

CRITICAL REVIEW

TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER: THE ROLE OF RADIATION THERAPY

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Pancreatic cancer remains associated with an extremely poor prognosis. Surgical resection can be curative, but the majority of patients present with locally advanced or metastatic disease. Treatment for patients with locally advanced disease is controversial. Therapeutic options include systemic therapy alone, concurrent chemoradiation, or induction chemotherapy followed by chemoradiation. We review the evidence to date regarding the treatment of locally advanced pancreatic cancer (LAPC), as well as evolving strategies including the emerging role of targeted therapies. We propose that if radiation is used for patients with LAPC, it should be delivered with concurrent chemotherapy and following a period of induction chemotherapy. © 2012 Elsevier Inc.

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INTRODUCTION

In 2010, pancreatic cancer was estimated to represent 3% of new cancer cases (approximately 43,140 cases diagnosed) and the cause of 6% to 7% of all cancer-related deaths (36,800 deaths) (1). Prognosis remains poor, with a 1-year survival rate of 25% and a five-year survival rate of less than 5%. Surgical resection offers the only potentially curative treatment, and patients can be classified as resectable, borderline resectable, locally advanced, and metastatic (Table 1). Select patients with borderline resectable disease who do not develop progressive disease after neoadjuvant therapy will benefit from surgical resection (2). For the remaining 30% of patients with locally advanced unresectable tumors, median survival ranges from 8 to 12 months.

The optimal treatment for patients presenting with locally advanced pancreatic adenocarcinoma (LAPC) remains unclear. Current National Comprehensive Cancer Network guideline treatment options include immediate chemoradiation, single- or multiagent chemotherapy alone, or chemotherapy followed by chemoradiation (3). Uncertainties about the treatment of LAPC include defining the optimal systemic regimen, determining whether radiation should

be added to systemic therapy and, if so, whether radiation should be given immediately or after a period of induction chemotherapy, determining how radiation should be delivered, and deciding what systemic therapy should be delivered concurrently with radiation. We review key studies regarding the treatment of LAPC as well as preliminary data regarding novel therapies that have shown promise for improving outcomes in LAPC.

TRIALS COMPARING CONCURRENT CHEMORADIATION TO SINGLE-MODALITY THERAPY

Concurrent chemoradiotherapy compared to radiation alone

Although pancreatic cancer is now recognized as a disease in which metastatic spread often overshadows local disease control, investigators previously performed two randomized phase III trials comparing concurrent chemoradiotherapy with radiation alone for patients with LAPC. Results of these trials are presented in Table 2. While the trial reported by Moertel *et al.* (4) showed a survival benefit for chemoradiation, the Eastern Cooperative Oncology Group (ECOG) E8282 trial did not (5). The lack of survival benefit with

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Table 1. Clinical classifications of pancreatic cancer

Resectable	Borderline resectable	Unresectable/locally advanced	Metastatic
No distant metastases	No distant metastases	No distant metastases	Distant metastases
Tumor does not distort SMV or PV	Tumor abuts but does not narrow SMV or PV	Involvement of nodes outside resection field	
No SMV or PV tumor thrombus or encasement	SMV or PV encased, but not neighboring arteries	Tumor encases more than half circumference of SMA	
Fat planes present radiographically around CA, HA, SMA	SMV or PV occluded with patent vessel proximal and distal	Tumor abuts or encases more than half circumference of CA	
	Tumor encases less than half the circumference of SMA	SMV or PV occluded without suitable vessel for reconstruction	
	GD encased up to HA, but not extending to CA	Aorta invaded or encased	

Abbreviations: CA = celiac axis; GD = gastroduodenal artery; HA = hepatic artery; PV = portal vein; SMA = superior mesenteric artery; SMV = superior mesenteric vein.

chemoradiation in that study has been attributed to differences in study design, including the requirement for surgical staging, as well as differences in systemic regimens, possibly resulting in worse toxicity profiles. A meta-analysis that included a combined analysis of the two larger randomized trials demonstrated a survival benefit for chemoradiation (6).

Chemoradiation compared to chemotherapy alone

There is considerable controversy over whether the local control benefits of adding radiation to systemic therapy outweigh the potential for increased toxicity. Data from patterns of failure at autopsy support a role for local therapy. A study of 76 patients with pancreatic cancer demonstrated that while 70% of patients died with widely metastatic disease, a significant fraction of patients died with locally aggressive disease. Of the 18 patients initially diagnosed with locally advanced disease, 30% of them had locally advanced tumors but no evidence of distant metastases at autopsy (7). Thus, local control seems to be an important factor not only for palliation of symptoms but also for improved survival.

Two small, early randomized studies compared chemoradiotherapy followed by maintenance chemotherapy to systemic therapy alone as the treatment for LAPC, and again, results were conflicting (Table 3). A Gastrointestinal Tumor Study Group (GITSG) trial, which enrolled patients from 1983 to 1985, demonstrated the superiority of concurrent chemoradiotherapy to chemotherapy alone,

with a median survival of 10.5 months versus 8 months ($p < 0.02$) (8). The ECOG also conducted a trial beginning in 1977 that compared systemic therapy alone to concurrent chemoradiotherapy followed by maintenance chemotherapy (9). In contrast to the GITSG study, the median survival rates for both treatment arms of the ECOG study were equivalent (8.3 months with concurrent treatment versus 8.2 months). The ECOG study included patients with residual disease after resection or recurrent disease, likely with worse prognoses. Therefore, it can be argued that the heterogeneity of the patient population may have diluted the ability to detect a significant benefit for chemoradiotherapy in LAPC. In addition, any benefit from radiotherapy may have been understated by outdated radiation planning, delivery, and dosage. A third small randomized trial also showed no benefit to combined modality therapy, but that study suffers from many of the same issues as the ECOG trial (10). Because of the small numbers of patients and outdated techniques employed, a definite conclusion about the benefit of adding radiation to chemotherapy cannot be drawn from these early, conflicting studies.

Early trials used radiation and chemotherapy treatment methods and dosages that are now outdated. Furthermore, combined modality therapy had not yet been compared in a randomized fashion to gemcitabine-based chemotherapy, already known to yield improved outcomes for patients with advanced disease (11). Between 2000 and 2005, investigators of the Federation Francophone de la Cancerologie

Table 2. Trials comparing chemoradiation to radiotherapy alone

Study, author, year (ref.)	No. of patients	Treatment	Median survival (months)	<i>p</i> value (RT vs. CRT)	Comments
GITSG randomized, Moertel <i>et al.</i> , 1981 (4)	194	60 Gy	5.7	<0.01	2-week break after 20 Gy
		60 Gy plus 5-FU (B)	10.1		
		40 Gy plus 5-FU (B)	10.6		
ECOG randomized, Cohen <i>et al.</i> , 2005 (5)	114	59.4 Gy vs.	7.1	NS	Increased toxicity with CRT regimen
		59.4 Gy plus 5-FU (ICI) plus mitomycin	8.4		

Abbreviations: B = bolus; CRT = chemoradiotherapy; ICI = intermittent continuous infusion; NS = nonsignificant; RT = radiotherapy.

Table 3. Trials comparing chemoradiation to chemotherapy alone

Study, author, year (ref.)	No. of patients	Treatments	Median survival (months)	<i>p</i> value (CT vs. CRT)	Comments
GITSG randomized (1988)	43	SMF (streptozocin, mitomycin, 5-FU) 54 Gy plus 5-FU (B) -> SMF	8 10.5	<0.02	Accrual limited
ECOG randomized, Klaassen <i>et al.</i> , 1985 (9)	91	5-FU (B) 40 Gy plus 5-FU (B) -> 5-FU	8.2 8.3	NS	Includes patients with recurrence or residual Dx after resection; lower RT dose
Canadian randomized, Hazel <i>et al.</i> , 1981 (10)	30	5-FU plus methyl-CCNU 46 Gy plus 5-FU (B) -> 5-FU plus methyl CCNU	7.3 7.8	NS	Lower RT dose
FFCD/SFRO randomized, Chauffert <i>et al.</i> , 2008 (12)	119	Gemcitabine 60 Gy plus 5-FU (CI) plus cisplatin -> gemcitabine	13 8.6	0.03	Terminated early due to toxicity of CRT regimen
ECOG randomized, Loehrer <i>et al.</i> , 2008 (13)	74	Gemcitabine 50.4 Gy plus gemcitabine -> gemcitabine	9.2 11	0.04	Abstract only
Phase II, Ioka <i>et al.</i> , 2010 (14)	80	Gemcitabine 50 Gy plus gemcitabine	12.2 12.8	<0.02	Abstract only

Abbreviations: B = bolus; CCNU = Lomustine; CI = continuous infusion; CRT = chemoradiotherapy; CT = chemotherapy; NS = nonsignificant.

Digestive and the Societe Francophone de Radiotherapie Oncologique (FFCD/SFRO) conducted a phase III trial evaluating the role of chemoradiotherapy followed by maintenance systemic therapy versus chemotherapy alone for locally advanced patients (12). In that study, 119 patients were randomized to receive 60 Gy of radiation concurrently with continuous infusions of 5-fluorouracil (5-FU) and cisplatin or gemcitabine alone. All patients then received gemcitabine until disease progression. Conformal radiation techniques were used, but elective nodal regions were also treated. The very aggressive experimental arm, which featured two-drug cisplatin-based chemotherapy combined with a higher-than-standard radiation dose, was inferior to gemcitabine alone, and accrual was terminated early. Patients treated in the chemoradiotherapy arm had lower median survival (8.6 months versus 13 months, $p = 0.03$) and 1-year survival (32% versus 53%). The poor outcomes from chemoradiotherapy were likely due in large part to the significantly increased percentage of Grade 3 to 4 treatment-related toxicities, which were seen during both the induction and the maintenance phases, resulting in an increased number of treatment interruptions and a large fraction of patients who did not receive the full, intended course of treatment. Moreover, it is difficult to draw conclusions regarding the potential benefit of radiotherapy in combination with chemotherapy, as the chemotherapy differed between the two treatment arms, with the combined modality patients receiving a more toxic regimen that included cisplatin.

Most recently, the ECOG E4201 phase III trial compared concurrent radiotherapy plus gemcitabine with gemcitabine alone for treating LAPC (13). Accrual was slow, and enrollment was terminated early at only 74 patients. Radiation was delivered to 50.4 Gy, using an involved field approach,

along with weekly administration of gemcitabine (600 mg/m²) and was followed by five cycles of gemcitabine alone (1,000 mg/m² weekly for 3 of 4 weeks). Patients in the chemotherapy-alone arm received seven cycles of gemcitabine in the above-described dosages for adjuvant treatment. Combination therapy was associated with a marginally significant survival benefit, with a median survival of 11 months compared to 9.2 months ($p = 0.044$) and 1-year survival of 50% versus 32% ($p = 0.034$), respectively. Grade 4 hematologic and gastrointestinal toxicities occurred more often in the combined modality treatment arm. Overall, this better-tolerated combined modality regimen demonstrated a higher survival benefit from chemoradiation than from therapy with gemcitabine alone. A Japanese randomized phase II trial of chemoradiation with gemcitabine versus gemcitabine alone was recently presented. Eighty patients with LAPC were enrolled and randomized to receive gemcitabine, 1000 mg/m² weekly for 3 of 4 weeks, with or without 50-Gy radiation delivered to the tumor alone. Median survival time (12.8 months versus 12.2 months, respectively, $p < 0.02$), progression-free survival (7.8 months versus 4.2 months, respectively, $p < 0.01$), and 2-year and 3-year survival rates were improved with combined modality therapy (14). Although these two more recent studies demonstrated a modest benefit from gemcitabine-based chemoradiation versus chemotherapy alone, it must be noted that both studies are small and have been published only as abstracts.

A number of recent phase II trials have studied concurrent chemoradiotherapy with 5-FU-based regimens in LAPC, resulting in median survival times of 9 to 14 months (15–18). Survival outcomes below this range were generally reported for the phase III trials, which showed equivalent or inferior outcomes with chemoradiation, supporting the fact that treatment-related toxicities, patient selection criteria,

and older radiation techniques may have contributed to the observed outcomes and masked any potential benefit of concurrent therapy. In summary, although recent trials suggest moderate dosages of chemoradiation to 50 Gy with modern techniques may be superior to gemcitabine alone, definitive evidence is lacking.

Chemoradiotherapy compared to supportive care

For patients considering supportive care only, it is important to recognize that chemoradiotherapy does provide palliation of symptoms and improved quality of life as well as an overall survival benefit, compared to best supportive care. In a small randomized trial, 31 patients with LAPC were treated with radiotherapy to 50.4 Gy with concurrent continuous infusion of 5-FU or with supportive care only. Chemoradiation improved median survival time to 13.2 months, with a 1-year survival rate of 54% compared to 6.4 months and 0% survival, respectively, in patients who received supportive care only. Moreover, the average monthly Karnofsky performance status score was significantly higher in the treated patients ($p < 0.0001$). Treatment with chemoradiation also resulted in fewer hospital admission days and improved durable pain relief (19). Therefore, chemoradiation offers not only a survival advantage but also palliative benefit for patients with locally advanced disease who might otherwise decline treatment.

RECENT ADVANCES IN SYSTEMIC THERAPY

Systemic therapy is a cornerstone in the management of advanced pancreatic cancer, including LAPC, as almost all patients will eventually develop distant metastases. Before 1996, 5-FU therapy was a treatment routinely used for metastatic pancreatic cancer. Rubin *et al.* (20) performed a phase II study of 5-FU plus leucovorin in 31 patients with pancreatic cancer. No objective response was observed, with a median overall survival of 5.7 months (20). Burris *et al.* (11) performed a multicentered randomized phase III clinical trial that compared 5-FU to gemcitabine therapy (11). Treatment with gemcitabine compared to that with 5-FU resulted in a relative improvement of 36% in median overall survival (5.7 months versus 4.2 months, respectively) and 1-year survival rates (18% versus 2%, respectively). In addition to survival benefit, gemcitabine therapy was also superior to 5-FU therapy in producing clinical response (24% versus 5%, respectively). That study led to the approval of gemcitabine as a first-line chemotherapy agent for treating advanced disease.

Over the last decade, multiple cytotoxic and targeted agents have been combined with gemcitabine in randomized phase III trials, and none of those combinations showed clear superiority over single-agent gemcitabine. A randomized phase III study of pancreatic cancer treatment that compared erlotinib plus gemcitabine versus gemcitabine alone demonstrated the superiority of a gemcitabine-containing combination over single-agent gemcitabine, although the survival benefit was minimal (21). Data from a French and Italian Intergroup study comparing gemcitabine plus oxaliplatin to

gemcitabine and a German multicenter trial comparing gemcitabine plus cisplatin versus gemcitabine were included in a pooled analysis based on individual patient data (22). Results showed that the effect of platinum-based combination chemotherapy was considerably greater in the group with locally advanced disease only (median progression-free survival 35 versus 21 weeks; $p = 0.051$). Most of those studies included both patients with metastatic pancreatic cancer and patients with LAPC. As described previously, recent randomized trials by the FFCO-SFRO (12) and ECOG (13) have provided conflicting results. Therefore, some investigators have continued to advocate treating LAPC with systemic therapy alone.

Most recently, a randomized study compared therapy that combined 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) with gemcitabine therapy in advanced pancreatic cancer (23). A total of 342 patients were randomized to receive FOLFIRINOX or gemcitabine. The FOLFIRINOX regimen showed statistically significant improvements in response rate compared to that of gemcitabine (31.6% versus 9.4%, respectively; $p < 0.001$) and in median overall survival (11.1 months versus 6.8 months, respectively; hazard ratio [HR], 0.57; $p < 0.001$) and 1-year survival (48.4% versus 20.6%, respectively). Patients treated with the combination regimen experienced a higher incidence of Grade 3 or 4 toxicities including neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and neuropathy. Despite increased toxicities resulting from FOLFIRINOX, patients treated with this regimen were able to maintain a significantly better quality of life than patients receiving gemcitabine, based on quality of life questionnaires. Decrease in quality of life at 6 months was reported by 31% of patients in the FOLFIRINOX treatment arm compared to 66% of patients in the gemcitabine treatment arm (HR, 0.47; $p < 0.001$). This non-gemcitabine-based regimen, which appears very promising for treating metastatic disease, has not yet been studied in treatment of LAPC.

OPTIMIZING CHEMORADIATION

Induction chemotherapy followed by concurrent chemoradiation

The high rate of occult metastatic disease in those patients who present with locally advanced disease has led to the use of induction chemotherapy to identify the patients destined to rapidly progress with metastatic disease. Studies have demonstrated a benefit to aggressive local therapy with chemoradiation after a period of induction chemotherapy (Table 4). A retrospective analysis was completed of 181 patients with LAPC enrolled in phase II and III studies by the Groupe Co-Opérateur Multidisciplinaire en Oncologie (GERCOR). These patients had received a minimum of 3 months of induction chemotherapy followed by either chemoradiotherapy or continued chemotherapy (24). Chemotherapy was gemcitabine-based. Twenty-nine percent of patients developed metastatic disease during the 3-month period of induction chemotherapy. Of those remaining, 56% of patients were

Table 4. Induction chemotherapy followed by chemoradiation

Study, author, year (ref.)	No. of patients	Treatments	Median survival (months)	<i>p</i> value	% patients who progressed on induction CT
GERCOR retrospective, Huguet <i>et al.</i> , 2007 (24)	181	Gem-based CT Gem-based CT × 3 months → 55 Gy plus 5-FU (CI)	11.7 15	0.0009	29
MDACC retrospective, Krishnan <i>et al.</i> , 2007 (25)	323	30 Gy plus 5-FU (CI) or Gem or Cap* Gem-based CT × 2.5 months → CRT as above	8.5 11.9	<0.001	NR
Phase II, Schneider <i>et al.</i> , 2005 (26)	23	Gem plus cisplatin × 2 cycles → 50.4 Gy plus Cap	12.8		22
Phase II, Mishra <i>et al.</i> , 2005 (27)	20	Irinotecan plus Gem → 50.4 Gy plus Gem	9.6		33
Phase II, Ko <i>et al.</i> , 2007 (28)	25	Gem plus cisplatin × 6 cycles → 50.4 Gy plus Cap	17		32
Phase II, Moureau-Zabotto <i>et al.</i> , 2008 (29)	59	GEMOX × 4 cycles → 55 Gy plus 5-FU (CI) plus oxaliplatin	12.6		15

Abbreviations: Cap = capecitabine; CI = continuous infusion; CRT = chemoradiotherapy; CT = chemotherapy; Gem = gemcitabine; GEMOX = gemcitabine-oxaliplatin; GERCOR = Groupe Cooperateur Multidisciplinaire en Oncologie; NR = not reported.

* Most patients were treated to 30 Gy; only 11% of patients were treated to 50.4 Gy.

treated with chemoradiotherapy, while 44% of patients continued taking chemotherapy. Radiation was delivered to a dose of 55 Gy to the gross tumor volume and regional lymph nodes by using three-dimensional treatment planning. Continuous infusion 5-FU was given with radiotherapy. Concurrent therapy after induction chemotherapy improved median survival (15 versus 11.7 months, respectively; $p = 0.0009$) and 1-year survival rates (65.3% versus 47.5%, respectively). That study suggests that locoregional tumor control with chemoradiotherapy likely translates into a significant survival benefit for patients with locally advanced disease after induction chemotherapy selects the 30% of patients with occult metastatic disease. The 15-month median survival exceeds that seen in any of the preceding randomized trials, again arguing in favor of this treatment approach. Because this is a retrospective study, the potential that bias affected the selection of patients receiving combined modality treatment must be recognized. Nonetheless, the two treatment groups were balanced for performance status, age, sex, type of chemotherapy received, and chemotherapy response.

A second large retrospective study evaluated the benefit of concurrent chemoradiation administered to patients either initially or in those patients whose disease did not metastasize after a period of treatment with induction systemic therapy (25). A total of 323 patients with LAPC were treated between 1993 and 2005 with chemoradiation. Of those, 76 patients received a median of 2.5 months of induction gemcitabine-based chemotherapy. The median survival was 11.9 months in patients who received induction chemotherapy compared to 8.5 months in patients treated with initial chemoradiation. Median times to both local and distant progression were improved in those patients who received induction therapy. Patterns of failure were not significantly different between the two treatment groups, with locore-

gional recurrence as the initial site of failure in approximately 25% of patients, distant disease as the initial site of failure in approximately one-third of patients, and failure both locally and distantly occurring in approximately 10% to 20% of patients.

Additional phase II trials have evaluated the role of induction chemotherapy followed by concurrent treatment and similarly have shown promising survival outcomes (Table 4) (26–29). Despite the lack of randomized data, evidence to date from phase II and retrospective studies indicates that a period of induction chemotherapy is beneficial in selecting a subgroup of patients who are likely to benefit from aggressive local therapy with chemoradiation and offers these patients the most promising outcomes yet reported, with median survival of 15 and 12 months in the two largest, albeit retrospective, studies. The fact that a quarter of patients in the MD Anderson study experienced locoregional recurrence as their first failure suggests that further intensification of local therapy may improve outcomes (25).

Advances in radiation delivery

The relatively high percentage of patients with local recurrences following chemoradiation suggests that radiation dose escalation may offer an improved survival benefit if tolerated. Stereotactic body radiotherapy (SBRT) has shown the ability to deliver high rates of local control in tumors of the lung, liver, and spine, with low toxicity. However, series using SBRT for LAPC have so far failed to show a meaningful survival benefit, and some studies have demonstrated significant toxicity (Table 5).

A series of trials of 25 Gy delivered in a single fraction with CyberKnife conducted at Stanford University yielded median survival times of 11, 8.3, and 11.4 months for SBRT alone and as a boost after chemoradiation and

Table 5. Experience with SBRT

Study (ref.)	No. of patients	Treatment (s)	Median survival (months)
Koong <i>et al.</i> , 2004 (30)	15	15 Gy, 20 Gy, or 25 Gy × 1	11
Koong <i>et al.</i> , 2005 (31)	19	45 Gy IMRT plus 5-FU → 25 Gy × 1 SBRT	8.3
Hoyer <i>et al.</i> , 2005 (32)	22	15 Gy × 3	5.7
Schellenberg <i>et al.</i> , 2008 (33)	16	Gem × 1 cycle → 25 Gy × 1 → Gem	11.4
Chang <i>et al.</i> , 2009 (34)	77	25 Gy × 1	6.7
Mahadevan <i>et al.</i> , 2010 (35)	36	8–12 Gy × 3 → Gem × 6 months	14.3

Abbreviations: Gem = gemcitabine; IMRT = intensity-modulated radiotherapy; SBRT = stereotactic body radiotherapy.

interdigitated with gemcitabine (30, 31, 33). Chang *et al.* (34) reported outcomes for 77 patients at Stanford treated with one fraction of 25 Gy. Patients included those with locally advanced disease, medically inoperable tumors, metastatic disease, and recurrent pancreatic tumors. Local control was excellent, with a local recurrence rate of 5% at 1 year. Overall survival at 1 year was 21%, but outcomes for the 81% of patients with locally advanced disease were poor, with a median survival of 6.7 months. Twenty-five percent of patients experienced Grade 2 or higher late toxicities at 1 year (34). Outcomes were similarly poor for LAPC patients in Denmark treated with SBRT to 45 Gy in 3 fractions. Moreover, severe acute treatment-related toxicities were reported, including severe mucositis, ulceration of the stomach or small bowel, and a nonfatal perforation of the stomach (32). Finally, Mahadevan *et al.* (35) reported results of a series of 36 patients treated with SBRT to 24 to 36 Gy in 3 fractions followed by 6 months of gemcitabine therapy. Radiation dose depended on the proximity of the tumor to the duodenum. Median survival was promising, but again, toxicities were significant (35). Further prospective studies are required to determine the optimal dose fractionation scheme to maximize therapeutic ratio and to examine whether improved local control with SBRT can ultimately be translated into a survival benefit. Furthermore, the technical difficulties associated with defining the extent of the tumor and managing organ motion are significant. The proximity of the duodenum poses a particular challenge, as hypofractionated radiation to the bowel can cause late stenosis, ulceration, or perforation.

Several studies have demonstrated improved local control and a marginal survival benefit with intraoperative radiation (IORT). A series of 150 patients with LAPC were treated at Massachusetts General Hospital with IORT to 15 to 20 Gy, following external beam radiotherapy (EBRT) to the primary tumor and regional lymph nodes to either low (10–20 Gy) or high (37–40 Gy) doses. Low-dose patients received additional EBRT following the intraoperative radiation, typically with a concurrent bolus of 5-FU. Median survival was 13 months, and the 1-year survival rate was 54%. Long-term survival greater than 3 years was observed in 8 patients (36). A study in which a series of 49 patients was treated with chemotherapy and IORT followed by concurrent EBRT and 5-FU also demonstrated promising outcomes, with freedom from local progression of 71% and median survival of 16 months (37). Although results are still

preliminary, they suggest that improved local control achieved with dose-escalated radiation delivered intraoperatively may translate into a survival benefit. Limitations to the use of IORT include the ability to deliver only a single fraction and the need for specialized expertise and equipment, which would make performing a prospective multicenter trial difficult.

Intensity-modulated RT (IMRT) has also been studied as a possible way to intensify treatment and reduce toxicity. An early phase I trial of concurrent gemcitabine and IMRT was closed early due to excessive toxicity (38). However, additional studies have demonstrated favorable toxicity profiles with IMRT and concurrent chemotherapy (39, 40). Notably, Ben-Josef *et al.* (41) reported a phase I study that attempted to intensify local therapy for patients with LAPC using IMRT and concurrent gemcitabine. Patients received two cycles of induction gemcitabine followed by IMRT to doses ranging from 50 to 60 Gy with concurrent and adjuvant gemcitabine. Treatment volumes included a 1-cm margin around the primary tumor, with additional measures taken to account for tumor movement. The initial analysis of 27 enrolled patients indicated that treatment was well tolerated and demonstrated a very promising median survival of 23.1 months, with local progression in only 1 patient (41). As with SBRT, the proximity of pancreatic head tumors to the duodenum and the proximity of body and tail tumors to the stomach make sparing of the surrounding normal tissues challenging, even with IMRT. Motion of the primary tumor due to respiration also presents a problem in the design of highly conformal radiation fields. Notably, recent series suggest that elective irradiation of regional lymph nodes can be omitted with a low risk of isolated nodal failure, thereby dramatically decreasing the treatment volume. Overall, results of these preliminary studies indicate that the use of IMRT provides a promising means of intensifying treatment without adding excessive toxicity.

Which radiosensitizer to use? Gemcitabine versus 5-FU

Early GITSG trials established chemoradiation with 5-FU as a standard treatment, but further studies have evaluated the role of concurrent therapy with other radiosensitizers. Compared to 5-FU, gemcitabine is a more potent radiosensitizer. A small randomized trial compared chemoradiation with gemcitabine versus bolus 5-FU (44). Thirty-four patients with LAPC were randomized to receive gemcitabine (600 mg/m²/week for 6 weeks) or bolus 5-FU, along

with three-dimensional conformal radiotherapy to doses of 50.4 to 61.2 Gy, followed by maintenance gemcitabine therapy (44). Results indicated improved outcomes for patients receiving chemoradiotherapy with gemcitabine, with a median survival of 14.5 months versus 6.7 months, respectively ($p = 0.027$). That study has been criticized for its significant treatment-related toxicities in both treatment arms and unusually poor outcomes in the 5-FU arm.

Phase I trials have indicated that a regimen consisting of full-dose gemcitabine given concurrently with radiation is associated with severe dose-limiting toxicities (45). Other studies have evaluated concurrent therapy with altered doses of gemcitabine or radiation, highly conformal radiation, or reduced treatment volumes as ways of lessening toxicity (46). Crane *et al.* retrospectively compared 114 patients with LAPC treated with radiotherapy to 30 Gy concurrently with seven cycles of weekly gemcitabine (250–500 mg/m²) or continuous infusion 5-FU (200–300 mg/m²). There was a trend toward improved outcomes with gemcitabine, despite the fact that those patients had larger tumors. The rate of severe toxicities was increased with gemcitabine, indicating a narrow therapeutic index when used with radiation (48). Phase II studies have evaluated chemoradiation with lower dose twice-weekly gemcitabine, but survival outcomes were comparable to those of historical controls (49).

Promising outcomes have been seen when gemcitabine is used in combination with conformal radiotherapy. Mattiucci *et al.* (50) conducted a phase II trial in which 40 patients were treated with weekly gemcitabine concurrently with three-dimensional conformal radiotherapy to 50.4 Gy to the primary tumor and 39.6 Gy to regional nodes, followed

by maintenance gemcitabine. Grade 3 and 4 toxicities occurred in 53% of patients. Two-year local control was 39.6%, two-year overall survival was 25%, and median survival was 15.5 months (50). Additional studies have explored the use of conformal radiotherapy to fields encompassing only the primary tumor, without elective nodal irradiation. Murphy *et al.* (51) treated 74 patients with gemcitabine (1,000 mg/m² weekly) and conformal radiation to 36 Gy in 15 fractions. The use of limited fields reduced toxicity. Treatment for only 5% of patients failed in the peripancreatic nodes, with one marginal failure, and the median survival was 11.2 months (51). A multicenter phase II trial reported by Small *et al.* (55) demonstrated that full-dose gemcitabine given concurrently with highly conformal radiotherapy to 36 Gy was well tolerated and clinically effective. Only gross tumor and involved nodes were treated, with 0.5-cm expansions for clinical and planning target volumes, respectively. One-year survival was 47% for patients with locally advanced unresectable disease (47). Therefore it appears that the radiosensitizing potential of gemcitabine can be harnessed in combination with limited-volume, conformal radiation. Many clinicians favor radiation with infusional 5-FU or capecitabine, but data indicate that gemcitabine-based concurrent therapy offers the potential for improved outcomes if the increased toxicities of gemcitabine are successfully mitigated.

Novel radiosensitizers and targeted biological agents

There has been great interest in evaluating novel radiosensitizers for treatment of LAPC, and pertinent studies are summarized in Table 6. RTOG trial 98-12 was a multicenter

Table 6. Selected novel radiosensitizers and biological agents

Agent, study (ref.)	No. of patients	Treatment	Median survival (months)	Comment
Paclitaxel/RTOG protocol 98-12, Rich <i>et al.</i> , 2004 (42)	132	50.4 Gy plus weekly paclitaxel	11.2	
Paclitaxel/RTOG protocol PA-0020, Rich <i>et al.</i> , 2006	195	50.4 Gy plus weekly paclitaxel and Gem -> with or without R115777	11.7	No benefit to R115777
S-1, Sudo <i>et al.</i> , 2010 (52)	34	50.4 Gy plus twice daily S-1	16.8	S-1 is classified as an investigational drug in the United States
Bevacizumab/RTOG protocol 04-11, Crane <i>et al.</i> , 2009 (54)	82	50.4 Gy plus Cap plus Bev -> Gem plus Bev	11.9	35% with grade 3 gastrointestinal toxicities
Bevacizumab, Small <i>et al.</i> , 2011 (55)	32	Gem plus Bev ×3 wks -> 36 Gy plus Gem plus Bev -> Gem plus Bev	11.8	
Nelfinavir, Brunner <i>et al.</i> , 2008 (56)	12	50.4–59.4 Gy plus Gem plus Cis plus nelfinavir	NR	Complete resection in 6 of 10 patients
Erlotinib, Duffy <i>et al.</i> , 2008 (58)	17	50.4 Gy plus Gem plus erlotinib -> Gem plus erlotinib	18.7	
Cetuximab, Crane <i>et al.</i> , 2010 (59)	69	Cetuximab plus Gem plus Oxali ×2 months -> 50.4 Gy plus Cap plus cetuximab -> cetuximab plus Gem	18.8	One-year survival of 68%

Abbreviations: Bev = bevacizumab; Cap = capecitabine; Cis = cisplatin; Gem = gemcitabine; NR = not reported; Oxali = oxaliplatin; R115777 = investigational farnesyl transferase inhibitor.

phase II trial that enrolled 132 patients with unresectable disease (43). Treatment consisted of 50.4 Gy with paclitaxel. Median survival was improved compared to that in previously reported studies evaluating radiation with 5-FU (42). RTOG trial PA-0020, presented in abstract form, showed similar results with a gemcitabine-paclitaxel-radiation regimen. The compound S-1 is a combination of tegafur (a pro-drug converted to fluorouracil), gimeracil (an inhibitor of an enzyme which degrades fluorouracil), and oteracil (an inhibitor of fluorouracil phosphorylation in the gastrointestinal tract that acts to decrease toxicities). To evaluate S-1 in the treatment of LAPC, 34 patients were treated with 50.4 Gy concurrently with twice-daily oral S-1, followed by maintenance S-1 therapy. Toxicity rates were acceptable, and outcomes were promising, with a median overall survival of 16.8 months and 1-year survival rate of 70.6% (52). Further evaluation of S-1 as a novel radiosensitizer is warranted, although it should be noted that non-Asian patients appear to metabolize S-1 differently from Asian patients, so additional safety studies will likely be required for non-Asian populations (53).

Ionizing radiation is known to induce expression of vascular endothelial growth factor (VEGF), with a resultant protective effect in endothelial cells. Therefore VEGF inhibition by bevacizumab may potentiate the effects of radiotherapy. Eighty-two patients with LAPC were enrolled in RTOG trial 0411 and received 50.4 Gy with capecitabine and bevacizumab (54). Although outcomes were comparable to those of previously reported studies, with a median survival of 11.9 months, 35% of patients experienced Grade 3 gastrointestinal toxicities. In contrast, a recently published phase II trial in which 32 LAPC patients received gemcitabine and bevacizumab concurrently with radiation to 36 Gy reported a median survival of 11.8 months and a treatment regimen that was better tolerated (55).

Promising results were seen in a phase I trial of the protease inhibitor nelfinavir in combination with chemoradiation (56). Human immunodeficiency virus (HIV) protease inhibitors have been shown to downregulate the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, which is often activated in human tumors and is associated with radioresistance (57). Twelve patients received oral nelfinavir for 3 days prior to and concurrently with radiation to 50.4 to 59.4 Gy and weekly gemcitabine and cisplatin. Toxicity levels were acceptable. Five patients had partial responses, while 5 patients had complete responses, as assessed by imaging. Of note, complete resections were attained in 6 of the 10 patients, indicating that the addition of nelfinavir may enhance local tumor response to therapy and increase the potential for possibly curative resection.

Pancreatic tumors are known to overexpress human epidermal growth factor receptor (EGFR), and therefore, biologic agents targeting the EGFR pathway have been evaluated in the treatment of pancreatic cancer (21, 58, 59). A phase I trial examined the role of erlotinib in combination with concurrent chemoradiation, and results were promising, with partial responses seen in 35% of

patients (58). Results from a phase II trial of 69 patients with LAPC treated with 2 months of induction cetuximab, gemcitabine, and oxaliplatin, followed by concurrent capecitabine and cetuximab with 50.4 Gy of radiation to the tumor alone and maintenance gemcitabine and cetuximab therapy, were recently presented in abstract form. The treatment was well tolerated, and after chemoradiation, a partial response was seen in 19% of patients, while 17% had a minor response, and 45% had stable disease. Survival data were very promising. Median survival was reported at 18.8 months, median progression-free survival was 12.3 months, and the 1-year survival rate was 68%. R0 resections were achieved in 7 patients; 13% of patients progressed with local disease only, and the investigators reported late local recurrences, suggesting a possible benefit for further intensification of local therapy (59). The use of EGFR inhibitors with concurrent chemoradiation has shown promising outcomes and acceptable toxicity, and further evaluation is indicated (60).

CONCLUSIONS

The appropriate therapy for patients with LAPC remains controversial. Data exist to support treatment with chemotherapy alone, chemoradiation, or induction chemotherapy followed by combined modality treatment. The evidence to date appears to support the use of induction chemotherapy to select the subset of patients without early metastatic disease who can benefit from more aggressive local therapy with gemcitabine or fluoropyrimidine-based chemoradiation. Despite the current lack of randomized phase III data, large retrospective series demonstrate median survival of up to 15 months (24, 25), which significantly exceeds that seen for patients treated initially with chemoradiation or chemotherapy alone. The optimal induction therapy should have minimal toxicities that could potentially defer concurrent treatment and be effective at controlling both micrometastases and the primary tumor prior to commencing locoregional treatment. Patients who develop metastases while undergoing induction therapy are spared the toxicity of chemoradiation, although patients taking excessively prolonged induction therapy run the risk of progressing locally or distantly before receiving the benefit of chemoradiotherapy. Studies to date have demonstrated that gemcitabine is generally well tolerated, making it an appealing choice around which to design induction and maintenance regimens, although the emergence of FOLFIRINOX in the metastatic setting should spur interest in the study of this regimen in LAPC (23). The recently reported phase II experience from MD Anderson Cancer Center and Brown University applied many of these principles, resulting in a median survival time of 18.8 months (59). Continued high local failure rates after current therapies indicate that strategies such as radiation dose escalation and novel radiosensitizers are important avenues for future study to intensify local therapy in patients with LAPC. Improvements in local control may translate into an overall survival benefit as well as increased rates of potentially curative

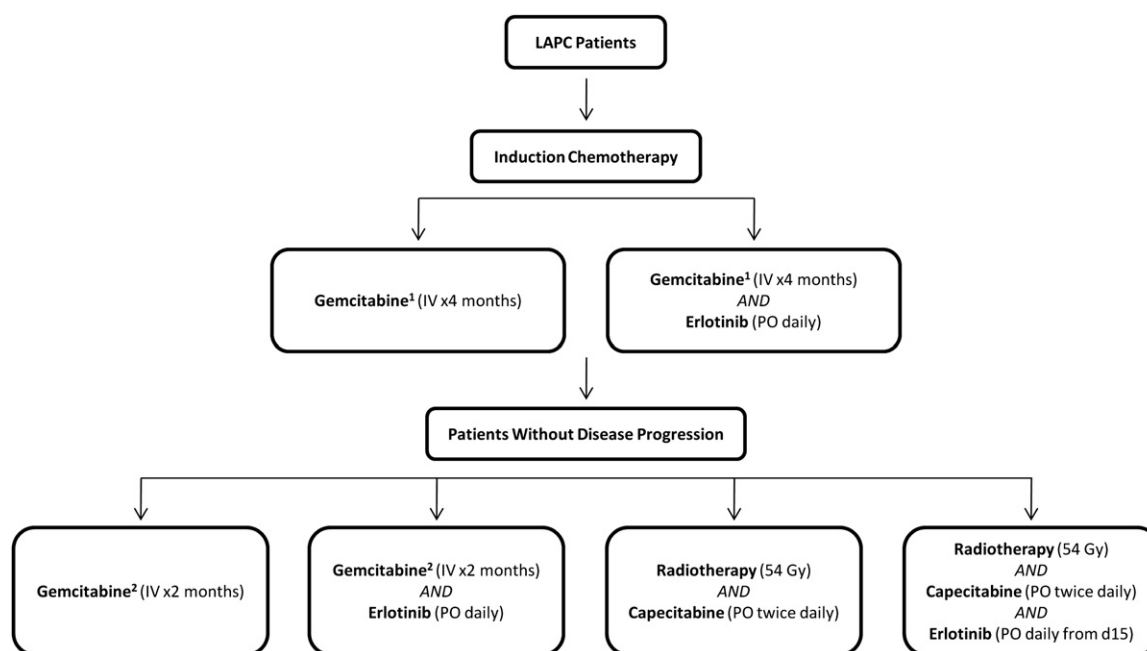


Fig. GERCOR LAP 07 Phase III Trial. Chemoradiation therapy flow diagram. 1 = d1, 8, 15, 22, 29, 36, 43; d57, 64, 71, 85, 92, 99. 2 = d113, 120, 127; d141, 148, 155. Gemcitabine dose schedule: 1 = days 1, 8, 15, 22, 29, 36, 43; 57, 64, 71, 85, 92, 99. 2 = days 113, 120, 127; 141, 148, 155".

resections. Finally, new radiation techniques offer the potential to minimize toxicity and treatment times for patients, important considerations given that LAPC remains essentially an incurable disease.

More high-quality data are still required to clearly define the role of radiation therapy in LAPC. The GERCOR LAP 07 phase III trial (www.clinicaltrials.gov, identifier code

NCT00634725) is designed to test the benefit of adding chemoradiation after induction gemcitabine and the benefit of adding biological therapy with erlotinib (Fig). A total of 820 patients will be enrolled, and the primary endpoint is overall survival. Results from this and other ongoing prospective studies will hopefully provide much needed insight into management of this difficult disease.

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