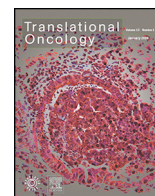




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## Original Research

## Analysis of the efficacy, safety and survival factors of stereotactic body radiation therapy in patients with recurrence of pancreatic cancer



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## ABSTRACT

**Objective:** This study aims to evaluate the efficacy and safety of stereotactic body radiation therapy (SBRT) using Cyber Knife (CK) in the treatment of patients with recurrent pancreatic cancer after surgery, and analyze its survival-related factors. **Methods:** The primary endpoint was freedom from local progression (FFLP) and local control (LC) rate after CK. The secondary endpoints were overall survival (OS), progression-free survival (PFS), symptom relief and toxicities. Receiver operating characteristic (ROC) curves were used to determine the optimal cut-off values of inflammatory composite indicators NLR, PLR, SII and PNI. The prognostic factors that affected these patients were analyzed by univariate and multivariate analysis, respectively. **Results:** A total of 27 patients were enrolled. Median local recurrence disease free interval (DFI) was 11.3 (1.3-30.6) months, LC was 81.5% and 37.0% at 6 and 12 months, respectively. Median PFS was 7.1 (1.3-27.1) months. Median OS was 11.3 (1.3-30.6) months. Symptom alleviation was observed in 16 of 17 patients (94.1%) within 2 weeks after CK. Subsequent chemotherapy, CA199  $\geq 50\%$  decrease after CK were independent prognostic factors for OS (all  $P < 0.05$ ). **Conclusion:** SBRT is a safe and effective treatment approach for recurrent pancreatic adenocarcinoma. Encouraging local control rate, low toxicity, and effective symptom relief suggests the vital role of CK in the treatment of these patients. This clinical application needs to be further studied in the combination of CK and multimodal therapy.

## Introduction

Pancreatic cancer is a common malignant tumor of the digestive system. However, its prognosis is extremely poor. Even with radical surgical resection, approximately 80% of patients will relapse within two years after surgery [1–5]. Furthermore, although the postoperative recurrence pattern of pancreatic cancer is well-known [6], its optimal treatment strategy remains unclear [7,8]. Due to the disorder of the anatomical structure of the pancreas and its surroundings in the first operation, in most cases, local recurrent disease cannot be re-operated [9–11]. In addition, patients with recurrence after surgery often have obvious local symptoms, including pain, biliary obstruction, etc. [12] Local progression is an important factor that affects quality of life, and is also correlated to short PFS [13]. Hence, it is particularly important to relieve the symptoms and improve quality of life through local radiotherapy.

Due to the special anatomic location of the pancreas, conventional radiotherapy has low fractionated doses, long treatment cycles and large adverse reactions, which may adversely affect other comprehensive treatments, such as chemotherapy. In addition, pancreatic cancer has low response to conventional radiotherapy and poor local control. Stereotactic body radiation therapy (SBRT) is a precise radiotherapy method. Its advantages are precise positioning, precise planning and precise irradiation. At

the same time, during high-dose irradiation, the doses to the surrounding organs are reduced, thereby reducing the incidence of serious adverse reactions. The present study aims to evaluate the efficacy, safety and survival of patients with recurrence of pancreatic cancer after CK.

## Materials and methods

## Study design and clinical data

The prospectively collected database of patients with recurrent pancreatic cancer of the investigators was retrospectively queried. Patients were treated with SBRT using CK between January 2009 and June 2019. Inclusion criteria: (1) any age; (2) imaging and clinical evidence supporting the local tumor recurrence; (3) complete clinical case data and follow-up data; (4) signed informed consent. Exclusion criteria: (1) previous radiation therapy; (2) contraindications to radiotherapy; (3) uncontrollable comorbidities. The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki, and was approved by independent ethics committees in Jinling Hospital. In addition, all included patients provided a written informed consent.

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The following were collected and recorded from the study subjects: the gender, age and pain level (based on the Numerical Rating Scale [NRS]), Eastern Cooperation Oncology Group (ECOG) score, tumor staging, systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutrition index (Prognostic nutritional index [PNI]) before treatment, median biological effective dose (BED<sub>10</sub>), serum CA-199 levels before and after treatment, and the presence or absence of follow-up treatment.

**Treatment plan implementation**

Preparation before treatment: Three 6.0 × 0.8 mm gold markers were implanted within or around the tumor using a CT-guided 19G needle. CT scan was performed to determine whether the markers were in the proper positions at 24 h after implantation. The CT scan was repeated at seven days after implantation. At this time, the local hemorrhage and edema subsided around the gold seed fiducial, and became relatively stable and immobile.

Tumor localization and target area delineation: The patient took the supine position, and was fixed with a vacuum pad. Then, CT enhanced scanning (layer thickness: 1 mm) was performed for positioning. The patients were fasted for more than 4 h before positioning. The oral contrast agents were taken before the CT scan to better display the gastrointestinal tract. The scanning range was 15 cm above and below the pancreatic lesion. The target area was delineated on the soft tissue window of the CT. The gross tumor volume (GTV) was the tumor volume observed through the imaging. The GTV was placed at 2–3 mm outward on all sides, in order to form a planning target volume (PTV). If the tumor was close to the organs at risk (OAR, the gap between the tumor and OAR was < 3 mm), the GTV was not placed in this direction. Normal tissues, including the esophagus, stomach, duodenum, small intestine, spinal cord, liver and kidneys, are sketched.

Treatment schedule: Before treatment, a respiratory monitoring device was used to continuously detect the position of the infrared generator placed on the patient's chest, in order to create a dynamic respiratory rhythm. Then, the X-ray digital imaging of the kV level was collected at different time points of the respiratory rhythm, in order to obtain the dynamics model between the gold seed fiducial (tumor) position and respiratory rhythm. Afterwards, the respiratory model was used to guide the accelerator in tracking the lesions within the pancreas, and provide dynamic radiation. The prescription dose provided to the lesions was 25–50 Gy (median dose: 40 Gy) once per day, at a fraction number of 4–7.

**Follow-up and adverse reactions**

These patients were observed at one month after completion of the treatment, every three months for the first year, and every six months thereafter, until December 2019. These patients were monitored for imaging data, related hematological indicators, adverse events, and compliance during follow-up. The OS, PFS and FFLP were recorded. The overall survival time was the time from the start of treatment to death or follow-up. The progression-free survival time was the time from the start of treatment to the progression of any lesion or onset of new metastasis. FFLP was the time from the start of treatment to the progression of the local lesion. Acute and long-term toxicities were defined as adverse events that occurred at < 3 months and > 3 months after SBRT, respectively. Toxicity was scored according to the Common Terminology Criteria for Adverse Events version 4.0.

**End point**

The primary end-point was the FFLP and LC rate after CK, which was determined using the Response Evaluation Criteria in Solid Tumors version 1.1.16. The LC rate for recurrent disease was assessed at six months after CK, in order to avoid the uncertainty associated with early transient

**Table 1**  
Summary of patient characteristics.

Name	Sex	Age (years)	Surgical staging	Type of surgery	Surgical pathology	Interval between surgery and recurrence (months)	Interval between surgery and SBRT (months)	ECOG	Symptoms	Synchronous metastases
LZJ	Male	46	T3N0M0	R0	Sarcomatoid carcinoma	1.3	1.7	2	Abdominal pain	Liver
WBH	Male	71	T3N1M0	R0	Adenocarcinoma	10.5	13.6	1	No	
LB	Male	56	T3N1M0	R1	Mucinous adenocarcinoma	13.1	16.2	1	No	
SXG	Male	50	T3N2M0	R0	Adenocarcinoma	10.6	11.5	3	Abdominal pain	
HXQ	Male	47	T4N0M0	R2	Adenocarcinoma	0	4.5	1	Abdominal pain	
WMH	Female	61	T4N0M0	R0	Adenocarcinoma	11.2	12.3	2	Lumbago	
ZXS	Male	72	T2N0M0	R0	Adenocarcinoma	34.2	37.2	2	Abdominal pain	
LQB	Male	68	T2N1M0	R0	Adenocarcinoma	6.4	11.5	1	No	
ZQ	Female	70	T3N0M0	R0	Adenocarcinoma	10.5	12.3	1	No	
WDC	Male	69	T1N0M0	R0	Adenocarcinoma	11.4	23.3	1	Lumbago	
ZH	Female	48	T3N1M0	R0	Adenocarcinoma	14.3	19.9	3	Lumbago	
YCH	Male	80	T3N1M0	R0	Adenocarcinoma with focal squamous cell carcinoma	4	5.4	2	No	
WZJ	Male	69	T3N0M0	R0	Adenocarcinoma	19	22	1	Abdominal pain	
LYM	Female	53	T3N1M0	R0	Adenocarcinoma	5.5	6.9	3	No	Lymphonodus of neck and armpit
ZL	Male	43	T3N0M0	R1	Adenocarcinoma	5.3	5.8	1	No	
WWJ	Male	79	T2N2M0	R0	Adenocarcinoma	10.9	11.5	2	No	
GLY	Female	81	T1N0M0	R0	Adenocarcinoma	10	10.9	2	Abdominal pain	
SST	Male	51	T3N0M0	R0	Adenocarcinoma	4.7	5.8	1	Abdominal pain and anorexia	
LW	Male	50	T4N1M0	R0	Adenocarcinoma	6	6.4	1	Abdominal pain	
XGD	Male	53	T3N0M0	R0	Adenocarcinoma	15.4	17.6	1	Lumbago	
ZJB	Male	53	T4N1M0	R2	Adenocarcinoma	0	2.3	1	Abdominal pain	
CQH	Female	60	T4N1M0	R0	Adenocarcinoma	3.7	8.6	2	No	
GHL	Female	74	T3N1M0	R0	Adenocarcinoma	9	10.6	2	Abdominal pain	
XZ	Male	73	T3N2M0	R0	Adenocarcinoma	7.7	8.3	2	Abdominal pain	
WHM	Female	56	T2N1M0	R0	Adenocarcinoma	10	12	1	Abdominal pain	
LAG	Male	56	T3N1M0	R0	Adenocarcinoma	12.2	13	1	Lumbago	
WYZ	Female	62	T2N0M0	R0	Adenocarcinoma	7	7.6	1	No	

Abbreviations: SBRT, stereotactic body radiation therapy.

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

**Table 2**  
Summary of treatment characteristics.

Name	Prescription dose (Gy)/fractionation	BED10 (Gy)	Isodose (%)	History of CT	Follow-up of CT	Location of PD	FFLP (months)	PFS (months)	OS (months)	Status (cause)
LZJ	50/5	100	71	No CT	Gemcitabine-based	Liver and adrenal gland metastasis	11.9	2.6	13.3	Death (tumor)
WBH	44/4	92.4	68	No	Gemcitabine-based	Liver metastasis	12.3	6.6	12.3	Death (tumor)
LB	40/5	72	70	Gemcitabine-based	No CT	No	3.6	3.6	3.6	Death (gastrointestinal hemorrhage)
SXG	40/4	80	77	No CT	No CT	Abdominal wall metastasis	2.9	1.3	2.9	Death (tumor)
HXQ	50/5	100	75	Gemcitabine-based	5-Fu-based	Liver metastasis	26.3	22.6	26.3	Death (tumor)
WMH	42/7	67.2	76	Gemcitabine-based	No CT	Liver and lung metastasis	6.8	3.3	6.8	Death (tumor)
ZXS	40/5	72	75	Gemcitabine-based	5-Fu-based	Liver metastasis	21.8	16.7	21.8	Death (tumor)
LQB	40/5	72	75	Gemcitabine-based	No CT	No	3.6	3.6	3.6	Death (heart accident)
ZQ	45/5	85.5	71	No CT	Gemcitabine-based	Liver metastasis	13.5	10.3	13.5	Death (tumor)
WDC	42/6	71.4	75	Gemcitabine-based	5-Fu-based	Liver and lung metastasis	30.6	27.1	30.6	Death (tumor)
ZH	50/5	100	75	Gemcitabine-based	No CT	Treatment site and liver metastasis	1.3	1.3	1.3	Death (tumor)
YCH	40/5	72	70	No	No CT	Liver metastasis	8.9	7.1	8.9	Death (tumor)
WZJ	42/7	67.2	81	Gemcitabine-based	5-Fu-based	Treatment site	22.3	22.3	26.5	Death (tumor)
LYM	40/5	72	70	Gemcitabine-based	5-Fu-based	Lymphonodus of neck and armpit	11.3	7.6	11.3	Death (tumor)
ZL	40/5	72	67	Gemcitabine-based	5-Fu-based	Liver and retroperitoneal metastasis	17.7	14.2	17.7	Death (tumor)
WWJ	40/5	72	80	No CT	5-Fu-based	Lung metastasis	15.2	9.3	15.2	Death (tumor)
GLY	35/5	59.5	75	No CT	No CT	Liver metastasis	6.9	4.3	6.9	Death (tumor)
SST	35/5	59.5	77	Gemcitabine-based	No CT	Peritoneum metastasis	5.3	4.1	5.3	Death (tumor)
LW	35/5	59.5	77	Gemcitabine-based	5-Fu-based	Liver metastasis	6.4	2.8	6.4	Death (tumor)
XGD	35/5	59.5	81	Gemcitabine-based	Gemcitabine-based	Liver metastasis	17.1	13.6	17.1	Death (tumor)
ZJB	35/5	59.5	79	No CT	Gemcitabine-based	Liver and lung metastasis	15.9	14.2	15.9	Death (tumor)
CQH	35/5	59.5	80	No CT	Oxaliplatin-based	No	11.9	11.9	11.9	Alive
GHL	35/5	59.5	77	No	Oxaliplatin-based	No	11.3	11.3	11.3	Alive
XZ	35/5	59.5	76	No CT	No CT	Peritoneum metastasis	7.5	5.9	7.5	Death (tumor)
WHM	25/5	37.5	75	Gemcitabine-based	5-Fu-based	No	9.1	9.1	9.1	Alive
LAG	35/5	59.5	75	Gemcitabine-based	Irinotecan-based	No	6.1	6.1	6.1	Alive
WYZ	30/5	48	83	Gemcitabine-based	Oxaliplatin-based	No	6.1	6.1	6.1	Alive

Abbreviations: BED, biologically equivalent dose; CT, chemotherapy; PD, progressive disease; FFLP, freedom from local progression; PFS, progression free survival; OS, overall survival time.

radiographic changes within the high-dose region. The secondary end points were OS, PFS, symptom alleviation and toxicity.

**Statistical analysis**

The SPSS 22.0 software was used for the statistical analysis of the research data. ROC curves were used to determine the best cut-off values for NLR, PLR, SII and PNI, and the area under the curve (AUC) was recorded. The OS and PFS rate estimates were calculated using the Kaplan–Meier method, and compared using the stratified log-rank test. The multivariate analysis of survival was carried out using the Cox’s regression model. P < 0.05 was considered statistically significant.

**Results**

*Clinical characteristics*

According to the inclusion criteria, the present study included a total of 27 patients: 18 male patients (66.7%), nine female patients (33.3%). Their median

age was 58 years old (43–81 years old). The median time from operation to recurrence was 10.0 (0–34.2) months, and the median time from relapse to CK was 1.6 months (0.4–11.9). The median time from surgery to CK was 11.5 (1.7–37.2) months. A total of 18 (66.7%) patients underwent follow-up chemotherapy after the CK. Tables 1 and 2 presents the summary of the clinical and treatment characteristics of all patients.

*Dosimetric index*

The isodose level of the prescription dose in the treatment plan was 82.33–94.66%, with a median value of 91%. The irradiation fields involved 150–200 non-coplanar fields. The treatment plan revealed that the median CI, nCI and HI of the pancreatic lesions in all patients was 1.13, 1.52 and 1.33 respectively (Table 3).

*Determination of critical values of inflammatory composite indicators*

The ROC curve for each inflammatory composite index was drawn with the survival time as the end-point (Fig. 1). The results revealed that the AUC

**Table 3**  
The dosimetry index of the patients during Cyber-Knife radiosurgery treatment.

Item	CI	n CI	HI	Coverage (%)	PTV (cm3)	Prescription dose (Gy)	BED <sub>10</sub> (Gy)	Isodose (%)
Range	1.01–1.56	1.15–2.28	1.2–1.52	82.33–94.65	18.38–170.38	25–50	37.5–100	67–83
Mean	1.16	1.52	1.33	89	87.13	39	70	75
Median	1.13	1.52	1.33	91	44.14	40	71.4	75

Abbreviations: Coverage: the coverage is volume of the tumor receiving greater than or equal to the prescription dose divided by the total volume of the tumor times 100; CI, conformity index; n CI, new conformity index; HI, homogeneity index.

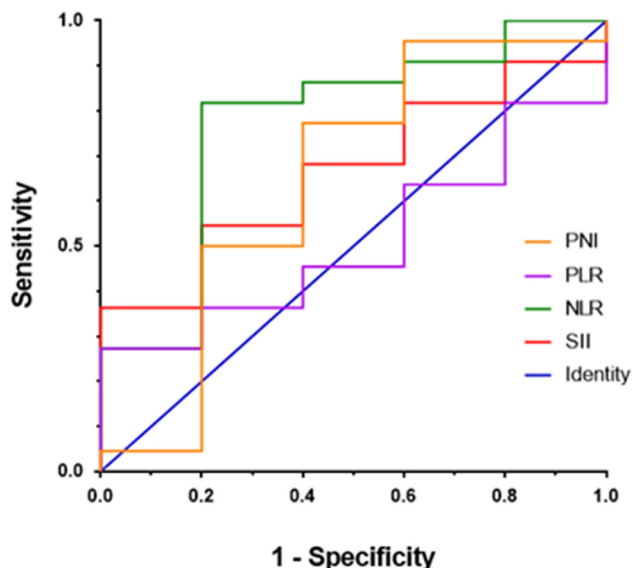


Fig. 1. Receiver operation characteristic curve of the patients according to the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic immune-inflammation index (SII) and prognostic nutrition index (PNI).

for SII, NLR, PLR and PNI was 0.6636, 0.7727, 0.5091 and 0.6455, respectively. The best cut-off values for each indicator in the present study were as follows: SII was 821.9, NLR was 1.26, PLR was 105.2, and PNI was 49.88. These were used to analyze the relationship between inflammatory composite indicators and OS, and PFS.

LC rate, OS and prognostic factors

Among the 27 patients, one (3.7%) patient achieved complete response, 18 (66.7%) patients exhibited partial response, six (22.2%) patients presented with a stable disease, and two (7.4%) patients developed progressive disease. The median local recurrence disease free interval (DFI) was 11.3 (1.3–30.6) months. The 6-month and 12-month LC rate was 81.5% and

37.0%, respectively. At six months after the CK, 16 (94.1%) of 17 patients with pain were relieved to varying degrees.

The median OS of the 27 patients was 11.3 months (1.3–30.6 months), and the median PFS was 7.1 months (1.3–27.1 months). The 6-month and 12-month survival rate was 81.8% and 40.7%, respectively, and the 6-month and 12-month progression-free survival rate was 63.0% and 26.0%, respectively (Fig. 2).

The univariate analysis results revealed the following: the ECOG score, postoperative lymph node staging, follow-up treatment, CA199 decline, SII, NLR, PNI and FFLP were factors correlated to OS (all,  $P < 0.05$ ; Table 4, Fig. 3). Patients with a lower ECOG score, no lymph node metastasis after surgery, continued treatment after radiotherapy, and a decrease in CA199 of  $\geq 50\%$  after treatment had a longer OS. Patients with  $SII < 821.9$  had a better OS, when compared to patients with  $SII \geq 821.9$  ( $P = 0.017$ ). The OS was shorter in the high NLR group than in the low NLR group. Patients with  $PNI \geq 49.88$  were significantly better, when compared to patients with  $PNI < 49.88$  ( $P = 0.019$ ). The ECOG score, follow-up treatment, CA199 decline after treatment, SII, PNI and FFLP were the related factors that affected PFS, (all,  $P < 0.05$ ; Table 4, Fig. 4).

The multivariate analysis results revealed that subsequent chemotherapy and the  $CA199 \geq 50\%$  decrease after CK are independent prognostic factors for OS, while subsequent chemotherapy was an independent prognostic factor for PFS (all,  $P < 0.05$ ; Table 5).

Side effects and patterns of failure

All patients completed the CK without treatment breaks or dose reductions. As indicated in Table 6, 21 patients (77.8%) experienced CTCAE version 4.0 grade 1–2 acute toxicities that manifested as diarrhea, abdominal distention, nausea and vomiting, thrombocytopenia, weakness and anorexia. One patient (3.7%) who received gemcitabine-based chemotherapy experienced grade 3 acute toxicity due to thrombocytopenia. These toxicities were generally transient, and were resolved with conservative management. One patient (3.7%) suffered from late grade 3 duodenal ulcer, which needed endoscopic treatment. No treatment-related deaths were observed.

Two patients (7.4%) exhibited relapse within the PTV. Furthermore, out-of-field progression was detected in 19 patients (66.7%) within a

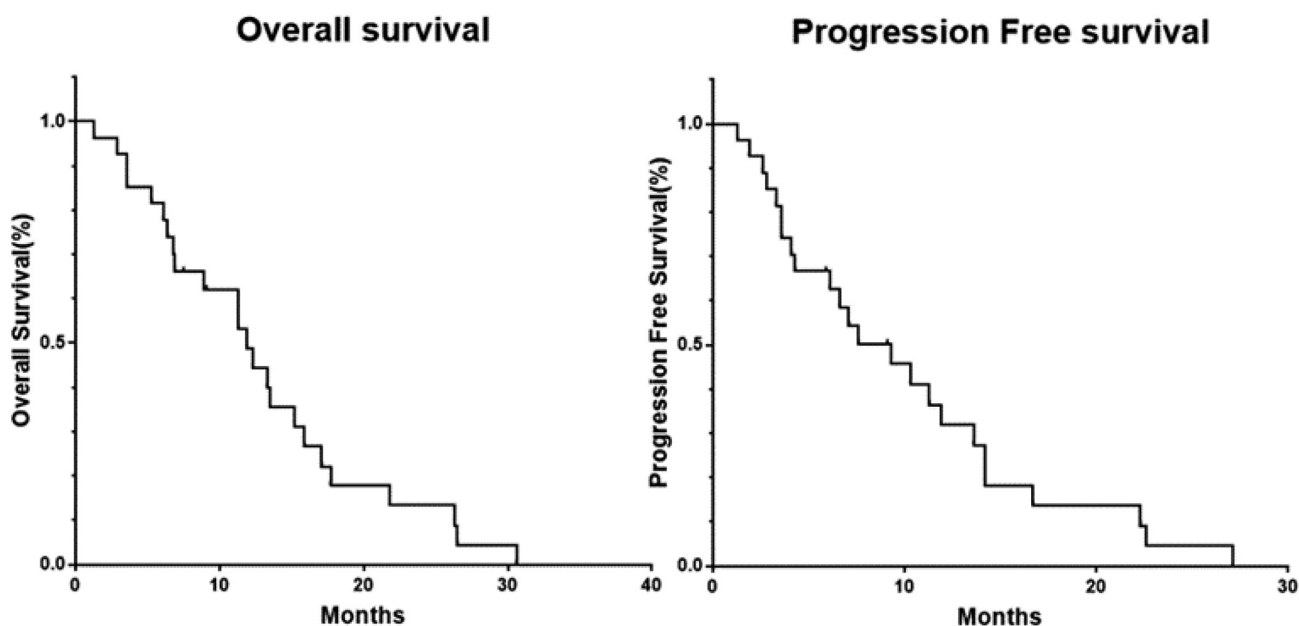


Fig. 2. Kaplan–Meier analysis of overall survival and progression free survival for patients.

**Table 4**  
The univariate analysis of OS and PFS.

Variable	N	OS Median (months)	P	PFS Median (months)	P
Gender					
Male	18	12.8	0.490	6.9	0.993
Female	9	9.1		7.6	
Age					
≤60	14	10.2	0.413	6.9	0.570
>60	13	11.3		7.1	
ECOG					
0–1	15	12.3	0.008	9.1	0.019
2	9	11.3		7.1	
3	3	2.9		1.9	
N stage					
N0	12	15.3	0.021	11.9	0.131
N+	15	8.9		6.6	
Follow-up chemotherapy					
No	9	5.3	<0.001	3.6	<0.001
Yes	18	13.4		10.8	
Degree of decline of CA199					
<50%	11	6.4	0.002	3.6	0.002
≥50%	16	11.6		9.8	
BED10					
≥60	16	12.8	0.834	7.4	0.637
<60	11	7.5		6.1	
NRS					
≤3	10	11.6	0.319	7.35	0.480
≥4	17	9.1		6.1	
SII					
≥821.9	8	9.4	0.017	4.8	0.017
<821.9	19	11.3		9.1	
NLR					
≥1.26	19	11.3	0.045	7.1	0.045
<1.26	8	9.05		8.7	
PLR					
≥105.2	21	8.9	0.052	6.1	0.107
<105.2	6	20.8		15.8	
PNI					
≥49.88	8	12.7	0.019	11.1	0.019
<49.88	19	7.5		6.1	
FFLP					
≥10	14	15.6	0.001	12.8	0.001
<10	13	6.1		4.1	

median of 7.1 months after the CK (range: 1.3–27.1 months), while progression was not observed after the CK in seven patients (25.9%).

**Discussion**

The treatment of patients with recurrent pancreatic cancer following surgical resection was mainly based on the comprehensive treatment, which included reoperation, chemotherapy and radiotherapy. Nevertheless, the treatment effect on these patients was not ideal, and most of these patients were not suitable for reoperation due to simultaneous distant metastases, vascular involvement, or poor physical condition [1,14]. The present results suggest that the CK is a safe and effective treatment approach for recurrent pancreatic carcinoma, and the related prognostic factors were analyzed for the first time.

Due to the high radiation accuracy of SBRT, tumors can be given higher radiation doses, while minimizing the radiation doses to the surrounding endangered organs. Compared with conventional radiation therapy, this can significantly shorten the treatment time without affecting the patient's overall treatment plan. The patient's local symptoms were effectively alleviated, and their quality of life was significantly improved, providing more time and opportunities for subsequent comprehensive treatment. The role of SBRT for advanced pancreatic cancer has been confirmed in many studies, but its application in patients with recurrent pancreatic carcinoma has been less studied. Five retrospective case series reported on SBRT for the treatment of isolated local recurrence (Table 7). In three studies, all patients

received prior radiation in association with initial surgical resection. Rwigema et al. [15] reported on 71 patients with advanced adenocarcinoma of the pancreas, who were treated with SBRT, and 11 (16%) of these patients had local recurrence following surgical resection. These patients had a median survival of 13 months, and no grade 3 or above toxicity was observed. Wild et al. [16] included 15 patients with isolated local recurrence after surgical resection and three patients with local progression after definitive chemoradiotherapy for locally advanced pancreatic cancer. All patients received GEM-based maintenance chemotherapy before SBRT. The median OS was nine months, and no acute toxicity of grade 3 or above was observed, while one patient developed grade 3 advanced toxicity (intestinal obstruction). Among the seven patients who presented with abdominal/back pain prior to SBRT, an effective symptom palliation was achieved in four patients. Dagoglu et al. [17] further described 15 patients with isolated local recurrence treated by SBRT. All of these patients received some form of chemotherapy prior to or after SBRT. The median OS was 13 months, and no acute or chronic toxicity above level 3 was found. Furthermore, all four patients who presented with pain symptoms experienced the alleviation of these symptoms as a result of the SBRT. Zeng et al. [18] reported 24 patients with SBRT after the recurrence of pancreatic cancer after surgery, with a median OS of 12 months and one year, and an LC rate of 83.8%. Nine patients developed grade 1–2 acute toxicity, and one patient developed grade 3 toxicity due to thrombocytopenia. However, no late toxicity was found. Comito et al. [19] reported 31 patients with isolated local recurrence after R0, and the median follow-up was 12 months. FFLP was 91% and 82% in one year and two years, respectively. The median OS was 18 months. No acute or chronic toxicity of grade 3 or above was observed, and the treatment was tolerable for all patients. In the present study, the median FFLP was 11.3 months, and the median OS and PFS was 11.3 and 7.1 months, respectively. The 6-month and 12-month LC rates were 81.5% and 37.0%, respectively. The 6-month and 12-month survival rate was 81.8% and 40.7%, respectively, and the 6-month and 12-month progression-free survival rate was 63.0% and 26.0%, respectively. Among the 27 patients, two patients had relapses within PTV, while the remaining patients had distant metastases. Therefore, SBRT should be combined with systemic therapy to reduce the rate of distant metastases.

Inflammatory response plays a vital role in all stages of tumorigenesis, development and treatment. The level of neutrophils, lymphocytes and platelets in peripheral blood are significantly correlated to tumor progression [20–23]. The combinations of different indicators, such as NLR, PLR and SII, have been shown to correlate with the prognosis of various malignancies. SII can more objectively reflect the balance between inflammatory and immune responses in patients [24–26]. The higher SII in tumor patients is associated with the high level of circulating tumor cells (CTCs) in the body, which in turn is associated with tumor invasion and metastasis, ultimately leading to poor prognosis. In addition, the prognostic nutrition index (PNI), which is a combination of serum albumin levels and lymphocyte counts, has also been considered to be correlated to the prognosis in a variety of tumors [27–29]. In the present study, the survival factors of recurrent pancreatic carcinoma after SBRT treatment were analyzed, and the relationship between inflammatory composite indicators and the prognosis of patients was initially explored. The univariate analysis results revealed that patients had a low ECOG score, good physical fitness (P = 0.008), no lymph node metastasis after the operation (P = 0.021), continued treatment after radiotherapy (P < 0.001), and a decrease in CA199 by ≥50% after treatment (P = 0.002), while patients with PFLP ≥ 10 months (P = 0.001) had a longer OS. Furthermore, patients with SII < 821.9 had a better OS than patients with SII ≥ 821.9 (P = 0.017). The OS of patients with high NLR was shorter, when compared to patients with low NLR (P = 0.045). The OS of patients with PNI ≥ 49.88 was significantly better than patients with PNI < 49.88 (P = 0.019). The ECOG score, radiotherapy follow-up treatment, CA199 degree after treatment, SII, PNI and FFLP were the related factors that affects a patient's PFS. The follow-up treatment of radiotherapy (P = 0.001) and the decrease in CA199 ≥ 50% after treatment (P = 0.001) were independent prognostic factors of OS. The follow-up treatment of radiotherapy (P = 0.005) was an independent prognostic

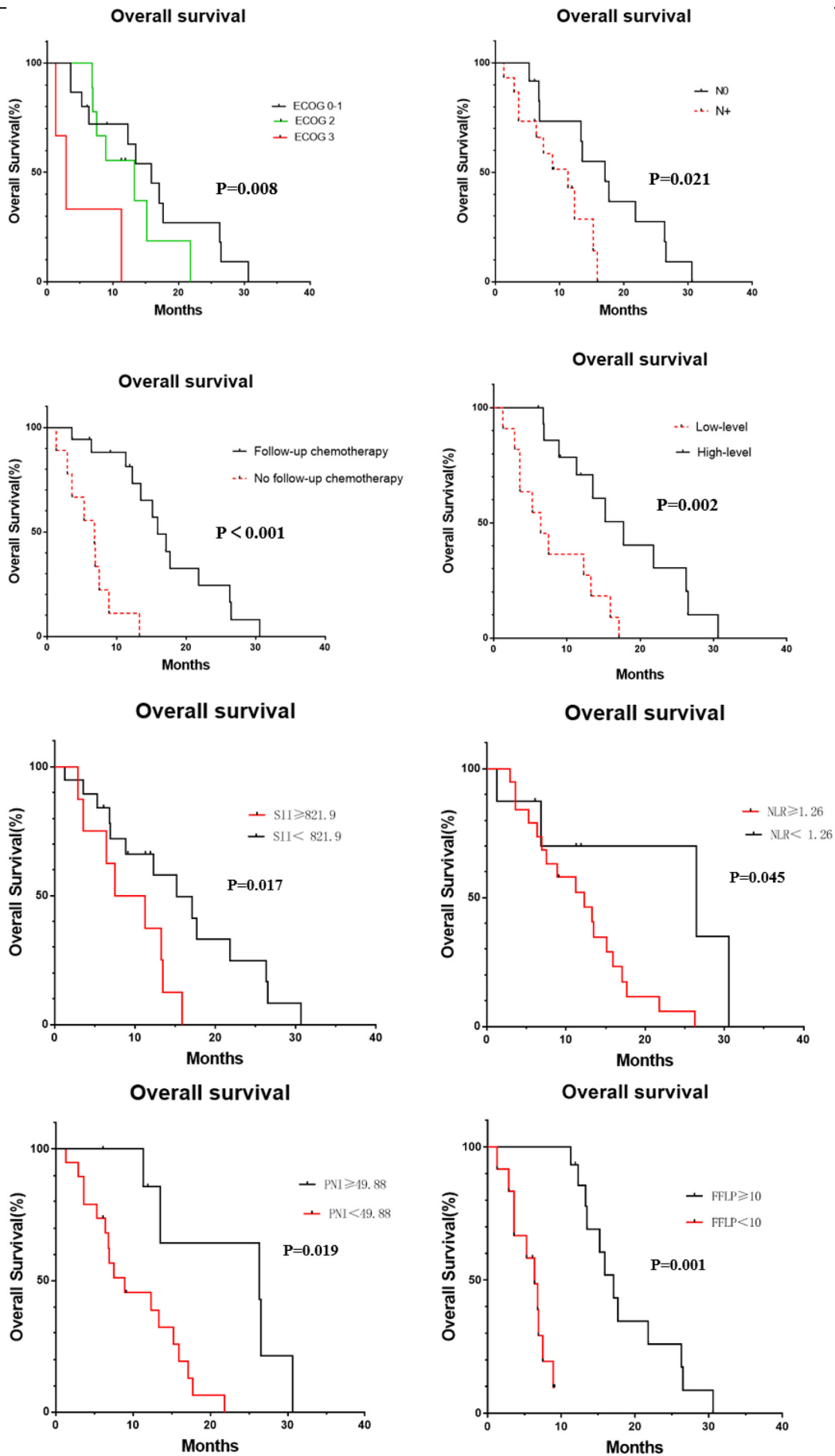


Fig. 3. Overall survival curves of 27 patients according ECOG score, postoperative lymph node staging, follow-up treatment, CA199 decline, SII, NLR, PNI, and FFLP.

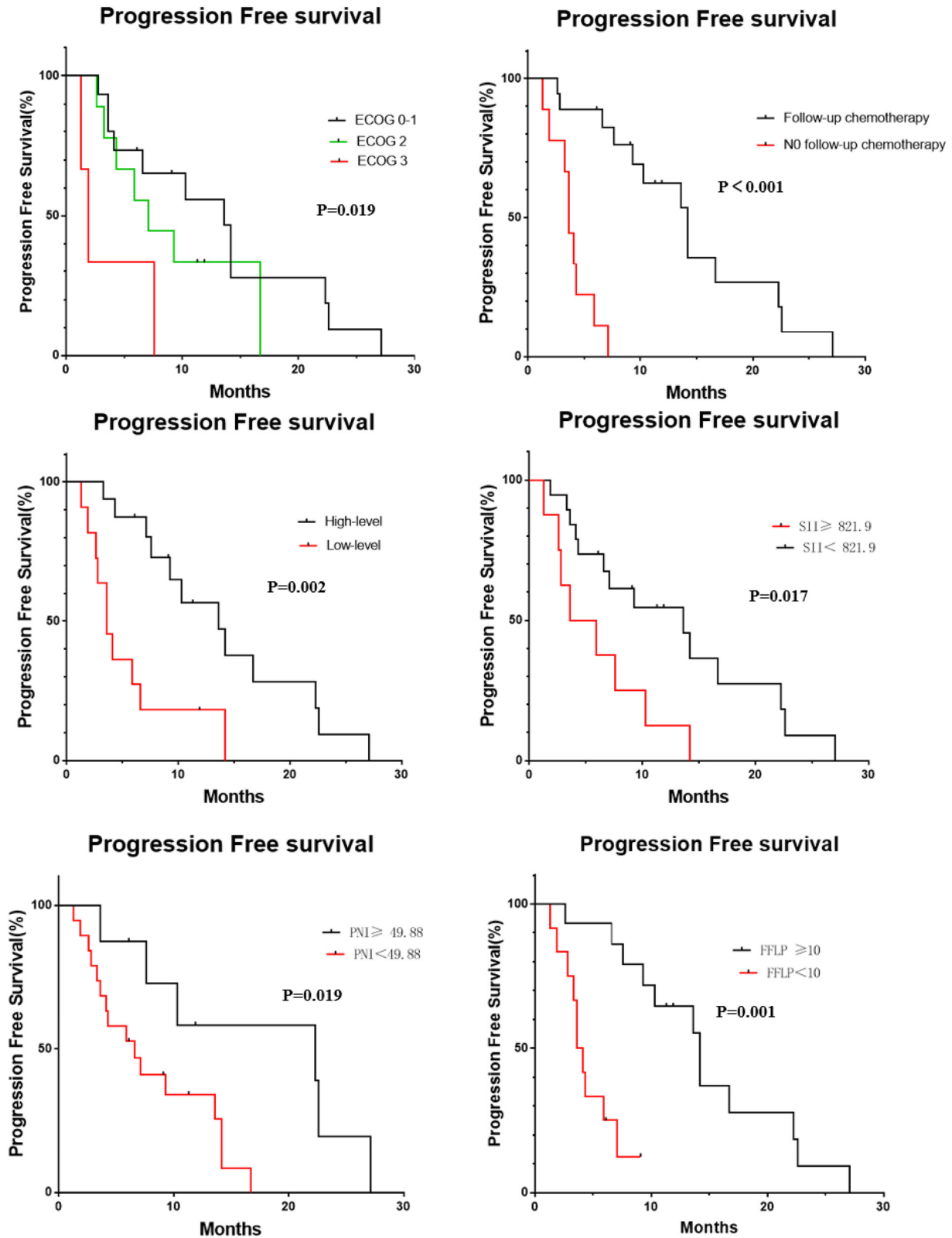


Fig. 4. Progression free survival curves of 27 patients according ECOG score, follow-up treatment, CA199 decline, SII, PNI, and FFLP.

factor of PFS. In the present study, two patients had a R1 resection and two patients had a R2 resection. Furthermore, two patients had distant metastasis at the time the recurrence was found, and nine patients did not follow-up treatment after SBRT. Patients with longer FFLP had a better OS. Therefore, more studies are needed to explore the combination of SBRT and other treatment models, providing a higher LC rate and better OS. Cytokines

secreted by neutrophils can change the tumor microenvironment through endogenous and exogenous pathways, in order to increase invasiveness and evade immune surveillance [30]. Furthermore, this can also lead to T lymphocyte activation disorders [26]. Lymphocytes mediate the body's immune response to tumor cells. By inducing cytotoxic cell death, and inhibiting the proliferation and migration of tumor cells, these play an

**Table 5**  
The multivariate analysis of OS and PFS.

Variable	OS					
	B	SE	Wald	P	RR	95% CI
Follow-up chemotherapy (no vs yes)	3.732	1.128	10.954	0.001	41.751	4.581–227.862
Degree of decline of CA199 (<50% vs ≥50%)	1.462	0.564	6.716	0.001	4.316	1.428–13.045
Variable	PFS					
	B	SE	Wald	P	RR	95% CI
Follow-up chemotherapy (no vs yes)	2.036	0.729	7.811	0.005	7.662	1.837–31.955

**Table 6**  
Side effects in 27 patents with pancreatic carcinoma in the treatment of Cyber-Knife.

	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
<i>Acute toxicities</i>				
Diarrhea	2 (7.4)	0	0	0
Abdominal pain	0	0	0	0
Abdominal distention	1 (4.2)	0	0	0
Agranulocytosis	0	0	0	0
Nausea and vomiting	10 (37.0)	0	0	0
Thrombocytopenia	1 (4.2)	1 (4.2)	0	0
Weak	3 (11.1)	0	0	0
Anorexia	5 (18.5)	0	0	0
<i>Late toxicities</i>				
Intestinal obstruction	0	0	0	0
Intestinal perforation	0	0	0	0
Gastric perforation	0	0	0	0
Stomach ulcer	0	0	0	0
Duodenal ulcer	1 (4.2)	1 (4.2)	0	0

important role in tumor defense and immune surveillance. When the number of CD4<sup>+</sup> T helper lymphocytes is reduced, the patient's anti-cancer ability is weakened, and the prognosis becomes poor [31]. Therefore, the immunotherapy of pancreatic cancer needs to select specific antigens for labeling, according to the heterogeneity. Furthermore, subsequent studies need to explore the changes in the immune inflammatory complex indexes of patients after SBRT treatment, in order to identify more accurate immunotherapy markers, and further explore the best mode of SBRT combined immunotherapy.

The whole management of patients with recurring pancreatic cancer after surgery remains as a challenging subject, because the disease typically causes symptoms that negatively impact the patient's quality of life, such as abdominal and back pain. These symptoms are not typically transient, and cannot be resolved with conservative management. However, in the present study, the majority of patients achieved complete symptoms relief, typically within two weeks of treatment. These present findings concur with published studies, suggesting that SBRT can reduce pain and improve the quality of life of patients with localized advanced pancreatic cancer. In the present study, most of the patients experienced CTCAE grade 1–2 acute toxic events, and most of these symptoms were

**Table 7**  
Study outcomes of stereotactic body radiation therapy for the treatment of locally recurrent pancreatic cancer.

Reference	Relevant patients (total)	Median radiation dose (Gy)	Acute toxicity ≥ Grade 3	Late toxicity ≥ Grade 3	LC (1 year)	Median survival (months)
Rwigema et al. [16]	11 (71)	24 (18–25)	3	0	19%	13
Wild et al. [17]	15 (18)	25 (20–27)	0	1	62%	9 (8–12)
Dagoglu et al. [18]	15 (30)	25 (24–36)	0	0	72%	16 (3–32)
Zeng et al. [19]	19 (24)	45 (42–50)	0	0	42%	12 (4–23)
Comito et al. [20]	31 (31)	45 (45–45)	0	0	91%	18 (11.1–24.9)
<b>Total</b>	<b>91 (174)</b>	<b>NA</b>	<b>3 of 135 (2.2%)</b>	<b>1 of 63 (1.6%)</b>	<b>NA</b>	<b>NA</b>

Abbreviations: NA, not available.

transient and resolved with conservative management. One patient developed grade 3 thrombocytopenia, and the blood returned to normal after symptomatic treatment. One patient developed grade 1 radioactive enteritis, which was cured after conservative medical treatment. One patient developed grade 3 radioactive enteritis, which required combined medical and surgical treatment. The patient's overall tolerance was better.

These present results confirm the efficacy and safety of SBRT using the CK for patients with recurrent pancreatic cancer after surgery. To the best of our knowledge, this study is the first to analyze the related prognostic factors, and explore the relationship between the inflammatory complex index and the prognosis of patients. However, the present study is limited by its retrospective nature, and the patient characteristics and treatment plan are not unified. However, in light of the paucity of literature on the outcomes of CK for these patients, these present results further recommend the clinical use of CK. At the time of precision therapy, more prospective studies are needed to combine SBRT with gene-guided multi-mode (chemotherapy, targeted therapy, immunotherapy and anti-vascular therapy) therapy, in order to achieve comprehensive treatment, provide a cure or control to the greatest extent, prolong patient survival, and improve the patient's quality of life.

**CRedit author statement**

Jing Li: Conceptualization, Methodology, Software, Writing - original draft preparation. Zhen Wang: Visualization, Investigation, Writing - review & editing, Formal analysis. Ao-mei Li: Project administration. Han Zhou: Data curation, Investigation, Writing - review & editing. Xi-xu Zhu: Funding acquisition, Supervision, Validation.

**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## References

- [1] J. Kleeff, C. Reiser, U. Hinz, et al., Surgery for recurrent pancreatic ductal adenocarcinoma, *Ann. Surg.* 245 (4) (2007) 566–572.
- [2] A. Vincent, J. Herman, R. Schulick, et al., Pancreatic cancer, *Lancet*. 378 (9791) (2011) 607–620.
- [3] S. Yamada, T. Fujii, M. Kanda, et al., Value of peritoneal cytology in potentially resectable pancreatic cancer, *Br. J. Surg.* 100 (13) (2013) 1791–1796.
- [4] W. Hartwig, J. Werner, D. Jäger, et al., Improvement of surgical results for pancreatic cancer, *Lancet Oncol.* 14 (11) (2013) e476–e485.
- [5] S. Moningi, A.S. Dholakia, S.P. Raman, et al., The role of stereotactic body radiation therapy for pancreatic cancer: a single-institution experience, *Ann. Surg. Oncol.* 22 (7) (2015) 2352–2358.
- [6] H. Oettle, S. Post, P. Neuhaus, et al., Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial, *JAMA*. 297 (3) (2007) 267–277.
- [7] O. Gangl, U. Fröschl, B. Dutta-Pügger, et al., Elective pancreatic resection – report of a series and review of the literature, *Eur Surg* 34 (1) (2010) 91–95 42.
- [8] I.D. Kyriazanos, G.G. Tsoukalos, G. Papageorgiou, et al., Local recurrence of pancreatic cancer after primary surgical intervention: how to deal with this devastating scenario? *Surg. Oncol.* 20 (4) (2011) e133–e142.
- [9] Y. Zhang, A.E. Frampton, C. Kyriakides, et al., Loco-recurrence after resection for ductal adenocarcinoma of the pancreas: predictors and implications for adjuvant chemoradiotherapy, *J. Cancer Res. Clin. Oncol.* 138 (6) (2012) 1063–1071.
- [10] D. Habermehl, I.C. Brecht, F. Bergmann, et al., Chemoradiation in patients with isolated recurrent pancreatic cancer - therapeutic efficacy and probability of re-resection, *Radiat. Oncol.* 8 (1) (2013) 27.
- [11] A. Nakamura, S. Itasaka, K. Takaori, et al., Radiotherapy for patients with isolated local recurrence of primary resected pancreatic cancer, *Strahlenther. Onkol.* 190 (2014) 485–490.
- [12] K. Ogawa, H. Shibuya, N. Uchida, et al., Postoperative external beam radiotherapy for resected pancreatic adenocarcinoma: impact of chemotherapy on local control and survival, *Anticancer Res.* 30 (2010) 2959–2967.
- [13] S. Rudra, A.K. Narang, T.M. Pawlik, et al., Evaluation of predictive variables in locally advanced pancreatic adenocarcinoma patients receiving definitive chemoradiation, *Pract. Radiat. Oncol.* 2 (2012) 77–85.
- [14] T. Zacharias, E. Oussoultzoglou, D. Jaeck, P. Pessaux, P. Bachellier, Surgery for recurrence of periampullary malignancies, *J. Gastrointest. Surg.* 13 (4) (2009) 760–767.
- [15] J.C.M. Rwigema, S.D. Parikh, D.E. Heron, et al., Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas, *Am. J. Clin. Oncol.* 34 (2011) 63–69.
- [16] A.T. Wild, S.M. Hiniker, D.T. Chang, et al., Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions, *J. Gastrointest. Oncol.* 4 (2013) 343–351.
- [17] N. Dagoglu, M. Callery, J. Moser, et al., Stereotactic body radiotherapy (SBRT) reirradiation for recurrent pancreas cancer, *J. Cancer* 7 (2016) 283–288.
- [18] X. Zeng, H. Wang, M. Meng, et al., Stereotactic body radiation therapy for patients with recurrent pancreatic adenocarcinoma at the abdominal lymph nodes or postoperative stump including pancreatic stump and other stump, *OncoTargets Ther.* 9 (2016) 3985–3992.
- [19] T. Comito, L. Cozzi, A. Zerbi, et al., Clinical results of stereotactic body radiotherapy (SBRT) in the treatment of isolated local recurrence of pancreatic cancer after R0 surgery: a retrospective study, *Eur. J. Surg. Oncol. (EJSO)* 43 (4) (2017) 735–742.
- [20] Eran Elinav, Roni Nowarski, A. Christoph, et al., Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms, *Nat. Rev. Cancer* 13 (11) (2013) 759–771.
- [21] E.Z. Chai, K. Siveen, M. Shanmugam, et al., Analysis of the intricate relationship between chronic inflammation and cancer, *Biochem. J.* 468 (1) (2015) 1–15.
- [22] J. Coolsartigue, J. Spicer, B. McDonald, et al., Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis, *J. Clin. Investig.* 123 (8) (2013) 3446–3458.
- [23] Labelle Myriam, et al., Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis, *Cancer Cell* (2011).
- [24] A. Passardi, E. Scarpi, L. Cavanna, et al., Inflammatory indexes as predictors of prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer, *Oncotarget* 7 (22) (2016).
- [25] C. Kyoung-Min, P. Hyunkyung, O. Do-Youn, et al., Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and their dynamic changes during chemotherapy is useful to predict a more accurate prognosis of advanced biliary tract cancer, *Oncotarget* 8 (2) (2017).
- [26] Y. Geng, Y. Shao, D. Zhu, et al., Systemic immune-inflammation index predicts prognosis of patients with esophageal squamous cell carcinoma: a propensity score-matched analysis, *Sci. Rep.* 6 (1) (2016) 39482.
- [27] Tateaki Naito, Fumihito Tanaka, Akira Ono, et al., Prognostic impact of circulating tumor cells in patients with small cell lung cancer, *J. Thorac. Oncol.* 7 (3) (2012) 512–519.
- [28] Tong Ys, H. Tan, Zhou Xi, et al., Systemic immune-inflammation index predicting chemoradiation resistance and poor outcome in patients with stage III non-small cell lung cancer, *J. Transl. Med.* 15 (1) (2017) 221–231.
- [29] K. Sun, S. Chen, J. Xu, et al., The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis, *J. Cancer Res. Clin. Oncol.* 140 (9) (2014) 1537–1549.
- [30] K. Wang, F. Diao, Z. Ye, et al., Prognostic value of systemic immune-inflammation index in patients with gastric cancer, *Chin. J. Cancer* 38 (09) (2017) 34–40.
- [31] S. Raghavan, M. Quiding-JaRbrink, Regulatory T cells in gastrointestinal tumors, *Expert Rev. Gastroenterol. Hepatol.* 5 (4) (2011) 489–501.