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ORIGINAL ARTICLE

Chemoradiotherapy after gemcitabine plus erlotinib in patients with locally advanced pancreatic cancer

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Summary

Purpose: *To evaluate the outcomes of chemoradiotherapy (CRT) after neoadjuvant chemotherapy consisting of gemcitabine and erlotinib for unresectable locally advanced pancreatic cancer.*

Methods: *Between 2010 and 2014, 24 patients with unresectable pancreatic cancer received neoadjuvant gemcitabine/erlotinib followed by CRT. There were 9 men and 15 women, and median age was 61 years (range 48-77). Radiotherapy (RT) was delivered to the tumor and regional lymph nodes with a median dose of 50.4 Gy (range 50.4-56). All patients received concurrent chemotherapy, with 5-fluorouracil (5-FU), capecitabine or gemcitabine and 17 patients received maintenance chemotherapy with gemcitabine plus erlotinib, 5-FU plus leukovorin or capecitabine plus oxaliplatin. The median follow-up period was 17 months (range 7-31).*

Results: *The median overall survival (OS) and post-RT OS (PROS) were 17.8 and 10.7 months, respectively. On multivariate analysis, RT dose (p=0.005) and maintenance chemotherapy (p=0.019) were significant prognostic factors for OS. In addition, RT dose ≥54Gy (p=0.021) and concurrent gemcitabine (p=0.012) were identified as favorable prognostic factors for PROS. Grade 3 hematologic and gastrointestinal toxicities occurred in 3 and 2 patients, respectively.*

Conclusions: *Intensive treatment with gemcitabine-based CRT, high RT dose, and maintenance chemotherapy may improve survival outcomes in locally advanced pancreatic cancer patients receiving neoadjuvant gemcitabine/erlotinib.*

Key words: *chemoradiotherapy, induction chemotherapy, pancreatic neoplasms, unresectable*

Introduction

Surgical resection offers the only curative chance for pancreatic adenocarcinoma patients. However, only 10-20% of patients are fit for surgical resection [1]. In patients with unresectable disease, the prognosis is poor with median survival ranging from 5 to 10 months [2]. Standard treatment for patients with locally advanced pancreatic cancer is still controversial. Treatment options include chemotherapy, RT, and CRT. In Korea, the total number of pancreatic cancer patients who received RT was increased from 566 in 2009 to 901 in 2013 [3]. Studies comparing CRT with chemotherapy alone have shown contradictory results. One phase III trial reported induction CRT was less effective than systemic chemotherapy alone [4]. However, Eastern Cooperative Oncology Group (ECOG) demonstrated improved survival with CRT compared to gemcitabine alone with acceptable toxicity [5]. The recent National Comprehensive Cancer Network guideline recommends chemotherapy or CRT as the first-line treatment for patients with good performance status [6]. In addition, several studies showed improved outcomes of CRT after induction chemotherapy [7-10]. From a systematic review of trials on CRT in locally advanced pancreatic cancer, induction chemotherapy followed by CRT is a promising option for patients not progressed with good performance status [11].

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In the current study, we retrospectively analyzed the outcomes of patients with unresectable pancreatic cancer who were treated with neoadjuvant gemcitabine plus erlotinib followed by CRT.

Methods

Patients

After the institutional review board approval, we reviewed the medical records of unresectable locally advanced pancreatic cancer patients who received neoadjuvant chemotherapy consisting of gemcitabine and erlotinib followed by CRT. Patients were examined with a complete blood count, liver function test, carcinoembryonic antigen level, cancer antigen 19-9 (CA 19-9) level, and imaging modalities.

Treatment

After categorized as unresectable disease based on computed tomography (CT) and/or magnetic resonance imaging (MRI), patients received gemcitabine (1000 mg/m^2 on days 1, 8, and 15) plus erlotinib (100 mg daily) on a 4-week cycle. Next, CRT was given for patients who did not develop distant metastasis while on chemotherapy. Patients were treated using either 3-dimensional (3D) conformal radiotherapy (n=22) or intensity modulated radiotherapy (IMRT) (n=2). The planning target volume included the tumor with regional lymph nodes. The median RT dose was 50.4 Gy in 28 fractions for 5 days per week (range 50.4-56). Concurrent chemotherapy given with RT included 5-FU, 1000 mg/m^2 on D1-3 and D29-31 (n=7), capecitabine (850 mg/m^2 bid; n=8) and gemcitabine (300mg/m^2 weekly;n=9). Seventeen patients received maintenance chemotherapy such as gemcitabine plus erlotinib (n=10), 5-FU plus leucovorin (n=5) and capecitabine plus oxaliplatin (n=2).

Statistics

OS was calculated from the starting date of gemcitabine/erlotinib, and PROS was estimated from the RT completion date. The survival rates were estimated by the Kaplan-Meier method. To verify the factors associated with survival, the log-rank test and the Cox proportional hazards regression model were used for the univariate and multivariate analyses, respectively. Factors with a p value <0.05 were considered as statistically significant. All analyses were performed in PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics

Between June 2010 and June 2014, 24 patients who were diagnosed as unresectable pancreatic cancer were treated with gemcitabine plus erlotinib followed by CRT. Nine were male and 15 were female (Table 1). The median patient age was 61 years (range 48-77). All patients but one had an ECOG performance status of 0 or 1. The median CA 19-9 level was initially 243 IU/ml (range 0.9-10648). The number of neoadjuvant chemotherapy cycles ranged from 2 to 12 (median 4). Fifteen patients showed stable disease, and 6 experienced progressive disease after neoadjuvant chemotherapy. Before CRT, median CA 19-9 level was 125.5 IU/ml (range 3-5438). After CRT, median CA 19-9 level decreased to 58.6 IU/ml (range 0.9-5790). Radiotherapy started at a median of 134 days after the initiation of neoadjuvant chemotherapy (range 68-354). Radiation doses were as follows; 50.4 Gy (n=16), 54 Gy (n=1), 55.8 Gy (n=6), and 56 Gy (n=1). All patients completed CRT without interruptions and 17 patients underwent maintenance chemotherapy.

Table 1. Patient and treatment characteristics

Variables	*No. of patients n (%)*	
Age (yrs)	61 (48-77)†	
Gender		
Male	9	(37.5)
Female	15	(62.5)
Performance status (ECOG)		
0	4	(16.7)
1	19	(79.2)
2	1	(4.2)
Histology		
Adenocarcinoma	20	(83.3)
Adenocarcinoma w/ mucin	2	(8.3)
Carcinoma	2	(8.3)
Initial CA19-9 (IU/mL)	243 (0.9-10648)†	
No. of cycles of gemcitabine/erlotinib		
#2	4	(16.7)
#3	4	(16.7)
#4	5	(20.8)
#5	2	(8.3)
#6	3	(12.5)
#7	1	(4.2)
#9	4	(16.7)
#12	1	(4.2)
Response to gemcitabine/erlotinib		
PR	3	(12.5)
SD	15	(62.5)
PD	6	(25.0)
Pre-RT CA 19-9 (IU/mL)	125.5 (3-5438)†	
Interval to RT from initiation of gemcitabine/erlotinib (days)	134 (68-354)†	
RT dose (Gy)		
< 54	16	(66.7)
≥ 54	8	(33.4)
Concurrent chemotherapy regimen		
5-FU #2	7	(29.2)
Capecitabine	8	(33.3)
Gemcitabine	9	(37.5)
Maintenance chemotherapy		
Yes	17	(70.8)
No	7	(29.2)
Maintenance chemotherapy regimen		
Gemcitabine/erlotinib	10	(41.7)
Fluorouracil/leucovorin	5	(20.8)
Capecitabine/oxaliplatin	2	(8.3)

†Values are presented as median (range).
ECOG: Eastern Cooperative Oncology Group, PR: partial response, SD: stable disease, PD: progressive disease, RT: radiotherapy, FU: fluorouracil

Survival and prognostic factors

Median OS and PROS for the entire cohort were 17.8 months (range 7.0-38.8) and 10.7 months (range 1.3-21.1), respectively. With the median follow-up period of 17 months (range 7-31), 17 patients experienced disease progression: local progression occurred in 8, distant metastases occurred in 16, 7 of whom had locoregional progression as well.

Table 2 displays the results from univariate and multivariate analyses for OS. On univariate analysis, RT dose ≥ 54 Gy improved OS (p=0.003). When age, initial CA 19-9 level, number of neoadjuvant chemotherapy cycles, response to neoadjuvant chemotherapy, pre-RT CA 19-9 level, RT dose, concurrent chemotherapy regimen, and administration of maintenance chemotherapy were incorporated into the Cox proportional hazard model, there was an improvement in OS with RT dose ≥ 54 Gy (p=0.005, Figure 1A) and the use of maintenance chemotherapy (p=0.019, Figure 1B).

As regards to PROS, we found that concurrent chemotherapy regimen was a significant prognostic factor (p=0.026) on univariate analysis (Table 3). In addition, the use of RT dose ≥ 54 Gy showed a trend toward better PROS (p=0.056). On multivariate analysis, high RT dose (p=0.021, Figure 2A) and gemcitabine-based CRT (p=0.012, Figure 2B) were independently associated with improved PROS.

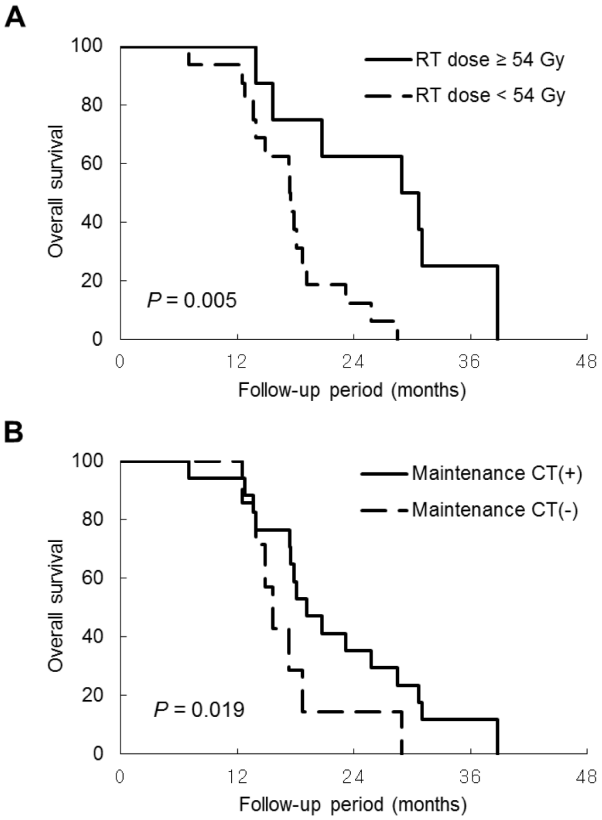

Figure 1. Overall survival rates according to **(A)** radiation dose and **(B)** maintenance chemotherapy. RT: radiotherapy; CT: chemotherapy

Table 2. Univariate and multivariate analyses for overall survival

Variables	*No.*	*Median OS (mo)*	*p value† (univariate)*	*p value‡ (multivariate)*
Age (yr)				
≤ 60	11	19.1	0.359	-
> 60	13	17.7		
Initial CA19-9 (IU/mL)				
≤ 37	4	17.4	0.203	-
> 37	20	17.8		
No. of gemcitabine/erlotinib cycles				
≤ 4	13	17.7	0.233	-
> 4	11	21.6		
Response to gemcitabine/erlotinib				
PR	3	18.4	0.635	-
SD	15	18.0		
PD	6	13.9		
Pre-RT CA19-9 (IU/mL)				
≤ 37	9	18.1	0.134	0.176
> 37	15	17.7		
RT dose (Gy)				
< 54	16	17.4	0.003	0.005
≥ 54	8	28.9		
Concurrent chemotherapy regimen				
5-FU-based	15	16.6	0.500	-
Gemcitabine	9	18.4		
Maintenance chemotherapy				
Yes	17	18.7	0.095	0.019
No	7	15.3		

†Log-rank test; ‡Cox-regression analysis. mo:months, OS:overall survival, PR:partial response, SD: stable disease, PD: progressive disease, RT: radiotherapy, FU: fluorouracil

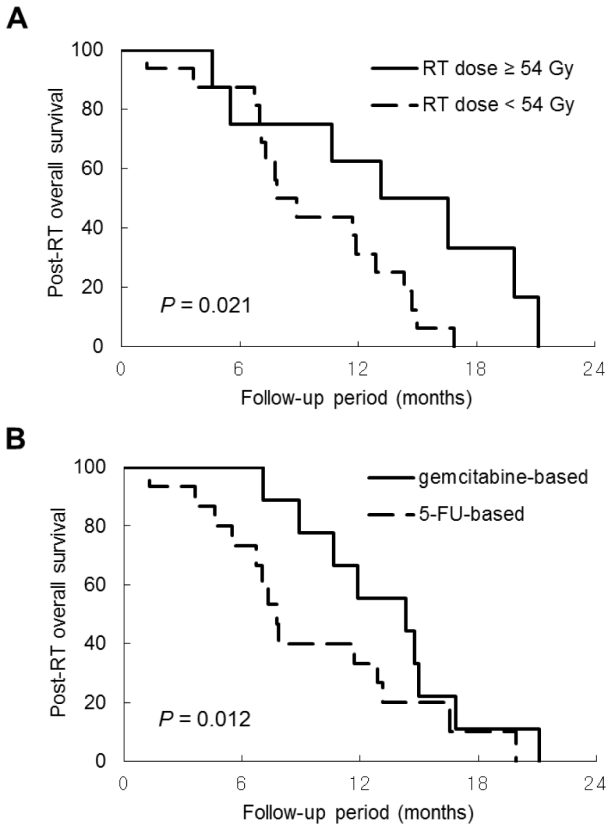

Figure 2. Post-radiotherapy overall survival rates according to **(A)** radiation dose and **(B)** concurrent chemotherapy regimen. RT: radiotherapy.

Treatment related toxicity

WHO grade 2 hematologic toxicity developed in 4 patients during neoadjuvant chemotherapy, and in 4 patients during CRT. Grade 3 hematologic toxicity was observed in 2 patients during neoadjuvant chemotherapy, and in 1 patient during CRT. Acute radiation morbidity was evaluated according to Radiation Therapy Oncology Group criteria. Acute grade 2 nausea developed in 2 patients, and grade 2 ulcer developed in 1 patient. With regards to late complications, 2 patients had grade 2 abdominal pain. Grade 3 gastric hemorrhage was observed in 1 patient who received 50.4 Gy and grade 3 duodenal stenosis in 1 patient who received 55.8 Gy. In addition, RT dose ≥ 54 Gy did not increase the acute and late toxicities (p=0.248 and 0.741, respectively).

Discussion

The treatment for unresectable locally advanced pancreatic cancer remains controversial. The current study indicates that CRT after gemcitabine plus erlotinib yields favorable survival outcome with median OS of 17.8 mo. Escalated RT dose (≥54Gy) and use of maintenance chemotherapy significantly improved OS with regards to survival after CRT, RT dose and concurrent chemotherapy regimen were independent prognostic

Table 3. Univariate and multivariate analyses for post-radiotherapy overall survival

Variables	*No. of patients*	*Median PROS (mo)*	*p value† (univariate)*	*p value‡ (multivariate)*
Age (yr)				
≤ 60	11	11.2	0.187	0.564
> 60	13	8.4		
Initial CA19-9 (IU/mL)				
≤ 37	4	10.7	0.502	-
> 37	20	8.9		
No. of gemcitabine/erlotinib cycles				
≤ 4	13	12.4	0.924	-
> 4	11	7.9		
Response to gemcitabine/erlotinib				
PR	3	9.3	0.658	-
SD	15	11.8		
PD	6	5.5		
Pre-RT CA19-9 (IU/mL)				
≤ 37	9	11.2	0.206	-
> 37	15	7.9		
RT dose (Gy)				
< 54	16	7.9	0.056	0.021
≥ 54	8	13.2		
Concurrent chemotherapy regimen				
5-FU-based	15	7.6	0.142	0.012
Gemcitabine	9	13.1		
Maintenance chemotherapy				
Yes	17	11.8	0.210	-
No	7	6.3		

†Log-rank test; ‡Cox-regression analysis. PROS: post-radiotherapy overall survival, mo: months, PR:partial response, SD:stable disease, PD:progressive disease, RT:radiotherapy, FU:fluorouracil

factors. Although patients remained in an unresectable status, our results suggest that neoadjuvant chemotherapy followed by CRT and maintenance chemotherapy may be one of the treatment options for patients with locally advanced pancreatic cancer.

Initial chemotherapy is the more often used treatment option for patients who have unresectable pancreatic cancer, because it helps physicians select those patient who show aggressive progression or metastasis [8-10]. As regards to chemotherapy regimen, several combination therapies including gemcitabine have been investigated [12-15]. Among them, gemcitabine/erlotinib regimen achieved longer progression-free survival and OS compared with gemcitabine alone, although a study failed to demonstrate a survival benefit of the regimen [9,16,17]. The combination regimen was accompanied with severe adverse events in the previous studies. However, our patients who received gemcitabine/erlotinib and CRT did not show detrimental toxicity during the overall treatment. Although two grade 3 hematologic toxicities occurred, they recovered without consequences.

Recent guidelines recommend CRT after neoadjuvant chemotherapy for locally advanced pancreatic cancer patients without progression [6,18]. The recent LAP07 study demonstrated no survival benefit from CRT compared to chemotherapy alone [9]. However, further analysis showed a trend toward improved progression-free survival by CRT, and significant local control improvement leading to prolonged treatment-free interval after CRT. In addition, a large population-based study showed the effectiveness of CRT over single-modality treatment even for elderly pancreatic cancer patients [19].

The optimal concurrent chemotherapy regimen is still under debate. Fluorouracil-based CRT has been used as early as 1980s since the report of Gastrointestinal Tumor Study Group study in locally advanced pancreatic adenocarcinoma [20]. Since gemcitabine was considered having the better radiation sensitizing effect, there were several trials comparing the clinical outcomes of gemcitabine- vs 5-FU-based CRT for locally advanced pancreatic cancer [21-23]. One small randomized trial showed that patients receiving gemcitabine lived significantly longer than those receiving bolus 5-FU [21]. Another study accruing a relatively large number of patients (n=74), however, showed non-significant differences in OS and progression-free survival [23]. In our study, there was no significant difference in OS according to concurrent chemotherapy regimen (5-FU-based vs gemcitabine). However, gemcitabine significantly increased PROS compared with 5-FU-based regimen (13.1 vs 7.6 months, p=0.012).

To improve the clinical outcomes of pancreatic cancer, RT dose escalation has been applied [24-27]. A recent study demonstrated that escalated regimen of 57.25 Gy in 25 fractions improved OS without additional toxicity [27]. In our analysis, the higher RT dose ranging from 54 to 56 Gy to boost the primary tumor showed benefits in both OS and PROS (p=0.005 and 0.021, respectively). Although late grade 3 gastric hemorrhage occurred in 1 patient with escalated dose, there was no significant difference in toxicity according to the RT dose. Our results suggest that the higher RT dose should be considered for unresected pancreatic cancer patients, although delivery of high RT dose is somewhat limited because pancreatic cancers are usually close to duodenum and small bowel.

There was a paucity of evidence examining the role of maintenance chemotherapy for unresectable locally advanced pancreatic cancer. Li et al. [21] demonstrated that additional gemcitabine following 5-FU- or gemcitabine-based CRT was tolerable, but survival was not improved compared to 5-FU-based CRT alone series. In the current study, patients receiving maintenance chemotherapy after CRT showed significantly improved OS (18.7 vs 15.3 months, p=0.019). Further studies are needed to demonstrate the role of maintenance chemotherapy after CRT for unresectable pancreatic cancer.

There are several limitations in our study. First, it was a retrospective study which is not free from statistical biases. For instance, maintenance chemotherapy regimens varied among patients. Second, it included a small number of patients. However, with the lack of data about CRT after neoadjuvant gemcitabine/erlotinib, our analysis may bring insights into the treatment of locally advanced pancreatic cancer.

In summary, we conclude that aggressive treatment such as escalated RT dose, gemcitabine-based CRT, and sequential use of maintenance chemotherapy improves survival in locally advanced pancreatic cancer patients treated with gemcitabine plus erlotinib. Further prospective studies with a large number of patients are needed to validate our conclusion.

Conflict of interests

The authors declare no confict of interests.

References

1. Garcea G, Dennison AR, Pattenden CJ, Neal CP, Sutton CD, Berry DP. Survival following curative resection for pancreatic ductal adenocarcinoma. A systematic review of the literature. JOP 2008;9:99-132.
2. Sun H, Ma H, Hong G, Sun H, Wang J. Survival improvement in patients with pancreatic cancer by decade: A period analysis of the SEER database, 1981-2010. Sci Rep 2014;23:6747.
3. Kang JK, Kim MS, Jang WI et al. The clinical utilization of radiation therapy in Korea between 2009 and 2013. Radiat Oncol J 2016;34:88-95.
4. Barhoumi M, Mornex F, Bonnetain F et al. Locally advanced unresectable pancreatic cancer: Induction chemoradiotherapy followed by maintenance gemcitabine versus gemcitabine alone: Definitive results of the 2000-2001 FFCD/SFRO phase III trial. Cancer Radiother 2011;15:182-191.
5. Loehrer PJ Sr, Feng Y, Cardenes H et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 2011;29:4105-4112.
6. National Comprehensive Cancer Network [homepage on the Internet]. Washington [cited 23 August 2016]. NCCN Clinical Practice Guidelines in Oncology: Pancreatic adenocarcinoma, version 2. 2016. Available from: http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
7. Krishnan S, Rana V, Janjan NA et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. Cancer 2007;110:47-55.
8. Huguet F, Andre T, Hammel P et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol 2007;25:326-331.
9. Hammel P, Huguet F, van Laethem JL et al.; LAP07 Trial Group. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. JAMA 2016;315:1844-1853.
10. Arvold ND, Ryan DP, Niemierko A et al. Long-term outcomes of neoadjuvant chemotherapy before chemoradiation for locally advanced pancreatic cancer. Cancer 2012;118:3026-3035.
11. Huguet F, Girard N, Guerche CS, Hennequin C, Mornex F, Azria D. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. J Clin Oncol 2009;27:2269-2277.
12. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group trial E2297. J Clin Oncol 2002;20:3270-3275.
13. Rocha Lima CM, Green MR, Rotche R et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 2004;22:3776-3783.
14. Louvet C, Labianca R, Hammel P et al. GERCOR; GISCAD. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 2005;23:3509-3516.
15. Oettle H, Richards D, Ramanathan RK et al. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. Ann Oncol 2005;16:1639-1645.
16. Moore M J, Goldstein D, Hamm J et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-1966.
17. Senderowicz AM, Johnson JR, Sridhara R, Zimmerman P, Justice R, Pazdur R. Erlotinib/gemcitabine for first-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas. Oncology (Williston Park) 2007;21:1696-1706.
18. Seufferlein T, Bachet JB, Van Cutsem E, Rougier P, ESMO Guidelines Working Group. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 (Suppl 7):vii33-40.
19. Krzyzanowska MK, Weeks JC, Earle CC. Treatment of locally advanced pancreatic cancer in the real world: population-based practices and effectiveness. J Clin Oncol 2003;21:3409-3414.
20. Moertel CG, Frytak S, Hahn RG et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 1981;48:1705-1710.
21. Li CP, Chao Y, Chi KH et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. Int J Radiat Oncol Biol Phys 2003;57:98-104.
22. Brasiūniene B, Juozaityte E. The effect of combined treatment methods on survival and toxicity in patients with pancreatic cancer. Medicina (Kaunas) 2007;43:716-725.
23. Mukherjee S, Hurt CN, Bridgewater J et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol 2013;14:317-326.
24. Wong AA, Delclos ME, Wolff RA et al. Pancreatic Tumor Study Group. Radiation dose considerations in the palliative treatment of locally advanced adenocarcinoma of the pancreas. Am J Clin Oncol 2005;28:227-233.

25. Zimmermann FB, Jeremic B, Lersch C, Geinitz H, Hennig M, Molls M. Dose escalation of concurrent hypofractionated radiotherapy and continuous infusion 5-FU-chemotherapy in advanced adenocarcinoma of the pancreas. Hepatogastroenterology 2005;52:246-250.
26. Golden DW, Novak CJ, Minsky BD, Liauw SL. Radiation dose ≥54 Gy and CA 19-9 response are associated with improved survival for unresectable, non-metastatic pancreatic cancer treated with chemoradiation. Radiat Oncol 2012;7:156.
27. Krishnan S, Chadha AS, Suh Y et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. Int J Radiat Oncol Biol Phys 2016;94:755-765.