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ORIGINAL RESEARCH

Stereotactic body radiation therapy for patients with recurrent pancreatic adenocarcinoma at the abdominal lymph nodes or postoperative stump including pancreatic stump and other stump

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Xian-Liang Zeng*
Huan-Huan Wang*
Mao-Bin Meng
Zhi-Qiang Wu
Yong-Chun Song
Hong-Qing Zhuang
Dong Qian
Feng-Tong Li
Lu-Jun Zhao
Zhi-Yong Yuan
Ping Wang

Department of Radiation Oncology, Tianjin's Clinical Research Center for Cancer and Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, People's Republic of China

*These authors contributed equally to this work

Background and aim: The aim of this study is to evaluate the efficacy and safety of stereotactic body radiation therapy (SBRT) using CyberKnife in the treatment of patients with recurrent pancreatic adenocarcinoma at the abdominal lymph node or stump after surgery.

Patients and methods: Between October 1, 2006 and May 1, 2015, patients with recurrent pancreatic adenocarcinoma at the abdominal lymph node or stump after surgery were enrolled and treated with SBRT at our hospital. The primary end point was local control rate after SBRT. Secondary end points were overall survival, time to symptom alleviation, and toxicity, assessed using the Common Terminology Criteria for Adverse Events version 4.0.

Results: Twenty-four patients with 24 lesions (17 abdominal lymph nodes and seven stumps) were treated with SBRT, of which five patients presented with abdominal lymph nodes and synchronous metastases in the liver and lung. The 6-, 12-, and 24-month actuarial local control rates were 95.2%, 83.8%, and 62.1%, respectively. For the entire cohort, the median overall survival from diagnosis and SBRT was 28.9 and 12.2 months, respectively. Symptom alleviation was observed in eleven of 14 patients (78.6%) within a median of 8 days (range, 1–14 days) after SBRT. Nine patients (37.5%) experienced Common Terminology Criteria for Adverse Events version 4.0 grade 1–2 acute toxicities; one patient experienced grade 3 acute toxicity due to thrombocytopenia.

Conclusion: SBRT is a safe and effective treatment for patients with recurrent pancreatic adenocarcinoma at the abdominal lymph node or stump after surgery. Further studies are needed before SBRT can be recommended routinely.

Keywords: stereotactic body radiation therapy, pancreatic adenocarcinoma, recurrent disease, overall survival

Introduction

The prognosis of pancreatic cancer remains poor with a 5-year overall survival (OS) rate <6%.[1,2] Surgical resection is the only curative treatment, but unfortunately, only 20% of patients appear to be candidates for surgery at diagnosis.[3] Even patients who undergo resection have a poor prognosis with a 5-year survival rate of 7%–25% due to frequent development of local and/or distant metastases.[4] The pattern of recurrence for patients with pancreatic cancer after surgery is well known;[5,6] however, the most effective therapeutic strategies are not well defined. Some surgeons attempted to re-resect in a small number of patients with recurrent pancreatic carcinoma but achieved a 5-year OS of only ≤5.6%.[7,8]

Correspondence: Mao-Bin Meng
Department of Radiation Oncology, Tianjin's Clinical Research Center for Cancer and Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin 300060, People's Republic of China
Tel +86 22 2334 1405
Fax +86 22 2334 4105
Email doctormm991@hotmail.com

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The National Comprehensive Cancer Network recommends chemoradiotherapy for patients with local recurrence if they have not received radiotherapy (RT), and alternative systemic chemotherapy or palliative and best supportive care if they have received prior RT.[9] As in the case of local advanced pancreatic cancer, the outcomes of these treatment strategies remain poor due to suboptimal local control (LC) and a poor median OS.[10] Therefore, treatment opinion for patients with recurrent pancreatic carcinoma, especially recurrent pancreatic adenocarcinoma, is deemed required.

Stereotactic body radiation therapy (SBRT) is a type of external beam RT that delivers radiation more accurately and precisely to the tumor than conventionally fractionated radiation therapy. SBRT can be delivered using either a traditional linear accelerator or a robotic arm (ie, CyberKnife). The purpose of this study is to evaluate the safety and efficacy of SBRT using CyberKnife for patients with recurrent pancreatic adenocarcinoma at the abdominal lymph node or stump after surgery.

Patients and methods

Study design and eligible patients

We retrospectively queried our prospectively collected database of patients with recurrent pancreatic cancer. Patients were treated with SBRT using CyberKnife between October 1, 2006 and May 1, 2015. The inclusion criteria were the following: 1) any age; 2) Karnofsky performance score ≥70; 3) recurrent pancreatic adenocarcinoma after surgery, confirmed by biopsy and histology and either computed tomography (CT) or positron emission tomography/CT (PET/CT) images; and (4) written informed consent for the treatment. Exclusion criteria were 1) history of prior RT, 2) contraindication for receiving RT, and 3) uncontrolled comorbidities (metabolic or psychiatric). The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the independent ethics committees at Tianjin Medical University Cancer Institute and Hospital. In addition, all inclusion patients gave written informed consent.

Treatment schedule

The treatment planning and SBRT with CyberKnife was performed as previously described.[11,12] The Xsight spine tracking system was used for patients with recurrent disease at the abdominal lymph node, and positional alignment was based on bony spinal skeletal structures. In contrast, it was recommended that gold fiducials were implanted at or near the recurrent stump for the gold fiducials tracking system which used B-ultrasound, endoscopic ultrasound, or CT guidance. Briefly, the patients were immobilized using a vacuum mattress before CT simulation.

A set of planning three-dimensional or four-dimensional CT images were obtained after intravenous radiographic contrast material infusion to highlight recurrent disease. The images included sufficient margins above and below the tumor, which were determined according to pretreatment planning CT and PET/CT images. The gross target volume (GTV) was defined as the volume of recurrent carcinoma, and the planning target volume (PTV) was defined as the GTV plus a margin of 0.3 cm in the *x*-, *y*-, and *z*-axis direction. The PTV was also amended to exclude the relevant anatomic boundaries when the target area was close to the duodenum, small bowel, or stomach in order to avoid damaging critical normal tissue. The normal tissue constraints were adopted from previous studies of advanced pancreatic carcinoma.[13–15]

Follow-up

The patients were observed at 1 month after completion of treatment, then every 3 months for the first year, and every 6 months thereafter until May 1, 2015. Imaging, adverse events, and compliance of all patients were monitored for the follow-up period using our clinical databases.

End points

The primary end point was the LC rate after SBRT, which was defined as complete response, partial response, or stable disease using the Response Evaluation Criteria in Solid Tumors version 1.1.[16] Local failure was defined as evidence of increased tumor size in the treated region. PET/CT scan was employed to differentiate radiation-related changes from local or regional recurrence. LC of recurrent disease was assessed after a minimum of 6 months after SBRT in order to avoid uncertainty associated with early transient radiographic changes within the high-dose region. The secondary end points were the following: 1) OS from diagnosis and SBRT, defined as the time between diagnosis or SBRT and death or last follow-up for censored patients. 2) The time to symptom alleviation or pain reduction: the time to symptom alleviation was defined as the time between SBRT and the date at which symptoms were alleviated or the date of the last follow-up for censored patients, and pain was evaluated from the pain status rated by patients on a visual analog scale (VAS) before and after SBRT (a score of 0 indicated no pain and a score of 10 represented maximum pain). A researcher trained to conduct clinical interviews then contacted the patients to conduct clinical interviews in person via telephone at fixed intervals after their treatment sessions (at 1 day, 1 week, 2 weeks, and

1, 2, 3, and 6 months) or until the patients died or were lost to follow-up. 3) Toxicity was evaluated through Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Acute toxicities and late complications were recorded. All symptoms and complications documented in patient records during and following SBRT were recorded.

Statistical analysis

LC and OS rates were estimated using Kaplan–Meier analysis. Curves were compared using the stratified log-rank test. A *P*-value of ≤0.05 was considered to represent statistical significance. Data were analyzed using the statistical software Intercooled Stata version 8.2 for Windows (StataCorp LP, College Station, TX, USA).

Results

Patients' characteristics

Between January 10, 2011 and June 19, 2014, 24 patients with 24 lesions (17 abdominal lymph nodes and seven stumps) were treated with SBRT using CyberKnife (Table 1). Five patients presented with abdominal lymph nodes and synchronous metastasis in the liver or lung. In addition to SBRT for abdominal lymph nodes, patients with synchronous liver metastasis received sequential palliative localized treatment, four patients with synchronous liver and lung metastases received adjuvant chemotherapy, and one patient with synchronous liver metastasis received no treatment.

Treatment characteristics

The treatment characteristics and treatment planning parameters for all patients are summarized in Table 2 and Figure 1. A total of 16 patients had negative margins (R0), four patients had microscopically positive margins (R1), and four patients had macroscopically positive margins (R2) after surgery. Eighteen patients had previously received gemcitabine-based chemotherapy, and three patients received other chemotherapy regimes.

The median PTV was 39.09 mL (range, 7.22–94.81 mL). Patients received a median of five fractions (range, five to eight fractions) with a median dose of 9 Gy per fraction (range, 6–10 Gy), and a total dose of 45 Gy (range, 42–50 Gy). The median biologically equivalent dose (α/β=10, linear-quadratic model used) was 85.50 Gy (range, 71.4–100 Gy). The dose was administered to the median 73% isodose line (range, 63%–79%), which encompassed 95% of the PTV (Table 3).

Table 1 Summary of patient characteristics

Name	Age (years)	Sex	No of lesions	Location of lesion	PTV volume (mL)	Interval between surgery and SBRT (months)	Symptoms	Synchronous metastases	Treatment of synchronous metastatic site
MWY	56	Male	1	Abd LN	31.65	8.77	Abdominal pain		
LYH	54	Male	2	Abd LN	71.85	36.87	Abdominal pain	Lung	CT
XDR	59	Male	1	Abd LN	24.33	15.80	None		
ZJQ	56	Male	1	Abd LN	38.20	4.30	Abdominal pain		
LJZ	71	Male	1	Abd LN	36.55	25.43	Abdominal pain		
CGS	62	Male	1	Abd LN	90.14	20.53	Anorexia and fatigue		
SJF	68	Female	2	Abd LN	7.22	14.80	None	Liver	CT
YJ	38	Female	1	Abd LN	32.32	20.23	None		
YSY	61	Female	1	Abd LN	25.48	6.47	Back pain		
ZL	27	Male	1	Abd LN	94.81	5.13	Abdominal and back pain		
ZLM	49	Female	2	Abd LN	49.48	11.53	None	Liver	CT
WGZ	50	Female	1	Abd LN	34.41	6.23	Abdominal pain		
GYQ	65	Female	1	Abd LN	75.08	14.07	None		
LZS	73	Male	2	Abd LN	41.50	9.53	Abdominal and back pain	Liver	None
SCL	60	Male	1	Abd LN	41.44	40.43	Abdominal pain		
ZY	60	Female	1	Abd LN	20.32	32.33	None		
ZBJ	47	Male	2	Abd LN	47.11	17.87	Back pain and jaundice	Liver	Biliary stenting
WJX	59	Male	1	Stump	39.98	16.63	None		
LCR	56	Female	1	Stump	34.09	20.53	Abdominal pain		
ZCF	64	Female	1	Stump	33.34	3.90	None		
LXY	57	Female	1	Stump	61.74	1.90	Back pain		
GWH	47	Male	1	Stump	30.84	6.47	None		
ZQG	40	Male	1	Stump	90.65	2.37	Abdominal pain		
ZXL	59	Male	1	Stump	40.82	55.03	None		

Abbreviations: PTV, planning target volume; SBRT, stereotactic body radiation therapy; Abd LN, abdominal lymph node; CT, chemotherapy.

Table 2 Summary of treatment characteristics

Name	Prescription dose/ fractionation	BED_{10} (Gy)	Isodose (%)	Type of surgery	History of CT	Time of symptoms disappearance and alleviation	Location of PD	LPFS (months)	OS (months)	Status (cause)
MWY	45/5	85.50	75	R0	Gemcitabine-based	No remission	Treatment site	18.07	23.30	Alive
LYH	42/6	71.40	63	R0	Gemcitabine-based	7 days	Lung metastasis	19.23	19.23	Alive
SJF	50/5	100.00	77	R0	No CT	NA	Liver metastasis	18.90	18.90	Alive
YJ	45/5	85.50	72	R1	No gemcitabine-based	NA	No	19.30	19.30	Alive
ZXL	45/5	85.50	76	R0	Gemcitabine-based	NA	Treatment site and liver metastasis	12.83	17.63	Alive
SCL	50/5	100.00	71	R0	No gemcitabine-based	9 days	No	22.90	22.90	Alive
LCR	45/5	85.50	70	R0	Gemcitabine-based	14 days	Abd LN	12.03	12.03	Alive
YSY	45/5	85.50	76	R1	Gemcitabine-based	9 days	Treatment site	8.40	10.53	Death (tumor)
ZL	48/6	86.40	70	R0	Gemcitabine-based	8 days	Abd LN	13.83	13.83	Death (tumor)
ZQG	48/8	76.80	75	R2	Gemcitabine-based	9 days	Liver metastasis	7.7	7.70	Death (tumor)
ZLM	45/5	85.50	76	R0	Gemcitabine-based	NA	Liver metastasis	28.17	28.17	Death (tumor)
WGZ	50/5	100.00	70	R1	Gemcitabine-based	5 days	Abd LN	11.73	11.73	Death (tumor)
GYQ	48/8	76.80	70	R0	Gemcitabine-based	NA	Abd LN	3.90	3.90	Death (tumor)
LZS	45/5	85.50	70	R0	Gemcitabine-based	No remission	Liver metastasis	3.77	3.77	Death (tumor)
WJX	45/5	85.50	66	R1	Gemcitabine-based	NA	Liver metastasis	12.50	12.50	Death (tumor)
ZY	45/5	85.50	75	R0	Gemcitabine-based	NA	Stomach metastasis	6.27	6.27	Death (tumor)
ZCF	42/6	71.40	72	R2	No gemcitabine-based	NA	Treatment site and Abd LN	6.8	12.50	Death (tumor)
LXY	45/6	78.75	76	R0	No CT	8 days	Liver metastasis	9.63	9.63	Death (tumor)
ZBJ	45/5	85.50	72	R0	Gemcitabine-based	7 days	Liver metastasis	9.77	9.77	Death (tumor)
XDR	50/5	100.00	75	R2	Gemcitabine-based	NA	Liver metastasis	12.93	12.93	Death (tumor)
ZJQ	50/5	100.00	79	R0	Gemcitabine-based	No remission	Liver metastasis	8.47	8.47	Death (tumor)
LJZ	45/5	85.50	74	R0	Gemcitabine-based	1 day	Liver metastasis	11.20	11.20	Death (tumor)
CGS	45/5	85.50	76	R0	No CT	5 days	Liver metastasis	10.03	10.03	Death (tumor)
GWH	48/6	86.40	72	R2	Gemcitabine-based	NA	Treatment site	10.80	12.20	Death (tumor)

Note: The R0, R1, and R2 were defined as negative margins, microscopically positive margins, and macroscopically positive margins after surgery, respectively.

Abbreviations: BED, biologically equivalent dose; CT, chemotherapy; PD, progressive disease; LPFS, local progression-free survival; OS, overall survival; Abd LN, abdominal lymph node; NA, not available.

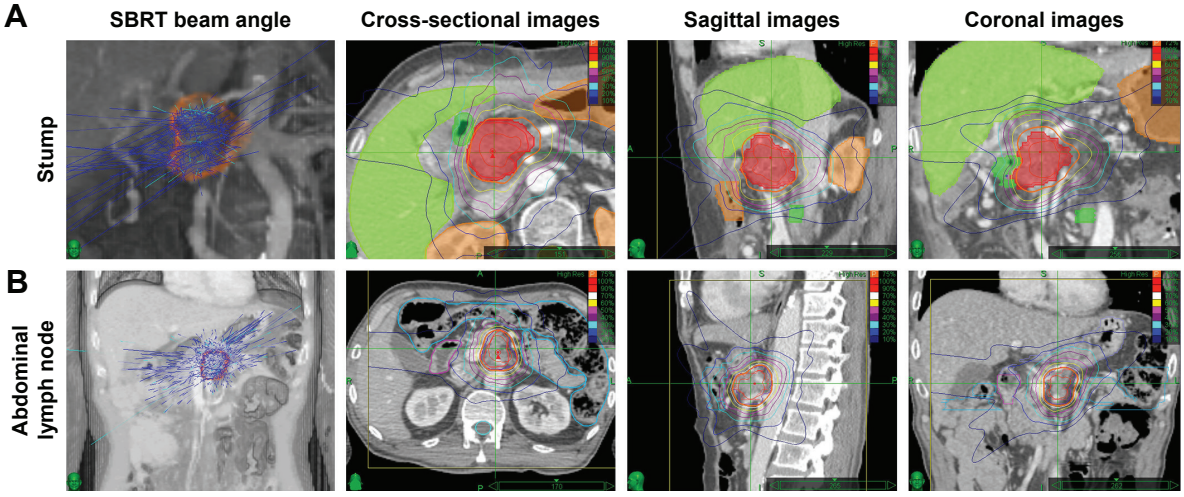


Figure 1 Representative planning CT and isodose distributions with SBRT using CyberKnife in patients with recurrent pancreatic adenocarcinoma at the abdominal lymph node or stump after surgery.

Notes: Each patient had SBRT beam angle, cross-sectional, sagittal, and coronal images taken, and red and purple lines indicate GTV and PTV, respectively. (**A**) A 64-year-old female treated for a solitary recurrent pancreatic adenocarcinoma at the stump. SBRT was performed using six fractions of 42 Gy prescribed to the 72% isodose line. (**B**) A 55-year-old male treated for a solitary recurrent pancreatic adenocarcinoma at the abdominal lymph node. SBRT was performed using five fractions of 45 Gy to the 75% isodose line.

Abbreviations: CT, computed tomography; SBRT, stereotactic body radiation therapy; GTV, gross tumor volume; PTV, planning target volume.

LC rate and OS

Out of 24 patients, five (20.8%) had a complete response, eight (33.3%) had a partial response, and nine (37.5%) had no response. The 6-, 12-, and 24-month actuarial LC rates were 95.2%, 83.8%, and 62.1%, respectively (Figure 2).

For the whole cohort, median follow-up time was 35.8 months (range, 14.2–72.7 months). The median OS from diagnosis and SBRT was 28.9 and 12.2 months, respectively (Figure 3A and B). It is worth noting that the rate of solitary recurrence and synchronous metastases did not differ significantly (P=0.31).

The time to symptom alleviation

Alleviation of symptoms was evaluated in 14 patients who reported symptoms (14/24, 58.33%, most commonly abdominal pain and back pain). Relief of symptoms was achieved in eleven patients (11/14, 78.57%), of which eight (8/14, 57.14%) reported complete relief of symptoms and discontinuation of medications. The remaining patients reported partial relief (3/14, 42.86%). Symptom improvement was reported after a median follow-up of 8 days (range, 1–14), and alleviation of symptoms continued throughout the follow-up period in all cases.

Pain was evaluated using a VAS score. VAS scores increased slightly from 7.2±2.5 at pre-SBRT to 8.9±1.2 24 hours after SBRT, and decreased from 7.2±2.5 at pre-SBRT to 2.7±1.3 1 week after SBRT. The VAS scores remained low throughout the follow-up period, 1.1±1.2 at 2 weeks, 1.4±1.3 at 1 month, 1.4±1.5 at 2 months, 1.3±0.9 at 3 months, and 1.2±1.4 at 6 months. Mean VAS differed significantly from the pre-SBRT baseline at each post-SBRT time point (all $P<0.05$).

Table 3 Summary of SBRT parameters

Parameter	Median (range)
PTV (mL)	39.09 (7.22–94.81)
Prescription dose (Gy)	45 (42–50)
Number of fractions	5 (5–8)
Dose per fraction (Gy)	9 (6–10)
BED_{10} (Gy)	85.50 (71.4–100)
Prescription isodose line (%)	73 (63–79)

Abbreviations: SBRT, stereotactic body radiation therapy; PTV, planning target volume; BED, biologically equivalent dose.

Patterns of failure

Five patients (5/24, 20.8%) exhibited relapse within the PTV. Out-of-field progression was detected in 17 patients (17/24, 70.8%) within a median of 10.0 months after SBRT (range, 3.8–28.2 months), and in only two patients (2/24, 8.3%) was progression not observed after SBRT.

Toxicities

All patients completed SBRT without treatment breaks or dose reductions. As indicated in Table 4, nine patients (37.5%) experienced CTCAE version 4.0 grade 1–2 acute toxicities manifested as diarrhea, nausea, vomiting, abdominal pain, and agranulocytosis. One patient (4.2%) who received

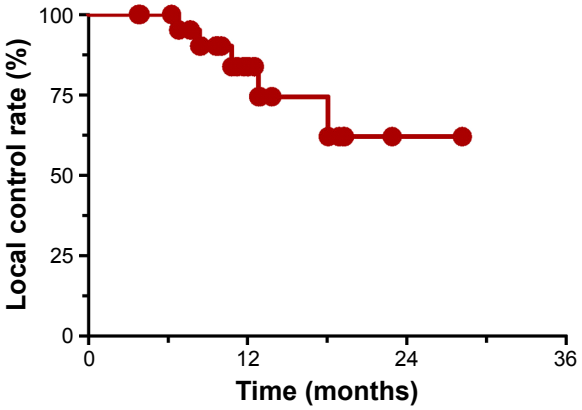


Figure 2 Actuarial rate of LC from SBRT using CyberKnife for patients with recurrent pancreatic adenocarcinoma at the abdominal lymph node or stump after surgery.
Abbreviations: LC, local control; SBRT, stereotactic body radiation therapy.

gemcitabine-based chemotherapy experienced grade 3 acute toxicity due to thrombocytopenia. These toxicities were generally transient and resolved with conservative management. No acute grade >3 toxicity or late toxicity was observed.

Discussion

The efficacy of treatments for recurrent pancreatic cancer following surgical resection is not well characterized. A majority of patients are not suitable candidates for surgery due to the presence of synchronous metastases, vascular involvement, or poor physical status, and for suitable patients, the rate of positive margin resection remains very high.[7,8] To our knowledge, this is the first study to evaluate the safety and efficacy of SBRT for patients with recurrent pancreatic carcinoma at the abdominal lymph node or stump after surgery. Our results demonstrate that SBRT using CyberKnife is a safe and effective treatment for these patients. Further studies will be required to identify which patients benefit most from this treatment modality.

SBRT is an attractive therapeutic option due to its short duration and proven efficacy and safety, which has been reported in many earlier studies on patients with localized advanced pancreatic cancer.[13–15,17–22] In the present study, the median OS of patients with recurrent pancreatic carcinoma treated with SBRT was 12.2 months; this is superior to the OS of 7.6–11.8 months of patients with localized advanced pancreatic carcinoma treated using SBRT,[17–19] and also superior to the OS of patients with recurrent pancreatic carcinoma who underwent re-resection.[7,8] However, the OS did not differ significantly between patients with solitary recurring and synchronous metastases, perhaps due to the small number of samples included, patients' status, and/or the characteristic of recurrent pancreatic adenocarcinoma.

SBRT achieves promising LC rates in patients with recurrent pancreatic cancer. The 6-, 12-, and 24-month actuarial LC rates were 95.2%, 83.8%, and 62.1%, respectively. However, a total of 22 patients (22/24, 91.67%) exhibited either relapse within the PTV or progression outside of the field. Of these patients, five exhibited relapse within the PTV, and 17 patients exhibited out-of-field progression within a median of 10.0 months of SBRT. Therefore, SBRT should be combined with systemic therapies to reduce recurrence of pancreatic cancer after surgery, and more studies will be required to confirm these findings.

The treatment of recurrent pancreatic cancer is a continuing challenge because the disease typically causes symptoms that negatively impact patients' quality of life, such as abdominal

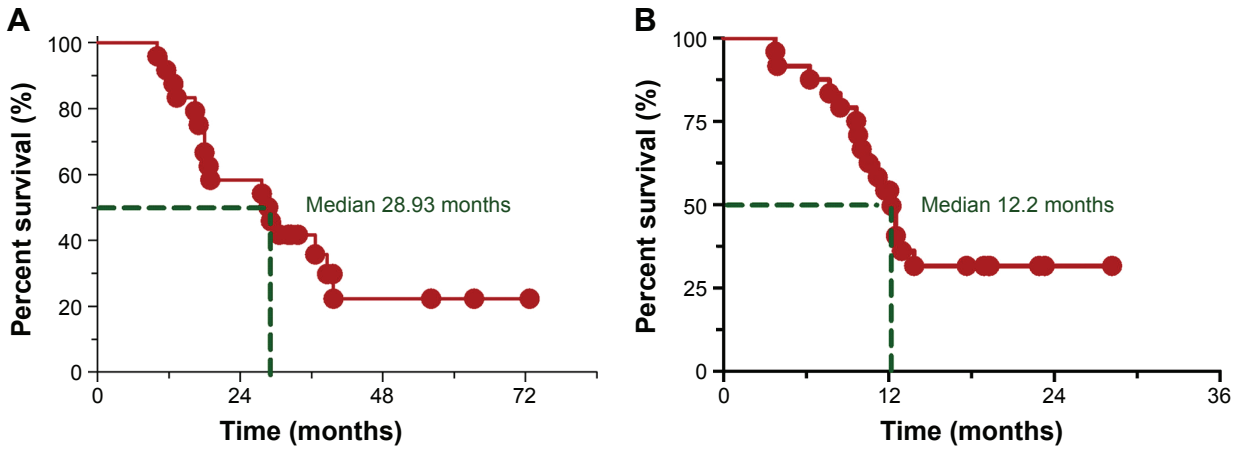


Figure 3 OS from diagnosis and SBRT using CyberKnife for patients with recurrent pancreatic adenocarcinoma at the abdominal lymph node or stump after surgery.
Notes: (**A**) OS from diagnosis. (**B**) OS from SBRT.
Abbreviations: OS, overall survival; SBRT, stereotactic body radiation therapy.

Table 4 Toxicities of pancreatic adenocarcinoma patients with recurrent disease treated with SBRT

	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Acute toxicities				
Diarrhea	2 (8.3)	0	0	0
Nausea and vomiting	1 (4.2)	0	0	0
Abdominal pain	5 (20.8)	0	0	0
Agranulocytosis	1 (4.2)	0	0	0
Thrombocytopenia	1 (4.2)	1 (4.2)	0	0
Late toxicities				
Intestinal obstruction	0	0	0	0
Intestinal perforation	0	0	0	0
Gastric perforation	0	0	0	0

Abbreviation: SBRT, stereotactic body radiation therapy.

and back pain. These symptoms are not typically transient and cannot be resolved with conservative management. However, in this study, the transient increase in pain observed 24 hours after SBRT could be attributed to edema, and the majority of patients in our study achieved complete symptoms relief, typically within 2 weeks of treatment. Our findings concur with published studies suggesting that SBRT can reduce pain and improve quality of life of patients with localized advanced pancreatic cancer.[23]

The low-toxicity profile observed in our study is of particular importance in cancer patients, who have received or will receive additional oncologic therapies. In previous trials in which 25 Gy was delivered in one fraction, grade ≥3 toxicities were reported in 5%–18.8% of patients.[18,24–26] However, some reports suggested that regimens of SBRT including two to five fractions for localized advanced pancreatic cancer are associated with better LC rates than those using single-fraction SBRT, and a lower incidence of high-grade toxicities.[14,15,27] In this study, most patients experienced CTCAE grade 1–2 acute toxic events, and most of these symptoms were transient and resolved with conservative management. No late toxicity was reported, although the relatively short median OS may have underestimated the rate of late toxicities following SBRT.

To our knowledge, our study is the first to demonstrate the efficacy and safety of SBRT using CyberKnife for patients with recurrent disease at the abdominal lymph node or stump after surgery originating from pancreatic cancer. This study is limited by its retrospective nature, and as our patient group encompassed a range of treatment sites, disease severities, fractionation regimens, and systemic therapies, interpretation of the results is somewhat difficult. However, in light of the paucity of literature on the outcomes of SBRT for these patients, our results further recommend the clinical use of SBRT. Further investigation will be required to identify which patients benefit most from this treatment modality, particularly in combination with other treatment modalities.

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Disclosure

The authors report no conflicts of interest in this work.

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