Pancreatic Cancer

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Contents

Abstract

Pancreatic cancer is an aggressive disease with high rates of disease-related mortality due to high rates of systemic disease spread. The role of radiation therapy for pancreatic cancer has been controversial to date. There have been significant advancements in effective systemic therapy regimens and radiation treatment delivery techniques, however, that are promising. This chapter aims to review all pertinent literature regarding the role of radiation therapy for pancreatic cancer.

1 Introduction

In 2014, pancreatic cancer is estimated to represent 3% of new cancer cases (36,888 diagnosed cases) and to cause 7% of all cancer-related deaths (39,590 deaths) (Siegel et al. 2014). In contrast to the stable or declining trends for most cancer types, pancreatic cancer incidence rates are rising (Siegel et al. 2014). Prognosis is poor, with 5-year survival rates of only 6% (Siegel et al. 2014). Surgical resection is the only potentially curative treatment, and patients are categorized as resectable, borderline resectable, locally advanced, or metastatic. Approximately one-third of patients present with unresectable disease; for these patients, median survival is only 8–12 months.

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Locally advanced pancreatic cancer (LAPC) is characterized by encasement (>180° involvement) of the celiac and/or superior mesenteric artery and/or obstruction of the portal and/or superior mesenteric vein. The ideal treatment paradigm for these patients remains unclear. The National Comprehensive Cancer Network guidelines recommend single- or multiagent chemotherapy alone, or chemoradiation (preferably preceded by chemotherapy) (Tempero et al. 2014). The role of chemoradiation for LAPC has been one of the most hotly debated topics in oncology. The uncertainty lies in whether localized therapy is warranted given the tendency of LAPC to spread systemically.

2 Chemoradiation Versus Radiation Alone

Two trials compare the use of chemoradiation versus radiation therapy alone. Prior to the use of gemcitabine for patients with LAPC, the Gastrointestinal Tumor Study Group (GITSG) randomized 106 patients with LAPC to external beam radiation therapy (EBRT) (60 Gy) alone or concurrent EBRT (either 40 or 60 Gy) and bolus 5-FU (Moertel et al. 1981). The GITSG-9273 trial was stopped early when the chemoradiation arms were found to be superior. The 1-year overall survival rates were 11% for patients who underwent radiation alone compared to 38% for patients receiving chemoradiation with 40 Gy and 36% for patients receiving chemoradiation with 60 Gy ($p < 0.01$). After 88 additional patients were enrolled in the chemoradiation arms, there was a trend toward improved survival in the 60 Gy arm as compared to the 40 Gy arm ($p = 0.19$).

While the GITSG-9273 trial showed a survival benefit for chemoradiation, the Eastern Cooperative Oncology Group (ECOG) E8282 trial did not (Cohen et al. 2005). In this trial, 114 patients were randomly assigned to receive radiation therapy (59.4 Gy) alone or with concurrent infusional 5-FU (1000 mg/m^2 daily on days 2–5 and 28–31) plus mitomycin (10 mg/m^2 on day 2). The median survival was 7.1 months in the radiation-alone arm as compared to 8.4 months in the chemoradiation arm ($p = 0.16$). The authors concluded that the addition of 5-FU and mitomycin increased toxicity without improving OS. However, the absence of a survival benefit with chemoradiation in the ECOG study has been ascribed to variation in study design, including the surgical staging requirement and different chemotherapy regimens. A subsequent meta-analysis that included both of these studies demonstrated a survival benefit for chemoradiation (Huguet et al. 2009).

3 Chemoradiation Versus Chemotherapy Alone

As it became evident that radiation therapy alone was insufficient, investigators evaluated the role of chemoradiation versus chemotherapy alone. The Fédération Francophone de Cancérologie Digestive-Société Française de Radiothérapie Oncologie (FFCD-SFRO) trial randomized 119 patients to chemoradiation (60 Gy in 2 Gy fractions with 300 mg/m^2/day of continuous-infusion 5-FU on days 1–5 for 6 weeks and 20 mg/m^2/day of cisplatin on days 1–5 during weeks 1 and 5) or gemcitabine (1000 mg/m^2 weekly for 7 weeks) (Chauffert et al. 2008). Patients in both arms received maintenance gemcitabine until disease progression or toxicity necessitated discontinuation. Although the study initially targeted accrual of 176 patients, the study was closed early after interim analysis demonstrated worse survival among patients randomized to receive chemoradiation. Median survival was superior in the gemcitabine arm (13 vs. 8.6 months, $p = 0.03$). In a per-protocol analysis of patients who received at least 75% of the planned treatment, the median survival was still only 9.5 months for the chemoradiation patients. In addition, there were more grade 3–4 toxicities recorded in the chemoradiation arm (36% vs. 22%). The authors concluded that chemoradiation with 5-FU is more toxic and less effective than gemcitabine alone. Of note, the dose intensity of maintenance gemcitabine was significantly lower in the chemoradiation arm because of more hematological toxicities.

The results of the ECOG E4201 study stand in contrast to the results of a study from the (FFCD-SFRO) trial. In the ECOG E4201 trial, 74 of a planned 316 patients were randomly assigned to either gemcitabine alone (1000 mg/m^2 × 7 cycles) or gemcitabine (600 mg/m^2) with 50.4 Gy of radiation followed by gemcitabine (1000 mg/m^2 × 5 cycles) (Loehrer et al. 2011). Median survival was superior in the chemoradiation as compared to the gemcitabine-alone arm (11.1 vs. 9.2 months, one-sided $p = 0.017$). As expected, grade 4–5 toxicities were more frequent in the chemoradiation arm as compared to the gemcitabine-alone arm (41% vs. 9%). The authors concluded that chemoradiation with gemcitabine had improved OS with increased, but acceptable, toxicity.

4 Induction Chemotherapy Followed by Chemoradiation

Given that a large percentage of patients who present with LAPC rapidly develop metastatic disease, investigators are pursuing a strategy of using induction chemotherapy to select the patients with localized disease. With this approach, the patients who do not progress after the several months of chemotherapy proceed to local therapy with chemoradiation. A retrospective study of 181 patients enrolled in phase II and III Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) trials demonstrated that 29% had metastatic disease during the 3-month period of gemcitabine-based chemotherapy (Huguet et al. 2007). For the remaining patients, survival was significantly longer among those treated with chemoradiation (55 Gy with continuous infusion 5-FU) as compared to patients treated with additional chemotherapy (15.0 months vs. 11.7 months, $p = 0.0009$). Although this strategy has yet to be validated in a prospective randomized phase III trial, it provides support for the use of consolidative chemoradiation after 3 months of induction chemotherapy in those patients with localized disease.

Based on these findings, the GERCOR group designed the LAP 07 study where 442 patients with LAPC were initially randomized to gemcitabine or gemcitabine plus erlotinib (Hammel et al. 2013). The 269 patients (61%) without disease progression after 4 months of chemotherapy were subsequently randomized to chemoradiation or 2 months of additional chemotherapy. With a median follow-up of 36 months, there was no statistically significant difference in overall survival between the arms (16.4 vs. 15.2 months in the chemotherapy-alone and chemoradiation arms, respectively). Unquestionably, the results of the LAP 07 trial have further confused the question of chemoradiation for the treatment of LAPC.

5 Controversies Regarding Local Therapy for LAPC

The rationale for delivering induction chemotherapy followed by chemoradiation to patients with LAPC is compelling, as these patients have the need for both distant and local control. While induction chemotherapy aims to clear micrometastatic disease in a high-risk population, chemoradiation is delivered with the goal of tumor downstaging to increase the chances of curative resection. However, this strategy has yet to be validated in a prospective randomized phase III trial. In fact, the LAP 07 study showed no statistically significant difference in overall survival between the induction chemotherapy followed by chemoradiation and the chemotherapy-alone arms. Given the randomized data supporting chemotherapy alone, how can one still argue for the use of chemoradiation?

A recent study by Iacobuzio-Donahue et al. recognized SMAD4, a tumor suppressor, as a possible predictor of local versus distant progression (Iacobuzio-Donahue et al. 2009). In this series, rapid autopsies were performed on 76 patients with pancreatic cancer. Patterns of failure (locally destructive vs. metastatic) and status of several genes were correlated. At autopsy, 30% of patients had locally destructive pancreatic cancer, and 70% had widespread metastatic disease. Although these differing patterns of failure were unrelated to clinical stage at initial pre-

sentation, treatment history, or histopathologic features, the investigators found a marked association between SMAD4 status and patterns of failure. Patients with intact SMAD4 expression were considerably more likely to have locally destructive disease as compared to those with loss of immunolabeling ($p = 0.007$).

The relationship between SMAD4 and pattern of disease progression has been confirmed at the M.D. Anderson Cancer Center in a phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for LAPC (Crane et al. 2011). In the study, 11 of the 15 patients (73.3%) with intact SMAD4 expression exhibited a local pattern of progression, whereas 10 of the 14 patients (71.4%) with SMAD4 loss displayed a distant pattern of spread ($p = 0.016$). Taken together, these studies suggest that identification of patients with intact SMAD4 at initial diagnosis might help identify patients who would benefit from aggressive local therapy.

In addition to the notion that there may be a subgroup of patients with SMAD4-intact cancer who can benefit from local therapy, one must also consider an important limitation of the LAP 07 study—gemcitabine as the choice of chemotherapy. With a superior regimen such as FOLFIRINOX, which has been studied in the metastatic setting, a benefit may have been detected with chemoradiation after improved systemic control. Furthermore, it is possible that with this more active regimen, tumor downstaging may be significant enough to increase the chances of surgical resection. This is being studied by the Radiation Therapy Oncology Group (RTOG) 1201, a phase II randomized trial of high versus standard intensity local or systemic therapy for LAPC. In the study, patients will undergo SMAD4 testing and will then be randomized to one of the three arms: (1) gemcitabine for 12 weeks followed by intensity-modulated radiation therapy to 63 Gy, given with concurrent capecitabine; (2) gemcitabine for 12 weeks followed by three-dimensional conformal radiation therapy to 50.4 Gy with concurrent capecitabine; or (3) FOLFIRINOX for 12 weeks followed by three-dimensional conformal radiation therapy to 50.4 Gy with concurrent capecitabine. Likewise, in the ALLIANCE/ECOG phase II trial, patients will receive eight cycles of FOLFIRINOX, and will then be randomized to an additional four cycles of FOLFIRINOX or chemoradiation with concurrent capecitabine. We eagerly await the results of these studies particularly with regard to subgroups of patients that may benefit from chemoradiation. Until then, based on the LAP 07 trial, we judge that chemotherapy alone is a reasonable option for patients responding to systemic therapy. However, we favor consolidative chemoradiation to optimize local control and surgical resectability for those patients with localized disease who have difficulty tolerating chemotherapy, patients suffering from local progression, or patients who may be candidates for surgical resection.

6 Stereotactic Body Radiation Therapy (SBRT) in Locally Advanced Pancreatic Cancer

Although neoadjuvant chemoradiation has many potential benefits, the standard regimen consists daily treatments over a 6-week period. This puts a substantial drain on ill patients with life expectancies on the order of 1 year. In addition, it delays the possibility of surgery, the only potentially curative procedure for these patients. SBRT allows for the delivery of chemoradiation over the course of 1 week, thereby reducing the delay to surgery and decreasing the burden of long radiation schedules.

SBRT has been studied in several of clinical trials as an alternative treatment for the management of locally advanced pancreatic cancer. However, the advantage of SBRT remains unclear since it may not improve survival and may be associated with significant toxicity as reported in selected studies (Koong et al. 2005; Hoyer et al. 2005; Chang et al. 2009; Schellenberg et al. 2008; Crane and Willett 2009; Mahadevan et al. 2010; Didolkar et al. 2010). For example, one phase II study of SBRT for locally advanced pancreatic cancer included 22 patients who received 45 Gy in three fractions over 5–10 days (Hoyer et al. 2005). SBRT

was associated with poor outcome and pronounced acute toxicity, with worsening performance status, nausea, and pain. In addition, four patients developed severe gastric or duodenal mucositis or ulceration, and one patient experienced a nonfatal gastric perforation. In another study of 77 patients (81% with locally advanced and 19% with metastatic disease) undergoing a single fraction of SBRT with 25 Gy (Chang et al. 2009), the overall survival rates at 6 and 12 months were 56% and 21%, respectively. The 6- and 12-month rates of grade ≥2 late toxicity (predominantly mucosal) were 11% and 25%, respectively. In another trial of 16 patients receiving SBRT (25 Gy in 1 fraction) in between cycles 1 and 2 of gemcitabine chemotherapy, late gastrointestinal toxicity was even more common, with 5 grade 2 ulcers, 1 grade 2 duodenal stenosis, and 1 grade 4 duodenal perforation (Schellenberg et al. 2008).

However, more encouraging results have been described in other studies using reduced treatment fields, more conformal methods, and more than one fraction (Mahadevan et al. 2011; Chuong et al. 2013; Schellenberg et al. 2011; Polistina et al. 2010). For instance, one single-institution retrospective series of 73 patients with locally advanced or borderline resectable pancreatic cancer treated with induction chemotherapy followed by SBRT (5 fractions of 7–10 Gy each) (Chuong et al. 2013) had more promising outcomes. Of the 57 patients with borderline resectable disease, 32 went on to have surgery and 31 had R0 resections. Median overall survival was 16.4 and 15 months for the borderline and initially unresectable patients, respectively. The 1-year local control rate for patients who did not proceed to surgery was 81%. Moreover, there was no grade ≥3 acute toxicity and only 5% of patients experienced grade ≥3 late toxicity. A prospective Italian study of 23 patients with locally advanced pancreatic cancer received SBRT (30 Gy in 3 fractions) and gemcitabine chemotherapy (Polistina et al. 2010). There were 14 partial and 2 complete responses. In addition, two patients proceeded to surgery. Median survival was 10.6 months and no grade ≥2 acute or late toxicities were reported.

Notwithstanding these promising results, and that it is undoubtedly preferable for patients to undergo treatments over a 1- rather than 6-week period, the data are not conclusive and there remains uncertainty regarding the possibility for toxicity. Until evidence from randomized trials comparing SBRT to conventional chemoradiation is reported, the role of SBRT in the treatment of locally advanced pancreatic cancer remains unclear. Therefore, we recommend that patients with pancreatic cancer undergo SBRT within the setting of a clinical trial.

7 The Role of Adjuvant Chemoradiation for Resectable Pancreatic Cancer

The use of adjuvant chemoradiation for patients with resected pancreatic cancer represents one of the most passionately debated topics within the field of gastrointestinal oncology. Resection remains the only potentially curative procedure for pancreatic adenocarcinoma. Nonetheless, the 5-year survival rate in patients undergoing surgery is less than 20% (Nitecki et al. 1995; Piorkowski et al. 1982; Gudjonsson 1987). Local-regional relapse (50–85%) and metastatic disease both account for the pattern of failure (Tepper et al. 1976; Kalser and Ellenberg 1985). The goal of adjuvant treatment is to prevent recurrence and increase survival. However, the data surrounding the utility of adjuvant chemoradiation is mixed.

Several trials support the role of adjuvant chemoradiation. In a randomized trial of 21 patients sponsored by GITSG, individuals were randomized to either surgery alone or adjuvant 5-FU chemoradiation followed by additional 5-FU. Patients who received adjuvant treatment had significantly improved median and 5-year overall survival rates as compared to those undergoing surgery alone (21 vs. 11 months and 5% vs. 5%, respectively, $p = 0.03$) (Kalser and Ellenberg 1985). In a similarly designed study, the EORTC randomized 114 patients to surgery alone or adjuvant radiation (40 Gy split course) with concur-

rent 5-FU (25 mg/kg per day by continuous infusion). Although not statistically significant, adjuvant chemoradiation was associated with a trend toward improvement in median survival and 2-year survival (34% vs. 26%, respectively, $p = 0.099$) (Klinkenbijl et al. 1999).

Despite these favorable results, the benefit of adjuvant radiation remains questionable. The European Study Group for Pancreatic Cancer-1 (ESPAC-1) trial was a phase III trial that randomized 541 patients to surgery alone or adjuvant treatment with six cycles of chemotherapy alone, chemoradiation alone, or chemoradiation followed by six cycles of chemotherapy. Concurrent chemotherapy consisted of bolus 5-FU and leucovorin and adjuvant chemotherapy consisted of 5-FU. Radiation was delivered AP/PA 40 Gy split course, although up to 60 Gy could be delivered. While the trial showed a benefit to chemotherapy (median survival 20 vs. 14 months for patients receiving and not receiving chemotherapy, respectively), chemoradiation was associated with decreased survival (15 vs. 16 months for patients undergoing chemoradiation and no chemoradiation, respectively) (Neoptolemos et al. 2001; Neoptolemos et al. 2004). However, the results of this trial are controversial because of concerns regarding trial design and radiation technique (Abrams et al. 2001).

The RTOG 9704 trial sought to determine whether the addition of gemcitabine to 5-FU-based chemoradiation improved survival for patients with resected pancreatic adenocarcinoma. After surgery, 451 patients were randomized to either continuous-infusion 5-FU or gemcitabine before and after chemoradiation (Regine et al. 2008). Chemoradiation was the same for all patients and consisted of 50.4 Gy in daily fractions of 1.8 Gy with continuous-infusion 5-FU. Although there were no differences in overall survival when taking into account the entire cohort, patients with pancreatic head cancers ($n = 381$) in the gemcitabine arm had a trend toward improved survival as compared to those in the 5-FU arm (median and 3-year survival of 20.5 months and 31% vs. 16.9 months and 22%, respectively, $p = 0.09$). In addition, pretreatment CA19-9 level > 90 IU/L strongly predicted survival.

Building on the results from RTOG 9704, RTOG 0848 is a randomized trial to determine whether the addition of erlotinib to adjuvant gemcitabine improves survival as compared to gemcitabine alone after resection of head of pancreas adenocarcinoma (Regine et al. 2008). In addition, it also seeks to determine whether concurrent chemoradiation with 5-FU following adjuvant gemcitabine-based chemotherapy improves survival. We hope that trial will conclusively show that adjuvant radiation with concurrent 5-FU improves survival for patients with resected head of pancreas adenocarcinoma who do not progress after adjuvant gemcitabine-based chemotherapy.

Conclusion

The role of radiation therapy in the treatment for pancreatic cancer is currently controversial. Recent advancements in systemic therapy, including establishment of gemcitabine/abraxane and FOLFIRINOX chemotherapy in the localized setting, may allow for improved systemic disease control. With improvement in systemic therapies, local control may potentially be more meaningful endpoint. There are numerous ongoing studies, including RTOG 0848, that hopefully will answer the question of the benefit of radiation therapy in the upcoming years.

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