Value of Neoadjuvant Radiation Therapy in the Management of Pancreatic Adenocarcinoma

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Introduction

Support for the role of neoadjuvant therapy in the management of nonmetastatic pancreatic adenocarcinoma is growing. With the high risk of rapid dissemination of disease, neoadjuvant therapy allows for the immediate delivery of systemic therapy to address micrometastatic disease present in most patients with localized pancreatic cancer at the time of diagnosis. This strategy will increase the number of patients who receive systemic therapy, since only approximately 50% of patients are able to receive a full course of chemotherapy after surgery.[1-4] Moreover, 2-4 months of neoadjuvant therapy provides a window to identify those patients who will develop early distant metastases. This selects patients with more favorable disease courses who may benefit from surgery, thus sparing patients with unfavorable tumor biology from undergoing a large surgical intervention. Such treatment sequencing is important and likely improves the overall survival (OS) of the entire population of affected patients.[5-8] However, the optimal neoadjuvant regimen has not been established.

The use of radiation therapy (RT) as a component of neoadjuvant therapy has been evaluated in several recent studies with conflicting results.[5,9] These studies have used various RT doses and modalities, making the existing data difficult to interpret across studies. Given the lack of definitive data and potential concerns about quality assurance when using newer RT modalities in patients with pancreatic cancer, the jury is still out as to the role of RT in the preoperative treatment of borderline resectable pancreatic cancer. In this commentary, we contend that there is strong rationale for continuing to study and refine the role of neoadjuvant RT for patients with pancreatic cancer, a disease where improvements in OS have been modest over the past four decades.

Surgery First Approach

Up-front surgical resection for resectable pancreatic cancer remains a standard that has been debated for over a decade. When patients undergo surgery first, the rate of positive margins range from 30% to 50% and local recurrence events range from 20% to 50%.[10] These event rates are five times higher than other types of adenocarcinoma treated with up-front surgical resection.[11,12] Although improving OS outcomes have been reported for patients who have successfully completed up-front surgical resection and adjuvant chemotherapy,[13] these OS data are at least partially driven by intense biological selection. Specifically, these outcomes are enriched by the inclusion of patients who withstood the challenges associated with surgical resection, recovery, postoperative restaging, and enrollment into a clinical trial. This timing of enrollment selects for patients without early disease progression on postoperative imaging. Biological selection, driven by surgery first (in sharp contrast to systemic therapy first), is not a strategy to meaningfully improve the OS of *all* patients with localized pancreatic cancer.

It is clear that the survival outcomes reported in adjuvant trials that enroll after postoperative restaging are not seen in patients who are enrolled and randomly assigned before surgical resection. As clear testament to this, the recently published SWOG 1505 trial (which enrolled patients with resectable disease before surgery) observed a median OS of 23.2 months using modified folinic acid, fluorouracil, irinotecan, and oxaliplatin (mFOLFIRINOX) perioperatively, whereas the PRODIGE-24-ACCORD trial, enrolling patients after surgery and recovery (again using mFOLFIRINOX adjuvantly), demonstrated a median OS of 54 months.[1,13] Does this mean that the best patient outcomes are achieved with a surgery first approach followed by adjuvant chemotherapy? No, to the contrary, a surgery first and adjuvant chemotherapeutic approach leaves meaningful numbers of patients excluded from the benefits of multimodality therapy. Patients who do not recover adequately from surgery, are incompletely resected, or develop early disease recurrence are never eligible for protocol enrollment. In other words, those patients with the worst outcomes are excluded from enrollment to such trials. For this reason, these results cannot be compared with outcomes in trials

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that enrolled patients before surgery or immediately after diagnosis. Optimal methods to evaluate the efficacy of novel therapies in patients diagnosed with pancreatic adenocarcinoma are most likely to be found by enrolling patients at the time of diagnosis/staging and examining patient outcomes with an intention-to-treat analysis.

Neoadjuvant Therapy

There have been several recent prospective trials that have examined neoadjuvant therapy as compared with surgery first. It is becoming more apparent that neoadjuvant therapy for patients with localized pancreatic cancer improves OS when compared with surgery first.[5-8] Although neoadjuvant therapy has shown considerable promise, the optimal regimen remains unclear. This lack of clarity is secondary to a paucity of randomized neoadjuvant trials. Whether chemotherapy alone or combinations of systemic chemotherapy and RT should be used, along with optimal dose, fractionation, and sequencing of these modalities remains unknown. It needs to be recognized that there is a near complete absence of well-powered, randomized trials that have met their initial accrual goals, robustly evaluating the utility (or absence of utility) for RT. The absence of such data limits conclusions that can be drawn comparing therapeutic interventions, leaving physicians to rely on single-institution and retrospective reports of different neoadjuvant regimens.

There have been numerous prospective, nonrandomized, phase II trials that have examined different types of neoadjuvant therapy for pancreatic adenocarcinoma.[14-17] It is important to recognize that nearly all these trials have included some type of concurrent chemotherapy and fractionated RT (CRT). Several have been conducted at single centers, which limits their generalizability as the supportive care provided to patients with pancreatic cancer greatly affects the successful receipt of all intended therapy.[18] A few multicenter, prospective studies have examined the role of neoadjuvant therapy (including CRT) compared with up-front surgery. As an example, Jang et al reported the results of a multicenter phase II/III trial evaluating neoadjuvant CRT followed by surgery or up-front surgery followed by the same CRT regimen. This randomized study was terminated early by the safety-monitoring committee after 58 patients were enrolled demonstrating a median OS in the neoadjuvant CRT arm of 21 months versus 12 months in the up-front surgery arm ($P = .028$). The R0 resection rate was also significantly improved with neoadjuvant CRT (51.8% *v* 26.1%; $P = .004$).[8] A second example is the recent PREOPANC randomized trial that compared neoadjuvant CRT, with concurrent gemcitabine and 36 Gy in 15 fractions followed by surgery, with up-front surgery followed by adjuvant gemcitabine. This study did not show an OS benefit in the intent-to-treat analysis in the initial manuscript publication,[19] but a more recent updated abstract demonstrated an OS improvement in the neoadjuvant arm.[5] The neoadjuvant CRT arm was associated with an improved R0 resection rate (71% *v* 40%; $P < .001$), a lower rate of node positivity (78% *v* 33%; $P < .001$), and an improved disease-free survival (8.1 *v* 7.7 months; $P = .03$).[19] Of note, when the preplanned subgroup of 120 patients who underwent successful surgery was analyzed, there indeed was a significant improvement in median OS with neoadjuvant CRT (35.2 *v* 19.8 months; $P = .029$). Although the full manuscript on these updated data is anticipated, it seems clear that neoadjuvant chemotherapy and RT improved OS.[5] What is not clear is if chemotherapy alone would have accomplished these same results. Exemplifying this uncertainty is the recently published SWOG1505 study of neoadjuvant chemotherapy alone (FOLFIRINOX *v* gemcitabine/nab-paclitaxel perioperatively), without RT, demonstrating a median OS of approximately 23.5 months in patients with resectable disease. There were no differences in response between FOLFIRINOX and gemcitabine/nab-paclitaxel. These modest OS outcomes in resectable disease suggest that chemotherapy alone may not be adequate for these patients.[1] Another recently reported neoadjuvant study was ESPAC-5F. This was a four-arm, multicenter phase II trial evaluating different methods of neoadjuvant therapy for patients with borderline resectable pancreatic cancer. Ninety patients were randomly assigned to receive immediate surgery or neoadjuvant therapy consisting of either two cycles of gemcitabine/capecitabine or four cycles of FOLFIRINOX or 50.4-Gy capecitabine-based CRT in 28 fractions.[7] The 1-year OS rate was 40% for immediate surgery and 77% for neoadjuvant therapy ($P < .001$). There was minimal power to cross compare groups on this study given the small numbers.[7] Taken together, these studies suggest that neoadjuvant therapy likely improves OS in patients with localized, operable pancreatic cancer; however, the optimal method of delivery remains unknown. With this magnitude of data including CRT, this would certainly suggest that RT is worthy of further investigation. Despite this, multiple neoadjuvant phase III trials have moved forward omitting RT entirely in pancreatic cancer (NCT03941093, NCT04340141, and NCT04617821), and National Comprehensive Cancer Network guidelines lack consensus as to the role of RT, reporting it as a consideration or as plus/minus.[20]

Neoadjuvant Stereotactic Body Radiation Therapy

There have been no prospective trials in pancreatic cancer directly comparing different RT strategies such as CRT or stereotactic body radiation therapy (SBRT). There have been multiple single-institution retrospective and prospective studies evaluating neoadjuvant SBRT for borderline and locally advanced pancreatic cancer (LAPC) demonstrating excellent R0 resection rates and promising OS.[21,22,24] These retrospective single-institutional reports are limited by selection bias, yet none of these series yielded a detriment to R0 resection associated with SBRT. Sharply conflicting with these results is the recent Alliance

randomized trial, A021501, that introduced SBRT to a multi-institutional National Clinical Trials Network (NCTN) study group. Unfortunately, this strategy was associated with low rates of pancreatectomy (35%) and treatment completion (18%).[9] Importantly, the use of SBRT deviated from the initial predicate of the Alliance A021101 feasibility study, which delivered historic and time-tested fractionated CRT. This approach had resulted in 68% of patients going on to surgical resection, of whom 93% (who went to surgery) had an R0 resection.[25] The reason for the critical differences in RT administration across these trials was multifactorial. This was partly based on the absence of benefit of low-dose fractionated RT and chemotherapy on the LAP-07 trial,[26] expert consensus from the committee designing the trial, and early data indicating favorable results with neoadjuvant SBRT. However, widely integrating FOLFIRINOX, SBRT, and surgery at multiple centers with limited experience using this approach was likely premature. Moreover, the original A021101 study was performed in a limited number of high-volume pancreatic cancer centers without an adaptive design; patients received 2 months of chemotherapy followed by CRT. Such high-volume centers had extensive multidisciplinary experience with neoadjuvant therapy in pancreatic cancer. It is also notable that other publications of neoadjuvant SBRT, in single-institution settings, yielded much higher R0 resection rates and better survival outcomes.[21,22,24] One such example is from the University of Colorado that demonstrated that among 103 patients with locally advanced (n = 18) or borderline resectable disease (n = 85) who received neoadjuvant chemotherapy followed by SBRT, 73 underwent definitive surgery and the R0 resection rate was 69% (97% in those who underwent surgery).[22] There are potential concerns about the appropriate volume for pancreas SBRT; specifically, smaller volumes are associated with the potential for marginal misses that could contribute to local recurrences, at either the celiac trunk or near the take-off of the superior mesenteric artery.[23,27] The A021501 trial illustrates the challenges of introducing an adaptive trial design and delivering SBRT followed by complicated surgeries across the NCTN. It appears that the introduction of SBRT may have been prematurely applied in this setting. Lower resection rates may also be in part because of the lack of experience with major pancreatic surgery after SBRT. Therefore, such a result should not be interpreted as closing the door on the potential benefits of RT, such as fractionated CRT, or magnetic resonance-guided adaptive SBRT, given after induction chemotherapy in the neoadjuvant setting. We simply do not understand the best type of neoadjuvant therapy. The only method to generate such understanding is additional, well-powered clinical trials.

The wide spectrum of RT modalities and delivery methods present a challenge when implementing such a treatment across a network of hospitals such as that in the NCTN. Compliance with RT treatment plans has been shown to potentially affect OS, specifically as it relates to the use of RT in pancreatic cancer trials, although this point is controversial.[28,29] If centers are less familiar with a specific RT approach, any complications in the neoadjuvant course can derail the treatment plan and negatively affect the ultimate goal of a grossly complete surgical resection. As more advanced RT modalities emerge, quality control remains of the utmost importance across the trajectory of care.[29]

Future Directions

The role of RT in the neoadjuvant setting has not been fully vetted. Current studies do not provide definitive answers as to how this modality should be applied to patients with borderline resectable pancreatic cancer. Excluding a potentially highly effective modality, in the absence of well-powered randomized data, is not a strategy to improve outcomes for patients with pancreatic cancer. Well-designed prospective studies that include adequate real-time quality assurance for the RT, have standards for defining resectability, and are powered to evaluate meaningful outcomes across therapy strategies are needed. The anticipated PREOPANC-II study (NTR7292) is comparing neoadjuvant FOLFIRINOX with neoadjuvant gemcitabine-based CRT for patients with borderline resectable pancreatic cancer; however, this study does not evaluate the addition of CRT after FOLFIRINOX and is still unlikely to fully clarify the true role of RT. There are other ongoing trials that will help in this regard. One such example is the MASTERPLAN study (NCT04089150), which is evaluating the addition of SBRT to FOLFIRINOX chemotherapy in operable, borderline resectable, and LAPC. This trial mandates central SBRT plan storage with real-time QA, in addition to central radiology review, and is likely to offer some further insight into the role of SBRT in patients with potentially operable and LAPC. A second example is the SOFT study (NCT03704662), which randomly assigns patients to either SBRT or fractionated CRT-based therapy (50.4-Gy in 28 fractions with concurrent gemcitabine) after neoadjuvant chemotherapy and before surgical resection. Without appropriate study designs, ideally randomized, we are not able to move beyond the fundamental question of the role of RT. We also cannot evaluate additional novel questions such as how to incorporate more sophisticated technologic advances and combinations of RT and novel concurrent agents. The methods for delivering RT and achieving tumor ablation while reducing the risk of toxicity are rapidly evolving.[30] One example is real-time magnetic resonance guidance, which offers an unparalleled ability to visualize normal organs in close proximity to a tumor. Novel methods of radiosensitization and radioprotectors are also continuing to emerge, and RT may be important as an immunomodulator, something that could potentially dramatically transform the treatment of pancreatic cancer.[31-33] We are only beginning to understand the incredible capabilities of RT and we simply cannot allow it to be absent

from routine consideration and robust prospective evaluation.[34]

In conclusion, prospective trials comparing different neoadjuvant management strategies are needed in pancreatic adenocarcinoma. Novel RT strategies should be refined and robustly evaluated prospectively to potentially improve outcomes in this devastating malignancy. Moreover, these studies will help to better define which patients are most likely to benefit from the incorporation of RT and which type of RT is most appropriate in different clinical scenarios. On the basis of existing prospective data, CRT should routinely be considered in the neoadjuvant management of pancreatic adenocarcinoma. Importantly, any local therapy (surgery or RT) will benefit only the subset of patients who successfully navigate the gauntlet of early systemic failure; this subset will continue to increase as systemic therapies improve. Therefore, rational and well-conducted studies, in which meaningful numbers of patients complete therapy, are critical to adequately evaluate the role of RT in the management of localized pancreatic adenocarcinoma. Going forward, a robust neoadjuvant study would ideally compare preoperative chemotherapy alone versus preoperative chemotherapy followed by CRT or hypofractionated RT/SBRT and incorporate clear criteria for resectability, assessment of intraoperative margins, and central review of all postoperative imaging for accurate assessment of patterns of recurrence. Pretreatment credentialing of sites and real-time QA for all RT planning is essential for the results of such a trial. We must continue to partner together in a multidisciplinary setting, focus on forming a better foundation of randomized data on which to draw reliable conclusions, and develop the ideal armamentarium to optimally treat patients with this challenging disease.

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