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Review

Neoadjuvant Chemoradiation for Resectable and Borderline Pancreatic Cancer

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Introduction

Pancreatic adenocarcinoma (PC) is arguably the most fatal of malignancies. Given the 37,000 cases diagnosed annually in the United States, it represents 2% of all cancer cases but 6% of all cancer deaths. It represents the fourth leading cause of cancer death, behind lung, colorectal, and breast cancer, despite the fact that each of these cancers has at least fourfold the incidence of PC.[1]

Two thirds of patients present with locally advanced or metastatic disease at presentation. For those patients who undergo surgery, 5-year survival ranges from 15%-20%.[2] Cure is rare, including in patients with resected cancer in whom disease recurs in 80% of patients within 2 years of diagnosis.

Improved pre-operative imaging, combined with neoadjuvant therapy, holds many potential advantages over traditional surgical approaches towards pancreatic cancer. Improvements in computerized tomography (CT) optimized for pancreas imaging and the use of EUS allow for more accurate staging. This, in turn leads to better prediction of positive margins and the presence of lymphadenopathy. We present evidence that positive margins at surgery result in worsened survival. The neoadjuvant approach also allows for earlier treatment of microscopic metastatic disease, which would otherwise remain unchecked until recovery from surgery. Furthermore, chemotherapy and radiation may be more effective in the setting of an uninterrupted vasculature. Finally, delaying surgery helps select those patients whose tumor biology is less aggressive, possibly resulting in better survival in those patients going to the operating room.

Predicting Vascular Involvement and Positive Margins

Positive surgical margins occur frequently even with procedures performed in high volume centers. Table1 lists a number of recent studies that demonstrate this incidence.

Table 1 - Incidence of positive surgical margin in pancreatic cancer

Institution	Ref	Year	Pts	Pos. Margin (%)
Millikan	3	1999	75	29
Sohn	4	2000	616	30
Benassai	5	2000	75	20
Neoptolomous	6	2001	541	19
Richter	7	2003	194	37
Takai	8	2003	94	68
Kuhlmann	9	2004	160	50
Smeenk	10	2007	218	21
Regine	11	2008	451	37

Recent improvements in CT technology have made staging of pancreatic cancer more accurate. Modern CT scanners utilize a multiphase, multi-detector technique to acquire thin image slices; at MDACC, we utilize a liver protocol that obtains fine cuts through the liver and pancreas. Indeed, the most recent NCCN guidelines[12] reflect the fact that staging may now be

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accomplished by CT, rather than through operative means.

A recent review compared surgical outcomes of 76 patients with the results of pre-operative CT imaging obtained by utilizing 3mm cuts through the pancreas.[13] CT findings for vascular involvement were associated with surgical outcome. No patient with mesenteric venous involvement greater than 180 degrees had a successful R0 resection, with four being locally advanced and three with R1 margin. As a predictive test, CT offered 50% sensitivity, 100% specificity, 100% PPV, 67% NPV, and 75% accuracy for this outcome. Likewise, CT venous involvement of greater than 90 degrees tended to predict for a R1 resection (p=0.09). Arterial involvement greater than 90 degrees was significantly associated with no patient achieving an R0 resection. CT scanning for such involvement was only 28% sensitive but highly specific (100%) for predicting an R1 resection. Biliary stents did not affect CT results, and the presence of lymphadenopathy did not correlate with R0 resection rates. A separate report by Valls and others[14] assessed 76 patients with CT scan prior to attempted resection. Of these, 55 underwent surgery and 39 were found to have a pancreatic cancer that was resected. The sensitivity of CT in showing portal or SMV invasion was 75%. Unfortunately, these authors do not distinguish between R0, R1, and R2 resections in their report.

One recent study by Zamboni and others[15] and others also undertook an assessment of the efficacy of preoperative vessel staging by using surgery as a "gold standard". These included the use of four-, eight-, 16-, and 64-row scanners, and included collimation ranging from 1.25mm to 0.5mm. These authors graded tumors into those considered resectable (with a fat plane or normal pancreas between tumor and vessel), questionable (with flattening and/or slight irregularity of one side of the vessel), or definitely unresectable (encased vessel with tumor extending around at least two sides, or with a major occluded vessel). Of 114 patients assessed, 88 had tumors that were considered resectable. Of these, 78 patients (89%) were ultimately resected; the remaining ten were found to be unresectable at the time of surgery. These authors also did not report rates of positive margins. Of note, the type of machine used was of lesser importance: seven (13% of 55) resections were aborted in the patients evaluated with four or eight row scanners, while three (9% of 33) were aborted among patients evaluated with 16 or 64 row scanners.

Endoscopic ultrasound also helps in the staging of pancreatic cancer. In the review by Bao[13], neither the findings of portal vein or SMV abutment or invasion was associated with a failure to obtain a R0 resection. However, EUS may be more accurate in the absence of a biliary stent. In these patients, visualization of venous involvement was significantly associated with incomplete resection, demonstrating a sensitivity of 79% and a specificity of 69%. EUS findings of arterial involvement were less accurate, however. The combination of CT involvement of 90 degrees and EUS findings of abutment or invasion resulted in a 73% accuracy rate for predicting the need for vein resection.

An analysis of these two modalities in 101 patients was also undertaken by Yovino and others.[16] As seen in the previous studies abutment of vessels, seen either on CT or EUS, was associated with a risk of unresectability on univariate analysis. These authors found CT to be rather insensitive (18%) for the presence of lymphadenopathy – as did Valls' group (16%).[14] Unlike Bao's study, these authors did find a correlation of lymphadenopathy with unresectability, though not due to pathological nodal involvement itself. Rather, the authors proposed that advanced (and more likely unresectable) tumors might cause either low grade cholangitis or pancreatitis, which in turn might cause lymphadenopathy.[14] Increasing visibility of lymph nodes and venous abutment via CT and EUS correlated with increasing unresectability.

An M.D. Anderson study compared CT with EUS (with or without FNA) for diagnosing pancreatic cancer. This retrospective review of 117 patients found no significant difference in overall accuracy between these modalities, though EUS was slightly more sensitive (99% vs. 93%).[17]

Thus, modern preoperative imaging can predict unresectability and margin positive surgery. The use of CT and EUS together allow both for a tissue diagnosis as well as optimal imaging. CT may predict for margin status, but, as pointed out in Bao's study, the combination allows better prediction of a need for venous resection. Patients with positive margins have a much worse survival than those patients with negative margins, and thus, such patients may not be benefiting from surgery in the first place.

Effect of Positive Margin on Survival in Pancreatic Cancer Patients

A number of studies suggest that the presence of a positive margin confers a worsened survival. A single-institution review[4] from Johns' Hopkins retrospectively

examined the survival of 616 patients who had undergone resection of a pancreatic tumor mass. These were mostly (85%) Whipple procedures. Of these, 30% had a positive margin. These patients had a significantly worse survival than those patients with negative margins, exhibiting a hazard ratio of 0.64 (p=0.0004). In this series, patients with negative resection margins had a 1 year survival of 69%, as compared with 49% among patients with positive margins. Likewise, patients with negative margins had a five year survival of 22%, as compared to 6% among patients with positive margins.

More evidence of improved five year survival with curative surgery is provided by Takada,[18] who examined survival of pancreatic cancer patients with or without chemotherapy. Those patients who underwent a R0 surgery had an improved five-year survival of roughly 20% vs. 3% among those patients undergoing surgery with positive margins or remaining lymph nodes.

Median survival is longer among patients whose surgeries result in negative margins. In the Hopkins' study, the difference was 20 months vs. 16 months. In the ESPAC-1 study, patients undergoing R0 resections had a median survival of 17 months, as compared to patients with R1 resections whose median survival was 11 months.[6] This was a large multicenter study where patients were stratified by margin status and randomized to either chemoradiation, chemotherapy, both, or none. Of note, in this study, larger tumor size was associated with worse survival in patients undergoing an R0 resection though it had no effect in R1 resections. Further, chemotherapy was more useful in patients who had undergone an R0 resection. In these patients, survival improved from 15 months to 20 months, while in those patients who had undergone an R1 resection, survival increased only from 10 to 11 months.

Other studies have shown a similar pattern (see Figures 1 and 2). Takai and others[8] demonstrated that patients with stage I-III cancers capable of undergoing R0 (or near R0) resection had a greater median survival (23 months) than those patients with stage IVa or IVb disease (8 months, p=0.0002). Benassai[5] and others found the resection margin to be the strongest predictor of decreased survival. Millikan and others[3] likewise found that the median survival of patients undergoing R0 resection was greater than those undergoing R1 resections–17 vs. 8 months (p=0.01).

While these individual studies suggest an improved overall survival amongst patients who have undergone R0 resections, it should be noted that a recent meta-analysis from the ESPAC[19] group did not. These authors noted a non-significant trend towards improved survival after the R0 resection - 16 vs. 14 months. Again, in this analysis, patients who underwent an R0 resection had a greater benefit from chemotherapy with a 7 month vs. 2 month increase in median survival. Resection margin status was an independent prognostic factor only when tumor grade and lymph node involvement were absent from the model. These authors postulated that the R1 tumors might represent a more aggressive disease type, rather than representing only surgical technique. However, the major criticism of this analysis is that the results do not correlate with what would be expected biologically: specifically, a higher 5-year survival rate in R1 patients not receiving chemotherapy (17%) than in R0 patients who did receive chemotherapy (10%)

Thus, despite the meta-analysis, the preponderance of the evidence does suggest that an R0 resection contributes to an improved survival. The logical next questions, then, address whether there is a subset of patients who might be made more likely to undergo an R0 resection, and whether doing so would improve survival.

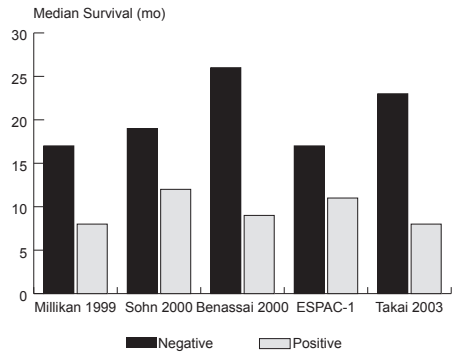

Figure 1 - A comparison of survival in pancreatic cancer patients with negative or positive margins

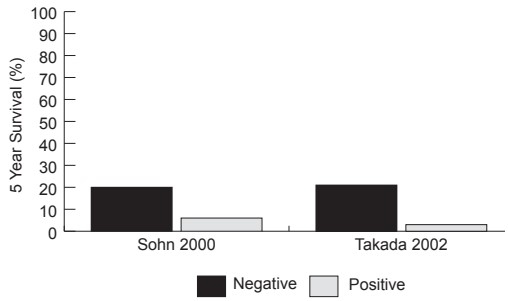

Figure 2 - Differences in 5-year survival in pancreatic cancer patients with negative or positive margins

Definition of Resectable and Borderline Resectable Disease

Resectable pancreatic adenocarcinoma is defined as presence of a normal tissue plane between tumor and adjacent arterial structures with a patent SMV-PV confluence (stage I/II). Locally advanced unresectable pancreatic adenocarcinoma is defined as tumor encasement (defined as > 180°) of adjacent arteries or obstructed SMV-PV confluence with no option of resection or reconstruction (stage III).

Early literature describing "borderline resectable" disease represents a somewhat amorphous category including both resectable and unresectable disease. In our institution, we currently address this concern by objectively defining respectability based on CT-based staging of tumors of the pancreatic head, neck and proximal body.[20] This technique is consistent with the AJCC classification method and is acknowledged in NCCN guidelines.[12] Borderline resectable patients are defined as having short segment hepatic artery involvement, without extension to the celiac axis, which is amenable to resection or reconstruction. The CHA is often redundant and amenable to resection or reconstruction. Likewise, tumors demonstrating <180 degree abutment of the circumference of the SMA and short-segment occlusion of the SMV, PV, or SMPV confluence with a suitable option for vascular reconstruction are also included in this definition. The involvement of the transverse mesocolon is not included in the definition, because even though it is technically challenging, it bears no impact on resectability or positive margin rates.

Our multidisciplinary approach has identified two subsets of patients who escape precise categorization into specific staging of disease: patients with undefined stage of disease or uncertain metastatic disease, and patients whose performance status or medical comorbidities result in insufficient performance status for pancreaticoduodenectomy. Including these patients under the borderline resectable category allows for precise staging for all patients who present with newly diagnosed pancreatic cancer and grouping patients resectable or operable based on the clinical criteria.

Preoperative Therapy Reduces Positive Margin Resection Rates and Improves Survival

Pre-operative chemoradiation shows promise in reducing positive margin resection rates when compared with patients who have had no preoperative intervention. Pinkpank and others[21] looked at the effect of preoperative chemoradiotherapy on patients undergoing pancreaticoduodenectomy. The researchers asked if the presence of multiple positive margins had an impact on survival compared to single positive margins. Patients with clearly identified resectable tumors confirmed by a CT scan received postoperative adjuvant therapy, either gemcitabine or 5-FU based. Patients of questionable resectability, SMA or SMV invasion, lesions that were larger in size, or those deemed unresectable at time of preoperative exploration were given neoadjuvant therapy of a full dosage of gemcitabine and radiation therapy or mitomycin C and 5-FU or preoperative gemcitabine/ radiation therapy.

These authors looked at a series of 100 such patients and compared the 53 patients who had preoperative chemoradiation with the 47 patients who had post-operative treatment. Patients were treated with either 5-fluorouracil or gemcitabine. Tumors were slightly larger in the group receiving pre-operative treatment (4.0 vs. 2.5cm), though other demographic factors were not statistically different.

The group undergoing neoadjuvant chemoradiation had a lower multiple margin positive rate (8% vs. 48%) and higher R0 rate (51% vs. 26%, p=0.01). The margin-negative patients had longer disease free (p=0.01) and overall survival (p=0.02) than margin positive patients. There was a trend towards improved survival in the neoadjuvantly treated group (p=0.07). Patients with borderline resectable tumors and patients who were deemed inoperable at time of previous diagnostic exploration showed a decrease in positive resection margins. This finding demonstrates the significant clinical impact that preoperative chemoradiation can have. The critique of this study it was not randomized and the number of patients treated pre-operatively who were not able to go to surgery were not reported, though the authors estimate this number at 25%.

Also examined was the effect of a single positive margin on survival. In spite of the amount of chemoradiation received, the presence of tumor at the SMV margin was the only site that indicated a decreased survival. The investigators found an increase in survival in margin-negative patients. There was a strong trend toward improved disease-free and overall survival is seen in patients with a single positive margin versus multiple positive margins. When the investigators stratified the data for individual margin status, survival was decreased in patients with positive superior mesenteric artery and

vein margins. This finding has not resulted in significant increase in disease-free or overall survival for patients receiving preoperative therapy.

A similar project was done at Mount Sinai hospital in New York.[22] Patients with pancreatic adenocarcinomas were assigned treatment to either surgical resection if feasible, or radiation with 5-fluorouracil, streptozocin, and cisplatin if unresectable. The group undergoing neoadjuvant treatment had larger tumors – all (100%) were T3 in size, as compared to only 30% of the resected group. The RT group had slightly more lymph nodes present (51% vs. 45%). Despite more advanced disease, the patients treated with neoadjuvant therapy had a longer median survival than patients undergoing initial surgery (23.6 vs 14 months, p=0.006). Of the 68 patients assigned to chemoradiation, 20 were ultimately able to undergo surgery. While on its surface this study does argue for neoadjuvant chemotherapy, it must be remembered that this is an older study where CT staging was likely less accurate. This makes interpretation of such studies difficult. The 20 patients who later underwent surgery may have been resectable or borderline had they been imaged with modern equipment and staged by current criteria.

A more recent examination of pancreatic cancer patients being treated with neoadjuvant chemotherapy and radiation comes from Columbia University.[23] This was a retrospective review of patients treated from 2000 to 2006, where 78 of 245 patients underwent chemotherapy and chemoradiation for initially unresectable disease. Reasons included invasion of the SMV or portal vein (43%), short segment venous occlusion or arterial abutment of the tumor <180 degrees (16%), and venous occlusion without technical options for reconstruction (41%). The GTX regimen[24] was used as chemotherapy; 50.4Gy was given in 180cGy fractions. The other 167 patients underwent initial attempts at surgery with 139 such patients successfully resected. These authors found that median survival for patients who received neoadjuvant therapy (503 days) was longer than those patients who initially attempted surgery (430 days). Even among successfully resected patients (those whose attempts at surgery were not abandoned), survival was longer among those patients undergoing neoadjuvant therapy (533 vs. 498 days). Margins were more frequently negative in the neoadjuvant group (15% vs. 27%), and particularly so for patients requiring vascular resection (25% vs. 58%). Positive lymph nodes were also less frequent in the neoadjuvant group (42% vs. 74%). Of note, however, complications were more frequent in the neoadjuvant therapy group (44% vs. 31%) and surgical mortality was higher (10.2% vs. 2.9%).

Taken together, these studies, though retrospective, provide some evidence that patients treated with neoadjuvant chemotherapy and radiation seem to have fewer positive margins and improved survival compared to patients whose tumors are smaller and are more likely to be considered for initial resection. However, critiques of these studies include a large variability in staging and under-appreciation of the differences in degrees of aggressiveness of individual pancreatic cancers. It may be argued that the benefit of neoadjuvant therapy may, in actuality, simply select patients who have less aggressive disease. Thus, while these studies generate hypotheses, their interpretation requires a degree of caution.

MD Anderson Cancer Center Experience: Neoadjuvant Therapy

Katz and others[25] recently analyzed patients with borderline resectable pancreatic cancer treated with neoadjuvant therapy at the M.D. Anderson Cancer Center. These were patients who had arterial or venous involvement as described above, but also included were patients for whom extrapancreatic metastases were of concern or patients with a poor performance status. As patients were treated generally off protocol, there was variation in both initial chemotherapy (5-FU, paclitaxel, gemcitabine, or capecitabine), and radiation schema (30Gy or 50.4Gy). In total, 160 such patients began treatment. Of these, 125 completed neoadjuvant therapy and underwent restaging; of these, 66 (41%) ultimately underwent a successful pancreatic resection. Only 6% of patients had an R1 resection, with a median of 3 positive lymph nodes. Median survival of this group was 40 months, with a 5-year survival of 36%. This figure is among the best of reported outcomes for pancreatic cancer resection.

If borderline tumors are best approached with neoadjuvant therapy, what, then, of tumors that fall under the 'resectable' category? U.T. MD Anderson Cancer Center has conducted sequential phase II trials of preoperative chemoradiation, without[30] or with[31] or with initial systemic chemotherapy, followed by pancreaticoduodenectomy (PD) for patients with stage I/II pancreatic adenocarcinoma. In one study, patients were treated with gemcitabine and cisplatin initially, followed by 30 gray of radiation using gemcitabine as

a radiosensitizer. Patients underwent re-staging 4-6 weeks after completion of chemoradiation, and went to surgery if still resectable. In the other study, the initial gemcitabine and cisplatin was omitted, and patients were treated with chemoradiation and weekly gemcitabine.

With induction chemotherapy, 79 of 90 patients (88%) completed chemotherapy and chemoradiation. Resection was ultimately performed in 52 (66%). With preoperative RT alone, 64 of 86 patients (74%) underwent a successful PD. Median survival for the resected groups was 31 and 34 months, respectively, while survival for the unresectable patients was 10.5 and 7 months, respectively. SMA margins were positive in only 2% and 6%, respectively. Median survival for the two study populations as a whole was 17.4 and 22.7 months, respectively. Five year survival from the Evans study (no gem/cis) was 36%.

Taken as a whole, these two trials suggest that the neoadjuvant strategy yields low rates of R1 resections and survival durations that compare favorably with previously published studies reviewed in this paper. It is intriguing that the survival outcomes in resectable patients were similar, but not superior to, the borderline patients as reviewed by Katz.[25] It leaves open the question of whether the neoadjuvant strategy is equally effective in both resectable and borderline settings.

Conclusions

Pancreatic cancer remains among the most lethal of malignancies. Even patients with early stage disease have a high chance of recurrence and death. Proper staging of disease – with modern CT equipment and EUS - is absolutely critical for determining t he resectability and need for vascular reconstruction in potential surgical candidates. We have demonstrated in this review that positive margins at surgery correspond with increased risk of death from the disease. Retrospective studies that selected patients for neoadjuvant therapy – due to more advanced tumors – suggest lower rates of positive margins and longer survival than patients treated with surgery prior to chemotherapy or radiation. Such studies must be interpreted with caution, however, as these improvements may reflect better biology rather than better treatment.

While there are no randomized studies to prove the point, the data we present here argue that the preoperative treatment approach leads to some of the best survival rates documented in the literature. Many questions do remain, such as the relative importance of chemotherapy and chemoradiation. The "best" chemotherapy regimen remains yet to be defined, though it appears that doublet (e.g. gemcitabine/cisplatin) and triplet chemotherapy regimens (GTX) work well in this regard. The role of and the optimal dose of radiation has yet to be defined as well. Nevertheless, taken as a whole, the strategy of neoadjuvant treatment does warrant further investigation.

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