Background: Surgery first (SF) versus neoadjuvant approach (NAT) to management of potentially resectable pancreatic ductal adenocarcinoma (PDAC) is controversial. This study aims to utilise institutional data to offer Markov decision analysis models for both 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 versus 21.85 QALMs) vs SF. 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 strategies. One-way deterministic sensitivity analysis showed that probability of resection and probability of receiving adjuvant therapy in SF pathway altered 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 basis Markov decision analysis. Markov cohort analysis of treatment received demonstrated benefit with NAT pathway.

METHODS

A Markov cohort decision analysis model was constructed using TreeAge Pro 2017 (TreeAge Software Inc., Williamsport, 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 complications, and receipt of adjuvant therapy based on postoperative complication occurrence. Results were adjusted based in quality-of-life indices 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 complications, adjuvant therapy and neoadjuvant therapy. Markov survival states included: disease free survival, alive with disease and dead.

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 superior outcomes with NAT pathway. One-way deterministic sensitivity analysis showed that probability of resection and probability of receiving adjuvant therapy in SF pathway altered pathway superiority. Two-way deterministic sensitivity analysis showed that probability of resection and probability of receiving adjuvant therapy in SF pathway altered pathway superiority. 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 complications, and receipt of adjuvant therapy based on postoperative complication occurrence. Results were adjusted based in quality-of-life indices for surgery, chemotherapy and/or radiotherapy, and no treatment were taken from published literature (Table 1).

CONCLUSIONS

In conclusion the Markov decision analysis showed superiorof 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 modelling 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.

REFERENCES