Review Article

Adjuvant chemoradiation for pancreatic cancer: what does the evidence tell us?

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Abstract: The role of adjuvant chemoradiation (CRT) for pancreas cancer remains unclear. A handful of randomized trials conducted decades of ago ignited a debate that continues today about whether CRT improves survival after surgery. The many flaws in these trials are well described in the literature, which include the use of antiquated radiation delivery techniques and suboptimal doses. Recent prospective randomized data is lacking, and we eagerly await the results the ongoing Radiation Therapy Oncology Group (RTOG) 0848 trial that is evaluating the utility of high quality adjuvant CRT in resected pancreas cancer patients. Until the results of RTOG 0848 are available we should look to other studies from the modern era to guide adjuvant treatment recommendations. Here we review the current state of the art for adjuvant pancreas CRT with respect to patient selection, radiation techniques, radiation dose, and integration with novel systemic agents.

Keywords: Pancreas cancer; adjuvant chemoradiation (CRT); radiation therapy (RT)

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Background

Minimal progress has been made to significantly improve treatment outcomes for pancreas cancer patients despite constant efforts to better understand this devastating disease. According to the American Cancer Society, the 5-year overall survival (OS) rate has only marginally increased from 2% between 1975-1977 to 6% between 2003-2009 (1). The roadblocks to major progress are predominantly related to limitations in early cancer diagnosis when tumors are more likely to be resectable as well as poor detection of occult locoregional and distant metastasis.

While the goal for pancreas cancer patients is ultimately to achieve a margin negative (R0) resection, this is not possible for the majority of newly diagnosed patients typically either due to distant metastatic spread or extensive locoregional involvement of critical vascular structures. The minority of newly diagnosed patients who successfully undergo a R0 resection are at an extremely high risk for both locoregional and distant disease recurrence (2-8). Therefore, adjuvant therapy is the standard of care for resected pancreas cancer. While the benefit of adjuvant chemotherapy is undisputed, the addition of radiation therapy (RT) remains hugely controversial (6,9,10). In this article we will review the published literature with respect to adjuvant RT and optimal patient selection, treatment techniques, and incorporation of systemic agents.

Historical randomized trials

The initial studies that evaluated the addition of postoperative chemoradiation (CRT) for pancreas cancer are extensively discussed and debated in the published literature. Fueling this debate is the combination of limited prospective randomized data comparing the use of adjuvant CRT to no adjuvant CRT, conclusions made by older trials that used outdated RT techniques, and numerous flaws in the design and execution of these historical trials. That being said, we should critically interpret these trials when making treatment recommendations to our patients and

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when designing future trials that further examine how best to implement adjuvant CRT.

The Gastrointestinal Tumor Study Group (GITSG) 9173 trial was the first to evaluate whether surgery followed by adjuvant CRT would improve outcomes over surgery alone for resected pancreas patients (11). This trial of 43 patients limited enrollment to only those with negative surgical margins. The authors reported a significant OS benefit favoring the CRT arm despite the trial closing early due to poor accrual. In contrast to how we would treat these patients today, RT was delivered to 40 Gy in 20 fractions with a planned 2-week break after 20 Gy. 5-fluorouracil (5-FU) was given concurrently and after RT for 2 years or until evidence of disease progression. After an additional 30 patients were treated on a non-randomized arm using the same CRT regimen and had similar survival as those from the randomized CRT arm, CRT was considered to be a new standard of care for resected pancreas cancer management (12).

Several European studies were subsequently conducted that challenged whether CRT actually improved survival. The European Organization for Research and Treatment of Cancer (EORTC) randomized patients to surgery alone versus surgery followed by CRT, as was done in the GITSG trial (13). The EORTC trial did not demonstrate a significant survival benefit favoring CRT, although a trend towards improved survival emerged for the subset of patients with pancreatic head tumors (13,14). While many interpret this as a negative trial, others have countered that a number of flaws in trial execution and design likely prevented any CRT benefit from being detected. First, whereas the GITSG only included pancreas cancers nearly 50% of the patients enrolled on the EORTC trial had periampullary tumors, which have a more favorable prognosis. Second, 20% of patients did not receive adjuvant therapy despite being randomized to receive CRT and 44% did not receive chemotherapy per protocol. Third, the EORTC enrolled patients with positive surgical margins without stratifying by margin status while the GITSG excluded patients with positive margins. Fourth, while patients on the GITSG trial received maintenance chemotherapy, this was not given in the EORTC trial. Lastly, some have argued that if the EORTC data were evaluated using a one-sided instead of a two-sided log rank test, then this would have provided statistical significance (P=0.049) to the survival improvement seen with adjuvant CRT (15). Still, Europeans cite this as a negative trial and typically recommend adjuvant chemotherapy alone.

The European Study for Pancreatic Cancer (ESPAC)-1 trial concluded that not only was there no survival benefit obtained by using adjuvant CRT, but also that CRT actually caused a detriment in survival (16). This is the largest prospective study to evaluate adjuvant therapy for pancreas cancer patients, randomizing 254 patients from 61 European institutions after surgery either to chemotherapy alone versus observation or CRT versus observation. An additional 285 patients were included in a 2×2 factorial randomization between observation, chemotherapy alone, CRT alone, and CRT followed by maintenance chemotherapy. In a 2004 report of the patients treated within the 2×2 factorial design, CRT negatively affected 5-year OS versus no CRT (10% *vs.* 20%; P=0.05) while chemotherapy improved 5-year OS compared to no chemotherapy (21% *vs.* 8%; P=0.009). This trial has been widely criticized due to the ability of the treating physician to choose the randomization, the use of "background" therapy, lack of central review, and longer time to treatment in the CRT arm (17,18). Several more recent studies have specifically refuted the claim that CRT is detrimental to survival (19,20). Kinsella *et al.* examined whether unfavorable results in the CRT arm from the ESPAC-1 trial could be related to inadequate radiation delivery (20). They matched pT3N1 patients from the ESPAC-1 trial who were treated per their institutional regimen of 63 Gy and concurrent chemotherapy and concluded that the observed survival outcomes from the ESPAC-1 trial were dramatically inferior to those that would be "expected" using modern and high quality CRT. In fact, the observed results were outside the 95% confidence intervals for "expected" survival. While speculative, these data emphasize that CRT was not fairly assessed in the ESPAC-1 trial.

The next phase III study to include adjuvant CRT was Radiation Therapy Oncology Group (RTOG) 9704, which randomized patients to 5-FU CRT sandwiched between either gemcitabine or 5-FU (21). After an initial report with a median follow up of 4 years showing a significant improvement in survival, with additional follow up (median =7 years), only a trend towards improved survival was detected for pancreatic head tumors treated with gemcitabine (median survival 20.5 *vs.* 17.1 months; P=0.08) (22). This was felt to be potentially related to the interruption of gemcitabine via the "sandwiched" 5-FU CRT and hence became a consideration in the design of the successor trial.

RTOG 0848, the successor study to RTOG 9704, is a phase III trial that is attempting to answer two questions,

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the first being whether there is a survival benefit for adding erlotinib to gemcitabine compared to gemcitabine alone among head of pancreas patients who have undergone either an R0 or R1 resection. The second question is whether the addition of CRT in patients who have no evidence of disease progression following a full course of gemcitabine is superior to full course of gemcitabine alone. The results of RTOG 0848 will be critical to shedding light on the role of CRT, and until they are available we have no choice but to look to published literature from the modern era to guide our clinical practice.

Recent studies using modern RT doses and delivery techniques do not universally agree that adjuvant CRT should be used over chemotherapy alone. For instance, results from a randomized phase II trial published in 2010 did not show a difference in survival among resected patients who received CRT in addition to gemcitabine versus gemcitabine alone, although the authors acknowledge that the trial was not designed to detect such a difference (23). Another recently published single institution study of 146 patients actually reported higher median survival in patients who received chemotherapy alone compared to CRT (21.5 versus 16.8 months), although this difference was not statistically significant (P=0.76). On the other hand, recent studies that perhaps most strongly advocate for the use of CRT are from the Mayo Clinic and Johns Hopkins University (19,24-26). A large collaborative study between these two high volume pancreas institutions included 1,386 resected patients (19). When compared to surgery alone, adjuvant CRT improved survival in propensity score analysis by 33% (P<0.001). Matched-pair analyses demonstrated prolonged median survival with CRT (21.9 *vs.* 14.3 months; P<0.001). The survival benefit favoring CRT over surgery alone was also reported individually by each institution (24-26). Interestingly, the median survival of 21.2 months reported in patients who received CRT at Johns Hopkins was remarkably similar to what was reported in the CRT arm of the GITSG trial (20 months) despite the Johns Hopkins patients having more high-risk features such as positive lymph nodes (80% *vs.* 30%) and positive surgical margins (45% *vs.* 0%). While a direct comparison cannot be made between these two studies, modern high quality RT likely improves outcomes compared to the poorly delivered RT used in the previously mentioned historical trials. This observation was demonstrated in RTOG 9704, the first phase III trial which required central quality assurance review of RT fields used (27).

Personalized therapy

Despite adjuvant CRT not being universally adopted, it is generally agreed that a subset of resected patients with a high risk for locoregional disease recurrence may particularly benefit from the addition of RT to chemotherapy (28). For example, RT did not seem to benefit patients in the aforementioned Mayo Clinic experience who did not have any specified negative risk factors while those with at least one negative risk factor did have significantly improved survival (24). Other studies support this strategy in patients with negative features such as older age, large tumor size, advanced tumor stage, high histologic grade, elevated CA 19-9 level, positive lymph nodes, and positive surgical margins (4,24,26,29-34). The literature supports pathologic lymph node status, surgical margin status, and CA 19-9 level as being among the most important.

Lymph node involvement is consistently described as one of the most significant negative prognostic factors for long-term survival after surgery for pancreas cancer (21,30-33,35-37). Merchant and colleagues published a review of 747 pancreas patients from across seven academic medical institutions who had either surgery alone (n=374) or surgery followed by CRT (n=299) (35). While median OS was longer in patients receiving CRT (20 *vs.* 14.5 months, P=0.001), subset analysis showed that only the node positive patients benefitted (HR 0.477; 95% CI, 0.357-0.638, P<0.0001). The survival benefit of CRT has repeatedly been demonstrated among node positive patients using the Surveillance, Epidemiology, and End Results (SEER) database, although Mellon *et al*. were the first to demonstrate that RT conferred a survival benefit despite including information on chemotherapy in their analysis (31,38-41). The importance of lymph node metastasis was also shown in the analysis of RTOG 9704 (21). The data from RTOG 9704 were further analyzed by Showalter *et al*. to better understand the importance of certain lymph node parameters beyond only classifying patients as either having or not having lymph node metastasis (32). Their conclusions were in agreement with work previously published by others that showed a significant association between worse OS and higher number of positive nodes (NPN) (33,42,43), fewer total nodes examined (TNE) (31,43-45), and higher lymph node ratio (LNR) (45-48). While there is substantial evidence that lymph node involvement portends worse outcomes, we should be aware that node positive disease does not necessarily preclude long-term survival as shown

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in a study by Schnelldorfer *et al*. in which 32% of the 62 patients alive at 5 years and 29% of the 21 patients alive at 10 years had pathologically positive nodes (37).

Surgical margin status has also been described as being a highly significant negative prognostic factor. Patients who undergo resection with negative surgical margins (R0) have prolonged survival over those who have either microscopically positive (R1) or grossly positive (R2) margins (20,26,33-35,49-51). However, some investigators question the significance of postoperative margin status (52-54). A Pancreatic Cancer Meta-analysis Group (PCMG) study suggested that resection margin status was not a significant factor for survival, although R1 patients had a 28% reduction in the risk of death after CRT (52). Perhaps the benefit of R0 resection is not uniform, as suggested by Tummala *et al*., who showed a dramatic improvement in survival for R0 versus R1 resection, but only for patients with tumors no larger than 25 mm who also had no more than one positive lymph node (55).

The importance of postoperative CA 19-9 levels was most prominently demonstrated by RTOG 9704 in which a secondary endpoint was survival based on a postoperative CA 19-9 cutoff of 180 U/mL. The 5-year survival of patients with CA 19-9 ≥180 U/mL was 0% compared to 25% and 18% in patients with CA 19-9 <180 U/mL treated with either gemcitabine or 5-FU, respectively. In addition, the authors analyzed the RTOG 9704 data using a threshold of 90 U/mL, inspired by the CONKO-001 trial that only included patients with values <90 U/mL. As was seen using the higher cutoff, patients with CA 19-9 <90 U/mL also had significantly higher 5-year OS (23% *vs.* 2%; P<0.0001). Finally, the most important independent predictor of survival in multivariate analyses from RTOG 9704 was postresection CA 19-9 using the cutoffs of 90 U/mL [HR 3.02; P<0.0001 (95% CI, 2.16-4.23)] and 180 U/mL [HR 3.18; P<0.0001 (95% CI, 2.09-4.84)]. Preoperative CA 19-9 level is also thought to be a useful prognostic factor as supported by multiple single institution retrospective reports (56-59), the largest of which was published by the Mayo Clinic (56). Of 226 patients, approximately half received adjuvant CRT alone (n=122) with the remainder receiving CRT followed by additional chemotherapy (n=23), chemotherapy alone (n=6), or observation (n=69). Adjuvant CRT was delivered to a median 50.4 Gy and nearly all received concurrent infusional 5-FU. Multivariate analysis showed preoperative CA 19-9 levels based on cutoffs of 180 and 90 U/mL to each significantly predict survival. Survival was significantly higher among the 101 patients with preoperative CA 19-9 ≥180 U/mL who received adjuvant CRT compared to those who did not (median survival 16.8 *vs.* 11.4 months; 5-year OS 24% *vs.* 5%; P<0.001). Lastly, the utility of preoperative CA 19-9 level may also include the ability to predict for tumor stage, nodal involvement, tumor grade, and surgical margin status. Prospective studies are needed to clarify the importance of preoperative CA 19-9, preoperative versus postoperative CA 19-9, and the ideal CA 19-9 cutoff.

There is increasing awareness that certain biomarkers may correlate with survival (60-62). Arguably the most promising of these is the tumor suppression gene DPC4 (SMAD4), which encodes the Smad4 protein involved in the transforming growth factor (TGF)-β signaling pathway. Smad4 status appears to be associated with patterns of failure; intact Smad4 patients seem to predominantly recur locally while those with loss of Smad4 are more likely to have distant progression (63-65). Herman *et al*. recently evaluated Smad4 status in 29 resected pancreas patients and discovered that recurrence-free survival was prolonged in patients with intact Smad4 (17.4 *vs.* 11.5 months; P=0.003), although there was no OS difference based on Smad4 status (64).

At this time, it is not clear how to precisely incorporate certain prognostic factors within our clinical practice. However, adjuvant CRT should be strongly considered in patients with multiple high-risk features such as positive lymph nodes and positive margins. If Smad4 status proves to reliably predict patterns of recurrence, then patients with intact Smad4 may particularly benefit from adjuvant CRT.

Evolution of radiation therapy (RT) techniques

We should be mindful that interpretation of study results should be within the context of the treatment era and the specific treatment delivered. The previously mentioned historical CRT trials used what is now undoubtedly considered to be antiquated RT including 2-dimensional planning and split-course radiation to a low dose.

In the decades that have followed these initial trials, technological advancements have included 3-dimensional conformal RT (3DCRT) and more recently intensity modulated radiation therapy (IMRT). IMRT is increasingly being used for pancreas cancer as well as other upper abdominal malignancies based on its superior ability to deliver sharp dose gradients at the periphery of the target volume, thereby significantly limiting unintended high dose to nearby normal tissues (*Figure 1*) (66-69). Even further normal tissue sparing may also be achieved using IMRT with noncoplanar beam angles (70), helical tomotherapy

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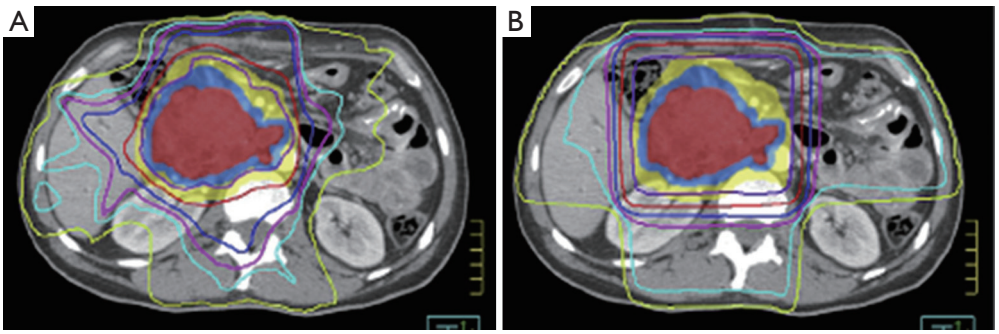

Figure 1 Isodose distributions from treatment plans using intensity modulated radiation therapy (A) and 3D conformal radiation therapy (B). Note the superior dose conformality, especially in the high dose regions, around the target volume using intensity modulated radiation therapy.

(69,71), and dose painting (72). Yovino *et al*. published the first comprehensive report of adjuvant IMRT in 71 pancreas cancer patients (34). They reported a low rate of locoregional failure (19%), alleviating concerns that the high conformality of IMRT did not lead to a compromise in treatment accuracy compared to less conformal techniques such as 3DCRT. In addition, treatment was very well tolerated with a much lower incidence of severe acute and late GI toxicity than would be expected using 3DCRT (34). Because of these favorable outcomes, both 3DCRT and IMRT may be used in RTOG 0848.

Although IMRT plans delivered using photons are incredibly conformal, the physical properties of protons allow for even greater sparing of normal tissues and delivery of lower integral dose. While dose in a photon beam decreases exponentially with increasing tissue depth, dose in a photon beam remains relatively constant until it reaches an area of maximal energy deposition, also known the Bragg peak. Thus, the main advantage of proton beam therapy (PBT) is that there is almost no dose delivered beyond the Bragg peak. While clinical PBT data is lacking for resected pancreas patients, there is data to suggest that PBT offers a dosimetric advantage over highly conformal photon therapy. Investigators at the University of Florida and University of Maryland generated PBT plans using simulation CT scans of eight resected patients who received IMRT. Each PBT plan was generated without knowledge of the corresponding IMRT plan dose distributions. The study authors demonstrated that the PBT and IMRT plans resulted in equivalent target coverage, although PBT was able to better limit dose to normal organs. PBT reduced median small bowel V20 from 47% to 15%, median gastric V20 from 20% to 2%, and median right kidney V18 from 51% to 27%. The University of Florida is now conducting a phase II trial (NCT01553019) of adjuvant CRT using PBT and concurrent chemotherapy.

Finally, there is increasing evidence that stereotactic body radiation therapy (SBRT) may benefit some patients with pancreas cancer although data in the postoperative setting is limited. SBRT is a technique that allows for large ablative doses to be precisely delivered to small focal targets in up to five fractions. Such large doses are thought to have a unique biologic effect and result in an enhanced local effect over standard fraction doses (73). While the pancreas SBRT literature focuses primarily on locally advanced disease (74,75), there is increasing enthusiasm to evaluate its use in borderline resectable (76) and even resectable patients (77). Rwigema *et al*. published a retrospective review of 24 resected pancreas patients who received SBRT, most commonly in a single fraction, for close or positive margins. No grade 3 or higher toxicities were noted while freedom from local progression was 95% at 6 months and 66% at 1 year. The utility of SBRT in the adjuvant setting remains to be seen.

Radiation dose and delivery schedule

Split-course RT, which was used in the GITSG, EORTC, and ESPAC-1 trials, prolongs overall treatment time and results in inferior local control due to accelerated repopulation (30,78). The use of a split-course approach to a lower dose than what is used today (40 Gy) was necessitated by the lack of highly conformal RT delivery resulting in significant dose to large amounts of normal organs. However, modern delivery techniques such as 3DCRT have allowed for doses of at least 50 Gy to be evaluated in prospective trials

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such as RTOG 9704 (21,79-81). Although we have the ability to safely deliver doses above 50 Gy, does it mean we should routinely do so? Few studies have measured the impact of RT dose on clinical outcomes for pancreas cancer (82,83). While dose escalation may benefit patients with gross disease (84), it remains unclear whether this holds true for patients with microscopic disease in the postoperative setting. Hall and colleagues recently examined the relationship between RT dose and survival in a cohort of 1,385 non-metastatic resected pancreas cancer patients (82). Most had positive lymph nodes (61.7%) and negative margins (71.3%). Median survival was longest in patients who received 50 to <55 Gy (n=498; 23 months) compared to those who received ≥55 Gy (n=89; 16 months), 40-50 Gy (n=634; 20 months), or <40 Gy (n=164; 15 months). Multivariate analysis revealed that in comparison to the reference range of 50 to <55 Gy, worse OS was predicted by <40 Gy [HR 1.30; (95% CI, 1.03-1.66); P=0.031], 40 to <50 Gy [HR 1.17; (95% CI, 1.00-1.37); P=0.05], and ≥55 Gy [HR 1.44; (95% CI, 1.08-1.93); P=0.013]. There was no significant difference between each group with respect to age, surgical margin status, nodal involvement, tumor size, or tumor stage.

Therefore, modern studies using highly conformal RT delivery and doses of approximately 50 Gy may better reflect the benefit of adjuvant CRT compared to older studies that used split-course RT to 40 Gy (24-26). Furthermore, these older studies did not require central quality assurance of RT plans, which we have learned is critical and can significantly affect OS (27).

What is the appropriate clinical target volume (CTV)?

The predilection of pancreas cancer to involve locoregional lymph nodes has long been recognized, with rates reported from clinical and pathological series of up to 80% (2-8). Imaging studies including CT, PET/CT, and MRI are not able to readily detect subclinical disease (6,85). Therefore, given the high likelihood of subclinical nodal involvement, many radiation oncologists agree that elective nodal irradiation (ENI) should be a standard component of treatment field design for both resectable and borderline resectable pancreas cancer. However, there is not a consensus regarding the use of ENI. Many have argued for omitting ENI altogether (86), particularly in the setting of locally advanced pancreas cancer, especially given the increasing use of SBRT (74,76). Others have favored extensive surgical lymph node interrogation of even the para-aortic nodes (87) despite data suggesting that this may not result in a survival benefit (88).

For the majority of radiation oncologists who utilize ENI, the required extent of lymph node coverage has been somewhat uncertain although this recently has become better characterized (89-92). Brunner *et al*. were the first to publish evidence-based guidelines for target volume delineation in resected head of pancreas patients. These were based on a histopathologic analysis of 178 patients who also had a formal regional systematic lymph node dissection (89). They described a systematic stepwise method by which radiation target volumes should be constructed based on factors including the frequency of nodal spread, respiratory motion, and expected treatment-related toxicity related to treatment volume. In accordance with previously published data, the peripancreatic and pancreaticoduodenal nodes were most commonly involved (93). The authors highlighted the importance of also including the celiac axis, para-aortic, superior mesenteric artery, and hepatoduodenal ligament regions based on their frequency of subclinical involvement. While coverage of these regions would significantly increase the treatment volume, the authors' opinion was that the likelihood of tumor recurrence was outweighed by a potential increase in normal tissue injury. These data has served as the foundation for CTVs that are currently used today.

Sun *et al*. performed an extensive review of the published literature to comprehensively evaluate lymph node positivity rates and patterns of nodal spread in both resected head and body/tail pancreatic cancer patients (91). They included 18 studies representing 5,954 patients that provided a detailed lymph node analysis, including the paper by Brunner and colleagues. They concluded that the pattern and frequency of subclinical nodal involvement was consistent across all of the included studies. Caravatta *et al*. developed guidelines for CTV delineation based on these data published by Sun and colleagues (92). Lymph node regions with at least 3% risk of involvement were considered to be at a clinically significant risk of recurrence, and therefore were included in the CTV. The authors justified this 3% threshold as being appropriate because if the more commonly threshold of 10-15% was used, several classically included nodal groups such as the celiac axis and hepatoduodenal ligament would be excluded. They admit that their proposed target volumes for head of pancreas cancers were actually "quite comparable" to those as described by Brunner and colleagues.

The RTOG has published target volume delineation

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guidelines in an attempt to standardize target volume delineation for patients treated on RTOG 0848, given the importance of delivering high quality RT (27,94). These guidelines are in large part based on the previously reviewed data that described patterns of spread. The authors admit that the appropriate CTV definition after a pancreaticoduodenectomy remains uncertain, and that the results of RTOG 0848 will hopefully clarify this.

Finally, some have challenged whether smaller target volumes may effectively allow for dose escalation and decreased treatment toxicity without compromising local control (90,95). To guide target volume construction, investigators from Johns Hopkins University first mapped local recurrences with respect to easily identifiable and reproducible vascular structures including the celiac axis, SMA, and renal veins (90). They suggested a stepwise CTV planning process based on their discovery that 90% of local recurrences were located within a 1-3 cm volumetric expansion from the combined celiac axis and SMA contours. Three simulated treatment plans were generated using these guidelines, and each was noticeably smaller than one generated based on recommendations per the RTOG (94).

Adding novel therapies to adjuvant chemoradiation (CRT)

Because of the limited progress made in treatment for resected pancreas cancer patients using traditional chemotherapy and CRT, novel therapeutic agents are needed.

Biologic agents that target specific molecular pathways potentially provide a novel approach in the fight against pancreas cancer (96). Investigators have developed agents against certain genes that are commonly mutated or overexpressed in pancreas cancer cells including vascular endothelial growth factor (VEGF) (97), human epidermal growth factor receptor type 2 (HER2) (98), and epidermal growth factor receptor (EGFR)/KRAS (99). While these targeted agents have shown anti-tumor activity *in vitro*, their clinical efficacy when added to chemotherapy has been disappointing (83,100-102). The most promising is erlotinib, a tyrosine kinase inhibitor (TKI) against ErbB1-phosphorylation (103). While it's unclear whether the addition of erlotinib to adjuvant chemotherapy and CRT is useful (104), marginal improvements in survival have been reported by the addition of erlotinib to gemcitabine over gemcitabine alone in locally advanced and metastatic pancreas cancer patients (103). RTOG 0848 will attempt to evaluate whether erlotinib improves survival in resected pancreas patients.

Another novel adjuvant treatment approach has been to harness the body's own immune response using vaccine therapy. Several types of vaccines have been evaluated including peptide, recombinant microorganism, and whole-cell vaccines (105). Promising results of a phase II study were published in which irradiated allogeneic granulocyte-macrophage colony stimulating factor (GM-CSF) secreting tumor vaccine was given postoperatively along with CRT (106). Hardacre *et al*. have described their experience using a vaccine that stimulates a hyperacute rejection-type response against two commonly expressed human pancreatic adenocarcinoma cell lines (107). In a phase II study, 70 resected pancreas patients received algenpantucel-L immunotherapy in addition to chemotherapy and CRT as per the gemcitabine arm of RTOG 9704. One-year disease free survival was 62% and OS was 86%, which paved the way for an ongoing phase III trial (NCT01072981).

Conclusions

The role of adjuvant CRT for resected pancreas cancer patients remains controversial, largely due to the conflicting results of several trials conducted decades ago that were plagued by a myriad of flaws. Studies from the modern era consistently demonstrate that adjuvant therapy, particularly including high quality RT, is beneficial especially among patients who have a particularly high risk of locoregional recurrence. In that regard, the results of RTOG 0848 are eagerly awaited. Radiation delivery techniques continue to evolve, as does our understanding of what is an appropriate adjuvant target volume, and both of these will further enhance the therapeutic ratio of RT. Lastly, novel treatments such as vaccine therapy hopefully will help us make desperately needed headway in the struggle against pancreas cancer.

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