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Pancreatic cancer

Long-term results of full-dose gemcitabine with radiation therapy compared to 5-fluorouracil with radiation therapy for locally advanced pancreas cancer [☆]

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ABSTRACT

Purpose: To retrospectively compare the efficacy and toxicity of full-dose gemcitabine based chemoradiotherapy (GemRT) versus 5-fluorouracil (5-FU) based chemoradiotherapy (5FURT) for locally advanced pancreas cancer (LAPC).

Methods: From January 1998 to December 2008, 93 patients with LAPC were treated either with 5FURT ($n = 38$) or GemRT ($n = 55$). 5FURT consisted of standard-field radiotherapy given concurrently with infusional 5-FU or capecitabine. GemRT consisted of involved-field radiotherapy given concurrently with full-dose gemcitabine (1000 mg/m² weekly) with or without erlotinib. The follow-up time was calculated from the time of diagnosis to the date of death or last contact.

Results: Patient characteristics were not significantly different between treatment groups. The overall survival (OS) was significantly better for GemRT compared to 5FURT (median 12.5 months versus 10.2 months; 51% versus 34% at 1 year; 12% versus 0% at 3 years; 7% versus 0% at 5 years, respectively; all $P = 0.04$). The OS benefit of GemRT was maintained on subset analysis without concurrent erlotinib or with sequential gemcitabine (all $P < 0.05$). The rates of distant metastasis, subsequent hospitalization, acute and late grade 3–5 gastrointestinal toxicities were not significantly different between the GemRT and 5FURT groups.

Conclusions: GemRT was associated with an improved OS compared to standard 5FURT. This approach yielded long-term survivors and was not associated with increased hospitalization or severe gastrointestinal toxicity.

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The current role of radiation therapy (RT) in the treatment of locally advanced pancreas cancer (LAPC) is unclear [1]. LAPC, defined as unresectable but non-metastatic disease at diagnosis, accounts for 30% of pancreas cancer and has a reported median survival of approximately 1 year [2]. Historically, 5-fluorouracil (5FU) based chemoradiotherapy (5FURT) was the standard approach for LAPC in the United States due to two randomized trials that showed that 5FURT was superior to RT alone or 5FU alone [3,4]. More recently, gemcitabine was shown to improve survival and palliation of symptoms compared to 5FU alone for LAPC and metastatic pancreatic cancer [5]. Further support for the role of

gemcitabine was demonstrated when gemcitabine alone was found to be superior to 5FU and cisplatin with RT followed by gemcitabine [6]. These randomized trials introduced gemcitabine alone as the first line therapy and challenged the role of the traditional 5FURT approach.

The importance of local control should not be dismissed in this disease. The primary tumor may be a source of development of therapeutic resistance, and it is unlikely that substantive progress will be made without improvements in both local and distant control [7]. Gemcitabine alone has relatively low response rate against pancreatic cancer, with a partial response rate of 5–10%, so simply deleting the RT may be disadvantageous [5]. Additionally, two retrospective studies supported the importance of local control, in that survival was superior with the addition of consolidative RT after gemcitabine [8,9]. Furthermore, gemcitabine is a potent radiosensitizing agent, with radiation enhancement ratios of 1.7–1.8 [10]. Thus, a combination of gemcitabine and RT is an attractive approach, using the radiosensitizing property of gemcitabine to improve local control and its chemotherapeutic benefit to improve systemic control.

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The purpose of this study was to retrospectively review our institutional experience comparing the efficacy and toxicity of the involved-field RT with full-dose gemcitabine (GemRT) compared to the standard 5FURT. Over the last decade, both approaches had been used to treat LAPC in our multi-institutional hospital system.

Methods

All patients diagnosed with LAPC and treated with definitive chemoradiotherapy at two different institutions of the William Beaumont Hospital (WBH) from January 1998 to December 2008 were retrospectively reviewed. All patients underwent a standard pre-treatment evaluation [11]. LAPC was determined based on helical CT scan, endoscopic ultrasound, and/or exploratory laparotomy using the criteria defined in the National Comprehensive Cancer Network guidelines for pancreas cancer [12]. Generally, patients with a good performance status were recommended for chemoradiotherapy rather than gemcitabine alone. Since WBH is a multi-institutional hospital system, different institutional preferences existed that influenced the selection between the two chemoradiotherapy approaches. Patients who underwent neoadjuvant chemoradiotherapy followed by surgical resection, those treated with standard field RT and reduced dose gemcitabine, and those with metastatic disease before the start of their chemoradiotherapy were excluded from the analysis. Medically inoperable patients were included. This study was reviewed and granted approval by the WBH Human Investigation Committee.

Chemotherapy

For the 5FURT group, chemotherapy was typically started concomitantly with RT on day 1 and constituted a continuous infusion of 5-FU (200–300 mg/m²) administered Monday through Friday, or bolus 5-FU (500 mg/m²) on day 1–3 and day 29–31, or oral capecitabine (1300–1600 mg/m² per day).

For the GemRT group, concurrent gemcitabine was administered as previously described [11]. Typically, a 30-min IV infusion at a dose of 1000 mg/m² was given on day 1, 8, and 15 of a 28-day cycle, with RT started on day 1. When included on an in-house research study, erlotinib was given at 100 mg per day orally [13].

Sequential chemotherapy either before (induction) or after (adjuvant) chemoradiotherapy were given as per the medical oncologist's and patient's discretion as part of their initial treatment course.

Radiation therapy

Three-dimensional conformal RT was used in most cases. Patients were immobilized in a foam cradle in a supine position, and the treatment planning CT was obtained on a helical scanner with oral contrast. The standard RT field of the 5FURT group encompassed the primary tumor and regional lymphatics, including the celiac axis, superior mesenteric vessels, and the porta hepatis for pancreatic head tumors. The large field was typically treated to 45 Gy, and the gross tumor was then boosted to a cumulative dose of 50.4–63 Gy. The standard field RT was always delivered at 1.8 Gy per fraction given 5 days a week.

The involved-field RT of the GemRT group treated only the gross tumor volume identifiable on CT scan with 1 cm margin, without prophylactic nodal irradiation [11]. Treatment planning was performed with the isocenter calculated at 100% and the 95% line encompassing the planning target volume. For the GemRT without concurrent erlotinib group, the RT was always given over a 3 week period for a total of 15 fractions, so the fraction size varied depending on the prescribed dose. The maximum tolerated dose (MTD)

was reached at 42 Gy in 2.8 Gy fractions (which would be biologically equivalent to 46 Gy in 1.8 Gy fractions for the primary tumor according to the linear quadratic formula, using an α/β value of 10) in the initial dose-escalation trial [11], and subsequent treatments used 36 Gy in 2.4 Gy fractions (which would be biologically equivalent to 38 Gy in 1.8 Gy fractions). The GemRT with concurrent erlotinib group were all treated as part of an in-house trial with the RT given at fixed 2 Gy fractions and dose escalation by adding fractions of 2 Gy. The dose was initially escalated from 30 Gy to 38 Gy [13].

Hospitalization and severe toxicity

All hospitalizations and grade 3 or higher toxicities after the start of RT were retrospectively reviewed. Toxicity was scored using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. We defined acute toxicity as within 6 weeks of chemoradiotherapy and late toxicity as after 6 weeks.

Statistical methodology

The primary endpoint of the analysis was overall survival (OS) measured from the time of diagnosis. The secondary endpoints were distant metastasis (DM), hospitalization, and toxicity. Local control and progression-free survival were not analyzed, because they represent poor surrogates for treatment efficacy of LAPC [14]. DM was defined as the unequivocal appearance of distant metastatic disease as determined on axial CT or with histopathological confirmation. Follow-up time was measured from the time of tissue diagnosis to the date of death or last contact. Rates of OS and DM were estimated with Kaplan–Meier analysis and compared using the log rank test. The unpaired Student's *t*-test and Fisher's exact test (or chi-square) were used to analyze continuous and categorical variables (including toxicities) between groups, respectively. A *P* value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed with SYSTAT Version 11.0 (SPSS Inc., Chicago, IL), and all statistical tests were two-sided.

Results

During the study time-frame, a total of 93 patients with LAPC were treated with chemoradiotherapy. The median follow-up was 11.2 months (range 1.5–96 months). Thirty-eight patients were treated with 5FURT, and 55 patients were treated with GemRT. Sixty-seven percent of GemRT group were treated on phase I protocols [11,13,15]. Three patients had non-diagnostic biopsies and were diagnosed based on radiological images and a markedly elevated Ca 19-9. Two patients with T2 N0 M0 disease were medically inoperable and were treated with GemRT. Sixty-one patients had sequential gemcitabine either before or after chemoradiotherapy; the remaining patients received either no additional chemotherapy (*n* = 24), 5-FU/capecitabine (*n* = 5), or unknown (*n* = 3).

The 5FURT and GemRT groups shared similar baseline characteristics including ECOG performance status, age, stage, tumor location or grade (all *P* = NS; Supplementary Table S1). Table 1 summarizes the treatment details of the different groups. The compliance of completing at least 75% of prescribed RT dose were excellent for both the 5FURT and GemRT groups (87% and 96%, *P* = NS). The GemRT cohort was more likely to have received adjuvant gemcitabine than the 5FURT group (*P* < 0.001).

At last follow-up, 88 of 93 patients have died, and the median OS was 11.2 months. One patient (in the GemRT group) was lost to follow-up after developing metastatic disease. The remaining four living patients (20.1 months, 20.2 months, 40.7 months, 96 months after their diagnosis) were all treated with GemRT

Table 1
Treatment characteristics.

	5FURT [*] N = 38 (%)	GemRT [*] N = 55 (%)	P
Phase I protocols	0 (0)	37 (67)	–
RT dose			
Median (Gy)	50.4	36	–
Range (Gy)	12.6–66	22–42	
RT fractions			
Median	28	15	–
Range	(7–35)	(11–19)	
RT duration			
Median (days)	42	18	–
Range (days)	8–66	14–57	
RT dose completed			
>75%	33 (87)	53 (96)	NS
<75%	5 (13)	2 (4)	
Type of concurrent			
Chemotherapy			
5FU [*]	30 (79)	–	–
CAP [*]	8 (21)	–	
G [*]	–	37 (67)	
GE [*]	–	18 (33)	
Sequential gemcitabine [†]			
Yes	14 (37)	47 (85)	<0.001
No	22 (58)	7 (13)	
Unknown	2 (5)	1 (2)	
Induction gemcitabine [‡]	3 (8)	10 (18)	NS
Adjuvant gemcitabine [‡]	11 (29)	37 (67)	<0.001

^{*} 5FURT = concurrent 5-fluorouracil or capecitabine and radiotherapy; GemRT = gemcitabine and radiotherapy with or without concurrent erlotinib; 5FU = intravenous 5-fluorouracil; CAP = oral capecitabine; G = full-dose gemcitabine without erlotinib; GE = full-dose gemcitabine with erlotinib.

[†] Sequential gemcitabine = gemcitabine given either before (induction gemcitabine) or after (adjuvant gemcitabine) concurrent chemoradiotherapy.

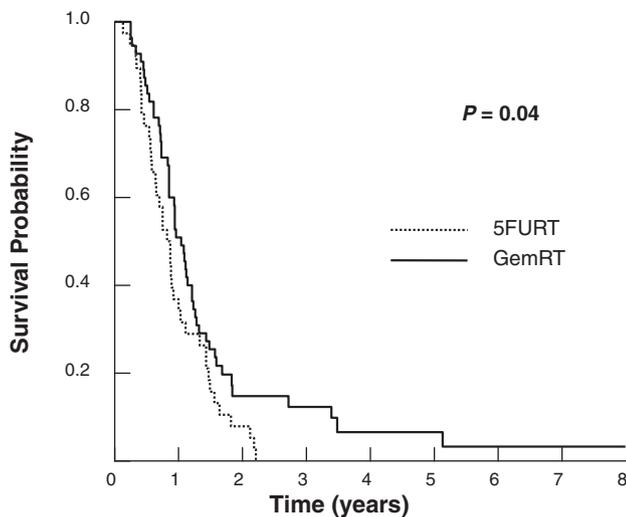
without erlotinib. Overall, the GemRT group had a significantly better OS than the 5FURT group, with a median OS of 12.5 months compared to 10.2 months, a 1-year OS of 51% compared to 34%, a 3-year OS 12% compared to 0%, and a 5-year OS of 7% compared to 0% (all $P = 0.04$, Fig. 1A). After excluding those who received concurrent erlotinib, the GemRT group still had significantly better

OS than the 5FURT ($P = 0.002$, Fig. 1B). Statistical analysis was not performed for the erlotinib subset due to its small sample size. Since 67% of the GemRT patients were prescribed to a range of different doses as per phase 1 protocols, dose–response to RT was tested. For the GemRT group, RT dose ≥ 36 Gy was associated with improved OS compared to RT dose < 36 Gy ($P = 0.02$, Fig. 1C), suggesting that improved local treatment can impact OS.

Patients who received sequential gemcitabine (of the entire cohort) also had an improved OS than those who did not ($P = 0.01$). To eliminate the possible confounding effect of sequential gemcitabine as well as concurrent erlotinib, we performed a subset analysis of those who received sequential gemcitabine without erlotinib. Of those who received sequential gemcitabine, the GemRT subset had a significantly better survival than the 5FURT subset, with a median OS of 15.1 months compared to 10.7 months ($P = 0.01$), a 1-year OS of 70% compared to 36%, a 3-year OS of 21% compared to 0%, and a 5-year OS of 11% compared to 0% ($P = 0.005$, Fig. 1D). The GemRT subset received their first dose of gemcitabine earlier than the 5FURT subset, at a median of 1 month after diagnosis compared to 3.7 months, respectively ($P < 0.001$). Of the 14 5FURT patients who received sequential gemcitabine, only 3 patients received induction gemcitabine. The total dose of gemcitabine was evaluable for 37 of the 47 patients above, and the median gemcitabine dose received were not significantly different, with 10,000 mg/m² for the GemRT subset and 7450 mg/m² for the 5FURT subset ($P = NS$).

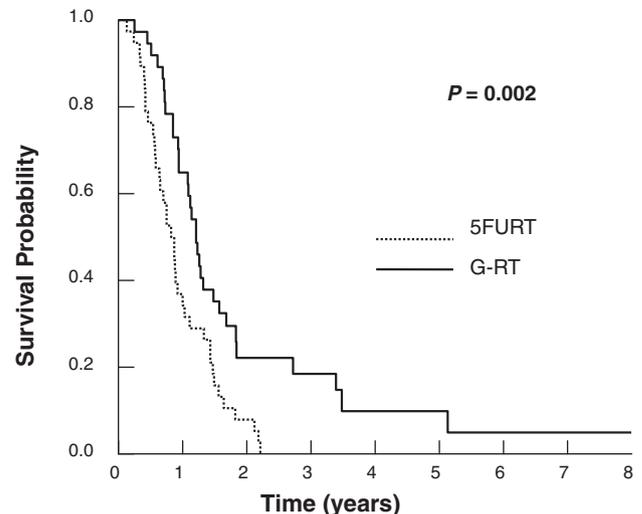
Sixteen (42%) of the 5FURT patients developed documented DM compared to 27 (49%) of the GemRT patients. The rates of DM were not significantly different among the two cohorts (34% at 1 year for both, $P = NS$). Of those who received sequential gemcitabine, the GemRT without concurrent erlotinib subset had significantly less DM than the 5FURT subset, with 1 year DM of 23% compared to 45% ($P = 0.04$). The longest surviving patient of our cohort is still alive 96 months after his diagnosis, without any signs of disease recurrence. He had biopsy proven T4 N1 LAPC and was treated with 39 Gy with concurrent gemcitabine followed by 16 additional weeks of full-dose gemcitabine.

There were a total of 224 documented hospitalizations for the entire group: 39% for cancer-related symptoms, 20% for GI



No at risk	38	14	3	0	0	0	0
5FURT:	38	14	3	0	0	0	0
GemRT:	55	28	6	5	2	2	1

Fig. 1A. Overall survival of 5FURT (concurrent 5-fluorouracil/capecitabine and radiation therapy) versus GemRT (gemcitabine and radiation therapy with or without concurrent erlotinib) [actual for 5FURT and Kaplan–Meier estimate for GemRT].



No at risk	38	14	3	0	0	0	0
5FURT:	38	14	3	0	0	0	0
G-RT:	37	24	6	5	2	2	1

Fig. 1B. Overall survival of 5FURT (concurrent 5-fluorouracil/capecitabine and radiation therapy) versus G-RT (gemcitabine and radiation therapy without concurrent erlotinib) [actual for 5FURT and Kaplan–Meier estimate for G-RT].

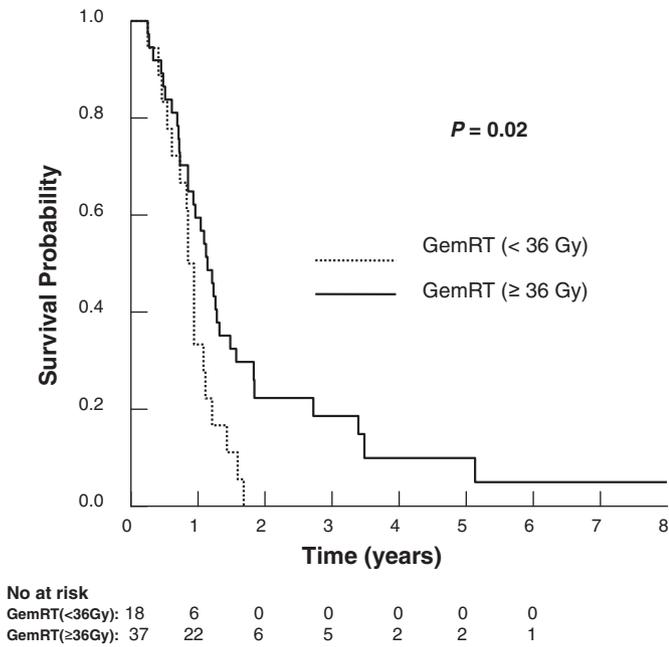


Fig. 1C. Overall survival of GemRT < 36 Gy versus GemRT ≥ 36 Gy [actual for GemRT < 36 Gy and Kaplan–Meier estimate for with GemRT ≥ 36 Gy].

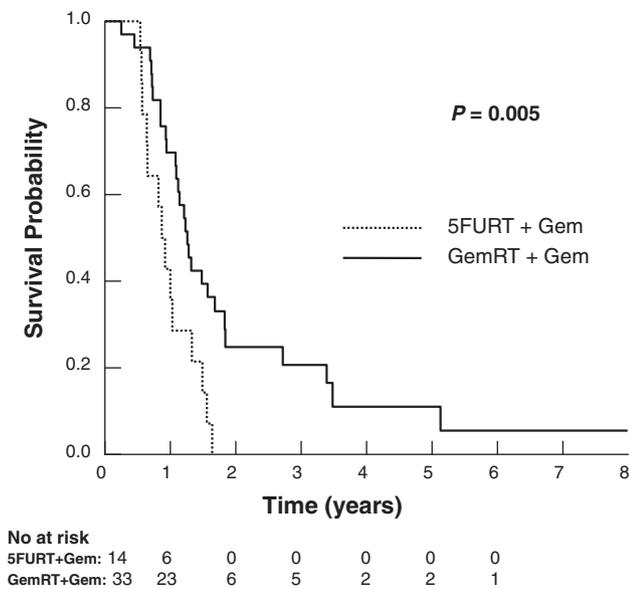


Fig. 1D. Overall survival of 5FURT with sequential gemcitabine (5FURT + Gem) versus GemRT without concurrent erlotinib but with sequential gemcitabine (GemRT + Gem) [actual for 5FURT + Gem and Kaplan–Meier estimate for GemRT + Gem].

toxicities, 17% for unrelated medical issues, 15% for infections, 3% for hematological complications. Total hospitalization days, percentage of survival time spent in hospital, and grade 3 or higher GI as well as hematological toxicities were not significantly different between the 5FURT and GemRT groups (Table 2). The severe late GI toxicities occurred between 1 and 39 months (median of 5 months) after chemoradiotherapy. There were two cases of grade 5 toxicities in each group due to GI perforation or bleeding. The two 5FURT patients received 63 Gy, while the two GemRT patients received 36 Gy and 39 Gy, respectively. The only renal toxicity occurred 12 months after GemRT and was due to gemcitabine-related renal failure.

Table 2
Hospitalization and Grade 3 or higher toxicity.

	5FURT [*] N = 38	GemRT [*] N = 55	P
Hospitalization time			
Median (days)	11	17	NS
Range (days)	0–70	0–109	
Percent of survival time spend in hospital			
Median (%)	3.8	3.9	NS
Range (%)	0–21	0–31	
Acute GI toxicity [†]			
N (%)	5 (13)	11 (20)	NS
Late GI toxicity [†]			
N (%)	4 (11)	10 (18)	NS
Acute hemetological toxicity [†]			
N (%)	3 (8)	2 (4)	NS
Late renal toxicity [†]			
N (%)	0 (0)	1 (2)	NS

^{*} 5FURT = concurrent 5-fluorouracil or capecitabine and radiotherapy; GemRT = gemcitabine and radiotherapy with or without concurrent erlotinib.

[†] Acute toxicity = occurred within 6 weeks of the completion of chemoradiotherapy; late toxicity = occurred after 6 weeks; all toxicities were grade 3 or higher and were scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Discussion

This study found that the GemRT was associated with a longer overall survival than the standard-field 5FURT. This was true whether or not sequential gemcitabine was given. Most remarkably, the GemRT produced promising long-term control of LAPC, including 5 year survivors. To our knowledge, there has been no other report of 5 year survivors for unresected LAPC in the literature. Considering the GemRT group had a lower RT dose than the 5FURT group, the improved efficacy agreed with preclinical data that gemcitabine is a better radiosensitizer [10]. Since the superior local therapy resulted in a longer OS, the results of this study further support validity of the importance of local control. In addition, the GemRT approach also reduced treatment time by 50% as compared to the 5FURT approach, which would translate to a significant reduction of burden from both patients and the health-care system.

The OS of our 5FURT group (median of 10.2 months) is comparable to recent studies investigating novel combinations of 5FU-based chemoradiotherapy: Uracil/Tegafur and leucovorin with or without celecoxib [16,17], or capcitabine and oxaliplatin [18]. Despite these attempts with combination chemotherapy, the median OS had not improved, ranging between 8.8 and 11.0 months. Therefore, future investigation on chemoradiotherapy for LAPC should strongly consider GemRT instead of 5FURT.

The finding of this study also challenges a prevalent thinking on the timing of radiation and chemotherapy, namely gemcitabine for 3 months followed by consolidative chemoradiotherapy [8,9]. Although induction gemcitabine for 3 months makes a great deal of sense if RT can only be given with 5-FU, so as not to delay immediate gemcitabine, its rationale of delaying local therapy is less clear if RT can be incorporated with full-dose gemcitabine. Obviously, induction gemcitabine can select out those who progress rapidly, but it may also risk missing the window of opportunity for local control and the chance for long-term cure for some patients.

This study did not detect significantly different toxicities between GemRT and 5FURT in contrast to the two previous studies [19,20]. This finding is even more remarkable since our GemRT used full-dose gemcitabine, whereas the other comparative studies used reduced-dose gemcitabine. It is likely that differences in the

reported toxicities were due to the difference in the RT fields. Unlike the other two studies, the RT field of this study incorporated only the gross disease with 1 cm margin and avoided prophylactic irradiation of the lymphatics. There is increasing evidence that the toxicity of GemRT is mainly related to the volume of irradiated normal mucosa [21,22] and that a limited radiation field does not increase local failures yet reduces gastrointestinal toxicity [22,23].

Since this study was retrospective, the finding should be viewed as hypothesis-generating. Although selection bias can never be completely excluded in a retrospective study, it is unlikely that overt patient selection influenced the results as the two groups were similar in patient characteristics, and the treatment assignment was systematic based on institutional preference. Furthermore, given the overall dismal prognosis of LAPC, it is unlikely that any unforeseen selection bias would explain the dramatic survival difference in this study, especially the promising long-term survival associated with the GemRT approach. This study was not designed to address the role of erlotinib to GemRT. The relatively small sample size of the concurrent erlotinib subset as well as the lower RT dose used (mostly less than 36 Gy) prohibited meaningful statistical comparison. Continued investigation will be needed to understand the optimal approach to incorporate erlotinib with GemRT [13].

This study highlights a need of systematic and well-designed randomized trials to clarify the optimal treatment approach for LAPC. Two key questions of controversy are the role of RT in the gemcitabine-era and the best way to incorporate RT with chemotherapy. Although two small randomized studies (published in abstract forms) have reported improved survival of GemRT as compared to gemcitabine alone [24,25], larger multi-institutional randomized studies with longer follow-up are needed to confirm the role of RT for LAPC. New RT techniques may also continue to increase the role of RT in treating LAPC. Intensity modulated RT (IMRT) and respiratory-gated RT technique may allow dose-escalation while decreasing the dose to critical structures to improve the therapeutic ratio of GemRT [26,27]. Stereotactic body RT (SBRT), which delivers a high dose of radiation to the gross tumor in one or a few fractions, represents a more extreme form of hypofractionated involved-field RT and avoids delay of systemic therapy [28,29]. A randomized phase II trial comparing GemRT (using IMRT) followed by gemcitabine versus SBRT followed by gemcitabine may provide important information for future large phase III trials.

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None.

Conflicts of interest

The authors have no conflicts of interest to report.

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Appendix Supplementary. data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2011.05.038.

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