The Role of Radiation Therapy in Pancreas Cancer

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ABSTRACT

The role of radiation therapy in pancreatic cancer continues to be investigated. Its use in the adjuvant setting remains controversial. Its use is more generally accepted in borderline resectable disease, but prospective data are sparse. Randomized trials have yielded conflicting data in locally advanced disease. Radiation techniques have improved over time, such that findings in older trials are not necessarily applicable in modern practice. This article reviews the role of radiation in resectable, borderline resectable, and unresectable pancreatic cancer.

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The American Cancer Society estimates that 37,680 people will be diagnosed with pancreas cancer and 34,290 people will die of the disease in 2008.[1] The overall 5-year relative survival rate for patients reported to the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute from 1996 to 2004 was 5.1%.[1]

Surgery remains the only potentially curative treatment modality for pancreas cancer. However, only a minority of patients are candidates for surgery at diagnosis, and only a minority of patients who undergo surgery are cured.[1–4] In an attempt to improve survival, chemotherapy and radiation therapy (RT) have been used both in the adjuvant setting and for locally advanced unresectable disease. Although chemotherapy has gained acceptance as an appropriate therapy, the role of RT remains controversial. This article reviews data on RT in both resectable and unresectable pancreatic cancer.

RESECTABLE PANCREAS CANCER

Adjuvant RT

To date, randomized trials (summarized in Table 1)[2,4,5] have failed to resolve the debate regarding the role of adjuvant RT in resectable pancreas cancer. An initial trial by the Gastrointestinal Tumor Study Group (GITSG) showed a survival benefit with the addition of chemoradiotherapy to surgical resection.[2,3] The RT dose was 40 Gy delivered via split course, with a 2-week break after 20 Gy. Patients received 5-fluouro-uracil (5-FU) chemotherapy during RT, followed by maintenance 5-FU chemotherapy for 2 years or until progression. Eligibility criteria included negative surgical margins and excluded periampullary tumors. The trial accrued only 43 patients over 8 years, and closed early both due to poor accrual and due to the detection of a survival benefit on interim analysis. After the randomized portion of the trial was closed, an additional 30 patients were assigned to the chemoradiotherapy arm, and results showed similar survival to the patients initially randomized to chemoradiotherapy.

A trial by the European Organization for Research and Treatment of Cancer (EORTC) did not show an overall survival benefit with the addition of chemoradiotherapy to surgical resection.[5] The RT dose was 40 Gy delivered split course with concurrent 5-FU chemotherapy, as in the GITSG trial. Unlike the GITSG trial, the EORTC trial did not include maintenance chemotherapy, and the eligibility criteria allowed periampullary and pancreatic head adenocarcinomas (the latter of which carries a worse prognosis). Positive margins were allowed, and 25% of patients had positive margins. In total, 53% of patients had N0 disease, whereas 28% of patients in the GITSG trial had node-positive disease. A trend toward improved survival ($P = .07$) was identified in an analysis including only patients with pancreatic head carcinoma (n = 81). One potential explanation for a lack of survival benefit observed in this trial as opposed to the GITSG trial is the absence of maintenance chemotherapy; other potential contributing factors are the inclusion of a greater proportion of patients with node-positive disease and the inclusion of patients with positive margins.

Both the GITSG trial and the EORTC trial evaluated the use of adjuvant chemoradiotherapy, but did not address the effects of adding RT to chemotherapy or vice versa. The European Study Group for Pancreatic Cancer (ESPAC)-1 trial featured four arms, consisting of (1) no adjuvant treatment, (2) adjuvant chemotherapy alone, (3) adjuvant RT with concurrent chemotherapy, and (4) adjuvant RT with concurrent chemotherapy followed by maintenance chemotherapy.[4] Enrollment criteria included ductal adenocarcinoma of the pancreas. Positive margins were allowed, and 18% of patients had positive margins. The trial allowed randomization by 2 × 2 factorial design to any of the four arms, or physicians could choose that patients be randomized between (1) no treatment vs. chemotherapy *or* (2) no treatment vs. chemoradiotherapy.

The ESPAC-1 trial enrolled 541 patients, and was initially reported in 1999. In part

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Table 1: Randomized trials of adjuvant radiation therapy in pancreatic cancer

Trial	Treatment	n	Local recurrence	Distant metastases	Disease-free survival	Overall survival	Median survival
GITSG[2]	(A) RT[a] and CT (bolus 5-FU during RT[b], then once weekly for 2 yrs starting one mo after RT)	21	47%	40% (liver)[c]	48% (2 yr)	14% (5 yr)	20 mo
	(B) Observation	22	33%	52% (liver)[c]	14%[d] (2 yr)	4%[d] (5 yr)	11 mo[d]
EORTC[5]	(A) RT[a] and CT (CI 5-FU during RT[e])	104	36% (14% LR only)	49% (31% DM only)	37% (2 yr)	28% (5 yr, all) 20% (5 yr, pancreas)[f]	24.5 mo (all) 17.1 mo (pancreas)[f]
	(B) Observation	103	36% (15% LR only)	49% (28% DM only)	38% (2 yr)	22% (5 yr, all) 10% (5 yr, pancreas)[f]	19 mo (all) 12.6 mo (pancreas)[f]
ESPAC-1[4,g]	(A) RT[a] and CT (bolus 5-FU during RT[b])	73	For all patients: 62% (35% LR only)	For all patients: 61% (34% DM only)		7% (5 yr)	13.9 mo
	(B) RT and CT (bolus 5-FU during RT[g] followed by 5-FU and folinic acid monthly for 6 mo[h])	75				29% (5 yr)	21.6 mo
	(C) CT[h] (5-FU and folinic acid monthly for 6 mo)	72				13% (5 yr)	19.9 mo
	(D) Observation	69				11% (5 yr)	16.9 mo

Abbreviations: CI = continuous infusion; CT = chemotherapy; DM = distant metastases; 5-FU = 5 fluorouracil; mo = month; LR = local recurrence; yr = year.

[a] All trials used 40 Gy RT delivered split course, with a 2-week break after 20 Gy.

[b] Bolus 5-FU 500 mg/m^2 on days 1–3 of each 20 Gy course of RT.

[c] Rate of liver metastases was reported, but not rate of any metastases.

[d] $P < .05$.

[e] CI 5-FU 25 mg/kg/24 hr during first course of RT and for 0, 3, or 5 days during 2nd course of RT, depending on toxicity during first course.

[f] Periampullary tumors were allowed in EORTC trial. When the subgroup of patients with only pancreas adenocarcinoma (n = 114) was evaluated, the difference in overall survival with the addition of adjuvant chemoradiotherapy approached, but did not reach, statistical significance ($P = .09$).

[g] Groups C and D (combined) were compared to groups A and B (combined), and the overall survival was higher in groups C and D (median survival 17.9 months, 5-yr overall survival 29%) compared to groups A and B (median survival 15.9 months, 5-yr overall survival 10%) ($P = .05$). Groups A and D (combined) were compared with groups B and C (combined), and overall survival was lower in groups A and D (median survival 15.5 months, 5-yr overall survival 8%) compared to groups B and C (median survival 20.1 months, 5-yr overall survival 21%) ($P = .009$).

[h] IV 5-FU 425 mg/m^2 and folinic acid 20 mg/m^2 daily for 5 days, monthly for 6 months.

due to criticisms regarding physician choice of randomization arms, the trial was republished in 2001, reporting only on the 289 patients who underwent randomization to any of the four arms. Median survival was 16.9 months with no adjuvant therapy, 21.6 months in patients who received adjuvant chemotherapy, 13.9 months in patients who received adjuvant chemoradiotherapy, and 19.9 months in patients who received adjuvant chemoradiotherapy plus maintenance chemotherapy. The authors did not report whether differences among the four treatment arms reached statistical significance.

One analysis was performed grouping patients who received chemotherapy vs. patients who received no chemotherapy. Patients defined as receiving chemotherapy included patients who received chemotherapy alone *and* patients who received chemoradiotherapy followed by chemotherapy. Patients defined as receiving no chemotherapy included patients who received no treatment *and* patients who received chemoradiotherapy but no maintenance chemotherapy. Patients who received chemotherapy (as defined above) had a survival benefit compared to those who did not ($P = .009$).

Another analysis was performed grouping patients who received RT vs. patients who received no RT. Patients who received RT included patients who received chemoradiotherapy alone *and* patients who received chemoradiotherapy followed by

Table 2: Comparison of gemcitabine arm of RTOG 97-04 trial and gemcitabine arm of CONKO-1 trial.

	RTOG 97-04[24]	CONKO-1[1]
Treatment	1 cycle gemcitabine → 5-FU/RT → 4 cycles gemcitabine	6 cycles gemcitabine
Patient characteristics		
Positive margins	34%	19%
CA 19-9 >90 U/mL	79%	100%
Node-positive	66%	71%
T3/4	75%	86%
Disease control		
3-year OS, all patients	33%	30%[a]
3-year OS in patients with CA 19-9 <90 U/mL	31%	30%[a]
Median survival, all patients	20.5 mo	22.1 mo
Median survival in patients with CA 19-9 <90 U/mL	22.8 mo	22.1 mo
Local recurrence rate	23%	25%
Distant metastasis rate	75%	67%
Toxicity		
Any grade 3 or higher	79%	14.5%[b]
Hematologic grade 3 or higher	58%	4%
Nonhematologic grade 3 or higher	58%	3.5%

Abbreviations: mo = month; OS = overall survival.
[a] Estimated survival.
[b] Serious adverse event, grade not specified.

maintenance chemotherapy. Patients who received no RT included patients who received no treatment *and* patients who received chemotherapy alone. Patients who received RT had a survival detriment compared to those who did not ($P = .05$). The authors concluded that adjuvant chemoradiotherapy has a deleterious effect on survival.

The ESPAC-1 trial has been criticized for lack of quality assurance of RT plans. RT field size and technique were not specified, and no central review of RT plans was performed. In the United States, the Radiation Therapy Oncology Group (RTOG) 97-04 trial of adjuvant chemoradiotherapy in pancreas cancer required central review of RT portals.[6] This trial delivered 5-FU concurrent with RT, and randomized patients between 5-FU and gemcitabine before and after concurrent 5-FU and RT. In the 5-FU arm of the trial, 51% of patients were treated per protocol-specified RT guidelines, 35% had acceptable variation, and 5% unacceptable variation. Corresponding median survival durations were 1.47 years, 1.34 years, and 1.18 years, respectively ($P = .055$). In the gemcitabine arm, 45% of patients were treated per protocol, 43% had acceptable variation, and 5% unacceptable variation. Corresponding median survival durations were 1.89 years, 1.41 years, and 1.37 years, respectively ($P = .023$). The quality of RT therefore had an effect on survival. These results highlight the importance of specifying RT technique and the necessity for quality review in clinical trials.

The GITSG, EORTC, and ESPAC-1 trials have been criticized for the use of split course RT and for low RT dose (40 Gy). In theory, split course therapy allows for accelerated repopulation of malignant cells, resulting in reduced tumor control.[7] Split course therapy has been associated with decreased effectiveness of RT in anal cancer, cervical cancer, and head and neck cancer.[7–10] Therefore, the split course radiation used in the above mentioned adjuvant RT trials may have impaired the effectiveness of RT.

In multiple sites including head and neck, breast, cervix, ovary, lung, and testes, doses of 50 Gy are required to control microscopic disease with RT in a majority of cases, raising concerns that doses of 40 Gy in pancreas carcinoma are inadequate.[11,12] Although concerns exist regarding inadequate dose of radiation in the trials discussed, a separate GITSG trial compared 40 Gy radiation alone vs. 40 Gy chemoradiotherapy vs. 60 Gy radiation alone in unresectable pancreas cancer, and showed no improvement in survival with higher-dose radiation.[13] However, since this trial used the split course technique and used 2-dimensional therapy with AP:PA (anteroposterior-posteroanterior) fields, the results may not be applicable to modern RT practice. In addition, this trial did not address important end points regarding radiation dose, including response rates or local control, and included only patients with unresectable disease, making it difficult to generalize findings to the setting of resected disease. Although single institution series have reported improved local control with the addition of intraoperative RT or I-125 brachytherapy to external beam RT, suggesting a dose response, dose response has not been confirmed in randomized trials.[14–17]

The aforementioned trials address the effect of adjuvant therapy on survival, but do not address local control, palliation of local symptoms, and quality of life. In the setting of pancreas adenocarcinoma, both local and distant recurrence rates are high following surgical resection (33%-86% and 23%-92%, respectively).[2,4,5,18–23] High rates of distant metastases argue in favor of chemotherapy. High rates of local recurrence argue in favor of RT. If local recurrences do not result in significant morbidity and are generally associated with distant recurrence, then local control becomes less important than distant control, and therapies to decrease local control may not be warranted.

In the ESPAC-1 and EORTC trials, 15% to 19% of patients had local failure alone, suggesting a role for modalities that improve local control. Distant metastases alone occurred in 18% to 29% of patients, and 15% to 20% had both local and distant failure. Local recurrence may be associated with pain and obstruction. Prospective trials are needed to accurately assess the effect of RT on local control and quality of life. The improvements in local control must be weighed against the toxicity of treatment.

The Charité Onkologie (CONKO)-1 trial evaluated surgery alone vs. surgery plus six cycles of adjuvant gemcitabine chemotherapy, without RT.[1] Chemotherapy consisted of gemcitabine 1000 mg/m^2 weekly for 3 of 4 weeks. The addition of chemotherapy to surgery improved progression-free survival, the primary end point of the study, but not overall survival. The trial supports the use of adjuvant therapy in pancreatic cancer, but does not address the role of RT. The results of the gemcitabine arm of the CONKO-1 trial have been compared to the gemcitabine arm of RTOG 97-04, which included RT.[24] Although intriguing, such comparisons are not statistically valid and cannot be used to draw conclusions regarding the benefit of RT in addition to chemotherapy, given differences in the two trials.

Perhaps the most striking difference is that the CONKO-1 study included only patients with carbohydrate antigen (CA) 19-9 serum values of less than 2.5 times normal, whereas RTOG 97-04 did not define an upper limit for CA 19-9. RTOG evaluated the subgroup of 200 patients with CA 19-9 values of less than or equal to 90 U/mL (approximately 2.5 times normal) treated in the gemcitabine arm of the 97-04 trial. Median survival in this subgroup was similar to that observed in the gemcitabine arm of the CONKO-1 trial. Local recurrence rates were also similar in the gemcitabine arm of both trials, despite the use of RT in the RTOG trial. However, the RTOG trial had a higher percentage of patients with positive margins compared to the CONKO-1 trial. Toxicity was higher in the RTOG trial compared to the CONKO-1 trial, but 90% of patients in the former completed therapy despite toxicities; transient toxicities may be acceptable if local control, survival, or quality of life is ultimately improved.

In summary, the CONKO-1 study supports the use of adjuvant chemotherapy in patients with CA 19-9 levels less than 2.5 times normal, but does not prove or disprove the value of RT in this setting. Comparisons of patient characteristics, toxicity, and outcome between the CONKO-1 and RTOG 97-04 trials are presented in Table 2.

During radiation therapy, 11% to 26% of patients experience distant progression.[24–27] A reasonable consideration in a disease with high distant metastases rates is to begin with adjuvant chemotherapy, followed by RT in patients who do not progress.

Preoperative RT

Preoperative RT has theoretical advantages compared to postoperative therapy, including improved tissue oxygenation (which may enhance effectiveness of RT), sterilization of the surgical field (which may minimize iatrogenic tumor seeding), and improved ability of the patient to tolerate and complete treatment. In addition, a proportion of patients will develop distant metastatic disease during preoperative therapy, and will be spared a major surgical procedure.

Potential disadvantages include the fact that, in the absence of staging laparoscopy, some patients with distant metastatic disease who are unlikely to benefit from RT will receive unnecessary treatment. Data from Massachusetts General Hospital and others suggests that nearly 30% of patients with pancreas carcinoma who have no evidence of metastatic disease based on radiographic data are found to have distant metastases at the time of staging laparoscopy.[28,29] Furthermore, it is possible that local progression during neoadjuvant therapy will preclude surgical resection, or that radiation-related toxicity may impair the patient's ability to tolerate surgery and increase risk of wound complications.

Evans et al reported results of a phase II study of 86 pancreas cancer patients with potentially resectable disease treated with preoperative chemoradiotherapy (7 weekly doses of gemcitabine 400 mg/m^2 plus 30 Gy radiation in 10 fractions).[30] Twelve percent of patients did not undergo surgery due to distant disease progression (9%) or decline in performance status (3%). An additional 10% were taken to surgery but found to have distant disease, whereas 74% underwent successful pancreaticoduodenectomy. Median survival was 7 months for patients who did not undergo pancreaticoduodenectomy and 34 months for those who did. No patient had isolated local progression alone precluding surgery. The authors concluded that preoperative gemcitabine-based chemoradiotherapy identified a subgroup of patients unlikely to benefit from surgical resection, without compromising survival in patients who ultimately undergo surgery.

An earlier phase II trial of 53 patients with resectable pancreas cancer by Hoffman et al used preoperative RT (50.4 Gy in 28 fractions) and chemotherapy (mitomycin-C and 5-FU).[24] Twenty-three percent of patients did not go to surgery; distant progression was the most common cause (13%), with other causes including decline in performance status (6%) and isolated local progression (6%). Therefore, unlike in the study by Evans et al, a small percentage of patients may have been excluded from potentially curative surgery through the use of neoadjuvant therapy. Median survival was lower than in the Evans et al trial, likely due to the use of 5-FU–based, rather than gemcitabine-based, chemotherapy.

A retrospective analysis of preoperative vs. postoperative chemoradiotherapy at M. D. Anderson Cancer Center did not note differences in toxicity or survival. However, this report did show that prolonged recovery following surgical resection prevented the delivery of adjuvant therapy in up to 25% of patients.[31] Randomized trials are lacking, but existing data support further exploration of neoadjuvant chemoradiotherapy.

UNRESECTABLE PANCREAS CANCER

The role of RT in unresectable, locoregionally advanced pancreas cancer remains controversial. On the one hand, RT may slow the progression of local disease and possibly alleviate or prevent symptoms including pain, biliary obstruction, bleeding, and bowel obstruction. On the other hand, the likelihood of micrometastatic distant disease is high, treatment is not expected to be curative, and radiation can result in toxicity.

A randomized study by GITSG demonstrated that the addition of chemotherapy (5-FU) to radiation improved overall survival.[13] Four other randomized trials have compared chemotherapy alone to chemoradiotherapy (see Table 3).[32–35] All four of these trials delivered chemotherapy during RT, as well as maintenance chemotherapy following RT.

Two trials demonstrated an advantage

Table 3. Randomized trials of radiation therapy in unresectable, locally advanced pancreatic cancer

Trial	Treatment	n	Median survival	Overall survival	Median time to progression	RT technique
ECOG (1985)[33]	(A) 40 Gy RT (2-wk break between each 20 Gy course) and 5-FU (600 mg/m^2 IV bolus on d 1-3 of each course of RT and weekly after completion of RT)	34	8.3 mo	28% (1 yr)	4.4 mo	AP:PA
	(B) 5-FU (600 mg/m^2 weekly)	37	8 mo	28% (1 yr)	4.2 mo	
GITSG (1981)[13]	(A) 40 Gy RT (2-wk break between each 20 Gy course) and CT (bolus 5-FU 500 mg/m^2 on d 1-3 of each course of RT and then every 4 wks for 2 yrs)	83	10 mo	40% (1 yr)	6 mo	AP:PA
	(B) 60 Gy RT (2-wk break between each 20 Gy course) and CT (bolus 5-FU 500 mg/m^2 on d 1-3 of each 20 Gy course of RT and then every 4 wks for 2 yrs)	86	10 mo	40% (1 yr)	8 mo	
	(C) 60 Gy RT (2-wk break between each 20 Gy course)	25	6 mo[a]	10% (1 yr)[a]	3 mo[a]	
GITSG (1988)[32]	(A) RT (2-wk break between each 20 Gy course) and CT (bolus 5-FU 350 mg/m^2 on d 1-3 of each course of RT, then SMF for 2 yrs starting d 64)	24	8 mo	19% (2 yr)	Not stated	CT plan, 3-4 fields
	(B) SMF chemotherapy for 2 yrs or until progression	24	10 mo[a]	41% (2 yr)[a]		
FFCD/SFRO (2008)[34]	(A) RT (60 Gy) and CT (5-FU/cisplatin during RT, and gemcitabine after RT)	59	8.4 mo	32% (1 yr)	6 mo[b]	Conformal RT recommended
	(B) Gemcitabine	60	14.3 mo[a]	53% (1 yr)	7 mo[b]	
ECOG 4201 (2008)[35]	(A) 50.4 Gy RT with concurrent gemcitabine 600 mg/m^2 weekly x 6, then gemcitabine 1000 mg/m^2 weekly x 3 of 4 wks for 5 cycles	74 total	11.0 mo	Not stated	6.3 mo	3D conformal RT
	(B) Gemcitabine 1000 mg/m^2 weekly x 3 of 4 wks for 7 cycles		9.2 mo[a]		6.1 mo	

Abbreviations: CI = continuous infusion; CT = chemotherapy; d = day; mo = month; SMF = streptozocin, mitomycin, 5-FU; 3D = 3-dimensional; wk = week; yr = year.
[a] $P < .05$.
[b] Estimated from graph.

with the addition of radiation to chemotherapy in terms of overall survival (1988 GITSG study,[32] Eastern Cooperative Oncology Group [ECOG] 4201 study published in 2008[35]), and two did not (Federation Francophone de Cancerologie Digestive/French Society of Radiation Oncology [FFCD/SFRO] study,[34] ECOG study published in 1985[33]). Heterogeneity of treatments and outcomes and the small number of patients accrued in these trials make it impossible to draw definite conclusions regarding the benefit of RT. However, some important observations can be made. To begin with, the GITSG trial and the initial ECOG study (published in 1985) did not incorporate gemcitabine chemotherapy, which has been shown to have a significantly higher response rate compared to 5-FU.[36] In addition, both of these trials used split course RT technique. Therefore, the application of these results to modern practice is questionable. The streptozocin, mitomycin, and 5-FU (SMF) chemotherapy used in the GITSG trial has greater toxicity compared to gemcitabine, and results achieved with such a regimen do not offer the added benefit observed when RT is used with gemcitabine.

The FFCD/SFRO study did not show an advantage to RT, and in fact was closed early when an interim analysis suggested that patients receiving RT did worse. This trial has been criticized for its use of high-dose radiation (60 Gy) given concurrent with aggressive chemotherapy (5-FU and cisplatin). The National Cancer Care Network (NCCN) considers single-agent 5-FU chemotherapy during 50.4 Gy RT to be standard treatment. The aggressive regimen used in the FFCD/SFRO study may have resulted in high toxicity and masked the benefits of RT.

The ECOG 4201 study, published in abstract form in 2008, addresses the most pertinent question in modern therapy: Does the addition of radiation to gemcitabine chemotherapy provide a benefit?[35]

Despite gross under-accrual (74 of a planned 316 patients), RT did result in prolonged median survival. This trial has strengthened and renewed interest in RT in locally advanced disease.

The above-mentioned studies used survival as a primary end point. In this disease, which is generally not curable, control of cancer-related symptoms and quality of life are of paramount importance. Cancer-related symptoms are not well reported in any trial. The GITSG trial showed greater weight loss and severe nausea/vomiting in the SMF chemotherapy arm compared to chemoradiotherapy. However, SMF chemotherapy is no longer standard. In this trial, rates of progression in the pancreas were equivalent with or without radiation, suggesting that radiation prolongs time to local recurrence rather than prevents it.

In the ECOG 4201 trial, quality of life parameters were examined, but results have not yet been reported. Rates of grade 4 toxicity (principally, gastrointestinal and hematologic) were 41% with chemoradiotherapy compared to 6% with chemotherapy alone ($P < .0001$), but the authors note that these toxicities were "generally manageable." An increase in acute toxicities (during and immediately following radiation) may be acceptable if patients recover from symptoms, and cancer-related symptoms and quality of life are ultimately improved.

Although some patients benefit from RT, we know that some do not. Future goals include the more accurate identification of patients who are likely to benefit, thus sparing patients with rapidly progressive, chemotherapy-resistant disease the toxicity of radiation. A simple yet seemingly effective method for identifying such patients is the test of time. Practitioners are increasingly using a 3-month trial of chemotherapy, followed by chemoradiotherapy in patients whose disease has not progressed and whose performance status has not deteriorated during this time.

The Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) completed a randomized phase II study and a randomized phase III study evaluating various chemotherapy agents.[37] In both trials, patients received 3 months of gemcitabine-based chemotherapy. If performance status was good (Zubrod score < 2) and disease had not progressed, physicians were encouraged but not required to deliver RT with concurrent chemotherapy. Approximately 30% of patients had progression of disease during induction chemotherapy. Of 181 patients who had not progressed, about half received RT; those who received RT had longer median survival compared to those who did not (15 vs. 11.7 months, $P = .0009$). In contrast, patients who progressed during chemotherapy had median survival of only 4.5 months. GERCOR is currently evaluating the use of RT after 3 months of induction chemotherapy in a randomized fashion.

Although surgery is generally considered the only curative treatment option for pancreas cancer, long-term (> 5 year) survivors treated with chemoradiotherapy have been reported. Willett et al published their results using intraoperative electron RT in addition to external beam radiation and 5-FU–based chemotherapy.[38] Five-year overall survival was 4%. The size of the intraoperative radiation field can be used as a surrogate for tumor size, with the size of the tumor being approximately 2 cm less than the field size. No patients who had 9-cm or greater intraoperative field size lived beyond 18 months. The highest 3-year overall survival (17%) was observed in patients with 5- to 6-cm intraoperative field size. These findings suggest that patients with locoregionally advanced disease do not necessarily have distant micrometastases at diagnosis. The trial also stresses the importance of patient selection; patients with small tumors may achieve long-term control with chemoradiotherapy.

BORDERLINE RESECTABLE PANCREAS CANCER

The goal of surgery is R0 resection (negative surgical margins). R1 resection (microscopically positive margins) is rarely curative and R2 resection (gross residual disease) is not curative.[39] Therefore, if either R1 or R2 resection is likely based on imaging, it is advisable to deliver neoadjuvant therapy.

Among patients with outright unresectable disease, 8% to 30% are converted to a resectable state following chemoradiotherapy.[24,40–43] Patients with borderline resectable disease are likely to ultimately undergo resection, and there is thus a strong rationale for use of local therapy (radiation) in addition to chemotherapy in these patients.

Although the definition of borderline resectable disease is debated, current NCCN guidelines define borderline resectable disease as severe unilateral superior mesenteric vein (SMV)/portal impingement, tumor abutment on superior mesenteric artery, gastroduodenal artery encasement up to the origin of the hepatic artery, tumors with limited involvement of the inferior vena cava, SMV occlusion, and colon/mesocolon invasion. In these patients, chemoradiotherapy rather than chemotherapy alone should be strongly considered.[44] In a retrospective study by Brown et al, specifically evaluating borderline resectable pancreas cancer patients, 11 of 13 patients receiving RT underwent R0 resection and 2 underwent R1 resection.[45]

RADIATION THERAPY TECHNIQUE

Many of the trials of RT in pancreas cancer have used 2-dimensional anterior:posterior techniques. Currently, 3-dimensional computed tomography (CT)-based treatment planning is standard. Three-dimensional planning allows the use of multiple custom-shaped radiation fields, with the angle of each field optimized to minimize dose to critical normal structures. Split course RT is no longer used due to concerns of accelerated repopulation during the split. Despite advances in radiation technique, the small bowel, which cannot be completely excluded from the radiation field given the proximity of the pancreas to the duodenum, remains a dose-limiting structure.

Intraoperative RT (IORT) has been studied in an attempt to increase radiation dose. Intraoperative RT allows dose limiting normal structures such as the bowel to be physically moved out of the radiation field. A randomized trial by the National Cancer Institute has demonstrated an improvement in local control with the use of 20 Gy IORT following surgical resection compared to standard therapy.[46] Standard therapy was defined as observation if disease was limited to the pancreas, or external beam RT if disease was extrapan-

creatic or lymph nodes were involved. In addition, the data from Massachusetts General Hospital suggest that some patients with small unresectable pancreas cancers may be cured with a combination of IORT and standard RT.[38] Although local control is likely improved with IORT, an improvement in survival has not been demonstrated, and a phase II study by RTOG using IORT in unresectable pancreas cancer showed survival rates very similar to trials that did not incorporate an RT boost.[47] Therefore, although IORT is promising, the technique has not been adopted nationwide.

Other radiation techniques being studied include stereotactic body RT (SBRT) and intensity-modulated RT (IMRT). SBRT delivers 1 to 5 high-dose radiation fractions, as opposed to conventional RT which delivers 25 to 28 low-dose fractions. The rationale behind conventional fraction RT is that delivering a lower dose of radiation per day minimizes damage to normal tissues. Therefore, substantial amounts of normal tissue can be included in the radiation field. With SBRT, the tissues within the radiation field receive extremely high doses and are expected to suffer significant radiation-related damage. Therefore, SBRT must be focused on gross disease, and areas at risk for micrometastatic disease, such as lymph node basins, are not included.

In RT for pancreas cancer, the duodenum is the primary dose-limiting normal tissue, and the primary concern with SBRT is small bowel ulceration, perforation, or obstruction. SBRT may be appropriate in unresectable pancreas cancer patients in whom cure is unlikely, and the primary goal of RT is local control. A phase II trial of SBRT by Hoyer et al used 30 Gy in 3 fractions. This study demonstrated a local control rate of 57% but unacceptable small bowel toxicity, with 18% of patients experiencing severe gastrointestinal mucositis/ulceration and 4.5% experiencing gastric perforation.[48]

A trial from the Stanford group using single-dose (25 Gy) SBRT and smaller radiation field size demonstrated more reasonable results, with an 81% local control rate accompanied by a 31.3% rate of grade 2 and 12.6% rate of grade 3 or 4 late gastrointestinal toxicity.[49] The addition of an SBRT boost to 45 Gy conventional fractionated RT has also been investigated by the Stanford group, with the strategy yielding a 94% local control rate and a 12.5% rate of late duodenal ulcers.[50] Although local control rates have been encouraging, median survival times in these trials have not been substantially different compared to historical controls (6 to 11 months), primarily due to the development of distant disease. Given the gastrointestinal toxicities observed, the benefits of local control vs. treatment toxicity must be carefully examined in future studies.

Intensity-modulated RT is typically delivered using conventional fractionation, but unlike conventional 3-dimensional RT, the intensity of the radiation within each radiation field is nonuniform. Dose distribution within each radiation field is designed to minimize the radiation dose to normal tissues. If normal tissue toxicity is decreased, dose escalation may also be achievable. Although IMRT has great potential, the accurate delivery of IMRT requires precise knowledge of the location of the target and critical normal structures at the time of treatment delivery.

Since the location of the pancreas tumor and abdominal organs varies with respiration and bowel filling, a precise knowledge of their location is difficult. The potential roles of daily pretreatment CT scans, implanted fiducial markers in the tumor, and respiratory gating (in which the radiation beam is only turned on during a particular part of the respiratory cycle) are all being explored.

Dosimetric planning studies comparing 3-dimensional RT to IMRT have demonstrated reduction in dose to normal tissues including the liver, kidneys, stomach, and small intestine with IMRT.[45,51] However, it is unknown if these planning studies will translate into decreased toxicity in the clinical setting. Small clinical trials employing IMRT have been completed.[45,51–53] To date, IMRT has not been proven superior to conventional 3-dimensional RT, but IMRT techniques are clearly worthy of further study.

RADIATION THERAPY FIELD SIZE

Radiation therapy field size is another topic of current clinical investigation. Traditionally, the RT field included the pancreas tumor with a wide margin (2–3 cm) and uninvolved regional lymph nodes in both resected and unresected disease, in an attempt to treat areas at high risk for micrometastatic disease. However, when large radiation fields are used, full-dose concurrent gemcitabine chemotherapy cannot be used due to toxicity.[40] If only gross disease with a minimal margin is included in the radiation field, full-dose concurrent gemcitabine can be used,[54] and effective chemotherapy to address distant micrometastatic disease is not delayed. Furthermore, it is possible that gemcitabine may be as effective as RT at controlling regional (nodal) micrometastatic disease. A phase I study by McGinn et al demonstrated the safety of full-dose gemcitabine chemotherapy concurrent with limited-field RT in unresected pancreas cancer, and only one of 23 patients developed regional recurrence.[54] Although these findings are encouraging, prospective randomized data do not yet exist to guide optimization of RT field size.

CONCLUSIONS

The role of RT in adjuvant therapy for pancreas cancer is not clearly defined by existing data and remains hotly debated. Randomized prospective data using modern RT techniques and dosing are needed. In locally advanced pancreas cancer, recent evidence using modern RT techniques and dosing suggests a continued role for RT. In both resected and unresected disease, further study is needed to define optimal radiation dose, field size, and technique, and to more closely assess the effect of radiotherapy, not only on survival, but also on local disease control and quality of life.

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Disclosures of Potential Conflicts of Interest

Dr. Hazard indicated no potential conflicts of interest.