World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i26.8156

World J Gastroenterol 2015 July 14; 21(26): 8156-8162
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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ORIGINAL ARTICLE

Retrospective Study

Stereotactic body radiotherapy using CyberKnife for locally advanced unresectable and metastatic pancreatic cancer

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Author contributions: Su TS and Liang P performed the majority of experiments and designed the study; Su TS wrote the manuscript; Lu HZ and Liang JN collected all the clinical materials; Liu JM, Zhou Y, Gao YC and Tang MY provided vital reagents and analytical tools and were also involved in revising the manuscript.

Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Rui Kang Hospital.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflict of interest to disclose.

Data sharing statement: Statistical code and dataset available from the corresponding author at sutingshi@163.com.

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Received: January 7, 2015
Peer-review started: January 8, 2015
First decision: January 22, 2015
Revised: February 3, 2015
Accepted: March 18, 2015
Article in press: March 19, 2015
Published online: July 14, 2015

Abstract

AIM: To evaluate the efficacy and toxicity of stereotactic body radiotherapy using CyberKnife for locally advanced unresectable and metastatic pancreatic cancer.

METHODS: From June 2010 to May 2014, 25 patients with locally advanced unresectable and metastatic pancreatic cancer underwent stereotactic body radiotherapy. Nine patients presented with unresectable locally advanced disease and 16 had metastatic disease. Primary end-points of this study were overall survival, relief of abdominal pain, and toxicity.

RESULTS: Fourteen patients were treated with a total dose of 30-36 Gy in three fractions and the remainder with 40-48 Gy in four fractions. Median follow-up was 11 mo (range: 2-25 mo). The median survival duration calculated from the time of stereotactic body radiotherapy for the entire group, the locally advanced group, and the metastatic group was 9.0 mo, 13.5 mo, and 8.5 mo, respectively. Overall survival was 37% and 18% at one and two years, respectively. Abdominal pain relief was achieved within 2 wk of completing radiotherapy in the patients who received successful palliation (13 of 20 patients had significant pain). Five patients (20%) had grade 1 nausea, and one (4%) had grade 2 nausea. No acute grade 3+ toxicity was seen.

CONCLUSION: Stereotactic body radiotherapy using the CyberKnife system is a promising, noninvasive, palliative treatment with acceptable toxicity for locally advanced unresectable and metastatic pancreatic cancer.

Key words: CyberKnife; Pancreatic cancer; Stereotactic body radiotherapy

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Core tip: Locally advanced unresectable and metastatic pancreatic cancer is the most common presentation of pancreatic cancer. The available therapeutic option is chemotherapy or chemoradiotherapy. The low-dose radiation of conventional radiotherapy has unsatisfactory results for survival and local control, at a cost of increased hematologic toxicity. Doses > 54 Gy may be considered if clinically appropriate. Stereotactic body radiation therapy has become an important research topic to provide a higher biologically effective dose. We evaluated the efficacy and toxicity of stereotactic body radiation therapy using the CyberKnife system for patients with locally advanced unresectable and metastatic pancreatic cancer.

Su TS, Liang P, Lu HZ, Liang JN, Liu JM, Zhou Y, Gao YC, Tang MY. Stereotactic body radiotherapy using CyberKnife for locally advanced unresectable and metastatic pancreatic cancer. *World J Gastroenterol* 2015; 21(26): 8156-8162 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i26/8156.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i26.8156

INTRODUCTION

Pancreatic cancer is both an aggressive and prevalent malignancy. It is the fourth leading cause of cancer mortality in men and women in the United States[1]. In the Asia-Pacific region, the age-standardized incidence reached a plateau after 1985, while the incidence continued to rise due to the aging population in the region[2]. Only approximately 20% of patients are amenable to surgery at diagnosis. It is a highly aggressive entity with approximately 40% presenting with locally advanced but unresectable disease and an additional 40% presenting with metastatic disease[3]. Surgical resection remains the only curative therapeutic modality for early-stage pancreatic cancer. Despite improvements in surgical technique and patient selection, as well as adjuvant chemotherapy, the five-year survive rate remains low, ranging from 10% to 20%, following curative surgery[4-6]. In patients with locally unresectable pancreatic cancer, the only therapeutic option is chemoradiotherapy. The local control rate after chemoradiotherapy is still relatively low, ranging from 40% to 55%, with a median survival ranging from 5 mo to 14 mo[7-9]. The conventional radiation dose is usually between 45 and 54 Gy in 1.8-2.5-Gy fractions. These limited doses have a poor curative effect. Doses > 54 Gy may be considered if clinically appropriate[10-12]. Recently, stereotactic body radiotherapy (SBRT) has become an important research topic to provide a higher biologically effective dose. The conformity and rapid dose fall-off associated with SBRT offer the potential for dose escalation[13]. In this study, we analyzed the patients with locally advanced unresectable and metastatic pancreatic cancer who underwent SBRT.

MATERIALS AND METHODS

Patient population

Between June 2010 and May 2014, 25 patients with unresectable or metastatic pancreatic adenocarcinoma were included in this retrospective analysis. Ethical approval was given by the Medical Ethics Committee of Rui Kang Hospital, Guangxi, China. All patients gave written informed consent. Reasons for unresectability included the presence of metastatic disease and radiographic evidence of major vessel involvement, as determined by the surgeon and/or radiologist. Patients with metastatic disease who were treated with SBRT had distant disease that: (1) responded well to initial chemotherapy if the prognosis was that local disease potentially could lead to death or significant morbidity; or (2) the local tumor was causing symptoms of pain or obstruction. All patients' hospital charts and irradiation documents were carefully reviewed.

SBRT

Patients were immobilized in the supine position with arms over the head using a thermoplastic body mask and a styrofoam block provided abdominal compression to minimize internal organ motion (spontaneous or breath-induced). CT was performed with a slice thickness of 3 mm. The gross tumor volume was defined as the tumor visible on the CT scan, and in those with N1 disease, the nodes were not included in the target. The gross tumor volume was expanded by 1 or 2 mm to form the planning target volume (PTV). The dose-volume constraints for organs at risk were: duodenum, V 1 mL < 25 Gy; stomach and small bowel, V 1 mL < 25 Gy, and was strict with regard to keeping any 1 mL < 25 Gy; kidneys, 1/3 V_{tot} < 15 Gy; liver, total spared volume (V_{tot} - V 15 Gy) > 700 mL and V 15 Gy < 1/3 total volume; spinal cord, V 1 mL < 15 Gy, and strict with regard to keeping any 1 mL < 15 Gy. The radiosurgical plan was to deliver a dose of 30-36 Gy in three fractions or 40-48 Gy in four fractions. Plans were devised such that the prescription dose was the isodose line encompassing > 97% of the PTV. No more than 3% of the PTV was to receive < 93% of the prescription dose. For stereotactic localization, patients underwent a 4D-CT treatment

Table 1 Detailed information of pancreatic cancer patients treated with stereotactic body radiotherapy

Patient	Sex	T	N	M	CA19-9	Dose/No. of fractions	Live/dead	Survival time (mo)	Toxicity
1	Female	4	0	0	Positive	36 Gy/3	Live	4	G1
2	Male	3	0	0	Negative	45 Gy/4	Dead	9	
3	Male	3	1	1	Negative	48 Gy/4	Live	2	G1
4	Male	3	0	0	Positive	46 Gy/4	Dead	2	
5	Male	3	1	1	Positive	46 Gy/4	Dead	8	
6	Male	3	1	1	Positive	30 Gy/3	Live	8	G1
7	Female	3	0	0	Positive	36 Gy/3	Dead	4	
8	Female	3	1	0	Negative	31.5 Gy/3	Live	17	
9	Female	3	1	1	Negative	33 Gy/3	Dead	5	
10	Male	3	0	1	Positive	36 Gy/3	Dead	9	G1
11	Male	3	0	1	Positive	35 Gy/3	Dead	14	
12	Female	4	1	1	Positive	33 Gy/3	Dead	9	
13	Female	4	0	1	Positive	36 Gy/3	Dead	3	G1
14	Male	3	0	0	Positive	36 Gy/3	Live	6	
15	Male	3	0	1	Negative	40 Gy/4	Dead	3	
16	Female	3	0	1	Positive	45 Gy/4	Live	15	G1
17	Male	3	1	1	Negative	33 Gy/3	Dead	17	
18	Male	3	0	1	Positive	36 Gy/3	Dead	2	G2
19	Male	3	1	1	Positive	36 Gy/3	Dead	2	
20	Male	3	1	0	Negative	42 Gy/4	Dead	3	
21	Male	3	0	0	Negative	33 Gy/3	Live	3	G1
22	Male	4	1	1	Positive	40 Gy/4	Live	1	
23	Male	3	1	0	Positive	46 Gy/4	Live	25	
24	Male	3	1	1	Negative	48 Gy/4	Dead	9	
25	Male	3	0	1	Positive	40 Gy/4	Live	9	G1

CA19-9: Carbohydrate antigen 19-9.

simulation with the CyberKnife Robotic Radiosurgery System with the Xsight Spine Tracking System (Accuray Inc., Sunnyvale, CA, United States).

Response evaluation and follow-up

Patients were re-evaluated 1 mo after SBRT and then every 3 mo thereafter by the treating radiation oncologist. Clinical examination, determination of carbohydrate antigen 19-9 levels, and contrast-enhanced CT were performed at each step of follow-up. Acute and late toxicity was scored according to the NCI Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

Overall survival (OS) was calculated from the date of SBRT to the date of progression and to the day of last follow-up or death using the Kaplan-Meier method. Acute toxicity was defined as that occurring within 90 d of SBRT, and late toxicity as that occurring thereafter. SPSS version 17.0 (SPSS Inc., Chicago, IL, United States) was used for statistical analysis. All enrolled patients were included in the statistical evaluation. The statistical methods of this study were reviewed by Zhen-Dong Yang from Rui Kang Hospital, Guangxi Traditional Chinese Medical University.

RESULTS

Patient characteristics

Twenty-five patients were treated in our hospital with SBRT for pancreatic cancer. The median age was 63 years (range: 44-80 years) and 72.0% (18/25) were male. All patients were considered to have unresectable/locally advanced (9/25; 36.0%) and metastatic (16/25; 64.0%) disease as determined by experienced pancreatic surgeons and/or radiologists. Patients were diagnosed with pancreatic cancer at clinical stages T3 (21/25; 84.0%) and T4 (4/25; 16.0%). The majority of patients were N0, but 48.0% (12/25) had N1 disease. Clinical characteristics of selected patients are described in Tables 1 and 2.

SBRT

Fourteen patients treated with SBRT received a dose of 30-36 Gy in three fractions and the remaining 11 received 40-48 Gy in four fractions. The mean target volume was 43.27 mL (range: 8.80-96.39 mL). The CyberKnife platform utilized 150-180 beams. Maximum spinal cord point dose was a mean 730 cGy (range: 390-1430 cGy), which was strictly maintained at 1 mL < 15 Gy. Maximum bowel point dose was a mean 3361 cGy (range: 2792-4018 cGy) for the PTV, which was strictly maintained at 1 mL < 25 Gy.

Adjuvant therapy

Two patients received neoadjuvant gemcitabine-based chemotherapy. Another two patients received adjuvant gemcitabine-based chemotherapy. The choice of chemotherapy was at the discretion of the medical oncologist. During SBRT, combined adjuvant medication was given, consisting of Chinese herbs and

Table 2 Characteristics of pancreatic cancer patients treated with stereotactic body radiotherapy

Characteristic	*n*
Sex	
Male	18
Female	7
Age, yr	Median 63 (range: 44-80)
Stage[1]	
T3	21
T4	4
N0	13
N1	12
M0	9
M1	16
Dose (Gy)/No. of fractions	
30-36 Gy/3	14
40-48 Gy/4	11
Carbohydrate antigen 19-9	
Positive	16
Negative	9
Primary location of tumor	
Head of pancreas	20
Body or tail of pancreas	5

[1]According to 2010 AJCC staging system.

dexamethasone, vitamins, glutathione, and lansoprazole.

Toxicity

Twelve patients experienced grade 1 fatigue at 2 wk after SBRT, which required no treatment. Five patients (20%) had grade 1 nausea, and ondansetron was administered to one (1/25; 4%) patient with grade 2 nausea. None of these patients had persistent nausea after 1 mo. No acute grade 3+ toxicity was seen. Most toxicity was well tolerated.

Pain relief

According to the numerical rating scale scoring system, 20/25 (80%) patients experienced significant pain before SBRT. Abdominal pain relief was achieved within 2 wk of completing radiotherapy in the patients who received successful palliation. Ten patients achieved pain control after treatment, allowing suspension of analgesic administration. In three patients, analgesic dose was reduced by 50%, or the patients needed fewer analgesic drugs.

Survival

Survival data were available at a median follow-up of 11 mo (range: 2-25 mo). The median survival duration calculated from the time of SBRT for the entire group, the locally advanced group, and the metastatic group was 9.0 mo, 13.5 mo, and 8.5 mo, respectively. OS was 37% and 18% at one and two years, respectively (Figure 1).

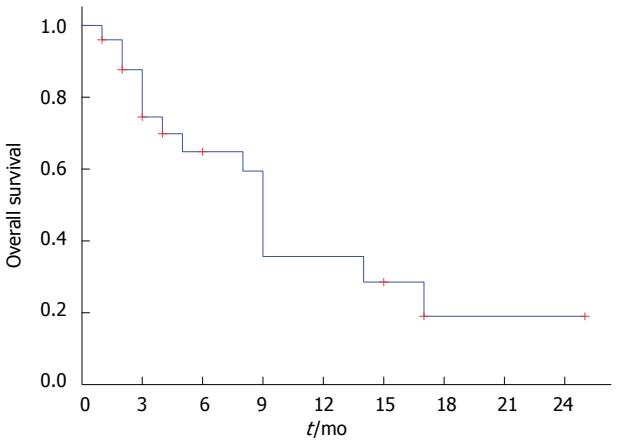

Figure 1 Kaplan-Meier curve for overall survival. Median overall survival was 9 mo, and overall survival was 37% and 18% at one and two years, respectively.

DISCUSSION

Locally advanced unresectable and metastatic pancreatic cancer is the most common presentation of pancreatic cancer. There have been many clinical trials conducted to evaluate novel system regimens for advanced pancreatic cancer. Chemotherapy alone reduces the incidence of distant metastases in patients with localized disease, even though it may hardly improve local disease control. Gemcitabine monotherapy has conventionally been considered the standard regimen for advanced pancreatic cancer on the basis of phase Ⅲ clinical trials. The median overall survival is limited to the range of 4.6 to 9.2 mo with gemcitabine treatment[12,13]. Among non-gemcitabine regimens, the most notable is FOLFRINOX. A phase Ⅲ clinical trial showed that OS was significantly longer in the FOLFRINOX arm (11.1 mo *vs* 6.8 mo). Nevertheless, the FOLFRINOX regimen was at the cost of increased hematologic toxicity[13,14]. The only therapeutic option available is gemcitabine- or capecitabine-based chemoradiotherapy. The median survival ranges from 11.1 mo to 15.2 mo[12,15,16]. The local progression rate reported with conventional fractionation of radiotherapy is still relatively low, at 40%-55%[7-9]. In recent years, the unsatisfactory results of conventional radiotherapy led to several studies that investigated the efficacy and safety of SBRT. Recent encouraging results of SBRT for pancreatic cancer are shown in Table 3. Improvement of local disease control was relevant in these studies, with a success rate of 57%-94%. Median OS was 5.7-20.0 mo. Survival was extended for most of the patients. However, acute and late toxicity are still challenging. The rate of late gastroduodenal toxicity of grade 2 or higher was 4%-47% in several studies.

We investigated the outcomes in a series of patients with locally advanced unresectable and metastatic pancreatic cancer who underwent SBRT. Radiotherapy comprised 30-36 Gy in three fractions or 40-48 Gy in four fractions, and the priority was to evaluate the safety of the surrounding normal tissue. According to the standard equation, 30-36 Gy in three fractions has a biologically effective dose

Table 3 Summary of treatment regimen, local control, progression-free survival, overall survival and late toxicity in previous studies compared with the present study

Ref.	No. of patients	SBRT dose (Gy/No. of fractions)	Gemcitabine-based chemotherapy	LC (%)	PFS (mo)	OS (mo)	Toxicity (≥ G2) (%)
Didolkar *et al*[17]	85	15-30 Gy/3	Sequential	91.7	-	18.6 from diagnosis 8.6 from SBRT	22
Polistina *et al*[18]	23	30 Gy/3	Prior	82.6	7.3	10.6	None
Mahadevan *et al*[19]	39	24-36 Gy/3	Sequential	85	15	20 from diagnosis	9
Schellenberg *et al*[20]	16	25 Gy/1	Sequential	81	9	11.4 from diagnosis	47
Hoyer *et al*[21]	22	45 Gy/3	Sequential	57	4.8	5.7 from diagnosis	18
Koong *et al*[22]	15	15-25 Gy/1	No	77	2	11 from diagnosis	None
Chang *et al*[23]	77	25 Gy/1	Prior	84	-	11.4 from diagnosis	13
Schellenberg *et al*[24]	20	25 Gy/1	Sequential	94	9.2	11.8 from diagnosis	20
Rwigema *et al*[25]	71	18-25 Gy/1	No	64.8	-	10.3	10
Pollom *et al*[26]	167	25-33 Gy/1-5	Sequential or concurrent	-	-	13.6 from diagnosis	12.3
Moningi *et al*[27]	88	20-33 Gy/5	Gemcitabine, cisplatin, FOLFIRINOX or paclitaxel	-	9.8	18.4 from diagnosis	5.7 G2 3.4 G3
Gurka *et al*[28]	38	25-30 Gy/5	Gemcitabine, mFOLFOX or capecitabine	79	9.2	14.3 from diagnosis	-
Present study	25	30-36 Gy/3 or 42-48Gy/4	4 patients, Gemcitabine	-	-	M0 group 13.5 M1 group 8.5 from SBRT	4

LC: Local control; OS: Overall survival; PFS: Progression-free survival; SBRT: Stereotactic body radiotherapy.

of 50-66 Gy, and 40-48 Gy in four fractions has a biologically effective dose of 68-88 Gy (assuming an α/β ratio of 10 for rapidly proliferating tumor cells and 3 for normal tissues). We found that the median OS was 9 mo. OS was 37% and 18% at one and two years, respectively. Palliative treatment with SBRT improved quality of life, especially palliation of pain, with acceptable toxicity. Our results support the use of palliative SBRT. The major advantages of this approach compared with conventional fractionated radiotherapy are: (1) more intensified treatment of the primary tumor; (2) increased patient convenience; and (3) minimal interference with the delivery of maximal systemic chemotherapy. We hypothesize that quality of life and OS benefit from local palliative SBRT for primary tumors, and large prospective clinical trials are warranted.

COMMENTS

Background

Locally advanced unresectable and metastatic pancreatic cancer is the most common presentation of pancreatic cancer. The available therapeutic option is chemotherapy or chemoradiotherapy. However, the low-dose radiation of conventional radiotherapy leads to unsatisfactory results for survival and local control, at a cost of increased hematologic toxicity. Doses > 54 Gy may be considered if clinically appropriate.

Research frontiers

Stereotactic body radiotherapy (SBRT) with conformity and rapid dose fall-off has become an important research topic, to provide a higher biologically effective dose. It has been used to treat many cancers. The current research hotspot is to evaluate the efficacy and toxicity of SBRT for patients with locally advanced unresectable and metastatic pancreatic cancer.

Innovations and breakthroughs

This study presented outcomes in a series of patients with locally advanced unresectable and metastatic pancreatic cancer who underwent SBRT using the CyberKnife system. The radiotherapy plan was 30-36 Gy in three fractions or 40-48 Gy in four fractions. The dose-volume constraints for organs at risk were: duodenum, V 1 mL < 25 Gy; stomach and small bowel, V 1 mL < 25 Gy, and was strict with regard to keeping any 1 mL < 25 Gy; kidneys, 1/3 V_{tot} < 15 Gy; liver, total spared volume (V_{tot} - V 15 Gy) > 700 mL and V 15 Gy < 1/3 total volume; spinal cord, V 1 mL < 15 Gy, and strict with regard to keeping any 1 mL < 15 Gy. According to the standard equation, 30-36 Gy in three fractions has a relative biologic effectiveness of 50-66 Gy, and 40-48 Gy in four fractions has a biologically effective dose of 68-88 Gy (assuming an α/β ratio of 10 for rapidly proliferating tumor cells and 3 for normal tissues). The authors found that median overall survival was 9 mo. Overall survival was 37% and 18% at one and two years, respectively. Palliative treatment with SBRT was effective for pain relief (65%), with acceptable toxicity (grade 1: 20%, grade 2: 4%). These results support the use of palliative treatment with SBRT. The major advantages of this approach compared with conventional fractionated radiotherapy are: (1) more intensified treatment of the primary tumor; (2) increased patient convenience; and (3) minimal interference with the delivery of maximal systemic chemotherapy.

Applications

This study supports the use of palliative treatment with the CyberKnife for locally advanced unresectable and metastatic pancreatic cancer. It is remarkably effective in palliation of pain, with acceptable toxicity.

Terminology

SBRT using the CyberKnife system is a promising noninvasive and palliative treatment with acceptable toxicity for locally advanced unresectable and metastatic pancreatic cancer.

Peer-review

This is an intriguing report on the experience with stereotactic body radiotherapy for locally advanced/metastatic pancreatic cancer, a topic of great interest for oncologists given the very difficult issue of local treatment/palliation in the setting of an aggressive histology with a high propensity to disseminate.

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P- Reviewer: Ryoo JJ **S- Editor**: Qi Y **L- Editor**: AmEditor
E- Editor: Zhang DN

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ISSN 1007-9327

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