Editorial Commentary

Clarifying the role of adjuvant therapy after multi-agent neoadjuvant chemotherapy for patients with pancreatic ductal adenocarcinoma

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Comment on: Sugawara T, Rodriguez Franco S, Sherman S, *et al.* Association of Adjuvant Chemotherapy in Patients With Resected Pancreatic Adenocarcinoma After Multiagent Neoadjuvant Chemotherapy. JAMA Oncol 2023;9:316-23.

Keywords: Pancreatic ductal adenocarcinoma (PDAC); adjuvant therapy; neoadjuvant therapy; survival

Submitted Apr 25, 2023. Accepted for publication Aug 08, 2023. Published online Aug 21, 2023.
doi: 10.21037/tcr-23-720
View this article at: https://dx.doi.org/10.21037/tcr-23-720

Pancreatic cancer is the 4th leading cause of cancer death in the United States, with an overall estimated 5-year survival rate of 12% (1), and pancreatic ductal adenocarcinoma (PDAC) accounts for the majority of pancreatic cancers (2). The standard of care for patients who present with resectable PDAC is curative-intent surgical resection, followed by adjuvant chemotherapy using regimens such as modified fluorouracil, irinotecan, oxaliplatin (mFOLFIRINOX) (2,3). Neoadjuvant therapy has been proposed as a way to improve R0 resection rates, tumour downstaging, limit systemic spread and treat micrometastases (3-7). At this time, neoadjuvant treatment is common practice for patients with borderline resectable disease (3).

The clinical benefit of neoadjuvant therapy in PDAC is supported by current and ongoing clinical trials (3). For example, the PREOPANC is a phase III clinical trial of 246 patients with resectable or borderline resectable PDAC, comparing preoperative chemoradiotherapy with gemcitabine followed by surgery and adjuvant gemcitabine with upfront surgery followed by adjuvant gemcitabine (5,8). While initial analysis did not demonstrate a survival benefit, analysis of long-term results demonstrated a significantly higher median overall survival (mOS) in the neoadjuvant chemoradiotherapy group (15.7 *vs.* 14.3 months), as well as 5-year OS of 20.5% *vs.* 6.5% (8). Analysis of long-term results suggests that neoadjuvant treatment is beneficial in both resectable and borderline resectable subgroups (8). Additional clinical trials are ongoing to define the role of neoadjuvant therapy in both resectable and borderline resectable pancreatic cancer (3).

Currently, only retrospective data is available regarding the role of adjuvant therapy for those patients that have received neoadjuvant chemotherapy for PDAC. Van Roessel *et al.* performed a multicenter retrospective cohort study of 520 patients that received neoadjuvant FOLFIRINOX followed by surgical resection, of whom 343 patients also received adjuvant chemotherapy (9). While there was no overall difference in OS between the adjuvant treatment and non-adjuvant treatment groups, they demonstrated that patients with pathology-proven node-positive disease had an improved median OS with adjuvant chemotherapy (26 *vs.* 13 months) (9). Swords *et al.* also performed a retrospective cohort study of 4,187 patients, demonstrating that postoperative chemotherapy after preoperative chemotherapy is associated with an improved OS in patients with lymph node ratios (LNR) 0.01–0.149 (mOS 34.5 *vs.* 26.5 months), but that this effect was not observed in node-negative disease or in patients with LNR ≥0.15 (10). A later study by Olecki *et al.* examined 3,897 patients who had received neoadjuvant therapy for pancreatic cancer, of whom 36.7% also received

adjuvant therapy (11). This study showed that the OS benefit of adjuvant therapy was specific to patients with low risk disease (N0, LNR 0–0.15, low grade histology) (11). Some of the conflicting findings in these studies may be explained by differences in sample sizes, the specific regimens used, different tumour characteristics for patients that are selected for adjuvant therapy, or the time period in which data was collected (11,12). While existing literature suggests a potential benefit of adjuvant chemotherapy after neoadjuvant therapy and surgical resection, it is yet unclear which specific subgroup of patients benefit from this strategy.

The current study by Sugawara *et al.* (12) is a retrospective, matched-cohort analysis of patients diagnosed with PDAC between the years 2010 and 2018 using data collected from the National Cancer Database (NCDB). From the NCDB, they created a dataset of 1132 patients who had received multi-agent neoadjuvant chemotherapy, of whom 492 also received adjuvant chemotherapy. Analysis of the dataset following propensity score matching revealed that adjuvant chemotherapy was associated with longer median survival than the non-adjuvant chemotherapy group (26.6 months compared to 21.2 months, P=0.002). Similarly, OS at 1- and 5-year was also higher for those patients who had received adjuvant chemotherapy. The authors then performed an interaction analysis to identify which patients are likely to derive benefit from the addition of adjuvant chemotherapy. They found that patients who were less than 75 years of age, had pathological T category of ypT3 or higher, and those with moderately or poorly differentiated tumours had a lower mortality when treated with adjuvant chemotherapy. Interestingly, they found that the survival benefit was preserved regardless of pathological N category and margin status (12).

Overall, although the role of adjuvant therapy after multiagent neoadjuvant therapy for PDAC is suggested by multiple retrospective studies [including the study from Sugawara *et al.* (12)], this conclusion is limited by the inherent biases associated with retrospective studies. Although the authors in the current study tried to mitigate some of these biases through the employment of propensity score matching, this does not negate completely these biases. The most notable bias would be the fact that patients who were offered adjuvant chemotherapy might be fitter with better performance status compared to those who were not offered such a treatment. It would be of interest to analyze post-operative complication rates in future studies, to identify any potential impact on eligibility for adjuvant chemotherapy.

In the current study by Sugawara *et al.*, information about the specific chemotherapy regimens used was also not available, which introduces a further confounding variable. Future studies will need to control for the specific treatment regimens used, and the cumulative dosages used during a patient's treatment course. Additionally, there is potentially an immortal time bias for patients receiving adjuvant chemotherapy due to the recovery period after surgery which would be difficult to control for.

Based on the currently available observational studies, it is unclear from the totality of the evidence which subgroup of patients is likely to derive benefit from adjuvant therapy, as well as what is the optimal regimen and duration of treatment. Future prospective randomized clinical trials will be important to clarify these uncertainties and might lead to the development of new treatment guidelines for patients with resectable or borderline resectable PDAC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-720/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-720/coif). OAR is part of the advisory board for Amgen, Eisai, Ipsen, Roche, Lilly, and Bayer. The other author has conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Lan X, Abdel-Rahman O. Clarifying the role of adjuvant therapy after multi-agent neoadjuvant chemotherapy for patients with pancreatic ductal adenocarcinoma. Transl Cancer Res 2023;12(8):2232-2234. doi: 10.21037/tcr-23-720

