Radiation Therapy in Operable and Locally Advanced Pancreatic Cancer

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Pancreatic cancer, chemoradiation, chemotherapy, adjuvant, locally advanced, stereotactic

Abstract
It is well established that the development of distant metastatic disease represents the dominant pattern of tumor recurrence/progression among patients with operable and locally advanced pancreatic cancer. However, the contribution of localized or locoregional tumor burden to pancreatic cancer–associated morbidity and mortality may be underappreciated, and therefore balancing competing considerations of systemic versus local disease control becomes important in therapeutic decision-making. The role of local therapies, particularly radiation therapy, has remained somewhat controversial in this disease context. Several phase II and III trials have sought to address the relative importance and role of radiation in both the localized and locally advanced settings, including the sequencing of this modality relative to systemic therapy and its optimal means of administration. However, differences and limitations in study design have produced mixed results, particularly in terms of the contribution of radiation to overall survival benefit. An emerging paradigm that makes conceptual sense and remains the subject of active investigation is to start with a defined period of systemic treatment, thus limiting radiation to the subset of patients who do not manifest with metastatic disease during initial therapy and are therefore most likely to benefit from local control. (JNCCN 2010;8:1022–1031)

When considering the role of radiation therapy in operable and locally advanced pancreatic cancer, it becomes necessary to examine the patterns of locoregional versus systemic failure in these disease settings. For example, data from single-institution series and from phase III trials of resected pancreatic cancer suggest that while distant metastatic disease tends to predominate as a pattern of recurrence, locoregional relapse is also common, occurring in anywhere from 33 to 73% of patients.1–5 A recently reported rapid autopsy series from Johns Hopkins showed that 15% of patients with previously resected stage I/II disease had recurrent cancer limited to the pancreatic bed only, and 28% of patients with stage III (locally advanced) disease had no evidence of metastases at the time of death.6 In total, 30% of patients in this series were classified as dying of locally destructive rather than widespread metastatic disease.

These findings suggest that, although the natural history of pancreatic cancer tends to be characterized by the development of metastatic disease at an exceedingly high frequency, local tumor burden may also contribute significantly to morbidity and mortality. Therefore, optimizing local disease control may be an essential component of treatment paradigms in both the localized and locally advanced pancreatic cancer settings. However, available data from phase II and III studies have failed to yield conclusive results regarding whether radiation produces improvements in patient outcomes and overall survival, partly because of differences and limitations in study designs. Additional questions, such as the sequencing of radiation relative to chemotherapy and the optimal means of delivering radiation, remain and must be addressed with greater clarity.

Potentially Resectable Disease
According to data from the SEER database, fewer than 10% of patients with pancreatic cancer have localized,
potentially operable disease at initial disease presentation.\textsuperscript{2} Long-term survival even in this group of patients remains relatively uncommon, with a 5-year survival rate of approximately 15 percent.\textsuperscript{3} Moreover, survival rates after pancreatic cancer resection do not seem to have substantially improved over the past several decades, despite evaluation of various chemotherapy and radiation regimens in the adjuvant setting. Several studies have shown that superior outcomes may be achieved when pancreatic cancer surgeries are performed at high-volume hospitals by experienced surgeons\textsuperscript{4,5}; however, even at these centers, the median survival is only around 18 months.\textsuperscript{6} These sobering statistics reflect the high rates of both local and distant recurrence that occur in patients who undergo surgery with curative intent. Therefore, the development of newer and more effective adjuvant strategies in this disease setting clearly includes a need to evaluate and refine approaches to achieve better local and systemic control.

**Early Adjuvant Studies**

Early evidence to support the use of chemoradiation in patients after pancreatic cancer surgery was provided in a clinical trial conducted by the Gastrointestinal Tumor Study Group (GITSG) in the 1970s and early 1980s.\textsuperscript{11} In this study, resected patients were randomized to receive either no further treatment or chemoradiation (4000 cGy delivered in two 2-week courses spaced apart by 2 weeks, with concurrent bolus 5-fluorouracil [5-FU], 500 mg/m\textsuperscript{2}, daily for 3 days at the start of each course) followed by bolus 5-FU chemotherapy for an additional 2 years. Although this study was closed early after accruing only 43 patients over 8 years, a statistically significant improvement was seen in the treatment arm for both median survival (20 vs. 11 months; adjusted \( P = .03 \)) and actuarial 2-year survival rate (43\% vs. 18\%). Notably, nearly one quarter of patients (24\%) randomized to the treatment arm never underwent therapy because of poor or prolonged postoperative recovery.

A subsequent phase III trial performed by the EORTC randomized 218 patients who had undergone resection of a pancreatic head cancer or periampullary cancer to receive either no further treatment or combined chemoradiation consisting of split-course radiation (similar to the GITSG study) with concurrent 5-FU given as a continuous infusion (25 mg/kg/d) for 5 days at the start of each radiation course.\textsuperscript{12} Distinct from the GITSG trial, however, was the absence of additional protocol-mandated maintenance chemotherapy after completion of chemoradiation. In the subgroup of the 114 patients with pancreatic head cancer, trends toward improved median survival (17.1 vs. 12.6 months; \( P = .099 \)) and 2- and 5-year survival rates (37\% vs. 23\% and 20\% vs. 10\%, respectively) were seen in patients enrolled on the treatment arm. However, these differences were not statistically significant (perhaps as a result of underpowering of the study), even after longer-term follow-up\textsuperscript{13}; hence, the investigators concluded that chemoradiation alone was not beneficial to patients in this setting.

**Recent Clinical Trials Examining the Respective Roles of Adjuvant Chemotherapy and Radiation**

More recently, several large phase III trials conducted in both Europe and the United States have sought to better define the roles and relative importance of chemotherapy and radiation as adjuvant therapy (Table 1). The ESPAC-1 trial,\textsuperscript{7} conducted by the European Study Group for Pancreatic Cancer, used a 2-by-2 factorial design in which patients were randomly assigned after surgery to 1 of 4 options: chemotherapy (bolus 5-FU plus leucovorin times 6 cycles), chemoradiation (split-course radiation with concurrent bolus 5-FU administered identically to the earlier GITSG trial), sequential therapy with chemoradiation followed by chemotherapy, or neither. The 4 arms were ultimately combined in 2 comparison groups for analysis: chemotherapy versus no chemotherapy, and chemoradiation versus no chemoradiation. Patients who underwent chemotherapy had a significantly improved median survival compared with those who did not, with an absolute difference in median survival of almost 5 months. Somewhat surprising, however, was the finding that patients who underwent chemoradiation not only did not benefit from this modality but actually had a shorter survival time than those who did not. Accordingly, investigators of the ESPAC-1 trial concluded that although chemotherapy should be offered to patients after pancreatic cancer resection, the role of chemoradiation was much more questionable and could not be recommended for routine use.

It should be pointed out that this study has been criticized on multiple fronts, including that fact that the lack of standardized trial methodology and suboptimal delivery and dosing of radiation may have
contribute to the high reported rates of local failure, and that a large number of patients did not receive the intended therapy. Nevertheless, these data further challenged the necessity of chemoradiation for treating resected pancreatic cancer.

A separate study led by the Radiation Therapy Oncology Group (RTOG 9704) in the United States compared gemcitabine with infusional 5-FU in the postoperative setting, with patients in both arms undergoing chemoradiation (5040 cGy given as split-course) followed by 5-FU/LV. The study design neither corroborated nor refuted the question raised by ESPAC-1 regarding the impact (either favorable or detrimental) of chemoradiation in this setting. Specific to tumors located in the pancreatic head, patients in the gemcitabine group of RTOG 9704 had a nonstatistically significant benefit in median survival that became more pronounced on multivariate analysis, with a 3-year survival difference of 31% versus 22% between the groups. This was the first phase III trial to use a chemoradiation regimen that is currently accepted as standard practice, in terms of both radiation therapy and chemotherapy. Therefore, this study design neither corroborated nor refuted the question raised by ESPAC-1 regarding the impact (either favorable or detrimental) of chemoradiation in this setting. Specific to tumors located in the pancreatic head, patients in the gemcitabine group of RTOG 9704 had a nonstatistically significant benefit in median survival that became more pronounced on multivariate analysis, with a 3-year survival difference of 31% versus 22% between the groups. This was the first phase III trial to use a chemoradiation regimen that is currently accepted as standard practice, in terms of both radiation therapy and chemotherapy.

### Table 1 Recent Phase III Trials Evaluating the Respective Roles of Chemotherapy and Radiation in the Adjuvant Setting for Patients After Pancreatic Cancer Resection

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample Size</th>
<th>Treatment Arms</th>
<th>Median Survival</th>
<th>P Value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPAC-1</td>
<td>75</td>
<td>Arm A: 5-FU/LV x 6 mo</td>
<td>Chemo (arms A+C): 20.1 mo vs.</td>
<td>.009</td>
<td>Bolus 5-FU/LV administered daily for 5 consecutive days every 28 days</td>
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<td></td>
<td></td>
<td>Arm B: 5-FU/XRT (4000 cGy given as split-course)</td>
<td>No chemo (arms B+D): 15.5 mo; P = .009</td>
<td></td>
<td>5-FU/XRT: Two 2-week courses of XRT, spaced 2 weeks apart; bolus 5-FU during first 3 days of each 2-week course</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>Arm C: 5-FU/XRT followed by 5-FU/LV</td>
<td>ChemoXRT (arms B+C): 15.9 mo vs.</td>
<td>.05</td>
<td>54% node-positive, 18% positive resection margins</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>Arm D: Observation</td>
<td>No chemoXRT (arms A+D): 17.9 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONKO-001</td>
<td>179</td>
<td>Gemcitabine x 6 mo</td>
<td>22.8 mo</td>
<td>.005</td>
<td>Gemcitabine standard infusion 3 weeks on/1 week off</td>
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<tr>
<td></td>
<td>175</td>
<td>Observation</td>
<td>20.2 mo</td>
<td></td>
<td>72% node-positive, 17% positive resection margins</td>
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<tr>
<td>RTOG 9704</td>
<td>221</td>
<td>Gemcitabine x 1 mo → 5-FU/XRT (5040 cGy) → Gemcitabine x 3 mo</td>
<td>20.5 mo</td>
<td>.09</td>
<td>5-FU given as a continuous infusion (250 mg/m²/d) in arm B and concurrent with XRT in both arms</td>
</tr>
<tr>
<td></td>
<td>230</td>
<td>5-FU x 1 mo → 5-FU/XRT (5040 cGy) → 5-FU x 3 mo</td>
<td>16.9 mo</td>
<td></td>
<td>XRT given in 28 consecutive fractions</td>
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<td></td>
<td>551</td>
<td>Gemcitabine x 6 mo</td>
<td>23.6 mo</td>
<td>.39</td>
<td>66% node-positive, 34% positive resection margins</td>
</tr>
<tr>
<td>ESPAC-3</td>
<td>537</td>
<td>Gemcitabine x 6 mo</td>
<td>23.6 mo</td>
<td></td>
<td>Survival results specific to pancreatic head tumors only</td>
</tr>
<tr>
<td></td>
<td>551</td>
<td>5-FU/FA x 6 mo</td>
<td>23.0 mo</td>
<td></td>
<td>72% node-positive, 35% positive resection margins</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; Chemo, chemotherapy; ChemoXRT, chemoradiotherapy; CONKO, Charite Onkologie Clinical Studies in GI Cancer; ESPAC, European Study Group for Pancreatic Cancer; FA, folinic acid; LV, leucovorin; RTOG, Radiation Therapy Oncology Group; XRT, radiotherapy.
tion dosing schedule and concurrent chemotherapy administration.

Two other large phase III trials from Europe also evaluated the role of gemcitabine in the adjuvant setting for pancreatic cancer. Notably, these studies were intended to exclusively address chemotherapy-specific questions, and thus neither of them included radiation as a protocol-mandated component of treatment. The first of these studies, CONKO-001, conducted by Charite Onkologie in Germany and Austria, compared adjuvant gemcitabine administered for 6 cycles with observation alone in 354 patients with completely resected pancreatic cancer. Patients receiving gemcitabine had a near doubling of median disease-free survival (13.4 versus 6.9 months; \( P \leq .001 \)), which translated into significant improvements in median, 1-year, and 3-year survival rates. In the second study (ESPAC-3), the investigators performed a direct comparison of gemcitabine versus 5-FU/folinic acid times 6 months in the adjuvant setting, similar to the RTOG trial but using bolus rather than infusional 5-FU, and without the confounding aspect of radiation. This study was originally designed to include a third arm, observation alone; however, as data emerged from other adjuvant trials regarding the benefits of adjuvant chemotherapy for pancreatic cancer, this arm was dropped. Still, ESPAC-3 represents the largest trial of its kind in pancreatic cancer, with a total of 1088 patients randomized between the treatment arms. No differences in either disease-free or overall survival were observed between patients receiving gemcitabine and those receiving 5-FU, with the only major distinction between the treatment arms being their respective toxicity profiles (more thrombocytopenia was observed in patients in the gemcitabine arm, whereas more grade 3/4 stomatitis and diarrhea was seen in the 5-FU arm).

Further prospective randomized studies, in which patients are assigned postoperatively either to undergo radiation or not, are required to sort out the relative importance of this modality in the adjuvant setting. One study conducted along these lines, designed by a European Intergroup (EORTC/FFCD/GERCOR 40013-22012/9203), was a multicenter phase II trial in which 90 patients were randomized after surgery to receive either gemcitabine alone for 4 months or gemcitabine for 2 months followed by concurrent gemcitabine/radiation. With a median follow-up of 27 months, no differences in overall or disease-free survival were observed between the arms (median survival, 24 months for both arms), although the rate of local recurrence was lower in the chemoradiation arm (11% vs. 24%; \( P = .16 \)). A larger phase III study that recently opened (RTOG 0848) will also be addressing this radiation/no radiation question. This trial, with an intended accrual of 950 patients, involves 2 separate randomizations. First, patients are randomized postoperatively to receive gemcitabine with or without erlotinib for 5 cycles. Patients confirmed to have no evidence of recurrence at the end of this period then undergo a second randomization, in which they receive either one final cycle of chemotherapy and then stop, or one cycle of chemotherapy followed by radiation with either capecitabine or infusional 5-FU. The primary end point of this study is overall survival.

**Alternative Strategies**

Although the previously mentioned studies all focused on the delivery of chemotherapy or radiation after patients had already undergone pancreatic cancer resection, a neoadjuvant approach to this disease offers several theoretical advantages, including no postoperative complications or delays; a positive selection for patients with favorable tumor biology (i.e., those who do not experience disease progression or develop metastases during neoadjuvant therapy); a potential increase in the likelihood of a successful R0 resection; and, from the standpoint of novel targeted agent development, the ability to evaluate on-target treatment effects in tumor tissue.

In the largest reported series of neoadjuvant therapy conducted at a single institution, gemcitabine-based chemotherapy (either alone or with cisplatin) plus an abbreviated course of chemoradiation (30 Gy in 10 fractions with concurrent weekly gemcitabine) was administered preoperatively to patients with resectable disease, with a resultant delay in surgery of 12 to 17 weeks. Of 176 patients, approximately 65% eventually underwent a successful operation; of these, median survival was greater than 30 months, reflecting the favorable selection of patients using this type of preoperative strategy. Although promising, this approach should still be considered experimental for patients with clearly resectable disease at baseline.

A similar strategy was used at the same institution in patients with borderline resectable pancreatic cancer, with treatment consisting of 4 months
of gemcitabine-based chemotherapy followed by radiation (50.4 Gy in 28 fractions) with concurrent gemcitabine. General agreement exists that radiation plays an important role in this subset of patients, in whom initial cytoreduction to achieve an R0 resection is the ultimate goal. In this series, 98% of patients with initial arterial involvement underwent successful resection with negative surgical margins. Moreover, median survival in this group was 40 months, suggesting an even greater surgical selection for patients with truly localized disease and an adequate performance status after prolonged systemic and radiation therapy.

Undoubtedly, novel therapeutic agents and new treatment paradigms will be required to make a significant impact in this disease setting. For example, the addition of an allogeneic pancreatic tumor cell vaccine to standard chemoradiation, and more aggressive combination chemoradiation platforms, each have shown provocative efficacy in phase II trials but require further validation in larger phase III studies before being considered appropriate options.

In the future, appropriate treatment selection may also be guided based on both pharmacogenetic analysis of the patient (looking for single-nucleotide polymorphisms in germline DNA) along with predictive biomarkers in resected tumor samples. An example of this latter possibility is shown through an analysis performed on tumor specimens available from the RTOG 9704 trial, in which the nucleoside transporter hENT1 proved to be a valuable biomarker of sensitivity to adjuvant gemcitabine but not 5-FU therapy.

In summary, the ability to molecularly interrogate both host and tumor may allow for greater success in refining the best therapeutic options for patients in the adjuvant setting, including determining not only the correct selection of drugs but also who is most likely to benefit from radiation.

**Locally Advanced Disease**

**Chemotherapy Alone Versus Chemoradiation in Locally Advanced Pancreatic Cancer: An Important Controversy?**

Several recent randomized clinical trials evaluating gemcitabine-based chemotherapy in advanced pancreatic cancer have included patients with locally advanced disease without planned radiotherapy. Median survival durations of between 9.1 and 9.9 months have been achieved in these subsets of patients (Table 2), although many of these patients also underwent radiotherapy. In comparison, very similar but slightly longer median survivals (11.3 and 11.9 months) were achieved in the last 3 phase II RTOG trials evaluating fractionated chemoradiation as an initial treatment strategy. The contribution of further systemic chemotherapy in these trials was not well documented.

Two recent phase III trials comparing initial chemotherapy to initial chemoradiation have reported conflicting results. The Fédération Francophone de Cancérologie Digestive and Société Française de Radiothérapie Oncologique (FFCD-SFRO) compared gemcitabine alone to an experimental chemoradiation regimen followed by gemcitabine. The median overall survival in the gemcitabine-alone arm was unusually high (14.3 months) and is not consistent with reported median survivals of the locally advanced subsets treated with gemcitabine-based chemotherapy alone in contemporaneous randomized trials (9.1–9.9 months; Table 2). Conversely, an unusually poor survival duration (8.4 months) was observed among the patients treated with chemoradiation followed by gemcitabine. One explanation is that the high rate of acute toxicity observed in the chemoradiation arm led to poor compliance with the regimen and declining performance status, and probably contributed to poor outcomes. The chemoradiation regimen in this trial was experimental, consisting of cisplatin (which is not considered standard in this setting) combined with an unusually high dose of infusional 5-FU (300 mg/m²/d); moreover, the dose of radiation (60 Gy) to large volumes exceeded the tolerance of the duodenum. The hypothesis was that intensification of chemoradiation would improve outcomes, which it clearly did not. The important lessons from the FFCD-SFRO study are that chemoradiation regimens must be well tolerated, and phase II multi-institutional studies must be conducted before phase III trials are undertaken.

The only other recent trial comparing induction chemotherapy with chemoradiation ECOG 4201. This trial compared gemcitabine-based chemoradiation (gemcitabine given at 600 mg/m² weekly with radiation to regional nodal volumes to a dose of 50.4 Gy in 28 fractions) followed by weekly gemcitabine (1000 mg/m² weekly, 3 of 4 weeks), with standard
treatment consisting of gemcitabine alone. Although it closed prematurely after accruing only 74 of a planned 316 patients, a statistically significant median survival benefit was seen in the arm that underwent chemoradiation compared with chemotherapy alone (11.0 vs. 9.2 months; \( P = .034 \); 2-sided, stratified log rank). This benefit came at the cost of increased gastrointestinal toxicity (grade 3–4, 38% vs. 14%; \( P = .03 \)) and fatigue (32% vs. 6%). Thus, the addition of chemoradiation before standard chemotherapy resulted in a modest prolongation of median survival at the cost of a modest increase in toxicity that remained manageable. The results from this trial are consistent with the results from contemporaneous cooperative group studies (Table 2).

**Does Sequencing of Chemotherapy and Chemoradiation Matter?**

The selection of patients who are most appropriate for chemoradiation may be best accomplished with an initial strategy of gemcitabine-based chemotherapy for 2 to 6 months, followed by consolidation with chemoradiation in patients who do not have rapidly progressive distant disease. Tolerability and response based on serial radiographic imaging and CA 19-9 measurement can be used to optimize the duration of systemic therapy. Chemoradiation directed to the gross tumor can only then be used as consolidation. Recent studies using this strategy of initial systemic chemotherapy followed by chemoradiation have reported median survival durations of 14.4 to 18.8 months (Table 2).

In summary, patients with locally advanced pancreatic cancer probably benefit modestly in different ways from both systemic therapy and chemoradiation. These approaches are complementary, and rational integration of both modalities should be considered in the care of all patients with locally advanced disease to maximize survival duration. Even when both modalities are used, however, distant and local tumor progression are frequent limitations of treatment.

For example, in one phase II trial at MD Anderson Cancer Center of 69 patients with stage III (locally advanced) disease, median survival was 18.8 months using a strategy of 2 cycles of chemotherapy followed by chemoradiation. This better-than-expected survival duration was long enough to reveal the limitations of local therapy: actuarial local tumor control was 90% up to 16 months, but eventually fell to less than 50% at 2 years. This time course to local tumor progression is similar to that in most solid tumors treated definitively with chemoradiation. As median survival durations continue to improve in patients treated for locally advanced pancreatic cancer, local persistence and progression of disease will probably be shown to be a common limitation to long-term survival.

**Radiation Technique**

**What Should the Target be?**

Patients treated with postoperative radiation therapy are typically treated with 50.4 Gy, given in 1.8-Gy fractions. Initial fields include the tumor bed, porta hepatis, superior mesenteric vessels, and the celiac axis. Field reductions off of the porta hepatis are often made after 45 Gy. Similar fields are used if the patient has a borderline resectable or resectable tumor unless concurrent gemcitabine is used. If concurrent gemcitabine is given, or if the patient has a locally advanced unresectable tumor, only the gross tumor should be treated.

In patients with unresectable tumors, no evidence shows that treatment of the para-aortic or porta hepatis lymph nodes leads to improved tumor control or survival. Treatment of the porta hepatis increases the dose to the duodenum and stomach, leading to increased rates of grade 3 gastrointestinal toxicity and fatigue.

In patients with poor performance status, the increased irradiated volumes can contribute to fatigue and a decline in performance status. In fact, the best results have been seen from treatment of the gross tumor only, which is better tolerated. Dual-phase, contrast-enhanced, thin-slice CT imaging is recommended to identify the tumor. A multiple-field technique with CT planning is recommended for 2-cm tumors to block margins used in the radial directions, and a 3-cm block margin should be used in the cranial and caudal directions to account for respiratory motion.

The standard dose of radiation is 50.4 Gy given in 28 fractions. In a recent RTOG phase II trial (RTOG 0411), major deviations from this technique were associated with increased grade 3 gastrointestinal toxicity; all were from inappropriately large treated volumes, possibly related to inadequate diagnostic imaging.
Stereotactic Body Radiation Therapy For Pancreatic Cancer?

Stereotactic body radiotherapy (SBRT) is capable of precisely delivering high doses of radiation to small tumor volumes. The CyberKnife is an innovative approach that incorporates real-time tracking of implanted fiducials to account for organ motion in real-time treatment delivery. Because tissue-ablative doses of radiation are delivered with SBRT, avoidance of sensitive normal tissues is critical in the application of this technology. For primary or metastatic tumors of the lung or liver, this approach is particularly appealing because these tumors move with respiration and the ablation of a small volume of surrounding normal liver or lung tissue to the tumor usually does not result in a significant clinical

<table>
<thead>
<tr>
<th>Reference</th>
<th>Radiation Dose (Gy)</th>
<th>Chemotherapy Agent</th>
<th>No. of Patients</th>
<th>Median Survival (mo)</th>
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<td><strong>Pre-CT–Era Studies</strong></td>
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<td>Moertel et al., 1969&lt;sup&gt;44&lt;/sup&gt;</td>
<td>35–40</td>
<td>5-FU</td>
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<td>5-FU and SMF</td>
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<td>CALGB 80303, 2007&lt;sup&gt;49&lt;/sup&gt;</td>
<td>–</td>
<td>Gemcitabine +/- bevacizumab</td>
<td>93</td>
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<td>Capecitabine + bevacizumab</td>
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<tr>
<td>Aarhus University, Denmark, 2005&lt;sup&gt;43&lt;/sup&gt;</td>
<td>45Gy/3 fx</td>
<td>–</td>
<td>22</td>
<td>5.6</td>
</tr>
<tr>
<td>Stanford University, 2008&lt;sup&gt;42,5&lt;/sup&gt;</td>
<td>25Gy/1 fx</td>
<td>–</td>
<td>56</td>
<td>6.7</td>
</tr>
</tbody>
</table>

All data are quoted are calculated from the date of enrollment or start of protocol therapy. Abbreviations: 5-FU, 5-fluorouracil; FFCD-SSRO, Fédération Francophone de Cancérologie Digestive and Société Française de Radiothérapie Oncologique; fx, fraction; GITSG, Gastrointestinal Study Group; MDACC, University of Texas MD Anderson Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center; RTOG, Radiation Therapy Oncology Group; SMF, streptozotocin, mitomycin, 5-FU; UCSF, University of California at San Francisco; UM, University of Michigan.

<sup>*</sup>Most (65%) patients received prior chemotherapy. Median survival was 11.6 months from the start of chemoradiation.

<sup>†</sup>Chemotherapy followed by chemoradiation in all patients.

<sup>‡</sup>Staging included laparoscopy

<sup>§</sup>Locally advanced patients
consequence. However, if a radiosensitive structure, such as the duodenum, small bowel, or stomach, is near the target, real-time motion tracking may minimize the volume of mucosa that receives a high dose, but large volumes receive intermediate doses that are many times higher than those received from a standard daily dose of 2 Gy. In particular for the gastrointestinal tract, the dose and volume safety constraints have not been defined.

The feasibility of SBRT as a pancreatic cancer treatment was evaluated in a phase I dose escalation trial at Stanford University in patients with locally advanced disease, consisting of a single fraction of radiation therapy. The recommended dose was 25 Gy. Subsequent studies by this same group examined different strategies for incorporating SBRT into treatment strategies, including 45 Gy of intensity-modulated radiation therapy with concurrent 5-FU followed by a 25-Gy SBRT boost, and gemcitabine given before and after a single 25-Gy fraction of SBRT. In this latter experience, late gastrointestinal toxicity was significant, including duodenal ulceration, stricture, and perforation. The updated pooled Stanford experience reported an actuarial 25% risk of late gastrointestinal toxicity (mostly ulceration of the gastrointestinal tract) and a median survival of only 6.7 months. Their experience is similar to what was reported in a phase I trial from Denmark using 3 fractions of 15 Gy. Investigators also reported unacceptable gastrointestinal toxicity, deterioration in performance status, and questionable palliative effect. Given the lack of any convincing prospective evidence for improved outcome, significant mucosal toxicity that could compromise survival, and no clear validated dose constraints for the gastrointestinal tract, SBRT has no role outside the setting of a clinical trial in patients with pancreatic cancer or at any other site around or near the gastrointestinal tract.

Conclusions

Randomized trial data in both the adjuvant and locally advanced disease settings have not provided clear evidence that chemoradiation improves survival outcomes. However, the high local tumor recurrence/persistence rate reported in all trials suggests that local control may be an important component in therapeutic management, even if the benefit is probably modest. The keys to the successful integration of radiotherapy in the care of patients with localized pancreatic cancer are sequencing, selection, and smaller treatment volumes. The recent rapid autopsy series from Johns Hopkins suggests that loss of the tumor suppressor gene DPC4 correlates significantly with patterns of failure (locally destructive vs. metastatic), and may be useful in the future in determining which patients may derive the greatest benefit from local tumor control.

A strategy of initial chemotherapy followed by consolidation with a well-tolerated chemoradiation regimen can be considered an acceptable approach in patients after resection and in those with locally advanced disease. Consolidative chemoradiation should only be considered in these settings after 6 months of initial chemotherapy in patients who have no evidence of tumor dissemination. Although many novel chemoradiation regimens have been investigated in clinical trials, none is clearly more efficacious than radiation with concurrent use of a fluoropyrimidine (5-FU or capecitabine), and they are typically more toxic. The use of concurrent gemcitabine with radiotherapy in this disease is also a reasonable option, because it is a proven systemic agent in pancreas cancer and has radiosensitizing properties, although it is potentially more toxic to the gastrointestinal mucosa. In the future, advances in systemic therapies used both concurrently and sequentially with radiation must occur if significant improvements in median survival are to be realized for this patient population.

References


Ko and Crane


