Int J Clin Exp Med 2017;10(1):979-985
www.ijcem.com /ISSN:1940-5901/IJCEM0039517

Original Article

The reirradiation of cyberknife treatment for locally advanced pancreatic cancer: initial clinical experiences

Shuiwang Qing, Huojun Zhang

Department of Radiation Oncology, Changhai Hospital, Shanghai, China

Received September 5, 2016; Accepted November 26, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: Background: The aim of this study was to evaluate the feasibility and safety of the reirradiation of CyberKnife (CK) for locally advanced pancreatic cancer (LAPC) patients in local control and pain relief. Methods: Four patients with unresectable LAPC were treated with CK robotic radiosurgery system and their treatment response was evaluated by response evaluation criteria in solid tumors (RECIST). Toxicity was evaluated according to the national cancer institute (NCI) common terminology criteria for adverse events (CTCAE) v4.0. The relief of abdominal or back pain was followed by numerical rating scale (NRS) scoring evaluation. Results: Two patient presented with stable disease (SD), the rest two patients were with partial response (PR) after first CK treatment course. The median overall survival (OS) and the median progression-free survival (PFS) were 20 months and 9.5 months respectively from the first CK treatment. The pain relief was observed less than 1 month after tCK procedures (3-22 days), and local control was achieved 3 months after CK treatment. All patients were with compliance to radiotherapy well, one patient with grade 1 nausea and vomitting in the first CK treatment, one patient with grade 1 leucopenia, grade 2 nausea and weakness, grade 3 vomitting were observed in CK reirradiation course, no grade 4 late toxicity was observed in both CK treatment courses. Conclusion: Selected LAPC patients can be reirradiated with CK after local failure of first CK treatment, the reirradiation was safe and effective to improve local control rate and relieve symptoms.

Keywords: Locally advanced pancreatic cancer, reirradiation, cyberknife

Introduction

Pancreatic cancer is one of the most invasive cancers with a poor prognosis, because early specific clinical symptoms were rarely shown, most patients had developed advanced stage at the time of diagnosis. For the current stage, surgery is the only curable treatment for pancreatic cancer, and around 15% of patients had received radical resection, however the median survival time is no less than 1 year [1].

Local recurrence rate or distant metastasis after radical surgery is still high and moreover few patients with LAPC are accessible for surgeries. Besides, 50% of patients with LAPC suffered from pains with varying degrees caused by ineffective local control which will lower the quality of life (QoL) [2]. Christine A [3] reported that about 30% of patients died with locally destructive pancreatic cancer without distant metastasis in autopsy, which suggested that local failure may play an important role in tumor recurrence with LAPC, and patients may enhance overall survival and QoL if local progression of the disease could be controlled.

Chemotherapy or radiotherapy is the conventional treatment for patients with LAPC, whereas it is not applicable in some circumstances. For pancreatic lesions located deep inperitoneal cavity, which is adjacent to critical organs such as stomach, small intestine, liver and kidney, it is difficult to elevate the prescription dose in conventional radiation therapy scheme even it is Intensity-modulated radiation therapy (IMRT).

Different from conventional therapy with relatively small doses over the course of several weeks, stereotactic body radiotherapy (SBRT) could deliver a greater dose of radiation over the course of far few treatments with highly precise treatment fields. SBRT has shown better

Table 1. Characteristics of 4 patients before the first-course CK treatment

Case	Gender	Age	Tumor location	Tumor maximal diameter	Lymph node metastasis	Tumor stage	KPS
1	Male	62	Head	4.0 cm	Negative	cT4N0M0	90
2	Male	77	Body	2.5 cm	Positive	cT2N1M0	80
3	Female	59	Body	2.6 cm	Negative	cT4N0M0	80
4	Male	55	Body	1.8 cm	Negative	cT3N0M0	90

Table 2. Dose-volume constraints for critical organs in the first course CK treatment

Critical structure	Volume of organ receiving radiation	Absorbed radiation (Gy) Mean (range)	Tolerance dose (Gy)
Liver	700 cc	3 (2.6-4.7)	21
Stomach	10 cc	12.5 (4.9-15.6)	18
Duodenum	5 cc	6.5 (2.7-15.6)	18
	10 cc	5 (2.2-10.9)	12.5
Bowel	5 cc	11.2 (7.43-18)	19.5
Left kidney	2/3	4.5 (2.3-6.27)	23
Right kidney	2/3	4.6 (1.6-7.84)	23

outcomes with more clinical benefit and less toxicity. And CK is one platform of SBRT with Synchrony® respiratory tracking system as well as real-time tumor tracking and adjustment keeps beam stationary to the target and reduces amount of dose to critical structures. The efficacy and safety of the CK in LAPC has been reported in several studies [4-9]. The range of median progression free and overall survival were 6.8 to 8.7 months and 12.2 to 14.3 months respectively. However, there were few studies on the subsequent therapy after the failure of local control. The aim of our study is to evaluate the safety and efficiency of the second course of CK treatment for LAPC patients in local control and pain relief.

Materials and methods

Patients

Between April 2013 and October 2013, four patients with unresectable LAPC received the first-course radiotherapy by CK, and from February 2014 to June 2014 the second-course of radiotherapy was delivered. The four patients with 3 males and 1 female, whose age ranged from 55 to 77 years, all were with a KPS ≥80 points. In which one was with pancreatic head carcinoma and the other three were with pancreatic body carcinoma. All patients were with variable degrees of abdominal or back pain with NRS scores from 5 to 7 before the first-course CK treatment. Two patients were diagnosed by histopathology via EUS-guided biopsy and the other two patients were diagnosed by clinical symptom, PET (positron emission tomography)-CT scan and a CA (glucoprotein antigen) 19-9 level. All patients had accepted any anti-tumor treatment before the first CK course radiation therapy (**Table 1**). The recurrence or progression was limited to the primary tumor or regional nodes.

Positioning and target delineation

Patients were placed in the supine position by a whole-body vacuum pad and underwent planning CT with a slice thickness of 1.5 mm. The normal organs at risk (OAR) include liver, kidneys, stomach, and small intestine. The gross tumor volume (GTV) was defined as the visible tumor and lymph node by CT images, while the clinical target volume (CTV) was equivalent to GTV, and planning target volume (PTV) was defined as the region of 2 mm outside CTV. When tumor is adjacent to critical organs especially duodenum, the expansion from CTV to PTV is avoided in this direction. The mean dose and range of doses to stomach, duodenum, small intestine and kidneys are listed in **Tables 2**, **3**.

Treatment planning and delivery

All patients were treated with CK robotic radiosurgery system (Accuray, Sunnyvale, USA) with different tumor tracking techniques for twice radiotherapy courses. Two patients were treated by spine tracking system and the other two patients were by both respiratory tracking system and fiducials tracking system by placing gold fiducials which are 0.9 mm in diameter and 3 mm in length (CIVCO, USA) to the region near to the tumor. Treatment planning CTs were performed at least 7 days after fiducial placement. The two patients received abdominal CT

Table 3. Dose volume constraints for critical organs in the second-course CK treatment

Critical structure	Volume of organ receiving radiation	Absorbed radiation (Gy) Mean (range)	Tolerance dose (Gy)
Liver	700 cc	1.8 (1.4-2.8)	21
Stomach	10 cc	7.74 (6.4-9.51)	18
Duodenum	5 cc	5.5 (2.3-9.33)	18
	10 cc	4.3 (1.9-8.17)	12.5
Bowel	5 cc	9.2 (6.7-12.05)	19.5
Left kidney	2/3	3.1 (1.58-3.7)	23
Right kidney	2/3	3 (1.47-4.5)	23

Table 4. Dose-volume parameters for the 4 patients before the first-course CK treatment

Case	GTV (cc)	PTV (cc)	Coverage (%)	CI	HI	Prescription dose (Gy)	Fractions
1	93.7	114	80.6	1.12	1.52	7	5
2	42	73.5	82	1.27	1.61	8	5
3	35.1	62.6	80	1.08	1.59	7.5	5
4	40.5	66.7	81	1.27	1.16	7	5

GTV, gross tumor volume; PTV, planning target volume; CI, conformality index; HI, homogeneity index.

Table 5. Dose volume parameters for the 4 patients before the second-course CK treatment

Case	GTV (cc)	PTV (cc)	Coverage (%)	CI	HI	Prescription dose (Gy)	Fractions
1	66.7	66.7	80.4	1.17	1.39	6	5
2	56	77.8	82	1.27	1.61	6.1	5
3	60.8	94.3	80	1.18	1.46	7.2	5
4	21.1	35	81	1.23	1.52	7	5

Table 6. Characteristics of the 4 patients with local recurrence before the second course CK treatment

Case	Tumor maximal diameter	Lymph node metastasis	KPS	Chemotherapy	PFS (m)	Best Response	OS (m)
1	3.4 cm	Negative	80	Gem+Oxa (4 cycles)	9	PR	24
2	2.5 cm	Positive	80	Gem (6 cycles)	11	SD	18
3	2.8 cm	Positive	80	None	7	SD	16
4	1.5 cm	Negative	80	Gem+S1 (3 cycles)	10	PR	22

PFS: progression free survival, Gem+Oxa: Gemcitabine plus Oxaliplatin (Gem 1 g/m^2/d1, 8; Oxa 130 mg/m^2/d1), Gem+S1: Gemcitabine plus S1 (Gem 1 g/m^2/d1, 8; S1 50 mg/m^2/d1-14).

scans about 1 week after fiducial placement. The three CT phases should be acquired under breath hold (end-expiratory). When the number of fiducials is less than three, fiducial tracking and x-sight spine tracking systems are applied.

Treatment characteristics

The median prescription dose was 36.25 Gy (35-40 Gy) in 5 fractions with the median coverage of 80.8% (80%-82%) for the first-course CK therapy (**Table 4**) and the second-course CK therapy, the median prescription dose was 32.75 Gy (30-36 Gy) in 5 fractions with the median coverage of 80.7% (80.4%-82%). The prescription isodose line was limited to 70%-75% (**Table 5**).

Patient follow-up

The patients had biological evaluations every month after CK treatment and underwent upper abdominal CT scans every 2-3 months. All patients' images will be assessed and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on RECIST. Toxicity was evaluated according to the NCI CTCAE v4.0. The relief of the abdominal or back pain was followed by NRS scoring evaluation.

Statistical analysis

All statistics were performed using SPSS 13.0 software. For survival analysis, progression-free survival was defined as the time interval between the date from treatment to the date of tumor progression, overall survival was defined as the time interval between the date from treatment to the date of death or the last follow-up. Survival curves were plotted using the Kaplan-Meier method. Statistical significance was set at $P<0.05$.

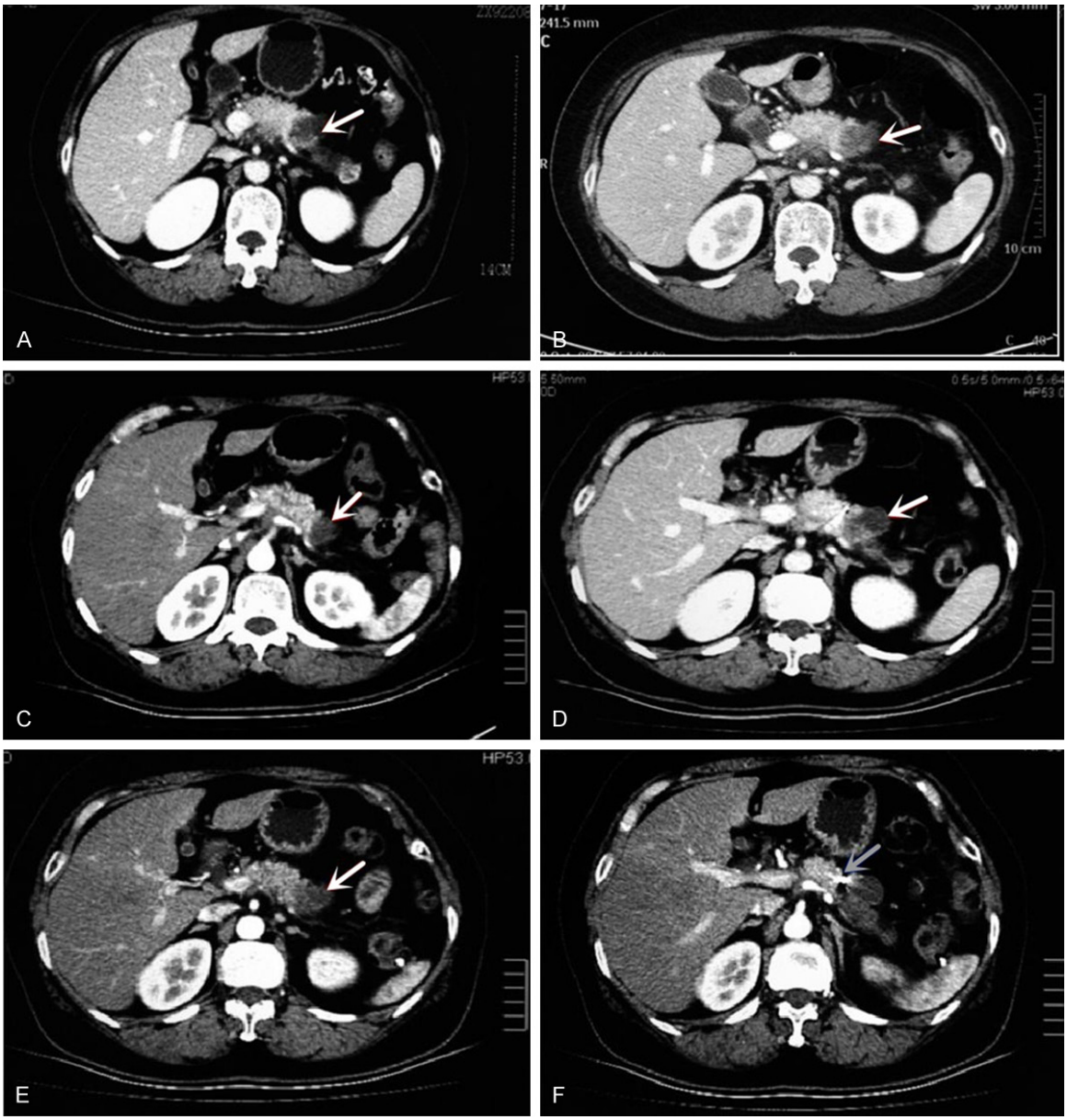

Figure 1. Computed tomography (CT) scan of case 3 with LAPC prior to and following the twice SBRT. A. CT scan prior to the first-course treatment shows a mass in the pancreatic body (white arrow). B, C. CT scan 3 months and 6 months following the first SBRT course (white arrow). D. CT scan prior to the second-course treatment shows the local recurrence of the tumor in the pancreatic body (white arrow). E. CT scan 2 months following the second SBRT course (white arrow). F. Fiducial showed in this picture (gray arrow).

Results

Tumor response and survival

The follow up upper abdominal CT scans were assessed for tumor response every two to three months, two patients showed SD, the other two patients were with PR after the first CK course illustrated in **Table 6**. And three patients accepted maintenance chemotherapy including Gemcitabine post-first CK course. The median OS and the median PFS were 20 months and 9.5 months respectively from the first CK course (**Table 6**). The CT images were shown in **Figure 1**.

Toxicities

All patients have shown good compliance to two courses radiation therapy. Only nausea and

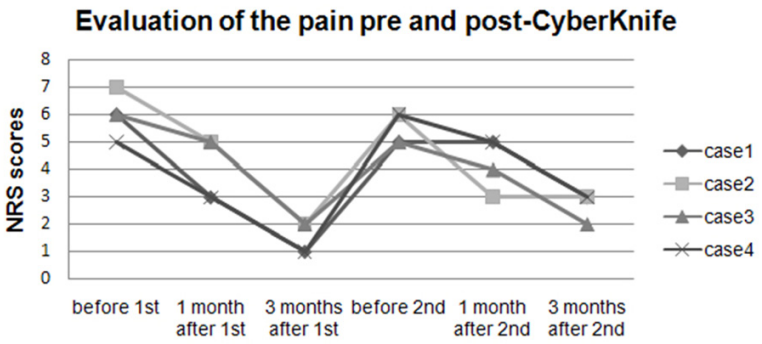

Figure 2. Evaluation of the pain relief in patients during the first and second CK course.

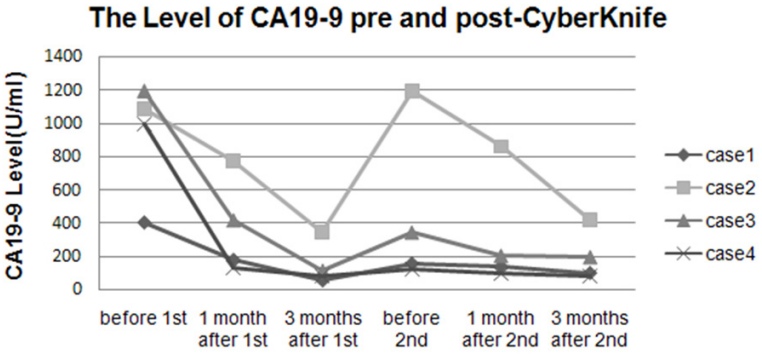

Figure 3. The level of CA19-9 in patients during the first and second CK course.

vomiting of grade 1 was observed after the first fraction during first course CK treatment. In the reirradiation of second-course CK treatment, leucopenia of grade 1 and nausea and weakness of grade 2 were observed, and one patient had temporary aggravated abdominal pain without increasing amylase. In the follow up, one case showed grade 3 vomitting, however no grade 4 of late toxicity was observed after CK reirradiation.

Pain relief

The pain suffered by the enrolled patients was assessed by NRS system with the range from 5 to 7 scores prior to radiation therapy. Opioids has to be prescribed to two patients to control the pain. The pain relief was observed after CK treatment with time range of 3 days to 22 days, and the best pain control was achieved in 3 months after CK treatment. The pain was relieved and controlled by 2 scores' reduction in all patients, moreover no medication was prescribed to the enrolled four patients (**Figure 2**). The pain relief rate was up to 100%. All patients complained that the pain aggravated to the range from 5 to 6 scores prior to the second CK course. And the second CK course relieved the pain with NRS scores down to 3.

The changes of the tumor markers

The difference of CA19-9 between pre- and post-CK is shown in **Figure 3**. In the follow-up of 18 months, the mean level of CA19-9 was found to be reduced from 925 to 151.8 U/ml which revealed the relevant tumor response after first course CK treatment. However the mean level of CA19-9 was increased to 457.7 u/ml just before CK reirradiation. In which the mean level of CA19-9 was reduced to 201 u/ml after the second course of CK treatment (**Figure 3**).

Discussion

The conventional external beam treatment to locally advanced pancreatic adenocarcinoma (LAPC) remains limited by relatively lower therapeutic ratio in the potential adverse effects than the gain in overall survival.

However, stereotactic body radiotherapy (SBRT) has shown the ability to deliver high doses for tumor control while keeping lower doses to the surrounding normal tissues and there were many experiences in SBRT shows that CK can get an advantageous survival rate and reduce the toxicity.

Gurka [10] had reported that 14 unresectable LAPC patients treated with prescription dose of 25 Gy in five fractions showed grade 1 to 2 gastrointestinal toxicity and no grade 3 or 4 radiation-related toxicities after SBRT treatment within 2 weeks, in the follow up, two patients had a partial response, and the left 12 patients showed stable disease. The median PFS and OS were 6.8 months and 12.2 months respectively.

The previous studies [11-13] have also demonstrated that hypo-fractionated approach in LAPC treatment is more effective in the radiation induced toxicity control. Koong and his coworkers [14] reported the first CK study on LAPC, the enrolled 15 patients were treated with doses of 15, 20, or 25 Gy in a single fraction. The local control rate was up to 100% and OS was 11 months. There wasn't any grade 3 toxicity observed in this study. The lower toxicity in LAPC SBRT treatment were also found in two studies with which achieved local control rate of 94% and 100% respectively by one fraction dose of 25 Gy. In addition, the increasing toxicity especially the late gastrointestinal (GI) toxicity was found to be well correlated with high local control rate in these studies.

Bae [15, 16] observed that a Dmax of 35 Gy and 38 Gy in 3 fractions of SBRT correlated with a 5% and 10% rate of grade 3 gastroduodenal toxicity respectively on abdominal malignant tumor. ASCO (American Society of Clinical Oncology) recommend [17] that five-fraction regimens (30 to 33 Gy in five fractions) have been shown to be associated with low incidence of GI toxicity, improvement in pancreatic pain, and 1-year local control of 78%. The optimal sequencing of chemotherapy and SBRT remains unknown; SBRT has been used as upfront treatment or as a sandwich regimen during ongoing chemotherapy.

In our study, a modest prescription dose of 30-40 Gy in five fractions (35-40 Gy in first course, 30-36 Gy in second course), which is equivalent to the conventional radiation therapy scheme dose of 2 Gy in 25-30 fractions in BED ($\alpha/\beta=10$) was prescribed to patients with LAPC.

The results showed that all four patients had a 100% local control rate, and the pain relief was accompanied with significant CA19-9 decrease even in reirradiation treatment. We observed that three patients received the maintenance chemotherapy post-first CK course. Maybe it is one of the reasons that preventing the there patients from the distant metastasis. The main toxicities in our study are transient grade 1 nausea and vomitting during the first CK course. Leucopenia of grade 1, nausea and weakness of grade 2 as well as vomiting of grade 3 were observed after the second CK treatment. There were no grade 4 late toxicity observed after CK treatment, the acute side effects were acceptable whereas more sample sizes and long term follow up were needed.

Our study has the limitation of small enrolled sample size, thus, we could not confirm that all LAPC patients can benefit from the repeated CK treatment. As an innovative new technology, the dose and fraction scheme of CK treatment is still under investigation. And from the experiences in this study the inclusion criteria of selected LAPC patients treated with CK re-irradiation were as follows: 1. The KPS scores should be more than 80. 2. Tumor located in pancreatic body or head without severe obstructive jaundice. 3. Patients with good clinical response after the first CK course. 4. The re-irradiation interval of CK treatment should be limited with at least 6 months from the first CK treatment, in the meanwhile, a reduced prescribed dose was delivered for the re-irridiation.

Conclusion

In the present study we have evaluated the outcomes in patients with LAPC treated with CK re-irridiation. Our study has shown that the repeated CK may be an alternative treatment in selected LAPC patients to improve the local control rate and quality of life with acceptable toxicity. Further studies based on larger sample size are needed.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Huojun Zhang, Department of Radiation Oncology, Changhai Hospital Affiliated The Second Military Medical University, No. 168, Changhai Road, Shanghai 200433, China. E-mail: correspondzhj@163.com

References

[1] Ghaneh P, Slavin J, Sutton R, Neoptolemos JP. Adjuvant therapy for pancreatic cancer. Word J Surg 1999; 23: 937-945.

[2] Willett CG, Czito BG, Bendell JC, Ryan DP. Locally advanced pancreatic cancer. J Clin Oncol 2005; 23: 4538-4544.

[3] Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, Vilardell F, Wang Z, Keller JW, Banerjee P, Herman JM, Cameron JL, Yeo CJ, Halushka MK, Eshleman JR, Raben

M, Klein AP, Hruban RH, Hidalgo M, Laheru D. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol 2009; 27: 1806-1813.

[4] Schellenberg D, Kim J, Christman-Skieller C, Chun CL, Columbo LA, Ford JM, Fisher GA, Kunz PL, Van Dam J, Quon A, Desser TS, Norton J, Hsu A, Maxim PG, Xing L, Goodman KA, Chang DT, Koong AC. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2011; 81: 181-188.

[5] Rwigema JC, Parikh SD, Heron DE, Howell M, Zeh H, Moser AJ, Bahary N, Quinn A, Burton SA. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. Am J Clin Oncol 2011; 34: 63-69.

[6] Chuong MD, Springett GM, Freilich JM, Park CK, Weber JM, Mellon EA, Hodul PJ, Malafa MP, Meredith KL, Hoffe SE, Shridhar R. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys 2013; 86: 516-522.

[7] Pollom EL, Alagappan M, Chan C, Shultz D, Kunz PL, Koong A, Chang DT. Outcomes and toxicity of SBRT for patients with unresectable pancreatic adenocarcinoma. J Clin Oncol 2014; 32: 546.

[8] Moningi S, Raman SP, Dholakia AS, Hackerprietz A, Pawlik TM, Zheng L. Stereotactic body radiation therapy for pancreatic cancer: single institutional experience. J Clin Oncol 2014; 32: 546.

[9] Gurka MK, Kim C, He AR, Charabaty A, Haddad N, Turocy J. Stereotactic body radiation therapy (SBRT) combined with chemotherapy for locally advanced pancreatic adenocarcinoma. J Clin Oncol 2014; 32: 546.

[10] Gurka MK, Collins SP, Slack R, Tse G, Charabaty A, Ley L, Berzcel L, Lei S, Suy S, Haddad N, Jha R, Johnson CD, Jackson P, Marshall JL, Pishvaian MJ. Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: a pilot trial demonstrating safety. Radiat Oncol 2013; 8: 44.

[11] Hoyer M, Roed H, Sengelov L, Traberg A, Ohlhuis L, Pedersen J, Nellemann H, Kiil Berthelsen A, Eberholst F, Engelholm SA, Von der Maase H. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. Radiother Oncol 2005; 76: 48-53.

[12] Koong AC, Christofferson E, Le QT, Goodman KA, Ho A, Kuo T, Ford JM, Fisher GA, Greco R, Norton J, Yang GP. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2005; 63: 320-323.

[13] Schellenberg D, Goodman KA, Lee F, Chang S, Kuo T, Ford JM, Fisher GA, Quon A, Desser TS, Norton J, Greco R, Yang GP, Koong AC. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2008; 72: 678-686.

[14] Koong AC, Le QT, Ho A, Fong B, Fisher G, Cho C, Ford J, Poen J, Gibbs IC, Mehta VK, Kee S, Trueblood W, Yang G, Bastidas JA. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2004; 58: 1017-1021.

[15] Bae SH, Kim MS, Cho CK, Kang JK, Lee SY, Lee KN, Lee DH, Han CJ, Yang KY, Kim SB. Predictor of severe gastroduodenal toxicity after stereotactic body radiotherapy for abdominopelvic malignancies. Int J Radiat Oncol Biol Phys 2012; 84: 469-474.

[16] Bae SH, Kim MS, Kim SY, Jang WI, Cho CK, Yoo HJ, Kim KB, Lee DH, Han CJ, Yang KY, Kim SB. Severe intestinal toxicity after stereotactic ablative radiotherapy for abdominopelvic malignancies. Int J Colorectal Dis 2013; 28: 1707-1713.

[17] Balaban EP, Mangu PB, Khorana AA, Shah MA, Mukherjee S, Crane CH, Javle MM, Eads JR, Allen P, Ko AH, Engebretson A, Herman JM, Strickler JH, Urba S, Yee NS. Locally advanced, unresectable pancreatic cancer: American society of clinical oncology clinical practice guideline. J Clin Oncol 2016; 67: 5561.