

Adjuvant radiotherapy for pancreatic cancer: rationale and results

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Abstract: Pancreatic cancer is a highly aggressive disease with a poor prognosis. The mainstay of curative treatment remains surgical resection. Adjuvant chemotherapy has been clearly shown to improve survival. Yet because local-regional recurrence after surgery is the predominant pattern of failure, chemoradiation is often used as a component of treatment. Despite several prospective, randomized trials evaluating adjuvant chemoradiation, controversy persists as to whether it confers a survival benefit. Here we review the rationale for adjuvant chemoradiation and the results of the major studies evaluating the impact of postoperative radiotherapy on disease control and patient survival.

Keywords: Radiotherapy; radiation therapy; pancreas cancer; gastrointestinal cancer; adjuvant therapy

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Introduction

Pancreatic cancer is the 12th most common cancer worldwide, with an estimated incidence of ~350,000 cases per year and an annual mortality rate nearly equaling the incidence (1). In 2015, the incidence of pancreatic cancer in the United States is estimated at 48,960 with 40,560 expected deaths (2). Despite advances in surgical techniques, systemic therapy, and radiotherapy, the survival outcomes for patients with pancreatic adenocarcinoma have not significantly improved in 3 decades and the prognosis remains dismal. The 5-year overall survival rate for pancreatic adenocarcinoma is ~6% (3). Surgery remains the mainstay of treatment with an R0 resection providing the best chance for cure. Nevertheless, at disease presentation, only ~20% of patients are eligible for curative resection. For this “fortunate” group of pancreas cancer patients, surgery is necessary for cure, although rarely sufficient. Surgery alone provides 5-year overall survival rates of approximately 15% (4,5). These poor outcomes provide the basis for the evaluation of adjuvant therapies to improve the survival of patients with adenocarcinoma of the pancreas. This

review discusses the rationale behind adjuvant radiotherapy and evaluates the evidence supporting its role in the postoperative setting.

Rationale for adjuvant radiotherapy

The high risk for local-regional recurrence forms the basis for adjuvant radiotherapy and chemoradiotherapy (CRT) in the treatment of pancreatic cancer. Local-regional recurrence in the resection bed or regional lymph nodes is the most common site of failure after curative resection for pancreatic adenocarcinoma, occurring in ~50–70% of patients treated with surgery. Approximately 20% of recurrences are local only, while the majority of patients ultimately develop distant metastatic disease (6,7). Pathologic studies have demonstrated that close or positive surgical margins are risk factors for local disease recurrence (8), while more recent tumor genetic subtyping has identified molecular markers that correlate with an increased risk of local failure (9,10). Recent radiographic mapping studies have been performed to improve our understanding of the highest risk areas for local-regional

recurrence (11).

It is with this risk in mind that we review the available literature with respect to the role of adjuvant radiation therapy and CRT for pancreatic adenocarcinoma.

The historical basis for adjuvant CRT

Early studies analyzing combined chemotherapy with radiation therapy showed improved response rates and survival in unresectable pancreatic adenocarcinoma compared to radiotherapy alone. Moertel *et al.* showed an overall survival benefit to radiotherapy and concomitant fluorouracil (5-FU) compared to radiotherapy alone for locally advanced disease (12). This finding led to the first prospective randomized study evaluating the role of postoperative concurrent CRT for pancreatic adenocarcinoma. The Gastrointestinal Tumor Study Group (GITSG) 9173 trial included patients with pancreatic adenocarcinoma (including head, neck, body, and tail lesions) after curative surgery with negative margins who were randomized to observation versus adjuvant CRT with 5-FU followed by 5-FU for 2 years or until disease recurrence (13). The study was terminated early after randomizing only 49 patients. Early closure was due to slow accrual and sufficient evidence that the adjuvant treatment arm had significantly improved disease-free and overall survival compared to surgery alone. Adjuvant CRT improved the median disease-free survival time by 2 months (11 *vs.* 9 months) and nearly doubled the overall survival time (20 *vs.* 11 months) (13). Five-year survival was improved with adjuvant treatment compared to observation: 19% *vs.* 5%, respectively. Following the closure of GITSG 9173, an additional 30 patients were treated adjuvantly per protocol confirming the reproducibility of the outcomes observed on the trial (14). Notably, the radiotherapy used in the trial was 40 Gy in 20 fractions given in a split course with a 2-week break after the initial 20 Gy. GITSG 9173 was the first prospective multi-institutional study to demonstrate improved survival with adjuvant therapy and established postoperative chemoradiation as the standard of care.

Subsequently, the European Organization for Research and Treatment of Cancer (EORTC) conducted a phase III trial in an effort to confirm the results of the GITSG trial with a larger sample size. EORTC 40891 included 218 patients with resected pancreatic head or periampullary adenocarcinoma (including those with positive margins) randomized to observation or postoperative CRT. Similar

to the GITSG trial, the radiotherapy was delivered as a split course to a total of 40 Gy over 6 weeks. Unlike the GITSG trial, however, there was no maintenance chemotherapy in the treatment arm. No statistically significant survival difference was observed between groups with a median overall survival of 19 months and 24.5 months in the surgery alone and adjuvant CRT arms, respectively. An underpowered subset analysis of pancreatic head tumors showed a trend toward improved median and 5-year survival times and rates with adjuvant therapy compared to observation of 17.1 *vs.* 12.6 months and 20% *vs.* 10%, respectively. Notably, there was no local control benefit seen in the adjuvant therapy arm in this trial (15).

Based on these data, the authors of the EORTC adjuvant trial concluded that there was no indication for concurrent 5-FU and radiotherapy in the postoperative setting. Yet several criticisms of the trial have arisen. One such critique points to the inclusion of ~45% of patients with periampullary tumors, which have a significantly more favorable prognosis compared to pancreatic cancers and are less likely to benefit from adjuvant CRT. Additionally, over 20% of patients in the adjuvant therapy arm did not receive adjuvant treatment (16). It has also been suggested that, given prior data supporting the benefit of adjuvant therapy, the EORTC statistical analysis inappropriately used a two-sided log rank test instead of a one-sided test. Reanalysis of the subset of patients with pancreatic head adenocarcinoma using a one-sided log rank test confirmed a statistically significant improvement in survival with adjuvant CRT ($P=0.049$) (17).

The European Study Group for Pancreatic Cancer (ESPAC)-1 trial followed in an effort to evaluate the impact of adjuvant chemoradiation or adjuvant chemotherapy alone on survival for pancreatic adenocarcinoma. The study was initially planned as a 2×2 factorial design following surgical resection (including positive or negative margins) with randomization to one of the following arms: observation, chemotherapy, CRT, or CRT followed by adjuvant chemotherapy. In an effort to “maximize” patient accrual, the trial was modified to allow physicians to select one of three possible randomization schemes: (I) a 2×2 factorial design (as noted above); (II) chemotherapy versus no chemotherapy; and (III) CRT versus no CRT. The chemotherapy and CRT regimens were similar to those used in the GITSG and EORTC trials

ESPAC-1 randomized a total of 541 patients: 285 to the 2×2 factorial design; 68 to CRT versus no CRT; and 188 to chemotherapy or no chemotherapy. The first

report of ESPAC-1 presented a pooled analysis of all three randomizations and compared the CRT group (including CRT and CRT plus chemotherapy) to the no-CRT group (including observation and chemotherapy alone) and separately compared the “chemotherapy” group (including chemotherapy alone and CRT plus chemotherapy) to the “no chemotherapy group” (including observation and CRT). The results showed a significant survival improvement for patients who received chemotherapy over no chemotherapy (19.7 *vs.* 14.0 months; $P=0.0005$) but no significant difference between the CRT and no-CRT groups (15.5 *vs.* 16.1 months; $P=0.24$). A subsequent report after 2-year follow-up for all patients again pooled the patients in groups including CRT versus no CRT or chemotherapy versus no chemotherapy. This analysis was conducted using only the data from patients enrolled in the 2×2 factorial design. Again, the chemotherapy group had improved survival compared to the no-chemotherapy group, with a 20.1-month *vs.* 15.5-month median survival times, respectively. In contrast, the CRT group had no survival benefit compared to the no-CRT group, with 15.9-month and 17.9-month median survival times, respectively.

Critics of the trial point to flaws that undermine the study’s validity, such as physician-selected patient randomization, the use of “background therapy” (either chemotherapy or CRT) before enrollment, and the lack of central radiotherapy review. Despite these criticisms, the results of ESPAC-1 and EORTC 40891 led many (particularly in Europe) to abandon postoperative CRT in favor of chemotherapy alone. In the United States, however, adjuvant CRT remains the standard of care.

Because of the mixed results among the phase III adjuvant pancreas trials (GITSG, EORTC 40891, and ESPAC-1) and strongly held positions on both sides of the debate over adjuvant therapy, several investigators have attempted to clarify the subject. A single-institution prospective non-randomized study conducted at Johns Hopkins Hospital (Baltimore, MD) included patients with resected pancreatic adenocarcinoma of the head, neck, or uncinate process who were assigned to one of the following: (I) no adjuvant treatment; (II) “standard” adjuvant chemoradiation similar to the GITSG study; or (III) “intensive therapy” consisting of higher-dose chemoradiation (50.4–57.6 Gy to the operative bed) with prophylactic hepatic radiation (23.4–27 Gy) followed by adjuvant chemotherapy for 4 months (18). The primary endpoint was survival. The standard adjuvant therapy arm revealed improved overall survival compared to the no-adjuvant-therapy arm: 21 *vs.* 13.5 months. There

was no survival benefit seen, however, with intensive adjuvant therapy compared to standard adjuvant therapy: 17.5 *vs.* 21 months, respectively (18). While limited in that it was a single-institution, non-randomized trial, it provides additional support for the benefit of adjuvant CRT.

Another study combined the efforts of Johns Hopkins University and Mayo Clinic (Rochester, MN) in a retrospective outcome comparison of patients with pancreatic adenocarcinoma treated with resection and either observation or CRT at these two high-volume centers (19). The study included 1,092 patients and showed improved survival in the cohort receiving adjuvant CRT compared to no adjuvant treatment: 21.1 *vs.* 15.5 months, respectively (19). To account for the selection bias and imbalances between cohorts inherent to a retrospective study, the authors performed a matched-pair analysis including 496 patients. The analysis confirmed the survival benefit of adjuvant CRT compared to surgery alone with median overall survival times of 21.9 and 14.3 months, respectively. While these studies showed improved survival with adjuvant CRT, they did not include a comparison with adjuvant chemotherapy only.

An international, multi-institutional pooled analysis included 955 patients with pancreatic adenocarcinoma who had received gross total resection and compared adjuvant CRT with adjuvant chemotherapy alone or no adjuvant therapy (20). Radiotherapy was delivered using contemporary treatment fields and modern doses (45–60 Gy). The median overall survival time and 5-year survival rate was highest after CRT (39.5 months and 41.2%, respectively) followed by chemotherapy alone (27.8 months and 25.7%, respectively) and then no adjuvant therapy (20.8 months and 23.5%, respectively) (21). Like the Johns Hopkins/Mayo Clinic pooled analysis described above, this study suffers from the selection biases and missing data inherent to a retrospective study. Nevertheless, it provides further support for the utility of adjuvant CRT.

A meta-analysis including nine randomized trials evaluated adjuvant chemotherapy (5-FU or gemcitabine), CRT, and CRT plus adjuvant chemotherapy. The authors compared survival outcomes and treatment-related side effects and reported a significant survival benefit for adjuvant 5-FU compared to observation, but no significant survival benefit for adjuvant gemcitabine, CRT, or CRT plus adjuvant chemotherapy compared to observation (22). The study is significantly limited by the use of summary statistics rather than individual patient data. Additionally, the data comparing CRT with observation were derived entirely from the ESPAC-1 and EORTC 40891 trials and

includes all of the limitations of those trials described above.

All of these studies were performed prior to the current era of more aggressive and active systemic treatments (e.g., FOLFIRINOX and Gem-Abraxane). It is uncertain how the previously described outcomes will compare to current treatment utilizing surgery and adjuvant chemotherapy with more effective systemic treatment. However, in the setting of improved systemic treatments, the importance of locoregional therapy may become even more relevant.

Contemporary adjuvant chemoradiation trials

With the conflicting outcomes between United States and European cooperative group trials, subsequent studies attempted to improve adjuvant treatment through various approaches. The United States RTOG 9704 trial (23) attempted to improve treatment using a CRT backbone. Meanwhile, the German/Austrian Charité Onkologie (CONKO) and the ESPAC-3 trials included only a postoperative chemotherapy regimen.

RTOG 9704 was a phase III postoperative adjuvant trial comparing CRT with 5-FU delivered in between either 5-FU or gemcitabine (23). The study included patients with pancreatic adenocarcinoma treated with primary gross total resection and randomized to one cycle of chemotherapy (5-FU or gemcitabine) followed by CRT before an additional 3 cycles of chemotherapy (5-FU or gemcitabine). Randomizing 451 patients, RTOG 9704 is the largest trial to date using adjuvant CRT for pancreatic adenocarcinoma. It was the first phase 3 adjuvant pancreas trial to require prospective radiotherapy quality assurance. Despite an initial survival difference observed between arms, the most recent update (with a median follow-up of 7 years for survivors) showed no significant survival difference between 5-FU and gemcitabine. A pre-planned subset analysis for pancreatic head tumors showed a trend toward improved median survival in the gemcitabine arm compared to the 5-FU arm: 20.5 vs. 17.1 months ($P=0.08$) (23,24).

Several findings from RTOG 9704 have revealed important implications for subsequent CRT treatments and trial design. The study used contemporary radiation doses, a continuous treatment course (45 Gy to the regional lymph nodes and 50.4 Gy to the operative bed), and 3-dimensional (3D) conformal radiotherapy fields (in contrast to the GITSG and ESPAC-1 trials). On multivariate analysis, a survival benefit was observed for patients treated per protocol-specified radiation treatment

parameters compared to those who failed to adhere to protocol radiation guidelines, with a median survival of 1.74 years compared with 1.46 years, respectively (25). The trial observed a relatively low rate of local recurrence (~25%) in comparison to outcomes in prior adjuvant CRT trials (47–63%), despite that one-third of the cohort had positive surgical margins (23). RTOG 9704 was also the first trial to prospectively evaluate cancer antigen (CA) 19-9 as a postoperative predictor of survival. Patients with a post-resection CA 19-9 level of either ≥ 90 U/mL or ≥ 180 U/mL had a significantly increased risk of death compared to their counterparts with lower levels (hazard ratio ~3.5 for both cutoffs) (26).

Many of the findings of RTOG 9704 led to the design of its successor trial, RTOG 0848, an ongoing 4-arm trial with 2 randomizations aiming to address two primary objectives: (I) does the addition of erlotinib (a tyrosine kinase inhibitor with a potent EGFR blockade) to gemcitabine improve survival compared to gemcitabine alone following gross total resection of pancreas adenocarcinoma? (II) does the use of concurrent 5-FU and radiation following adjuvant gemcitabine-based chemotherapy improve survival for patients compared to gemcitabine alone? The first randomization includes 5 cycles of gemcitabine versus 5 cycles of gemcitabine plus erlotinib, followed by restaging to ensure no progressive disease. The second randomization adds 1 cycle of chemotherapy or 5-FU-based CRT. RTOG 0848 builds upon the results of RTOG 9704, which showed relatively good local control with CRT, while attempting to improve distant control with improved chemotherapy before CRT. The results of this trial will be important in helping us answer ongoing questions regarding the benefit of adjuvant CRT. Based on the results of LAP07 (a phase 3 trial evaluating chemoradiation after induction gemcitabine +/- erlotinib) showing no benefit of the addition of erlotinib to gemcitabine in LAPC, the first randomization of RTOG 0848 was changed from a Phase III to a randomized Phase II design and was closed to further accrual.

The evolution of adjuvant radiotherapy

In addition to evaluating the survival benefit to postoperative CRT, the early randomized adjuvant CRT trials were important in confirming the safety and tolerability of adjuvant treatment. In the GITSG study, 14% of patients experienced severe (non-life-threatening) leukopenia and 5% (one patient) developed a minor skin rash. No life-threatening or deadly toxicities occurred as

a result of adjuvant CRT (13). In the EORTC trial, 44% of patients experienced grade 1 or 2 treatment-related toxicity. Grade 3 toxicity was observed in 9% of patients. One patient did not complete CRT owing to surgical complications (15). Notably, these studies used split-course CRT, a relatively low dose of radiation (40 NGy), and 2-dimensional or 3D radiation techniques.

RTOG 9704 used a more contemporary fractionation schedule and dosing (50.4 Gy). Grade 3 or higher treatment-related toxicity was observed in 62% and 79% of patients in the 5-FU and gemcitabine arms, respectively, including 1% and 14% grade 4 toxicity (23).

With advanced treatment planning and delivery techniques, intensity-modulated radiotherapy (IMRT) has been shown to be a safe and effective delivery technique for the adjuvant treatment of pancreatic cancer. This approach enables highly conformal dose delivery with significantly improved avoidance of organs at risk. Ben-Josef *et al.* published an early experience combining IMRT with capecitabine in 15 patients (seven patients had received a resection while eight had unresectable disease) (27). One grade 3 toxicity (gastric ulceration) and no grade 4 or 5 toxicities were observed.

Yovino *et al.* published the first large experience using IMRT as part of adjuvant CRT for resected pancreatic adenocarcinoma. Importantly, this series demonstrated no increased risk of local-regional recurrence (19%) as a result of highly conformal radiotherapy compared to historical treatments (28). The same group compared acute gastrointestinal (GI) toxicity using CRT with 5-FU and IMRT to those data from RTOG 9704 using 3D radiotherapy. IMRT yielded significant reductions in the rates of grade 3–4 nausea/vomiting and diarrhea compared to 3D techniques: 0% *vs.* 11% and 3% *vs.* 18%, respectively (29).

More recently, particle therapy using protons has shown promise for further improving the therapeutic ratio of adjuvant CRT in the treatment of pancreatic cancer. The dosimetric benefit of proton radiation therapy derives from the physical properties of the proton beam's "Bragg peak," which occurs at the end of the proton beam path where the majority of the proton energy is deposited without additional dose (called the "exit dose") beyond the beam's "peak." A summation of proton energies directed at the target leads to a "spread-out Bragg peak" that can deliver highly conformal radiation while minimizing dose to nearby normal tissues, and reduce the overall integral radiation dose. In contrast to X-ray (photon) therapy, proton therapy

deposits the majority of the radiation dose within the target as opposed to where it enters and exits the body.

Nichols *et al.* demonstrated the dosimetric benefit of protons compared to photon-based IMRT in the adjuvant setting with a blinded comparison study between two institutions: one providing optimized proton treatment plans and the other developing optimized IMRT plans (30). Proton planning showed reduced radiation doses to the stomach, small intestine, and kidneys. A prospective study from the University of Florida included 22 patients with resectable, borderline, or unresectable adenocarcinoma of the pancreas/ampulla treated with proton radiotherapy to doses between 50.4 Gy (RBE) and 59.4 Gy (RBE) and concurrent capecitabine. Three patients (14%) experienced grade 2 GI side effects and there were no grade 3–5 toxicities (31).

Photon-based stereotactic body radiotherapy (SBRT) is a technique used to deliver highly conformal radiation to relatively small targets using large doses per fraction. To date, it has typically been used for locally advanced pancreatic cancer, although there is increasing enthusiasm for its use in the postoperative setting without concurrent chemotherapy. The benefits of SBRT include a very short treatment course and very high, ablative doses of radiation. Rwigema *et al.* reported a retrospective review of pancreatic adenocarcinoma patients treated with SBRT (32). In their series, 12 patients were treated with postoperative SBRT for positive margins using single-fraction SBRT (18–25 Gy). The 1-year freedom from local progression rate was 71% in the adjuvant SBRT group. Prospective studies evaluating adjuvant SBRT are currently underway.

Because SBRT requires small treatment fields, it cannot be used to treat a large operative bed and cannot comprehensively treat regional lymph nodes. Efforts to improve our understanding of the highest risk areas for local-regional recurrence following a pancreaticoduodenectomy will help refine (and shrink) our treatment fields to enable these areas to be included as part of an SBRT treatment plan (11).

Patient selection

Numerous factors have repeatedly been shown to have prognostic value for determining survival in patients with pancreatic adenocarcinoma, including tumor grade, pathologic lymph node status, number of lymph nodes involved, margin status, tumor size, age, and postoperative CA 19-9 levels (24,33,34). Less-well characterized,

however, are factors that increase the risk for local-regional recurrence. Pathologic studies have implicated margin status as a risk for local-regional recurrence (7,8). Recent molecular studies have implicated tumor genotype in the risk for local recurrence versus distant recurrence (10). The evaluation of these factors coupled with staging studies to assess distant disease are critical for determining who will best benefit from aggressive local-regional therapy in the form of CRT. The challenge with pancreatic cancer is that despite a high risk for local-regional recurrence there is a competing risk for early distant metastases that may negate a survival benefit from improved local-regional control. Miller *et al.* evaluated data from the Mayo Clinic on 454 patients who underwent resection for pancreatic adenocarcinoma, 246 of whom received adjuvant CRT (34). On multivariate analysis, tumor grade and lymph node status were significant factors for overall survival. Patients with neither high-grade nor pathologically involved lymph nodes had no statistically significant survival benefit from adjuvant CRT. In contrast, patients with one or both adverse factors had significantly improved overall survival with adjuvant treatment. A multi-institutional prospective database analysis from the Central Pancreas Consortium evaluated 673 patients with pancreatic adenocarcinoma who underwent resection (R0/R1) followed by either observation (n=374) or CRT (n=299) (35). The group receiving adjuvant CRT experienced significantly improved overall survival compared to those who received surgery alone. The survival benefit of CRT was seen regardless of margin status (R0 and R1) but only in patients with lymph node involvement (35). In comparison, Hsu *et al.* showed in the combined Johns Hopkins/Mayo Clinic retrospective review that survival was improved with adjuvant CRT regardless of margin status, tumor stage, or lymph node status (19).

Conclusions

The debate over optimal adjuvant therapy for pancreatic adenocarcinoma is not yet settled. Regardless of one's position in this debate, there remains considerable work to be done to improve the outcomes of patients with this disease. Certainly, there are some high-risk features that warrant the use of postoperative CRT as a component of adjuvant treatment. As systemic agents become more effective in managing micrometastatic disease, local-regional control will become more impactful on overall survival. In the meantime, efforts to improve patient selection and radiation delivery techniques will hopefully

continue to increase the therapeutic ratio with the use of adjuvant radiotherapy and CRT.

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Footnote

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