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**ABSTRACT**

A Markov cohort decision analysis model was constructed using TreeAge Pro 2017 (TreeAge Software Inc., 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 complications, and receipt of adjuvant therapy based on postoperative complication occurrence. Results were adjusted based on quality-of-life indices for surgery, chemotherapy and/or radiotherapy, and no treatment was 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.

**METHODS**

A 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 pathway. 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 to give an additional 0.58 QALMs to give an additional 0.58 QALMs to the SF pathway superior to 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 demonstrated treatment superiority depended on resection rate and probability of receiving adjuvant therapy in the NAT pathway. Monte Carlo analysis demonstrated superiority of neoadjuvant pathway (Table 2). Conclusions: Optimal treatment pathway remains debateable on an intention-to-treat Markov decision analysis. Markov cohort analysis of treatment received demonstrated benefit with pathway superiority. Two-way deterministic sensitivity analysis showed probability of resection in the SF pathway must be greater than 0.82 to give an additional 0.58 QALMs to give an additional 0.58 QALMs to the SF pathway superior to 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 demonstrated treatment superiority depended on resection rate and probability of receiving adjuvant therapy in the NAT pathway. Monte Carlo analysis demonstrated superiority of neoadjuvant pathway (Table 2). Conclusions: Optimal treatment pathway remains debateable on an intention-to-treat Markov decision analysis. Markov cohort analysis of treatment received demonstrated benefit with pathway superiority.

**RESULTS**

In intention-to-treat analysis of the treatment pathways, NAT gave an additional 0.58 QALMs (22.43 vs. 21.85 QALMs). The results of Markov Cohort analysis: (Table 2) demonstrated superior treatment of SF 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 demonstrated treatment superiority depended on resection rate in each pathway (Figures 4&5) and receiving adjuvant therapy in SF pathway at 0.58 QALMs. The results of the 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 pathway. 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 to give an additional 0.58 QALMs to give an additional 0.58 QALMs to the SF pathway superior to 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 demonstrated treatment superiority depended on resection rate and probability of receiving adjuvant therapy in the NAT pathway. Monte Carlo analysis demonstrated superiority of neoadjuvant pathway (Table 2). Conclusions: Optimal treatment pathway remains debateable on an intention-to-treat Markov decision analysis. Markov cohort analysis of treatment received demonstrated benefit with pathway superiority. Two-way deterministic sensitivity analysis showed probability of resection in the SF pathway must be greater than 0.82 to give an additional 0.58 QALMs to give an additional 0.58 QALMs to the SF pathway superior to 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 demonstrated treatment superiority depended on resection rate and probability of receiving adjuvant therapy in the NAT pathway. Monte Carlo analysis demonstrated superiority of neoadjuvant pathway (Table 2). Conclusions: Optimal treatment pathway remains debateable on an intention-to-treat Markov decision analysis. Markov cohort analysis of treatment received demonstrated benefit with pathway superiority.

**CONCLUSIONS**

In conclusion the Markov decision analysis showed superior 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 different 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**