456: Markov Decision Analysis of Neoadjuvant Treatment Pathway versus Surgery First Pathway for Resectable Pancreatic Cancer

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ABSTRACT

Background: Surgery first (SF) versus neoadjuvant approach (NAT) to management of potentially resectable pancreatic ductal adenocarcinoma (PDAC) is controversial. This study is unique in utilizing institutional data to offer Markov decision-analysis of overall treatment pathways for resectable PDAC (RPC). **Methods:** An advanced Markov decision analysis model was constructed and populated with data from a retrospective institutional database. Patients presenting with resectable PDAC from 2008-2012 were included in the SF arm. Those presenting with resectable PDAC from 2012-2016 and treated within NAT pathway populated the NAT arm. Model uncertainties were tested with one and two-way deterministic sensitivity analysis and probabilistic Monte Carlo sensitivity analysis set to 1000 cycles with variables altered between highest and lowest observed values. **Results:** NAT pathway gave an additional 0.58 QALMs (22.43 vs. 21.85 QALMs). Monte Carlo analysis reported indifference between treatment strategies. One-way deterministic sensitivity analysis showed that probability of resection in the SF pathway must be greater than 0.82, or below 0.72 in NAT pathway, and probability of receiving adjuvant therapy above 0.6 to alter pathway superiority. Two-way deterministic sensitivity analysis demonstrated treatment superiority depended on resection rate in each pathway and receiving adjuvant therapy in SF pathway. Markov cohort analysis demonstrated superiority of neoadjuvant pathway (Table 2). **Conclusions:** Optimal treatment pathway remains debatable on an intention-to-treat Markov decision analysis. Markov cohort analysis of treatment received demonstrated benefit with NAT pathway.

OBJECTIVES

The aim of this study is to create a Markov decision analysis model based on a single institution database to compare SF versus NAT pathways for treatment of RPC. Approaches were assessed on an intention-to-treat basis and Markov Cohort analysis of treatment received.
Probabilities of interventions, clinical outcomes, and survival in both SF and NAT cohorts were calculated from the West of Scotland Pancreatic Unit prospective database which recorded data for a cohort of 201 sequential patients diagnosed with RPC and fit for surgery at initial staging. All patients underwent surgery in the West of Scotland Pancreatic Unit. SF pathway was exclusively performed from January 2008 to July 2012. From 1st August 2012-30th December 2015 100 patients with non-metastatic pancreatic ductal adenocarcinoma (PDAC) were treated in NAT pathway. For this model only those patients with resectable disease on completion of initial staging prior to commencing NAT were included (n=56). Borderline and locally advanced PC were determined according to AHPBA/ SSO/SSAT guidelines[1]. From August 2012 working backwards, 100 sequential patients in SF pathway who had resectable PC, and were deemed fit for surgery based on performance status score and CPET populated the SF arm of the model. No patients were lost to follow-up.
Neoadjuvant regime was FOLFIRINOX unless patients had: poor performance status, were aged over 70 years, or FOLFIRINOX was poorly tolerated, whereby they received Gemcitabine+Capcitabine (GEMCAP).
Ethical approval for data collection was granted by the West of Scotland Local Research Ethics Committee.

Survival State	Utility for QALM
Living with stable pancreatic cancer	0.81
Undergoing chemo/radiotherapy	0.81
Experiencing chemo/radiotherapy complications	0.53
Recovering from pancreatic surgery	0.59
Experiencing surgical complications	0.48
No treatment and pre-operative quality-of-life	0.65

Table 1: utilities for quality adjusted life month (QALM) survival from literatire [2-7]

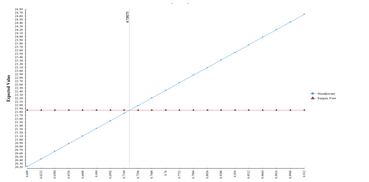


Figure 1: One-way sensitivity analysis showing threshold of probability of resection in neoadjuvant pathway that must be reached to maintain optimal strategy in ranking analysis. Y axis shows expected quality-adjusted survival, x axis shows probability of resection in NAT pathway.

METHODS

A Markov cohort decision analysis model was constructed using TreeAge Pro 2017 (TreeAge Software Ins., Williamstown, MA). The base case, surgery first followed by adjuvant therapy, was compared to neoadjuvant therapy followed by re-staging and, if appropriate, by surgical resection.
Transition nodes were based on outcomes of response to neoadjuvant therapy on repeat CT scan (for the neoadjuvant cohort only), operative intervention and outcome, post-operative complication, and receipt of adjuvant therapy based on postoperative complication occurrence. Results were adjusted based in quality-of-life indicies for surgery, chemotherapy and/or radiotherapy, and no treatment were taken from published literature (table 1).
Each cycle length was one month with a total number of 60 cycles. Patients cycled through the model until death or with a total follow-up time of 60 months for those still alive at model completion. For the Markov cohort analysis survival time was calculated from median survival time of each cohort based on: intervention, post-operative complication and neoadjuvant/ adjuvant therapy. Markov survival states included: disease free survival, alive with disease and dead.

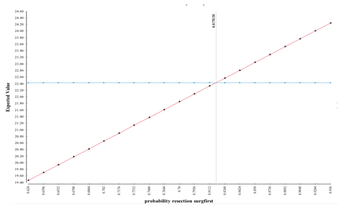


Figure 2: One-way sensitivity analysis showing threshold of resection in surgery first cohort that must be achieved to make SF optimal strategy in overall raking analysis. Y axis shows expected quality-adjusted survival, x axis shows probability of resection in SF pathway.

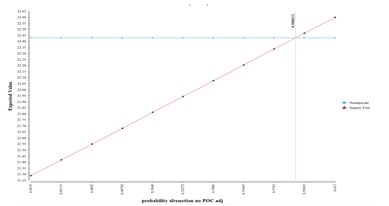
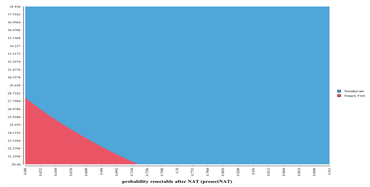


Figure 3: One-way sensitivity analysis showing threshold probability of receiving adjuvant therapy that must be achieved to make SF optimal strategy in overall raking analysis. Y axis shows expected quality-adjusted survival, x axis shows probability of receiving adjuvant therapy post resection in SF pathway.

4a)



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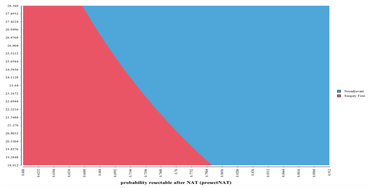

Figure 4: Two-way sensitivity analysis altering rate of resection following NAT and a) months to disease reoccurrence and b) months to death in neoadjuvant followed by resection group. Blue area depicts where neoadjuvant approach givens optimal quality adjusted survival. Y axis shows time in months

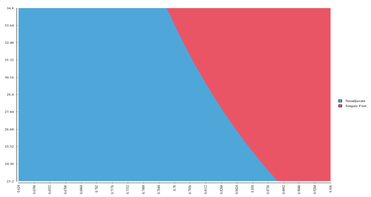

Figure 5: Two-way sensitivity analysis altering rate of resection in SF pathway and months to death. Blue area depicts where neoadjuvant approach givens optimal quality adjusted survival. Y-axis shows time in months.

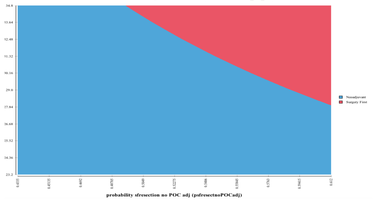

Figure 6: Two-way sensitivity analysis altering rate of adjuvant therapy following resection in SF pathway and months to death. Y-axis shows time in months. X-axis shows probability of receiving adjuvant therapy post resection. Blue area depicts where neoadjuvant approach givens optimal quality adjusted survival.

RESULTS

In intention-to-treat analysis of the treatment pathways, NAT gave an additional 0.58 QALMs (22.43 versus 21.85 QALMs). The results of Markov Cohort analysis (Table 2) demonstrated superiority of NAT pathway. One-way deterministic sensitivity analysis showed that probability of resection and probability of receiving adjuvant therapy in SF pathway altered pathway superiority (Figures1-3). Two-way deterministic sensitivity analysis demonstrated treatment superiority depended on resection rate in each pathway (Figures 4&5) and receiving adjuvant therapy in SF pathway (Figure 6). Probabilistic Monte Carlo sensitivity analysis set to 1000 cycles reported indifference between pathways when indifference threshold was set greater than 0.5 months.

	NAT Pathway	SF Pathway
Resection	OS: 37.97 months (34.12 QALMs) DFS: 19.83 months (19.42 QALMs)	Received adjuvant therapy: OS: 31.32 months (25.24 QALM); DFS: 17.53 months (13.99 QALM) No adjuvant therapy: OS: 21.83 months (18.92 QALMs) DFS: 13.15 months (10.65 QALMs)
Non-resection surgery	OS: 13.56 months (10.82 QALMs)	OS: 13.07 months (10.43 QALMs)
No surgery	OS: 13.97 months (9.08 QALMs)	

Table 2: Results of Markov Cohort Analysis

CONCLUSIONS

In conclusion the Markov decision analysis showed superiority of survival time, and quality adjusted survival time, with NAT pathway when all treatment modalities (i.e. surgery and chemotherapy) were completed.

This finding in the context of an absence of conclusive superiority of one pathway over another on an intention-to-treat basis highlights two important directions for future research based on Markov decision analysis:

1) cost-effectiveness analysis of neoadjuvant versus upfront surgery
2) exploring methods of predictive statistical modeling to identify patients who are more likely to receive and benefit from differing treatment modalities.

By moving research in this direction it is hoped that we can find a path from ambiguity to precision medicine with associated benefit to patients and resource utilisation.

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