Management of Localized Pancreas Adenocarcinoma

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Summary

The term localized disease as it applies to pancreas adenocarcinoma encompasses distinct entities with varied prognosis and therapeutic recommendations. These include three disease categories (1) disease that is localized and resectable, (2) localized disease that is borderline resectable, and (3) unequivocally unresectable pancreas cancer, all representing a continuum. The incorporation of systemic chemotherapy into the management of pancreas cancer at all stages has become standard of care, and the basis for this is discussed with reference to the major clinical trial landmarks. The role of radiation therapy (in association with concomitant chemotherapy) in the management of localized pancreas cancer has however become less clear and represents an area of management confusion in this disease. Going forward, with the future hope and expectation of new and improved systemic agents, loco-regional tumor control and hence, chemoradiotherapy, is anticipated to have a greater role and impact.

Introduction

Pancreas adenocarcinomas is a very challenging malignancy. About 38,000 people were anticipated to be diagnosed in 2008 in the United States and over 200,000 worldwide[1]. In the US the expected mortality this past year was approximately 33,000. Many factors contribute to these statistics – insidious clinical presentation and late symptom manifestation, lack of screening and early detection and limited effectiveness of the best currently available therapies. Surgical removal of locally-confined disease is the only realistic curative option. Even in that circumstance however, the relapse rate is high such that surgical resection followed by adjuvant chemotherapy is viewed by many as delaying rather than eliminating disease recurrence. Similarly, for patients with localized disease which is unresectable and unequivocally T4, treatment is essentially palliative in intent.

In discussing the management of localized pancreas cancer – with regard to both standard therapies and areas of controversy – it is important to delineate various categories which are distinct both with regard to prognosis and therapeutic approach. The most important distinction to be made is between resectable and unresectable localized disease. For localized disease that is resectable, the focus will be one key question: (1) What is the benefit of adjuvant therapy. For localized disease that is unresectable, there is a distinction to be made between borderline unresectable disease and disease that is unequivocally inoperable. For discussion of these categories, the focus will be on two questions: (1) What is the role of (chemo)radiation therapy?, (2) What is the optimal systemic therapy or combination of systemic drugs?

Localized Resectable Pancreas Adenocarcinoma

In the case of pancreas cancer, the precedent for adjuvant chemotherapy has been established relatively recently although the historical precedent for adjvuant chemoradiotherapy and chemotherapy dates back to the Gastrointestinal Tumor Study Group (GITSG) trial[2]. Older small randomized studies of adjuvant systemic therapy (without chemoradiation) using a variety of 5-FU-based regimens did not show a significant survival benefit compared to observation[3-5]. In 2004, Neoptolemos et al. published the updated report of the ESPAC-1 trial in the New England Journal of Medicine evaluating the role of adjuvant therapy in pancreas cancer[6]. The complex study design allowed the investigators to isolate and compare the relative benefits of chemotherapy and chemoradiation. The median survival was 20.1 months (95% CI, 16.5 to 22.7 months) for those who received chemotherapy and 15.5 months (95% CI, 13.0 to 17.7 months) for those who did not receive chemotherapy (hazard ratio for death, 0.71). Two-year and five-year survival estimates were 40 percent and 21 percent, respectively, among patients who received chemotherapy compared to 30 percent and 8 percent, respectively, among patients who received no chemotherapy. The investigators concluded that 5-FU-based chemotherapy offered a survival advantage and that chemoradiation offered no such benefit and may in fact be detrimental to outcome.

Given that gemcitabine has modestly more efficacy in metastatic disease than 5-FU, the rationale was strong to consider it's use in the adjuvant setting. The RTOG 9704 trial compared gemcitabine and 5-flourouracil in a 451 patient U.S. study[7]. The chemotherapy was given for one month prior to, and 3 months following chemoradiation. There was a benefit to gemcitabine but only for patients with tumors in the head of the pancreas. For patients with pancreatic head tumors the median survival was 20.5 months and a 3-year survival of 31% in the gemcitabine group vs 16.9 months and 22% in the fluorouracil group (HR, 0.82 [95% CI, 0.65-1.03]; P = .09). This reached statistical significance when a multivariate analysis was performed evaluating pre-planned stratified variables. These included nodal status, which was found to strongly affect survival (P = .001)

and the effect of gemcitabine which yielded a HR of 0.80 (95% CI, 0.63-1.00; P = .05) toward improved survival.

Perhaps the best data with regard to adjuvant gemcitabine is derived from the CONKO-001 study, published in 2007 and recently updated[8, 9]. The design of the CONKO-001 trial was somewhat purer than the RTOG study as none of the patients received chemoradiation. It was a direct comparison of chemotherapy versus observation following resection. The trial met it's primary endpoint with disease free survival being 13.4 months in the gemcitabine arm and 6.9 months in the observation arm, $p < 0.001$. Estimated disease-free survival at 3 and 5 years was 23.5% and 16.0% in the gemcitabine group vs. 8.5% and 6.5% in the observation group, respectively. Gemcitabine significantly improved median overall survival (22.8 months versus 20.2 months, p=0.005). Estimated survival at 3 and 5 years was 36.5% and 21.0% for the gemcitabine-treated group compared to 19.5% and 9% for the observation group.

To summarize, we now have level 1 evidence supporting gemcitabine's use in the adjuvant setting for resected pancreas adenocarcinoma. Ongoing and planned adjuvant phase III adjvuant studies in europe will address the benefit of the addition of erlotinib to gemcitabine (CONKO-006 and RTOG 0848) and capecitabine to gemcitabine (ESPAC-4). The role of chemoradiation in the adjuvant treatment of pancreas cancer has diminished both in the context of stronger evidence for systemic therapy alone and also a fuller understanding of the biologic behavior of this disease. The expectation however is that when systemic therapy improves in this disease, loco-regional tumor control will gain in relative importance.

Locally Advanced Unresectable Pancreatic Adenocarcinoma (LAPC)

For a pancreatic tumor to be clearly resectable, the following three criteria need to be satisfied[10]: no evidence of distant metastases, a clear fat plane around the celiac and superior mesenteric arteries (SMA) and patency of the superior mesenteric and portal veins (SMV-PV). Patients with unresectable disease have encasement of celiac or SMA, defined as involvement of > 180°, or occlusion of the SMV-PV confluence. In recent years a subset of patients have been defined as having disease that is borderline resectable, for whom surgical resection may yet be a possibility in their management. Given that there is little to be gained from attempting surgery when the chances of obtaining negative margins are not high, there is a strong rationale for a neoadjuvant approach to this setting.

The MD Anderson group recently reported their experience of neoadjuvant therapy in eighty-four patients who were borderline-resectable based on their own anatomic criteria (in addition to another seventy-six patients who they deemed borderline resectable on the basis of performance status and suspicion of metastatic disease)[11]. Thirty-two (38%) of the patients who were borderline resectable on anatomic criteria were able to undergo a (partial) pancreatectomy following neoadjuvant therapy, the vast majority of whom (97%) had clear margins. Similar to other reports relating to this specific entity[12, 13], this was not a prospective study, and in the absence of a control group it is impossible to know whether these patients did better or worse following the addition of neoadjuvant therapy. In addition, there was a heterogeneity in the neoadjuvant therapy used, although all these patients did receive chemoradiation. Clearly prospective randomized studies would of course be ideal but it is unlikely that the benefit of neoadjuvant therapy could be purely quantified, as there would be ethical concerns about having a 'straight-to-surgery' control group in a situation where the chances of obtaining negative margins are not high.

For disease that is clearly unresectable according to the criteria mentioned above, the role of surgery with curative intent is minimal except for the anecdotal patient. Likewise the role of radiation has grown increasingly controversial in this setting, as in the adjuvant setting, largely due to a fuller appreciation of the biology of pancreas cancer and the demonstration of benefit of systemic therapy, albeit in relative terms, modest. These issues diminish the importance of local control measures for this cohort of patients in general, based on the assumption that the majority of them will have sub-radiologic metastatic disease, which will in time be the main determinant of their prognosis.

The foothold of chemoradiation for LAPC was established on the basis of a number of small clinical trials stretching back to the 1960's. Two of these studies demonstrated a survival benefit for (5-FU based) chemoradiation compared to radiotherapy alone[14, 15]. Two other studies from the same era compared chemotherapy alone to chemoradiation. In a trial by the Gastrointestinal Tumor Study Group (GITSG) a benefit was demonstrated for chemoradiation plus chemotherapy compared to chemotherapy alone[16]. The chemotherapy consisted of streptozocin, mitomycin and 5-FU and the 1-year survival benefit was 41% compared to 19%. The other trial, by the Eastern Cooperative Oncology Group (ECOG)[17], compared 5FU-chemoradiation with chemotherapy alone, failing to demonstrate a survival benefit.

The value of chemoradiation in LAPC has not been quantified in the modern clinical trial epoch. In an attempt to address this question in the era of gemcitabine a phase III study was performed by the FFCD – SFRO (Fédération Francophone de Cancérologie Digestive - Société Française de Radiothérapie Oncologique) in France[18]. In this study, the first for nearly 20 years to address this question, 119 patients (of a planned 176) were randomized to undergo induction chemoradiation (with 5-FU 300 mg/m2/24 h as a continuous infusion, day 1–5 every week and cisplatin, 20 mg/m2/d, day 1–5 at week 1 and 5) followed by gemcitabine, or straight to chemotherapy with gemcitabine. The study was stopped prior to its planned enrollment due to an inferior survival in the chemoradiation group (median survival 8.6 v 13 months, p = 0.014). Although this study is not a definitive answer to the question of chemoradiation, it does add to the growing body of opinion that the benefit of chemoradiation in LAPC is most likely confined to a carefully selected subgroup. Recently a not dissimilar study design by ECOG[19] of initial systemic therapy compared to chemoradiation was reported comparing gemcitabine alone (1,000 mg/m2 weekly x 3 every 4 weeks for 7 cycles) to chemoradiation (RT 50.4 GY in 28 fractions plus gemcitabine 600 mg/m2 weekly x 6) followed by 5 cycles of gemcitabine alone (1,000 mg/m2 weekly x 3 every 4 wks). The trial was stopped early due to slow accrual (N = 74, out of a planned 316). The median survivals were 9.2 months (95% CI 7.8 - 11.4) and 11.0 months (95% CI 8.4 - 15.5) for the two arms respectively (p=0.044).

In an interesting attempt to tease out the benefit of chemoradiation, investigators from the Groupe Coordinateur Multidisciplinaire en Oncologie (GERCOR)[20] performed a retrospective analysis of 181 patients with locally advanced PAC who had been entered on prior prospective GERCOR studies and who had been offered chemoradiation (at the discretion of the investigator), but only if they had remained metastasis-free after a 3-month period. For those patients who were metastasis-free after initial chemotherapy, there was a survival advantage if they proceeded to chemoradiation compared to those who continued with chemotherapy alone (median OS 15.0 and 11.7 months, respectively; P = .0009). These data suggest that radiation may offer a survival benefit in selected patients who have disease that is proven to be localized after a test of time. This is an attractive concept as it allows patients to be selected for chemoradiation whilst receiving

systemic therapy for their disease and also gives time for the logistics of the chemoradiation to be organized.

To summarize, the role of chemoradiation in the management of locally advanced, clearly unresectable pancreas cancer, has changed in recent times with a trend towards induction systemic therapy. This seems to be the most pragmatic approach for selecting out the patients who will genuinely benefit from local therapy and avoiding intensive chemoradiation in patients who in all likelihood will not benefit from it.

Leaving aside the chemoradiation question, what is the best systemic therapy for LAPC? Gemcitabine became established as a cornerstone drug in pancreas adenocarcinomain 1997 following a phase III study which demonstrated an improvement in clinical benefit and survival (a secondary endpoint in the study) compared to 5-FU[21]. Progress since then has been modest and mixed. Phase III co-operative groups studies exploring the addition of the biologic agents, bevacizumab[22] and cetuximab[23], to gemcitabine in advanced pancreas adenocarcinoma have been negative in this disease, a particularly disappointing outcome given their demonstrated efficacy in other gastrointestinal cancers and the preclinical rationale for their use in PAC.

Cytotoxic combinations of gemcitabine with capecitabine and platinum agents do appear to offer a small incremental benefit, particularly in patients with good performance status. Heinemann et al. performed a randomized study of gemcitabine in combination with cisplatin versus gemcitabine alone[24]. This study showed an overall survival benefit which was not statistically significant (7.5 v 6.0 months, HR = 0.80; P = 0.15). A meta-analysis of randomized trials indicated a significant survival benefit for combination regimens when gemcitabine was either combined with platinum analogs (HR 0.85; 95% CI: 0.76 - 0.96, p = 0.010) or fluoropyrimidines (HR 0.90; 95% CI: 0.81 - 0.99, p = 0.030). In a subgroup analysis patients with a good PS appeared to benefit from cytotoxic combinations (HR = 0.76; 95% CI: 0.67 - 0.87; p < 0.0001), whereas patients with a poor PS seem to have no survival benefit from combination chemotherapy[25]. The first trial to show a survival benefit for any combination therapy in pancreas cancer and which led to FDA approval of this combination in the front-line treatment of pancreas cancer in 2005, was a study by Moore et al., in which 569 patients with untreated locally advanced or metastatic pancreas cancer were randomized to receive gemcitabine with either erlotinib or placebo[26]. There was a very modest but statistically significant improvement in progression-free (HR .77,95% CI, .64-.92;P= 0.004), one-year survival (23% v 17%; P=.023) and median overall survival (6.24 months v 5.91 months, HR 0.82, 95% CI, .69-.99;P= 0.038) favoring the erlotinib arm.

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