

Impact of neoadjuvant therapy on the surgical management of pancreatic cancer: a literature review

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Abstract: Survival after surgery for pancreatic cancer remains poor despite the use of multimodality treatment. Neoadjuvant strategies for patients with resectable, borderline resectable and locally-advanced disease are gaining acceptance and may improve outcomes. In this review we will summarize some of the studies supporting the use of neoadjuvant treatment and focus on the perioperative/operational aspects of executing a neoadjuvant treatment program. Currently, while neoadjuvant treatment is supported for borderline resectable and locally advanced patients, the evidence is equivocal on its use in the resectable setting. There appears also to be relatively little guidance from studies so far in assessing resectability after neoadjuvant treatment. Other issues that are not fully resolved include the timing of surgery, the use of vascular reconstruction, and assessing response to neoadjuvant treatment. Neoadjuvant treatment strategies appear to be feasible and relatively safe in terms of surgical morbidity and mortality. Response to treatment appears to be prognostic, but we lack reliable predictors of response to treatment prior to initiation. Our final discussion proposes areas of research that will aid surgeons and multidisciplinary teams in applying neoadjuvant strategies to pancreatic cancer.

Keywords: Combined modality therapy; neoadjuvant therapy; pancreatectomy; pancreatic neoplasms; pancreaticoduodenectomy

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Introduction

Pancreatic adenocarcinoma represents the fourth most common cause of cancer-related death in the United States (1). Survival, however, remains low and there is now an increasing fraction of cancer mortality within the past five years due to pancreatic cancer (1). Neoadjuvant therapies have been developed with the intent to improve upon this significant mortality over the past two decades.

Through mostly phase I and II trials at high-volume academic institutions, different combinations of neoadjuvant therapies have been studied. The initial efforts focused on the potential to downstage locally-advanced or unresectable

tumors to resectable, given the significant survival benefit seen historically with resection. Although survival benefit has been demonstrated in this setting, neoadjuvant therapy in initially resectable cancer has not yielded a clear survival benefit. The development of neoadjuvant therapies has led to a more standardized staging terminology necessary in assigning patients to appropriate neoadjuvant or upfront treatment regimens. Similarly, improved multidisciplinary care models have been developed as a result of neoadjuvant therapy regimens which has resulted in a more consistent completion of existing treatment protocols.

Nevertheless, with slow progress in survival there remains significant debate on the efficacy of neoadjuvant

treatment, and whether it is worth pursuing, at both the individual and the population level. In comparison to upfront surgery for all pancreatic cancers, a cost-analysis of neoadjuvant therapy was shown to reduce overall treatment-related costs (2). Furthermore, despite the perceived physiological challenge imposed by neoadjuvant therapies, the use of neoadjuvant therapy in elderly patients may improve overall treatment adherence and both disease-specific and overall survivals (3). Here we briefly review the evidence regarding the efficacy of neoadjuvant chemotherapy, radiation and chemoradiation. We will focus on perioperative issues surrounding neoadjuvant therapy for pancreatic cancer, including its impact on the performance of pancreatic resections and their complications. Finally, we conclude with a discussion of issues as yet unresolved and potential future directions.

Summary of evidence for neoadjuvant therapy

One of the earliest feasibility studies of a neoadjuvant approach to pancreatic cancer was reported by Evans *et al.* (4). On twenty eight patients with pathologic evidence for pancreatic cancer. The patients were given 50.4 Gy of radiation with 5-fluorouracil (5-FU) as a radiosensitizer, and all 28 completed this phase of treatment. Of these, 17 underwent resection successfully, while the remaining 11 either demonstrated progressive disease on restaging prior to surgery or were found to be unresectable at the time of operation. This was taken as a demonstration that a neoadjuvant approach could avoid surgery in patients with aggressive disease. Critics interpreted the approach as one that simply introduces a delay in care that allows progression of disease. There was no survival data or trials that could support either position at the time. Early data on survival with neoadjuvant therapy for resectable pancreatic cancer were reported by the Eastern Cooperative Oncology Group (ECOG) that consisted of mitomycin- and 5-FU-based chemoradiation (5). This small trial reported results of 53 patients, of whom 24 were resected with mixed results. These initial results were not convincing in terms of benefit to a neoadjuvant approach as only 24 of the 53 underwent resection with a median survival of 15.7 months. More importantly, the median survival for the group was 9.7 months, suggesting that, at least by an intent to treat analysis, the neoadjuvant approach was of questionable value.

The University of Texas MD Anderson Cancer Center has conducted a number of trials that may support neoadjuvant therapy in pancreatic cancer. In 2009, Katz

et al. published a retrospective analysis of 329 patients who underwent surgical resection for pancreatic ductal adenocarcinoma from 1990 to 2002, and reported a 27% 5-year overall survival (6). The majority (77%) of these patients were treated with some form of neoadjuvant therapy, and most of these patients were treated with chemoradiation. Some of these patients were also treated preoperatively with systemic chemotherapy, but few were treated with systemic therapy alone. Eighteen percent of the cohort received adjuvant treatment. Only 8% of patients were treated with surgery alone. When compared to other contemporary series, the median survival of 23.9 months and 27% 5-year survival appear to be a significant improvement and support the argument that multidisciplinary treatment of pancreatic cancer had potential to improve survival. In 2012, Estrella *et al.* provided an updated summary of the institutional experience from 1999-2007, but only for those patients undergoing pancreaticoduodenectomy, and reported 33.5 months survival for patients treated with neoadjuvant therapy versus 26.5 months for patients treated with a surgery first approach (7).

One important critique that has been raised about the MD Anderson experience is that the analyses do not include an intent-to-treat analysis that incorporates patients who started neoadjuvant therapy, but were then not resected. When the MD Anderson group first reported the results of smaller trials using various regimens, the resection rate varied from 57-74%, indicating a significant dropout rate. Furthermore, there were significant differences in the protocols in terms of time from diagnosis to preoperative restaging that also coincides with the replacement of 5-fluorouracil or capecitabine with gemcitabine, both as radiosensitizer and as systemic therapy (one trial). The “summary studies”, therefore, encompass a highly variable, non-randomized patient population. From an institutional point of view, the study periods also represent a time in which the technical aspects of surgery at the institution were in evolution, most markedly in the growing experience with vascular resection. It could be argued that this surgical ability was necessary if patients who had undergone neoadjuvant radiation were to be resected. Finally, it was also a period in which the optimal timing and sequencing of treatments were still being worked out, and therefore treatment schedules were somewhat variable among patients treated under different protocols.

Gillen *et al.* presented an excellent meta-analysis of neoadjuvant therapy for pancreatic cancer. They reviewed 111 trials in which 4,394 patients were treated. As noted

in the analysis, none of the studies were phase III trials (8). As these trials predated the results of the PRODIGE 4/ACCORD 11 study, none used FOLFIRINOX as the chemotherapeutic regimen (9). A complete response was only observed in 3.9% of patients, while 29.1% had a partial response, 43.9% had stable disease, and 20.8% had progression. The meta-analysis estimates of survival show a median overall survival of 22.4 months (9-62 months) for patients who underwent resection, and 9.5 months (6-21 months) for those patients who were not resected. Among patients felt to be resectable prior to the initiation of treatment, median survival was 23.3 months (12-54 months) for the resected patients and 8.4 months (6-14 months) for those who did not undergo resection. For those felt to be locally advanced prior to treatment, patient who ultimately could be resected had a median survival of 20.5 months (9-62 months), while non-resected patients had a median survival of 10.2 months (6-21 months). Overall, only about half of patients underwent resection, but this reflects that many of the studies were designed for locally advanced patients. The authors include an analysis variance that also shows that “institution” was a factor that also accounted for a significant fraction of the variability, in a relative way, to outcome measures such as resection rate, exploration rate, pathologic response, toxicity, morbidity and mortality.

Some studies are now reporting results in small trials on the use of FOLFIRINOX as a neoadjuvant regimen. As with other regimens, FOLFIRINOX seems to be capable of “conversion” to resectability. Petrelli *et al.* (2015) analyzed 13 studies including 253 patients in a meta-analysis that included both borderline resectable and locally advanced patients, reporting an R0 resection rate of 63.5% for borderline and 22.5% for locally advanced patients (10). It remains to be seen whether FOLFIRINOX will make a difference in terms of overall survival. Ferrone *et al.* issued a retrospective report on 47 patients who were treated with neoadjuvant FOLFIRINOX. Seven remained unresectable, but the regimen appeared to be well-tolerated with a median of 8 cycles (11). Twenty-four of the patients also received 5-FU based chemoradiation. Intraoperative radiation therapy was administered as a boost to 12 patients undergoing resection. Six patients were treated with proton beam therapy and capecitabine. Despite this variability, the R0 resection rate was 92%. The authors reported increased operative time and blood loss, but a lower complication rate. Most significantly, neoadjuvant therapy with FOLFIRINOX appears to be associated with an improved median survival when compared to a contemporary group

of patients resected for pancreatic cancer who received no neoadjuvant therapy, with a median survival of 34 months. Other studies suggest an effect on overall survival as well. Blazer *et al.* reported on FOLFIRINOX use in 43 patients with locally advanced and borderline resectable disease, and found a median overall survival for the group of 21.2 months, resected patients not having reached median after 13 months of follow-up and non-resected patients surviving a median of 12.7 months (12). Likewise, Khushman *et al.* reported the use of FOLFIRINOX in 51 patients with locally advanced disease (13). The median overall survival was 35.4 months for the whole group; only 10 patients had successful R0 resections. Potentially, FOLFIRINOX may therefore be the preferred option for locally advanced and borderline resectable patients at an intent-to-treat level. Trials are ongoing using a variety of regimens as neoadjuvant treatment in the locally advanced and borderline setting, but relatively few neoadjuvant trials are available for patients in the resectable category.

Neoadjuvant therapy impact on surgical management

Assessment of resectability

After completion of neoadjuvant therapies, the multidisciplinary team decision for recommending surgical exploration and possible resection is determined predominately on clinical status. Clinical factors involved in the decision-making process for suitability for surgical resection are medical co-morbidities precluding general anesthesia such as decompensated cardiac disease, poor functional status (ECOG greater than 2), and patient desire for surgery. Of the clinical factors evaluated in patients undergoing neoadjuvant therapy, both quality of life and weight loss have been shown to impact survival. In a retrospective study by Naumann *et al.* of patients undergoing neoadjuvant chemoradiation there was a greater likelihood for non-resectable disease at exploration for patients with a greater than 7.5% weight loss during neoadjuvant therapy, whereas body-mass index was not shown to correlate with resectability (14). While this demonstrates an association of weight loss to the resectability of disease, there was no correlation to survival or morbidity and cannot therefore be used to contraindicate potential curative resection in patients. Quality of life measures have similarly been correlated to decreased overall survival without an association to resectability status. In a

prospective study of patients undergoing a phase II trial of neoadjuvant chemoradiation, Serrano *et al.* showed no correlation with neoadjuvant therapies or surgical resection and eventual overall functioning, emotional functioning, or physical well-being scales despite an initial decrease in physical functioning during the neoadjuvant period (15). The only correlation to survival shown in this study was the association of baseline global health scales with overall survival rather than any interval decrease associated with either neoadjuvant or resection.

Assessment of resectability following neoadjuvant therapies has unfortunately not proven reliable utilizing traditional radiologic studies. Multidimensional computed tomography (MDCT) with dedicated pancreatic protocol remains the primary modality recommended for radiographically evaluating pancreatic tumors for resectability status (16-18). While the pretreatment evaluation of resectability status for pancreatic tumors is reliable, the use of MDCT following neoadjuvant therapy has failed to demonstrate reliable findings to determine resectability status or predict a pathologic response (19). In a matched cohort of patients with resectable, borderline resectable, and unresectable tumors undergoing either upfront surgery or neoadjuvant therapy Cassinotto *et al.* demonstrated MDCT was capable of determining resectability in only 58% of patients compared to 83% of upfront surgery patients (20). The group identified that the reliability of MDCT in evaluation of pathologic tumor size was 39% following neoadjuvant therapy with a mean error of +10 mm compared to initial CT with a reliability of 78% and a mean error of -2 mm. A review of the MDA group experience with neoadjuvant chemotherapy, chemoradiation, or combined chemotherapy and chemoradiation showed that re-staging MDCT response according to RECIST criteria is neither predictive of overall survival nor surgical resectability in their cohort (19). Further, they showed that in these patients undergoing neoadjuvant therapy radiologically stable disease occurs in 69% of which 83% were able to undergo resection with an overall 80% incidence of R0 resection.

Furthermore, MDCT has been shown to fail to demonstrate any response in the vascular involvement of pancreatic tumors following neoadjuvant therapies (21,22). In an evaluation of borderline and unresectable patients undergoing a neoadjuvant chemoradiation, Dudeja *et al.* showed a 0% response rate of vascular involvement on MDCT although there was a R0 resection achieved in each patient (22). Similar findings were found by the MDA group in a retrospective review of cases with less than 1%

change in vascular involvement following neoadjuvant chemotherapy, chemoradiation, or combined chemotherapy and chemoradiation (19). In a detailed assessment of MDCT changes to vascular involvement following neoadjuvant combined chemotherapy and chemoradiation, Cassinotto *et al.* demonstrated decreased contact of the SMV-PV or SMA as the only radiologic factors correlated to R0 status (21). This group failed, however, to demonstrate a correlation of the SMV-PV luminal obstruction or stenosis with R1 status, suggesting that limited fixation of vascular structures without radiographic tumor progression should not prevent surgical exploration. Tran Cao *et al.* performed a pathologic correlation of MDCT determined tumor-vein interface and showed that radiographic involvement can predict need for vascular reconstruction if there is any involvement (sensitivity of 91.8%) and that involvement beyond 180° is a more specific finding predicting this need for vascular resection (specificity 97.4%) (23). The authors were able to show a lower median overall survival and progression-free survival in patients with a tumor-vein interface beyond 180° (30.9 *vs.* 37.3 months and 15.9 *vs.* 18.2 months respectively), however they did not determine if this difference remained significant when accounting for pathologic invasion. Other radiologic findings which have been studied and failed to demonstrate an ability to predict resectability, resection status, or survival are tumor density changes (based on Hounsfield units) and tumor short and long-axis dimensions (21,22).

Similar to computed tomography (CT), positron emission tomography (PET) has failed to show benefit in the assessment of patients following neoadjuvant therapies. Specifically, in a study of patients with resectable disease, Heinrich *et al.* were able to demonstrate an elevated uptake of approximately 85% of primary tumors prior to any therapy with a mean standardized uptake value (SUV) of 4.4 (24). Of the patients with an elevated uptake, those with a lower SUV before treatment (3.5 *vs.* 6.6) and after treatment (2.9 *vs.* 4.4) had a greater likelihood for any histologic response to neoadjuvant chemotherapy on final pathology. However, the study showed CT/PET was unable to predict the presence or absence of metastatic or regional nodal metastases. Furthermore, the authors showed that CT/PET in the setting of pancreatic cancer was associated with a high rate of false positive findings in the liver and regional lymph nodes that did not correlate to pathologic tumoural involvement after resection. Despite the need for a modality to predict regional nodal disease and distant metastases, CT/PET has yet to demonstrate an ability to

aid in the evaluation either before or after neoadjuvant therapy.

In addition to utilizing imaging modalities, the use of serum CA 19-9 as a marker for response to neoadjuvant therapies has received significant research attention. Several large retrospective and some prospective series have failed to demonstrate any reliable correlation of serum CA 19-9 as a predictive tool for assessing candidacy for resection. In one of the largest studies, a retrospective evaluation from the MDA group showed that serum CA 19-9 elevation and response were unrelated to either the histologic treatment effect or histologic grade on final pathology (25). Furthermore, the group showed that in those patients with a decrease in CA 19-9 following neoadjuvant chemoradiation there was an improved survival (25.7 months compared 10.4 months); however there was no difference among patients who underwent resection with decreased, stable or increased CA 19-9 after chemoradiation. Similarly, a retrospective study by Tzeng *et al.* showed that although normalization of CA 19-9 following neoadjuvant therapy was associated with an improved overall survival (37.9 *vs.* 26.0 months in resected patients; 15.0 *vs.* 11.0 months in unresectable patients), which remained significant on multivariate analysis, the CA 19-9 before and after neoadjuvant therapy was not predictive of resectability alone (26). Although serum CA 19-9 has not shown a reliable predictor of pathology or spread, those patient with a significant pathologic response have been demonstrated to have a significant responses in CA 19-9. In a retrospective analysis of patients with an initial elevated CA 19-9, Boone *et al.* demonstrated that patients with at least 90% tumor destruction were more likely to have a greater than 50% reduction in CA 19-9 values (27).

Surgical decision-making

As demonstrated, there are limited evidence-based recommendations which can be made for determining which patients are not likely to benefit from potential resection after neoadjuvant therapy. In the absence of either distant metastases or inadequate physiologic function to undergo surgery, all patients after neoadjuvant therapy should be offered surgical exploration and potential resection with the existing limitations of staging modalities. Further, there exists no studies to date that identify the period of time needed following neoadjuvant chemotherapy, chemoradiation, or the combined chemotherapy and chemoradiation protocols to minimize operative morbidity.

A majority of prospective trials and retrospective series utilize a “Recovery Phase” ranging between 2-8 weeks. Extrapolation of retrospective studies from rectal and esophageal cancer patients undergoing neoadjuvant chemoradiation has shown that a delay of surgery after completing neoadjuvant therapy may improve pathologic complete response and 30-day readmission rate (28,29). However, no study to date has demonstrated any survival benefit from increased delay to surgery and no impact on peri-operative morbidity or mortality. Further studies on the outcomes of delayed surgery after neoadjuvant therapy in pancreatic cancer patients is necessary before any recommendation can be made.

Following neoadjuvant therapies there are a number of changes which alter the traditional surgical planning for pancreatic adenocarcinoma. Firstly, as a number of patients undergoing neoadjuvant therapy have been diagnosed with borderline or unresectable disease prior to neoadjuvant therapy the operative plan is more likely to involve the use of staging laparoscopy and biopsy to exclude abdominal metastases which may or may not have been visualized on pre-neoadjuvant imaging (16). Additionally, although there remains limited support for minimally-invasive pancreatectomy techniques, the post-treatment fibrosis and need for vascular control makes these techniques less likely to be able to be utilized following neoadjuvant therapy.

One of the major considerations in pancreatectomy for pancreatic cancer is the need for vascular resection and reconstruction. Due to inherent limitations in evaluating intra-operative margins along vascular planes for the degree of vascular involvement if any following post-neoadjuvant fibrosis, many surgeons elect to proceed with empiric vascular resection if the setting of uncertain vascular involvement. The post-treatment fibrosis and inability to distinguish fibrosis from tumoural extension along vascular planes has been shown to lead to a significant increases in the use of vascular resection following neoadjuvant therapy (30). In those patients with borderline or unresectable disease undergoing surgical resection multiple authors have demonstrated the likelihood of vascular resection can increase from 1.4-2.8 that of upfront surgery (30-32). However, in patients with initially resectable disease undergoing neoadjuvant therapy, Papalezova *et al.* showed there was no difference in the rate of vascular resection compared to those undergoing upfront surgery (18% *vs.* 22%) (33).

In those patients who are deemed to require a vascular resection and reconstruction following neoadjuvant therapies, there is demonstrated benefit to performing

the resection despite the elevated morbidity associated with these procedures. In a retrospective evaluation of the MDA results, Wang *et al.* showed that among all patients undergoing vascular resection after neoadjuvant therapy that the performance of a vascular resection did not alone impact overall survival or disease-free survival (34). In this analysis the authors demonstrated that tumor invasion alone was associated with a hazard ratio of 1.97, whereas the performance of a vascular resection was not significant among either those with or without venous involvement. Also, the analysis showed that the type of venous reconstruction was not associated with overall survival or disease-free survival among either those with or without vein involvement. With regard to potential risk for future locoregional recurrence, Takahashi *et al.* performed an analysis of patients in a Phase II trial undergoing neoadjuvant chemoradiation and showed there was no impact on the pattern of disease recurrence as either local, regional, or distant among patients which recur if a venous reconstruction was required (35). In concordance with these findings which have similarly been seen in other retrospective studies has led to the recommendation for venous resection and reconstruction when necessary to achieve an R0 outcome (17).

Unlike venous reconstruction, arterial resection and reconstruction has been met with significant challenges and may not commonly be performed. Nonetheless, the UPMC group and Stitzenberg and colleagues have retrospectively demonstrated potential survival benefits for patients undergoing neoadjuvant therapy and arterial resection in highly selected patients (36,37). In the Stitzenberg report, the presence of an arterial resection led to no significant difference in medial survival compared to a matched cohort not requiring arterial resection (37). The role for arterial resection following neoadjuvant therapy however remains of uncertain benefit given the overall lack of clear evidence for its efficacy (18).

With respect to the extent of regional lymphadenectomy performed as part of the pancreatectomy, there are no studies which evaluate the impact of an extended lymphadenectomy versus a standard regional lymph node dissection in the context of current chemotherapy regimens. Prior studies evaluating the impact of extended lymphadenectomy during pancreatectomy failed to demonstrate survival benefit and was associated with significant operative morbidity. These historical findings, despite occurring predominately before modern neoadjuvant therapies, have led to the current recommendation against

extended lymphadenectomy regardless of undergoing upfront surgery or following neoadjuvant therapy (17).

Operative outcomes and peri-operative complications

Although historical results for surgical resection of pancreatic adenocarcinoma were associated with a high rate of peri-operative morbidity and mortality, the significant experience gained in the past several decades has markedly decreased the anticipated morbidity and mortality following pancreaticoduodenectomy and distal pancreatectomy with splenectomy (38,39). Major operative challenges such as intra-operative hemorrhage and prolonged operative durations as well as peri-operative morbidity remain important issues in performing pancreatectomy. Multiple studies have demonstrated the marked reduction in peri-operative morbidity and mortality as well as healthcare costs when pancreatectomy is performed by high-volumes pancreatic surgeons at high-volume centers (40,41).

The impact of neoadjuvant therapies on vascularization and fibrosis in the surgical field during pancreatectomy is challenging to quantify. Variables such as intra-operative blood loss and operative duration serve as indirect markers for the anatomic changes seen after neoadjuvant therapy, although some confounding can come from peritumoral desmoplastic reactions and concurrent vascular resections performed in these patients. Among all patients undergoing neoadjuvant therapy, the operative blood loss has been shown to be higher than in those undergoing upfront surgery (31,32,42). As expected, the performance of a vascular reconstruction has been shown to lead to significantly elevated blood loss (mean EBL of 2.2 *vs.* 0.9 L) (32). Wang *et al.* showed however that among patients undergoing a venous resection that tumor involvement of the vein was associated with a higher blood loss than those undergoing a venous resection without involvement (mean EBL 1.3 *vs.* 0.8 L) (34). The impact of an elevated intra-operative blood loss has been shown to correlate with both overall survival as well as progression-free survival by the MDA group, suggesting a role of blood loss as an indirect marker for regional tumor factors not yet elucidated (43).

Operative duration in contrast to blood loss is a more direct marker for the number of procedures required during an operation and the relative difficulty in performing a surgical resection. Across all patients undergoing surgical resection, the mean operative duration has been shown to be significantly longer following neoadjuvant therapy based on studies from the Columbia

University group (31,32). Although this finding in each of the studies the operative duration was significantly longer in the neoadjuvant groups, these groups also were known to have a higher rate of vascular reconstruction which alone has shown to account for a significantly longer operative duration (540 *vs.* 405 minutes) (32). In contrast, retrospective studies from Araujo *et al.* and Barugola *et al.* failed to demonstrate a difference in the operative duration for patients undergoing pancreatectomy following neoadjuvant therapy (44,45). In a study of patients undergoing pancreatectomy after neoadjuvant radiation therapy from the American College of Surgeons NSQIP database, Cho *et al.* identified the use of radiation therapy in neoadjuvant settings to account for a prolonged operative duration (423 *vs.* 368 minutes) (30). An important finding of this study was that in multivariate analysis, operative duration beyond eight hours was correlated to a 1.31 higher odds of developing a Clavien grade IV or higher complication (30,46). Unlike operative blood loss, no study has demonstrated an impact on either progression-free or overall survival on operative duration suggesting the technical difficulty involved in the resection is not a reliable marker for tumor biology or treatment effect (31,32,44,45).

As mentioned, the increased experience with surgical resection techniques has led to improved tolerance of pancreatectomy and remains advocated even among elderly patients due to the relative safety and significant improvement in overall survival (3,17). Nonetheless, resection techniques are associated with peri-operative complications of which the most common are delayed gastric emptying, pancreatic fistula, and hemorrhage (38). There are conflicting results on the impact of overall morbidity following neoadjuvant therapies. In a retrospective analysis of resectable patients undergoing neoadjuvant chemoradiation, Papalezova *et al.* showed no significant difference in peri-operative morbidity or mortality compared to upfront surgery patients (33). For borderline and unresectable patients, three separate retrospective studies by Epelboym, Arauja, Barugola failed to show any significant difference in overall morbidity and mortality following neoadjuvant therapy (32,44,45). In contrast however, Allendorf *et al.* showed retrospectively a 43% higher rate of post-operative hemorrhage, portal vein thrombosis, abdominal abscess, sepsis, gastric outlet obstruction, anastomotic leak, renal insufficiency, respiratory insufficiency, and need for reoperation following neoadjuvant chemoradiation compared to upfront surgery (31). The difference in this study however could be due to the markedly higher rate of vascular resection (76% *vs.* 20%) seen in

the neoadjuvant group which was not controlled for in the analysis of complications.

Of the complications associated with pancreatectomy, the development of a pancreatic fistula is the most studied complication with respect to the impact of neoadjuvant therapy. In a study of distal pancreatic cancers, Takahashi *et al.* demonstrated that patients with UICC T3 tumors of the body and tail who underwent neoadjuvant chemoradiation followed by distal pancreatectomy and splenectomy were less likely to develop a pancreatic fistula than those who underwent upfront surgery (14% *vs.* 67%) (47). Moreover, in this study the authors showed that those undergoing neoadjuvant therapy were less likely to develop a clinically significant pancreatic fistula requiring any intervention (11% *vs.* 37%). The authors attributed the decreased rate of pancreatic fistula to a higher rate of pancreatic fibrosis and atrophy based upon their grading scale. Similar results have been shown by the MDA group with respect to the impact of neoadjuvant therapies on pancreatic fibrosis and atrophy (48). In the retrospective pathologic review utilizing a unique grading scale, the group showed that neoadjuvant therapy led to moderate fibrosis and pancreatic atrophy in 68.3% and severe fibrosis and atrophy in 27.1% of resected patients compared to 27.7% and 9.2% of upfront surgery patients. The MDA group however did not assess the impact of the degree of fibrosis and atrophy with respect to peri-operative complications. In a matched analysis of patients undergoing pancreaticoduodenectomy following neoadjuvant chemoradiation, Cheng *et al.* showed the pancreatic fistula rate was lower as well following neoadjuvant therapy compared to upfront surgery (4.8% *vs.* 24.1%) (49). The study also showed that a pancreatic fistula was not correlated with pancreaticojejunostomy technique following neoadjuvant therapy, although the use of a duct to mucosa technique had a lower fistula rate compared to the invagination technique in upfront surgery patients (30.3% *vs.* 55.8%) (49).

Histopathology following neoadjuvant therapy

Neoadjuvant therapies have been shown to lead to significant changes in the primary tumor. In resectable patients, Papalezova *et al.* demonstrated that neoadjuvant chemoradiation produced a significant decrease in the primary tumor diameter (2.5 *vs.* 3.5 cm) compared to upfront surgery (33). For borderline and unresectable patients by radiographic imaging undergoing neoadjuvant therapy, retrospective studies by Estrella, Epelboym,

Araujo, Barugola, and Kang showed similar results of tumor downsizing (7,32,44,45,50). However, all studies to date have demonstrated no impact on overall survival or progression free survival difference associated with tumor diameter following neoadjuvant therapy. In contrast, the ability to perform an R0 resection has been correlated to improved overall and progression free survival following neoadjuvant therapy compared to an R1 in upfront surgery (7,51).

The evaluation of primary tumor viability has clinical significance following resection. Of the scales for evaluating response, the most widely utilized has been the Evans criteria developed by the MDA group (4,52). In an analysis of the MDA borderline and unresectable patients undergoing neoadjuvant therapy, the authors demonstrated that specimens with less than 5% residual tumor cells or a complete response was associated with a lower likelihood of local and distant recurrence (55% vs. 73%), improved disease free survival (36.8 vs. 48.2 months), and overall survival (55.8 vs. 79.2 months) (52). Similar results have been demonstrated with respect to overall and progression-free survival benefits by White *et al.* (53). The overall impact of a complete pathologic response however has yet to be clearly defined. In a study of 11 patients with a pathologic complete response, Zhao *et al.* did show a significantly longer median overall survival compared to patients with post-neoadjuvant residual tumor either T1 or T2, although they were not able to reach the median survival for the complete response group in their study (54).

Other potential histopathologic variables which have been studied following neoadjuvant therapy include the neural and perineural invasion and lymphovascular invasion. Among borderline and unresectable patients undergoing neoadjuvant therapy and subsequent resection, the MDA group demonstrated that any perineural or neural invasion was correlated to recurrence or distant metastases (78.1% vs. 60.7%) (55). Among these patients with perineural and neural invasion, the group showed that the presence of intra-neural invasion correlated the strongest with likelihood for recurrence or metastases (94.3%), while other factors such as intra or extra-pancreatic with perineural invasion were less significant findings with respect to perineural invasion. The group was able to demonstrate that the presence of perineural or neural invasion as a significant negative prognostic factor with respect to disease free survival and overall survival, with the presence of intraneural invasion again yielding significantly worse disease free and overall survival (55). A similar study by Takahashi *et al.* showed that perineural invasion was

predictive on multivariate analysis of abdominal recurrence (HR 2.48) (35).

Similarly, the presence of lymphovascular invasion is a negative prognostic factor following neoadjuvant therapies. In a retrospective review of pathology slides from borderline and unresectable patients, the MDA group separated the presence of muscular lymphovascular invasion from non-muscular lymphovascular invasion. They demonstrated that muscular lymphovascular invasion compared to non-muscular was a stronger predictor of the development of local or distant recurrence (90.6% vs. 67.2%) and positive intra-operative margins (7.5% vs. 20.3%) (56). Their study however failed to demonstrate a difference in overall survival or disease free survival between muscular and non-muscular sub-types (24.0 vs. 39.5 months and 9.0 vs. 12.8 months respectively). In the similar study by Takahashi *et al.*, they also failed to demonstrate any impact of lymphovascular invasion on either disease free survival or recurrence pattern (35).

Future of neoadjuvant therapy and surgical management

Neoadjuvant strategies are now a part of a majority of academic and community-based pancreatic cancer programs. Use of neoadjuvant protocols have significant evidence supporting the general utilization strategies used by the multidisciplinary care teams at these centers (57). Nonetheless, there remain a number of questions which must be addressed through existing and future research to better understand the optimal implementation of neoadjuvant therapy into the management of pancreatic cancers.

As mentioned earlier, the optimal neoadjuvant regimen remains uncertain for the resectable, borderline, and unresectable patient. The decision for a specific regimen and the concomitant use of radiation remains to be clearly delineated by level I evidence in the neoadjuvant setting. Moreover, the role of neoadjuvant therapy in the setting of resectable disease is more uncertain than that of borderline and unresectable disease. There are two trials currently underway in Europe which will attempt to provide prospective randomized evidence on neoadjuvant therapy in this setting, with no U.S. trials unfortunately at this time (58,59). Ultimately, evidence supporting neoadjuvant therapies in this setting may need to await the development of effective targeted or immunotherapies. At this time however, there has yet to be any strong supporting evidence for these targeted therapies in the treatment of pancreatic

cancers unlike that of other disease sites (13,60-65).

With respect to surgical decision-making after neoadjuvant therapies there are several issues which must be addressed in the future. First, there is little reliable data that correlate with pathologic response. Specifically, markers/factors predictive of overall survival, resectability, and histopathologic response to therapies would greatly aid in patient management. Currently, radiologic evaluation and CA 19-9 assessment appear to be reliable only in the few patients who show dramatic changes, but not in the majority of patients in whom radiographic changes may be subtle and the marker levels less convincing. Second, it is not clear if the choice of regimen can be specifically tailored to the patient's circumstance effectively. For example, if neoadjuvant treatment is to be used in resectable patients, there is no clear evidence that they should be treated under a different regimen than borderline patients, yet there remains considerable variability on this point. Finally, the basis for further adjuvant therapy, and what form that should take, is also unclear when patients have received neoadjuvant treatment. The challenge in this setting is the need for prospective randomized trials which can elucidate the true subset of patients who benefit from neoadjuvant therapies.

A final consideration in the surgical management of pancreatic cancer with neoadjuvant therapies is the role of other interventions as adjuncts to neoadjuvant therapy. Specifically, electroporation is an emerging technology which may aid in the treatment of unresectable or locally advanced tumors (66). Although a single early study from Martin *et al.* showed possible prolonged local and distant progression free survival and overall survival, results from a Phase II trial are still pending completion. Other ablative techniques utilizing high-intensity ultrasound, radiofrequency, or microwave technology have also been reported on and may demonstrate benefit with further experience and development (67). Overall, the addition of these surgical techniques to this subset of patients is an important area of study which may create a greater role for surgical therapies in this generally non-surgical population of patients.

Conclusions

Neoadjuvant strategies for pancreatic cancer are expanding options for patients and may provide benefit in terms of survival and the overall efficacy of multidisciplinary care. Challenges remain due to lack of data and the need for better systemic and locoregional treatment options. Nevertheless, implementation of an effective neoadjuvant

program is clearly a necessity for pancreatic cancer programs, and requires understanding of areas of both consensus and uncertainty surrounding it. Further research should focus on developing the clinical tools that will clarify decision points in the algorithms for the treatment of pancreatic cancer that specifically inform neoadjuvant therapy.

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