancer patients, and these studies provided evidence supporting a modest benefit for neoadjuvant therapy in this population. Van Houten et al. (2012) reported a LE of 18.6 versus 17.7 months for patients treated with neoadjuvant therapy and initial surgery, respectively, whereas Sharma et al. (2015) demonstrated a slightly larger gain in LE (22 versus 20 months) and QALE (20 versus 18 quality-adjusted months) in favor of a neoadjuvant therapy.^{31,32}

Markov decision analysis models are powerful analytical tools that have been widely utilized to address complex problems in medical decision-making. Using Markov modeling to compare the treatment strategies available for patients with resectable pancreatic cancer offers the

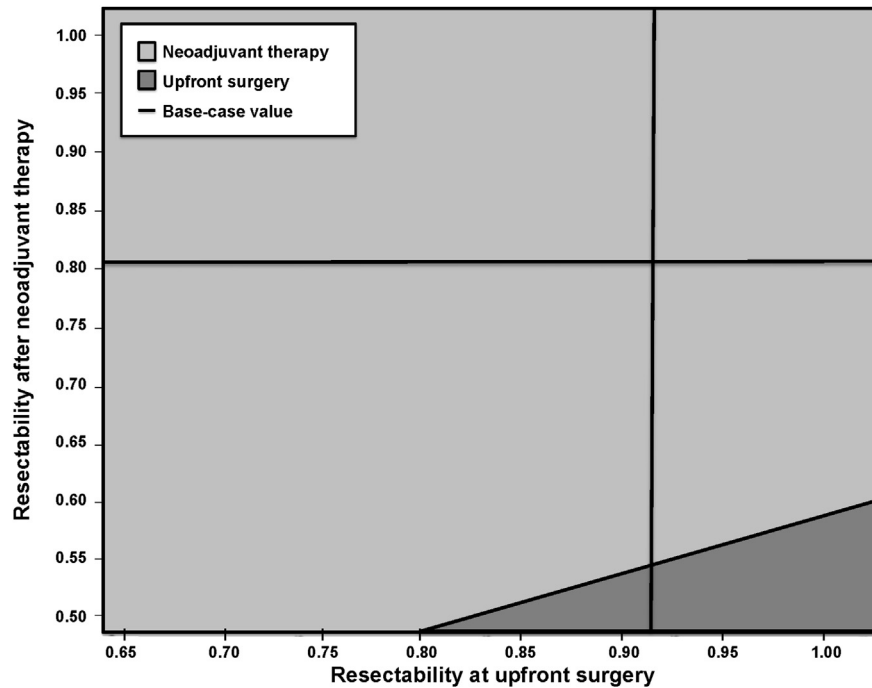


Figure 2. Two-way sensitivity analysis plotting rate of resectability after neoadjuvant therapy and rate of resectability at upfront surgery in resectable pancreatic cancer patients. Shaded regions reflect the optimal treatment strategy, in terms of life expectancy, for the corresponding values of resectability after neoadjuvant therapy and at upfront surgery.

opportunity to adjust for treatment delays and incorporate quality-of-life data. In concordance with our findings, previous studies using decision analysis modeling have also shown benefits in terms of overall and quality-adjusted

survival in favor of neoadjuvant therapy-based management of potentially resectable pancreatic cancer.³² Our study was able to advance on preceding decision analysis studies by solely investigating the value of neoadjuvant therapy in

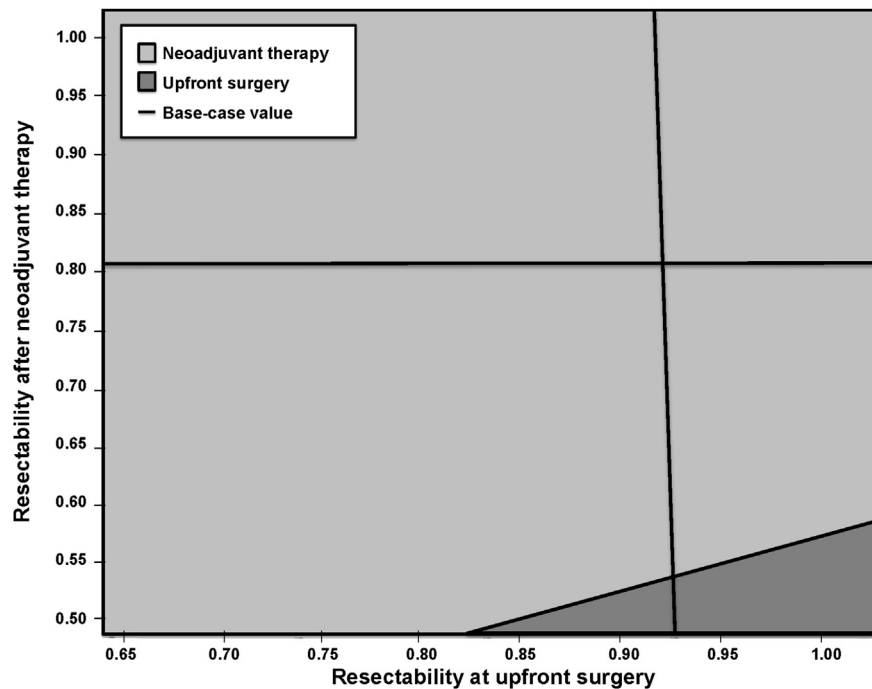


Figure 3. Two-way sensitivity analysis plotting rate of resectability after neoadjuvant therapy and rate of resectability at upfront surgery in resectable pancreatic cancer patients. Shaded regions reflect the optimal treatment strategy, in terms of quality-adjusted life expectancy, for the corresponding values of resectability after neoadjuvant therapy and at upfront surgery.

resectable pancreatic cancer patients, as neoadjuvant therapy has already gained wide acceptance in the treatment of borderline resectable pancreatic cancer. Furthermore, this study improved on previous iterations by employing a robust systematic literature review with recent data as well as a comprehensive probabilistic sensitivity analysis to address the uncertainty in the Markov decision analysis model.

Decision analysis is invariably limited by the data used to inform the model, since assumptions are necessarily made in constructing the decision tree. Although probability estimates used in the model reflect the best available clinical data, the outcomes of the studies included were heterogeneous. Additionally, most articles available for this analysis are retrospective in nature and may be biased toward positive results. Different radiation doses, fields, and schedules, as well as diverse chemotherapy agents were used, which may be associated with variable response rates and complication profiles. Also, published studies often utilized different staging protocols, different definitions for radiographic resectability, and different criteria for surgical resectability. In addition, it is unknown how the more effective combination systemic therapies such as FOLFIRINOX or gemcitabine/nab-paclitaxel, which have proven effective in advanced pancreatic cancer, may impact the efficacy of neoadjuvant therapy, the interval between treatment modalities (chemotherapy, chemoradiation and surgery).³³ Finally, some studies providing survival data for the neoadjuvant therapy and surgery arm also included patients that received adjuvant therapy; due to lack of data on the probability of receiving adjuvant therapy, patients who received additional adjuvant therapy could not be included in the model separately.

Despite its limitations, our study is the first decision analysis model to compare neoadjuvant therapy to the conventional upfront surgery in resectable pancreatic cancer patients. While a randomized controlled trial would provide conclusive evidence for the utility of neoadjuvant therapy in the care for resectable pancreatic cancer patients, we do not foresee such additional studies in the near future and decision analysis studies may serve as an interim source of information. This study accurately reflects the key tradeoffs between neoadjuvant therapy and upfront surgical strategies in patients with resectable pancreatic cancer, and is populated by recent data obtained from a robust systematic literature review. Importantly, using Markov decision analysis allowed for the inclusion of patients that did not proceed to surgery in the neoadjuvant therapy arm, accounting for the probability of loss of the “window of resectability”. Furthermore, in sensitivity analysis the model responded in an intuitive manner to changes in variables within clinically plausible ranges, giving our results face validity.

In this Markov decision analysis simulation informed by the most recent data available on resectable pancreatic cancer patients, neoadjuvant therapy, as opposed to upfront

surgical strategies, was the preferred treatment strategy in terms of LE (32.2 vs. 26.7 months) and QALE (25.5 vs. 20.8 quality-adjusted life months). In addition, probabilistic sensitivity analyses showed neoadjuvant therapy associated with favorable LE and QALE in 59% and 60% of cases, respectively. Although theoretical, these results suggest that neoadjuvant therapy holds promise to improve the care of resectable pancreatic cancer patients. They also lend support for further prospective randomized trials, especially in light of imminent advancements in systemic treatment.

Conflict of interest

None of the authors of this study have any financial and personal relationships with people or organizations that could inappropriately influence (bias) their work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejso.2016.07.016>.

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