

HIGHLIGHT ARTICLE

Is there an Optimal Neoadjuvant Therapy for Locally Advanced Pancreatic Cancer?

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Practice Points

1. Radiation therapy alone is a sub-optimal treatment.
2. Chemoradiotherapy using infusional 5-FU is a reasonable choice. No data supporting at this time that using gemcitabine or paclitaxel with radiation therapy has a better outcome than using infusional 5-FU.
3. Substituting infusional 5-FU with capecitabine is reasonable in patients for whom pump is not feasible.
4. Gemcitabine chemotherapy alone has been increasingly used approach instead of 5-FU-based chemoradiotherapy but there are no randomized data showing that gemcitabine alone is superior to conventionally dosed radiation therapy using concomitant infusional 5-FU.
5. If available, patients should be encouraged to enroll in clinical trial.

Research Agenda

1. Randomized trial comparing chemotherapy vs. chemoradiotherapy should be attempted again in order answer to clarify the role of radiation therapy in locally advanced pancreatic cancer.
2. Using chemotherapy plus novel targeted agents such as cetuximab with radiation therapy in order to increase the response rate to downstage the tumor leading to possible resection of the tumor.
3. Need to further investigate the role of chemotherapy followed by chemoradiotherapy in order to maximize local and systemic disease control.

Summary

Treatment of locally advanced pancreatic cancer is challenging. Despite continuing research, effective treatments continue to be elusive with median survival of only 8-12

months. Treatment options for locally advanced pancreatic cancer include radiation therapy, concurrent chemoradiation or chemotherapy. It is felt that radiation therapy is a suboptimal treatment as most of patients will die of systemic disease. In the past, radiation with 5-FU was the standard treatment for locally advanced pancreatic cancer. But now radiation has been used with combination other chemo agents such as paclitaxel or gemcitabine in order to increase the efficacy. Chemotherapy such as gemcitabine alone or gemcitabine doublet also has been studied in patients with locally advanced pancreatic cancer as well with overall survival being approximately the same magnitude as chemoradiation. The exact role of chemoradiation or chemotherapy in treatment of locally advanced pancreatic cancer is yet to be defined. Hence, this review summarizes and compares of role of radiation, chemoradiation and chemotherapy in treating this disease.

Introduction

About 33,730 people will develop pancreatic adenocarcinoma each year in the United States, and 32,300 people will die from the disease representing the fourth most common cause of cancer mortality [1]. Pancreatic cancer patients can be divided into three categories: those with resectable disease,

those with locally advanced tumor and those with metastatic disease. Surgical resection offers only chance of cure but unfortunately only 15-20% of patients with pancreatic cancer are amenable to surgery. Approximately 40% of patients with pancreatic cancer will present with locally advanced, unresectable disease and rest will present as metastatic disease. Generally, pancreatic cancer is deemed unresectable if there is evidence of involvement of the superior mesenteric artery or celiac axis (isolated splenic artery involvement is not a contraindication) or extrapancreatic involvement and/or metastatic disease [2]. Tumor encasement or occlusion of the superior mesenteric vein, or the superior mesenteric vein-portal confluence does not rule out resection, as some centers are demonstrating the feasibility of superior mesenteric vein reconstruction [3].

Treatment of locally advanced pancreatic cancer is challenging and requires multidisciplinary approach. Median survival of locally advanced disease is 8-12 months [4, 5]. Surgery is not a good option as locally advanced pancreatic lesions have a high probability of incomplete surgical resection due to residual cancer at the surgical margin or in draining lymph nodes. There are data that microscopically positive surgical margin (R1 resection) or gross residual disease (R2 resection) following pancreatic resection can substantially compromise or eliminate the survival advantage associated with complete

surgical (R0) resection [6, 7]. Given the limitations of surgery for locally advanced pancreatic cancer, chemotherapy and radiation have been used in the neoadjuvant setting in an effort to improve local and distant tumor control. Minority of patients with unresectable tumor may become resectable after neoadjuvant treatment [8].

In this review article we will review the therapeutic options for locally advanced pancreatic cancer including radiation therapy, chemotherapy or combined chemoradiotherapy.

Radiation Therapy Alone vs. Chemoradiotherapy

Locally advanced tumor can be encompassed in conventional external beam radiation therapy (EBRT) portal but in most setting EBRT by itself does not provide optimal palliation or tumor control. There are 3 prospective randomized trials comparing EBRT to combined chemoradiotherapy which came to opposite conclusions. In the Mayo clinic trial and the Gastrointestinal Tumor Study Group (GITSG) trial, patients who were randomized to received EBRT only had a median survival of 5.3-6.3 months which was inferior to EBRT plus 5-fluorouracil (5-FU) (Table 1) [9, 10].

In the Eastern Cooperative Oncology Group (ECOG) trial patients were randomized to received EBRT (59.4 Gy) alone or EBRT with concurrent infusional 5-FU (1,000

Table 1. Radiation therapy vs. chemoradiotherapy.

Series	Number of patients	Median survival time	1-year survival
Mayo Clinic [9]			
EBRT (35-40 Gy/3-4 weeks) only	32	6.3 months	6%
EBRT (35-40 Gy/3-4 weeks) + 5-FU	32	10.4 months	22%
GITSG [10]			
EBRT (60 Gy/10 weeks) only	25	5.3 months	10%
EBRT (40 Gy/6 weeks) + 5-FU	83	8.4 months	35%
EBRT (60 Gy/10 weeks) + 5-FU	86	11.4 months	46%
ECOG [11]			
EBRT(59.4 Gy/five 1.8-Gy fractions/week)	49	8.2 months	NR
EBRT + 5-FU and mitomycin (10 mg/m ² on day 2)	55	8.2 months	NR

NR: not reported

mg/m²/day as a continuous infusion on days 2-5 and 28-31) plus mitomycin (one-time bolus of 10 mg/m² on day 2). There was no benefit with addition of chemotherapy as response rate (9% vs. 6%), median disease-free survival (5.0 vs. 5.1 months) and overall survival (7.1 vs. 8.4 months) were similar, respectively [11]. But the lack of survival benefit seen in this study was attributed to method of 5-FU administration which was given in intermittent high dose fashion and addition of toxicity secondary to mitomycin. Generally it is believed that EBRT alone is a suboptimal treatment for locally advanced pancreatic cancer as most patients will die of systemic disease.

Chemoradiotherapy

There are numerous studies done using variety chemotherapy agent and radiation therapy in locally advanced pancreatic cancer for local control of the disease and to increase the survival. But the survival benefit is modest at best and best optimal combination chemoradiotherapy is yet to be defined.

Radiation Therapy plus 5-Fluorouracil

For the past three decades combination of 5-FU and radiation therapy has been considered a standard care for locally advanced pancreatic cancer based on the Mayo Clinic and GITSG trial results [9, 10]. The second GITSG trial also supported the role of 5-FU in combination with radiation therapy [12]. In this trial, 143 assessable patients with unresectable disease were randomized to receive 60 Gy split-courses EBRT with concurrent and maintenance 5-FU or 40 Gy continuous-course radiation with weekly concurrent doxorubicin chemotherapy, followed by maintenance doxorubicin and 5-FU. No survival difference was observed between the two groups but there was increase in treatment toxicity in doxorubicin arm.

Most of the trials done in 80s used bolus 5-FU with radiation therapy. But today infusional 5-FU is most commonly used approach in

combination with radiation based on mostly experience in other gastrointestinal malignancies such as rectal cancer. There are limited data in pancreatic cancer using infusional 5-FU with radiation therapy. Phase I ECOG trial was done in patients with residual, or unresectable pancreaticobiliary carcinoma which demonstrated that concurrent radiation with protracted 5-FU infusion at 250 mg/m²/day was well tolerated with median survival duration of all patients treated was 11.9 months and the 2-year survival rate was 19% [13]. Phase II trial done by Ishii *et al.* came to similar conclusion. In this trial, 20 patients with locally advanced pancreatic cancer received protracted 5-fluorouracil infusion (200 mg/m²/day) with concurrent radiotherapy (50.4 Gy in 28 fractions over 5.5 weeks) [14]. The median overall survival and 1-year overall survival rate were 10.3 months and 41.8%, respectively (Table 2). There are no phase III data comparing bolus vs. infusional 5-FU with radiation therapy in locally advanced pancreatic cancer.

Radiation Therapy plus Oral Fluoropyrimidine

Capecitabine (which is a rationally designed oral fluoropyrimidine carbamate that is absorbed intact through the intestinal wall, and then converted to 5-FU in three sequential enzymatic reactions) has been used in combination with radiation therapy. Oral capecitabine has been used in other tumors such as rectal cancer as a radio-sensitizing agent but in pancreatic cancer the data is limited. Phase I study done by Saif *et al.* showed that capecitabine 800 mg/m² bid with concurrent external radiation therapy is feasible in patients with locally advanced pancreatic cancer [15]. This approach offers an easy alternative to intravenous fluorouracil as a radiosensitizer but more studies are needed to be done.

S-1 is novel oral fluoropyrimidine with two modulators, 5-chloro-2,4-dihydropyridine (CDHP) and potassium oxonate (OXO), at a molar ratio of 1:0.4:1 [16]. CDHP is a

reversible competitive inhibitor of dihydropyrimidine dehydrogenase, so therefore it is expected to yield prolonged 5-FU concentration in serum and tumor tissue. S1 drug is currently commercially available in Japan for treatment of gastric cancer. But the data as a radio sensitizing agent in pancreas cancer is very limited. In the 2007 Gastrointestinal Cancers Symposium (Orlando, FL, USA; January 20th), phase I data from Japan recommended S-1 80 mg/m² once a day with concurrent radiotherapy [17]. The median progression-free survival time, median survival time and 1-year survival rate for all patients were 8.9 months, 11.0 months, and 40.8%, respectively. Phase II trial using similar regimen is ongoing at this time.

Radiation Therapy plus Gemcitabine

Gemcitabine is the standard chemotherapy used in metastatic pancreatic cancer and has been shown to have improvements in clinical benefit and survival, compared to 5-FU [18]. Gemcitabine also has potent radiation sensitizing effects as well and these characteristics of gemcitabine have led to investigators using combination of gemcitabine and radiation therapy in locally advanced pancreatic tumor.

There are many phase I and II trials using different doses of gemcitabine and different

schedules and doses of radiation. MD Anderson published phase I study using dose escalation of gemcitabine (350 mg/m² to 500 mg/m² weekly for 7 weeks) and hypofractionated radiation therapy (3,000 cGy in 10 fractions) in patients with locally advanced pancreatic cancer [19]. Median survival for the entire group was 6 months secondary to the toxic effects of the large radiation fields. The recommended phase II dose of gemcitabine was 350 mg/m² weekly from this trial [19].

Another phase I data published by Blackstock *et al.* showed that twice-weekly gemcitabine at a 40-mg/m² dose with 50.4 Gy of radiation to pancreas was feasible and generally well tolerated with thrombocytopenia, neutropenia, and nausea/vomiting being the dose-limiting toxicities [20]. The median survival in the small cohort of eight assessable patients was encouraging at 11.1±2.3 months. The promising result from this phase I trial led to phase II trial by Cancer and Leukemia Group B (CALGB) using the same dose/schedule of gemcitabine and radiation as above [21]. The result was somewhat disappointing as this treatment strategy produced good local regional control but the median overall survival was only 8.2 months.

Other phase II trials using gemcitabine and radiation therapy produced similar results.

Table 2. Phase II-III trials using infusional 5-FU or other chemo agents with radiation therapy.

Study	Regimen	Number of patients	Median survival time	1-year survival
GITSG [12]	RT (60 Gy/10 weeks) + 5-FU	73	8.5 months	33%
	RT (40 Gy/4 weeks) + doxorubicin	70	7.6 months	27%
Ishii <i>et al.</i> [14]	Infusional 5-FU (200 mg/m ² /day) with concurrent RT (50.4 Gy)	20	10.3 months	41.8%
Blackstock <i>et al.</i> [21]	Twice-weekly gemcitabine at a 40 mg/m ² dose + concurrent RT (50.4 Gy)	39	8.2 months	NR
Moore <i>et al.</i> [22]	Weekly gemcitabine (600 mg/m ²) + concurrent RT (50.4 Gy)	28	7.9 months	31.1%
Epelbaum <i>et al.</i> [23]	Gemcitabine 400 mg/m ² weekly x3 every 28 + concurrent RT (50.4 Gy)	20	8 months	NR
Rich <i>et al.</i> [27]	Paclitaxel 50 mg/m ² weekly + concurrent RT (50.4 Gy)	109	11.2 months	43%
Haddock <i>et al.</i> [29]	Gemcitabine 30 mg/m ² twice weekly and cisplatin 10 mg/m ² + concurrent RT (50.4 Gy)	20	8.8 months	29%

NR: not reported

RT: radiation therapy

Hoosier Oncology Group tested weekly gemcitabine (600 mg/m²) plus concurrent radiation therapy (50.4 Gy), followed by gemcitabine alone in 28 patients with locally advanced pancreatic cancer [22]. Median survival time was 7.9 months and one-year survival time was 31.1%. Epelbaum *et al.* did a similar study using gemcitabine 400 mg/m² weekly x3 every 28 days for 2 cycles, given concurrently with radiotherapy, for a total dose of 50.4 Gy in 28 fractions [23]. The median survival for the entire group was 8 months (Table 2).

Other alternative strategy is use to standard dose of gemcitabine with escalating dose of radiation therapy. McGinn *et al.* investigated weekly full dose gemcitabine (1,000 mg/m² on days 1, 8, and 15 of a 28-day cycle) combined with radiation therapy at escalating doses in a phase I trial of 37 patients with locally advanced or incompletely resected pancreatic cancer [24]. Radiation dose of 36 Gy in 2.4-Gy fractions was recommended on the basis of tolerance and patterns of failure for the phase II trial. The median survival for the entire group was 11.6 months. These findings led to phase II trial which has met its accrual but the results have not been reported.

Radiation Therapy plus Paclitaxel

Paclitaxel is a potent chemotherapeutic agent that interferes with mitotic spindle function to block cells at G2M, the most radiosensitive phase of the cell cycle [25]. Data in paclitaxel as radiation sensitizer is limited but promising. The Brown University Oncology Group used paclitaxel at 50 mg/m² on days 1, 8, 15, 22 and 29 along with radiation (50.4 Gy) in 44 patients with locally unresectable pancreatic cancer [26]. Results were promising as overall response rate was 26%. The median survival was 8 months, and the 1-year survival was 30%. These finding led to phase II trial by the Radiation Therapy Oncology Group (RTOG) [27]. One-hundred and twenty-two patients with locally advanced unresectable disease were enrolled in this trial. The median survival was 11.2 months (95% CI 10.1-12.3) with estimated 1- and 2-year survivals of 43% and 13%, respectively. The median survival

was better than historical results achieved with irradiation and 5-FU (Table 2).

Radiation Therapy plus Combination of Chemo-Agents

Combination of chemotherapy has been tried with radiation for better local control and to increase overall survival.

Cisplatin and gemcitabine with radiation therapy has been tried but with limited efficacy. The results of a phase I trial suggested that the recommended dose for phase II trial was gemcitabine 30 mg/m² twice weekly and cisplatin 10 mg/m² twice weekly with radiation therapy (50.4 Gy in 28 fractions) [28]. The phase II trial by Haddock *et al.* used the same regimen in 48 patients (only 20 were evaluable for survival endpoints). The results were disappointing as survival at one year was 30% and median survival was 8.8 months [29].

Combination of gemcitabine and 5-FU with radiation therapy has been tried as well. ECOG investigated in phase I trial using combination of protracted venous infusion of 5-FU (200 mg/m²/day) with gemcitabine doses of 50 to 100 mg/m²/week. But this regimen was felt to be too toxic as three patients developed gastric or duodenal ulcers with severe bleeding requiring transfusion and one patient developed severe thrombocytopenia lasting longer than 4 weeks [30]. However, CALGB trial is now testing the same regimen in phase II trial.

In the 2007 Gastrointestinal Cancers Symposium, Fogelman *et al.* presented data in 14 patients with locally advanced pancreatic cancer who received chemotherapy GTX (capecitabine at 750 mg/m² twice daily for 14 days with gemcitabine (750 mg/m² over 75 minutes) and docetaxel (30 mg/m²) on days 4 and 11) for 3 cycles followed by weekly gemcitabine (250 mg/m² over 30 minutes) while receiving radiation [31]. Median overall survival has yet to be reached with 9 patients still alive but more importantly 57% patients were successfully converted to operability.

Preliminary results using continuous infusion (CIV) 5-FU and oxaliplatin with radiation therapy in locally advanced

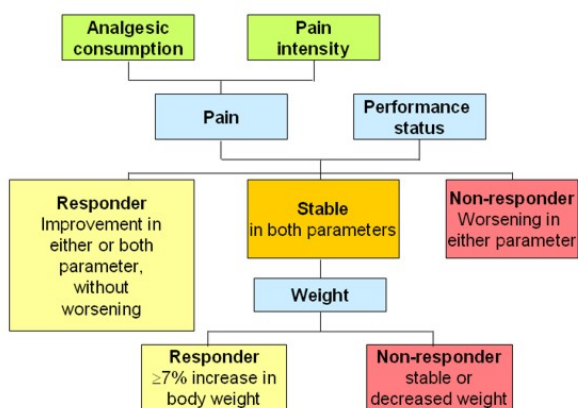


Figure 1. Clinical benefit algorithm.

pancreatic cancer were also presented at the 2007 Gastrointestinal Cancers Symposium [32]. In this phase I/II trial patients with locally advanced pancreatic cancer received CIV-5FU plus oxaliplatin with radiation therapy. In phase I portion, the treatment was well tolerated as all 15 patients finished neoadjuvant therapy. The recommended dose for phase II trial which is currently ongoing at this time is CIV-5FU 200 mg/m² and oxaliplatin (60 mg/m²/week) x 5 weeks with concurrent radiation therapy.

Chemotherapy Alone

Many contemporary phase III trials evaluating systemic therapy have included not only stage IV patients but also locally advanced patients. In order to assess the palliative benefit of chemotherapy drugs such as gemcitabine, Burris *et al.* [18], developed the concept of clinical benefit response (CBR) as a method to assess the positive palliative effects of

chemotherapy. Therefore, the primary efficacy measure of the pivotal trial was CBR, which was a composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit required a sustained (equal to, or greater than, 4 weeks) improvement in at least one parameter without worsening in any others (Figure 1).

Most of the trials used gemcitabine doublets including combination with molecular targeted agents such as erlotinib, bevacizumab, cetuximab and tipifarnib. But the results were disappointing as most of the phase III trials were found to have no survival benefit over single agent gemcitabine. One exception is the combination of erlotinib plus gemcitabine which was shown to have modest survival benefit over gemcitabine alone (median survival 6.4 vs. 5.9 months) [33].

Some investigators have questioned the role of radiation therapy as poor overall survival in locally advanced pancreatic cancer is attributed to distant metastases. Current trials which have included locally advanced pancreatic cancer suggest that impact of gemcitabine-based chemotherapy on survival may be of approximately the same magnitude as that achieved by chemoradiotherapy.

One of the largest trial using chemotherapy in patients with locally advanced pancreatic cancer was done in Europe [34]. In this phase III trial, 688 patients (164 patients with locally advanced pancreatic cancer) with advanced pancreatic cancer were randomized to gemcitabine or gemcitabine and tipifarnib

Table 3. Phase III chemotherapy studies in advanced/locally advanced pancreas cancer (median survival reflects patients with locally advanced pancreas cancer only).

Study	Chemotherapy	Number of patients		Median survival time
		Total	LAPC	
Rocha Lima <i>et al.</i> [35]	Gemcitabine/irinotecan	360	51	9.8 months
	Gemcitabine			11.7 months
Louvet <i>et al.</i> [39]	Gemcitabine/oxaliplatin	326	98	10.3 months
	Gemcitabine			10.3 months
Van Custem <i>et al.</i> [34]	Gemcitabine/tipifarnib	688	164	10.5 months
	Gemcitabine			10.5 months
Bramhall <i>et al.</i> [40]	Gemcitabine/marimastat	239	68	8.9 months
	Gemcitabine			9.7 months

LAPC: locally advanced pancreatic cancer

(farnesyltransferase inhibitor). The median survival of patients with locally advanced disease in both groups was 10.5 months.

Another phase III study which compared gemcitabine with or without irinotecan. The median survival was 11.7 and 9.8 months in the patients with locally advanced disease in the gemcitabine alone and gemcitabine/irinotecan arms, respectively (Table 3) [35]. In most other phase III trials, median survival for patients with locally advanced pancreatic cancer was not reported.

Chemotherapy vs. Combined Chemoradiotherapy

There are only few trials which directly compared chemotherapy to chemoradiotherapy in patients with locally advanced pancreatic cancer.

Early trial done by ECOG compared 5-FU alone to 5-FU with concurrent external radiation therapy followed by maintenance 5-FU [36]. This trial included 148 patients with unresectable cancer of the stomach and pancreas. There was no difference in median survival. But the study was criticized for using suboptimal external radiation therapy (40 Gy).

GITSG trial came to different conclusion. In this trial 43 patients with locally advanced pancreatic cancer were randomized to streptozocin, mitomycin, and 5-fluorouracil (SMF) vs. radiation combined with 5-FU followed by the same three-drug SMF combination [37]. The survival benefit for chemo arm was 32 weeks and the combination arm was 42 weeks which was statistically significant. But streptozocin and mitomycin has fallen out of favor because of its toxicities.

Recently in the ASCO 2006 Annual Meeting, data from the French Federation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique (FFCD-SFRO) phase III trial were presented [38]. The trial was halted because of poor accrual but 109 patients were available for evaluation. The patients with locally advanced pancreatic cancer were randomized to receive either radiation therapy (60 Gy)

plus concomitant 5-FU (300 mg/m² over 24 hours five days per week) and cisplatin (20 mg/m² on days 1 through 5 during weeks 1 and 5) followed by gemcitabine (1,000 mg/m² weekly for three of every four weeks) until progression or gemcitabine (1,000 mg/m² weekly for seven of the first eight weeks, then for three of every four weeks) alone. In a preliminary report (median 16-month follow-up), the group receiving gemcitabine alone had significantly better one-year (82% vs. 51%) and median survival (14.3 vs. 8.4 months). The high dose of radiation therapy along with addition of cisplatin may have had a detriment effect on the combination arm.

Conclusion

Treatment of locally advanced pancreatic cancer is challenging and needs multidisciplinary approach from surgeons, oncologists and radiation oncologists.

Currently most of the oncologists use 5-FU concurrently with radiation therapy to treat patients with locally advanced pancreatic care based on Mayo and GITSG trial [9, 10]. Palliation can be achieved on patients through combined modality treatment but no significant impact on long-term survival has been accomplished. Also there are conflicting results from randomized trial which questions the necessity of radiation therapy. Unfortunately, ECOG 4201, phase III trial comparing gemcitabine alone vs. gemcitabine and radiation therapy in locally advanced pancreatic cancer, was closed prematurely because of poor accrual. This study would have answered the role of radiation therapy in treatment of locally advanced pancreatic cancer.

Finally, at present the answer to the question "Is there an optimal neoadjuvant therapy for locally advanced pancreatic cancer?" is "No". However, our hope is that the trials in progress will give soon a definitive answer to this important question.

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Abbreviations ASCO: American Society of
Clinical Oncology; CALGB: Cancer and
Leukemia Group B; CBR: clinical benefit
response; CDHP: 5-chloro-2,4-
dihydroxypyridine; CIV: continuous
infusional; EBRT: external beam radiation
therapy; ECOG: Eastern Cooperative
Oncology Group; FFCF-SFRO: Federation
Francophone de Cancerologie Digestive and
Societe Francaise de Radiotherapie
Oncologique (GITSG: Gastrointestinal Tumor
Study Group; OXO: potassium oxonate;
RTOG: Radiation Therapy Oncology Group;
SMF: streptozocin, mitomycin, and 5-
fluorouracil

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