Neoadjuvant chemoradiation for resectable and borderline resectable pancreatic cancer: is there a benefit?

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Pancreatic ductal adenocarcinoma (PDAC) is a highly fatal malignancy for which resection is considered the only potential cure. However, most patients are not surgical candidates either because of distant metastasis or involvement of major vascular structures. While some with extensive vascular involvement are considered to have locally advanced disease, others with borderline resectable disease have more limited involvement (1). Only about 15% of PDAC patients have resectable disease at initial diagnosis although nearly all will experience disease recurrence distantly and/or locoregionally within 2 years after surgery (2).

Adjuvant chemotherapy is routine after PDAC resection due to the high likelihood of recurrence. Modern multi-agent chemotherapy regimens such as modified FOLFIRINOX (mFOLFIRINOX) have achieved substantially higher median overall survival (OS) compared to now antiquated single-agent strategies. For example, the PRODIGE24/CCTG PA.6 trial achieved median OS of 54 months with adjuvant mFOLFIRINOX compared to 35 months with gemcitabine (P=0.003) although these impressive results were in part achieved because of strict patient selection criteria including CA19-9 <180 U/mL prior to start of chemotherapy (3).

Adjuvant radiation therapy (RT) may also be considered although the benefit over chemotherapy alone remains controversial. However, modern RT techniques and prescription doses may especially benefit patients with pathologic risk factors for recurrence such positive margins or involved lymph nodes (4).

While there are clear advantages of adjuvant therapy there are also significant challenges. First, determination of surgical resectability on diagnostic imaging can be challenging; approximately 30% of patients in the SWOG S1505 randomized trial deemed initially to have technically resectable PDAC were found to have unresectable PDAC after central review of imaging (5). Second, more than half of PDAC patients deemed initially resectable will have a positive surgical margin as shown in multiple prospective trials (6). Third, about 20% of (borderline) resectable patients are understaged and found to have occult metastasis or locally advanced disease upon exploration (7). Fourth, only about 50% of patients who undergo complete resection will receive adjuvant therapy largely due to surgical morbidity and postoperative complications (8). Lastly, some resected patients experience a short interval to cancer recurrence likely as a result of occult micrometastatic disease being present at the time of initial diagnosis (2).

Efforts to improve outcomes for patients with (borderline) resectable PDAC through a shift to neoadjuvant therapy are ongoing. Neoadjuvant therapy offers the potential to increase the likelihood of margin-negative (R0) resection, address occult micrometastatic

disease, and enhance patient selection for surgery based on biologic selection. Promising outcomes including improved OS have been demonstrated using neoadjuvant therapy compared to upfront surgery in resectable patients, albeit in retrospective and meta-analyses with varied chemotherapy and RT approaches. In spite of the low level evidence to date the National Comprehensive Cancer Network (NCCN; v1.2020) and American Society for Clinical Oncology (ASCO) Clinical Practice Guideline (9) endorse consideration of neoadjuvant therapy for select resectable PDAC patients. Beyond consensus statements and retrospective data, there is clearly a need for well designed prospective studies to validate the benefit of such neoadjuvant strategies as standard of care. Furthermore, prospective data are emerging. A Korean randomized phase II/III trial of neoadjuvant chemoradiation (CRT) versus adjuvant CRT in borderline resectable PDAC patients closed early due a large median and 2-year OS advantage favoring the neoadjuvant arm (10). Although currently reported only in abstract form, the Japanese Prep-02/JSAP-05 randomized phase II/III trial showed improved median and 2-year OS with neoadjuvant gemcitabine and S-1 compared to upfront resection for resectable PDAC (11).

Versteijne *et al*. should be commended for completing the Dutch multicenter randomized phase III PREOPANC Trial, which lends support to neoadjuvant therapy for resectable and borderline resectable PDAC. Patients were randomized 1:1 across 16 centers to either neoadjuvant gemcitabine and gemcitabine-based CRT (36 Gy in 15 fractions) or immediate surgery, with the intent for all patients to receive adjuvant gemcibinate. Although the primary endpoint of median OS by intention to treat (ITT) was not met (16.0 *vs.* 14.3 months, P=0.096), there was a trend towards significance on per-protocol analysis favoring neoadjuvant CRT (20.2 *vs.* 16.8 months; P=0.073). However, in the predefined subgroup of patients with borderline resectable PDAC there was improved median OS (17.6 *vs.* 13.2 months, P=0.029) with neoadjuvant therapy although a significant difference was not found in the resectable subgroup. The R0 rate in the upfront surgery arm was 40% versus 72% in the neoadjuvant CRT arm (P<0.001). Neoadjuvant CRT also achieved a lower incidence of pathologic lymph node involvement (33% *vs.* 78%, P<0.001), perineural invasion (39% *vs.* 73%, P<0.001), and venous invasion (19% *vs.* 36%, P=0.024).

A strength of the study was analysis by ITT, which reduces potential bias and reflects actual clinical practice. With that in mind, patients who received neoadjuvant CRT had significantly higher median DFS (8.1 *vs.* 7.7 months; P=0.032) and LFFI (not reached *vs.* 13.4 months; P=0.0034). While the median DMFI was higher (17.4 *vs.* 12.5 months), the difference was not statistically significant.

Several study limitations should be recognized. First, the trial was likely underpowered to detect an OS difference because the actual median OS in the immediate surgery arm was 3 months longer than assumed in the study design. Second, there was a substantial dropout rate in the neoadjuvant arm (24%) due to various causes including metastatic disease found at laparoscopy and disease progression prior to CRT. Third, although baseline CA19-9 is an important prognostic biomarker for PDAC the study protocol did not include CA19-9 within the exclusion criteria. The median CA19-9 was 111 U/mL in the neoadjuvant arm (range: 26–603) although was more than twice as high in the upfront surgery arm at 257 U/mL (range: 83–727).

Although neoadjuvant therapy has been a standard of care for borderline resectable PDAC, we are in the midst of what is potentially a paradigm shift from adjuvant to neoadjuvant therapy for resectable PDAC. The PREOPANC trial provides additional evidence that neoadjuvant therapy should be strongly considered although several important questions have yet to be answered including the optimal chemotherapy regimen given that regimens such as mFOLFIRINOX are now preferred over gemcitabine monotherapy. The ideal RT dose fractionation approach needs to be better understood especially given that the moderately hypofractionated RT dose fractionation schedule used in the PREOPANC trial is uncommon whereas standard CRT and stereotactic body radiation (SBRT) are more routinely used in the clinic and have been evaluated in other clinical trials.

It is clear that there has been rapidly growing interest for neoadjuvant therapy for resectable PDAC based on a growing signal from the existing literature. This signal is strengthened with the publication of the PREOPANC trial results. The enthusiasm to further evaluate neoadjuvant treatment strategies is evident with over 10 ongoing or planned randomized trials and additional non-randomized studies that we expect will soon provide additional guidance about how modern chemotherapy and RT should be applied. We strongly encourage enrollment to such trials and are encouraged that progress is being made in the quest to further improve long-term outcomes for PDAC patients.

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Footnote

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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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