Symptom Relief is the Most Significant Prognostic Factor for Unresectable Locally Advanced/Recurrent Pancreatic Cancer Receiving Chemoradiotherapy: Analysis of 65 Cases

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Research

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Abstract

Background

Pancreatic cancer is the fourth leading cause of cancer-related death throughout the world. For local advanced and recurrent pancreatic cancer (LAPC/LRPC), chemoradiotherapy (CRT) is a main choice which may prolong their survival and ease patients' symptoms.

Methods

We constructed a database of 65 patients with LAPC/LRPC treated from June, 2004 to February, 2018. We used log-rank test to evaluate the different overall survival (OS) rates of all factors involved, and used cox regression model to find out independent prognostic factors for these patients.

Results

The median OS time for 65 eligible patients was 23.6 months. 47 (72.3%) and 18 (27.7%) patients had unresectable LAPC and LRPC, and median OS time was 17.2 and 40.7 months (*P*= 0.02), respectively. The mean biological effective dose (BED) to gross tumor volume (GTV) was 64.8Gy (46.7-85.5 Gy). 11(16.9%) and 54(83.1%) patients had BED> 72 Gy and BED≤ 72 Gy, and their mOS was 31.8 and 21.9 months (*P*= 0.08), respectively. Simultaneous dose boost to interval GTV (GTVin) was applied to 23 patients (35.4%). Patients with large GTV volume (≥ 109.2 cm^3) may benefit from radiation dose boost (mOS: 27.6 vs. 5.3 months, *P*= 0.004). Patients with symptom relief including relief of pain, jaundice, and/or diarrhea had higher OS rates than those without response (mOS: 25.7 vs. 13.2 months, *P*< 0.01) and multivariate cox regression analysis suggested symptom relief was the most significant prognostic factor for OS (HR= 0.44, 95%CI 0.35-2.36, *P*= 0.02).

Conclusion

CRT with simultaneous integrated boost of radiation dose may bring survival benefit for LAPC/LRPC patients with bulk tumor. Symptom relief is the most significant prognostic factor for LAPC/LRPC patients after comprehensive CRT.

Introduction

As one of the malignant digestive tract tumors, pancreatic cancer has an increasing trend at home and abroad. Chemoradiotherapy (CRT) is a main choice for local advanced and recurrent pancreatic cancer, which may prolong their survival and ease patients' symptoms.[1] This study retrospectively enrolled all the local advanced or recurrent pancreatic cancer (LAPC/LRPC) patients received definitive CRT in XXX hospital, to evaluate the effect of the treatment and analyze the prognostic factors for those patients.

Materials And Methods

Patient characteristics

Patients diagnosed with primary unresectable LAPC or LRPC after radical resection in our hospital from June, 2004 to February, 2018 were retrospectively reviewed. All of them received definitive CRT with or without neoadjuvant chemotherapy. Unresectable cancer was defined as superior mesenteric artery or celiac axis encasement> 180 degrees, unreconstructible superior mesenteric vein (SMV) / portal occlusion, or aortic invasion. Exclusion criteria included: (1) distant metastasis before radiotherapy, (2) patients received tumor resection after CRT, (3) LRPC patients with adjuvant RT after tumor resection before local recurrence, (4) missing data of clinical treatment. Detail of patients enrollment is shown in Fig. 1.

Totally, 65 patients are included into our study, with 47 unresectable LAPC patients and 18 unresectable LRPC patients. Among the 47 patients, primary tumor lay in pancreatic head, neck or uncinate process, and body or tail in 22, 7 and 18 patients, respectively. Among the 18 unresectable LRPC patients, tumor recurred in situ, at regional lymph nodes, and at both sites in 8, 6 and 4 patients, respectively.

The median age for all patients were 58 years (range 33-82 years). Male and female patients accounted for 60% and 40%, respectively. Other clinical characteristics are shown in Table 1.

All the radiologic image data were re-evaluated by a senior radiologist to assess the possibility of radical resection according to the guidelines from National Comprehensive Cancer Network[2] and tumor response according to the RECIST criteria V1.1.[3]

Radiation treatment

To fully appreciate the location of the gross tumor volume (GTV), the tumor is evaluated on all triphasic diagnostic scans (CT/MR) as well as on CT simulation images, to create an GTV. In recent years, an internal GTV (GTVin) is also defined by omitting the tumor part invading or locating approximate to the gastrointestinal tract, as shown in Fig. 2, for dose escalation, to treat GTVin volume to a higher dose level respecting the gastrointestinal tract tolerance. The clinical target volume (CTV) comprises a 5-10mm expansion from the GTVin all directions and may need to be further expanded to include areas at risk of microscopic extension, as well as nodal elective irradiation around the celiac axis, superior mesenteric artery (SMA), and SMV (generally starting at the origin of the arteries and including the vessels at the same axial slice levels as the GTV). The CTV can extend into bowel structures, ensuring coverage of microscopic risk of disease in the adjacent duodenum and nodal basins. Planning treatment volume (PTV) was generated by adding a 5-mm margin in all directions to the CTV in consideration of respiratory management.

There were 5 radiation techniques, including CT-SIM, 3D-CRT, IMRT, VMAT and SBRT. 17 patients accepted CT-SIM/3D-CRT radiation, 42 patients were treated with IMRT/VMAT and SBRT was applied to 6 patients. Radiotherapy delivered doses from 33 to 61.6 Gy, in 5-30 fractions. The majority of dose fraction was mainly conventional fraction (1.8-2.9 Gy) and a small part of patients received high-dose fraction (3.8-9

Gy) radiation. In addition, 23 person (35.4%) accepted contaminant boost radiation for GTVin. The average dose boost is totally 6 Gy (4-8 Gy). Biological effective dose (BED) equals to nd×[1+d/(α/β)]. (n refers to fraction times, d refers to fraction dose, and nd refers to total dose. The α/β was assigned as 10.) BED_{10} of the whole cohort ranged from 46.7 to 85.5 Gy. (Fig. 4)

Chemotherapy

46 patients accepted neoadjuvant chemotherapy before irradiation: 7 (10.8%) with single-agent gemcitabine or tegafur (S1), 30 (46.2%) with GS-based agents, 9 (13.8%) with FOLFIRINOX. 37 patients received concurrent chemotherapy, mainly using S1. 34 patients received adjuvant chemotherapy, including Gemcitabine, S-1, mFOLFOX or FOLFIRINOX.

Follow-up

The follow-up was performed regularly after treatments. Physical examination, serum CA199 detection and imaging examination (abdomen CT or magnetic resonance imaging) were implemented at follow-up. Afterwards the patients were followed by an outpatient interview or household registration system. The last follow-up was completed on 1 April, 2020.

Statistical analysis

Overall survival (OS) was defined as the time from the start of CRT to death or the last follow-up. All statistical analyses were conducted using the R statistical package (R software version 4-0.0; R foundation for statistical computing. Vienna, Austria). The Kaplan-Meier method was used to analyze OS. Differences between two groups were tested using Log-rank. Variables with $P< 0.22$ in the univariate analysis were subjected to the multivariate model. Cox proportion hazards model was performed to analyze variables. A two-sided P-value < 0.05 was considered statistically significant.

Results

Short-term outcome

According to the RECIST criteria, 10, 28 and 5 patients had partial response (PR), stable disease (SD) and progressive disease (PD), respectively. The length of 18 patients' lesions contracted less than 30% and 3 patients’ tumor increased less than 20% among SD patients. For all evaluated patients, the total rate of disease control was 88.4%.

Pain, jaundice, and diarrhea was alleviated in 72.7% (32/44), 88.2% (15/17), 66.7% (2/3) patients. According to the symptom and sign relief, we divided 65 patients into two groups, with 49 responded patients (Yes) and 16 non-responded patients (No).

Survival analysis

Until the last follow-up, death was recorded in 52 (80.0%) patients. The median overall survival (mOS) of the whole cohort was 23.6 months. OS rate at 1, 2, and 3 year was 78.0%, 46.2% and 27.3% respectively (Fig. 3a).

In univariant survival analysis, as shown in Table 2, symptom relief (Yes vs. No), tumor status (LAPC vs. LRPC), CA199 (≤ 115 U/mL vs. > 115 U/mL) are significant prognostic factors for OS (*P*= 0.004, 0.022, 0.021), as shown in Fig. 3b-d.

Since the year of 2012, most patients accepted radiation therapy with higher BED_{10} (Fig. 4a). As shown in Table 1 and Fig. 4b, 11 and 54 patients received radiation with BED_{10} > 72 Gy vs. ≤ 72 Gy according to ROC curve, and their mOS was 31.8 and 21.9 months (*P*= 0.200). In subgroup analysis, patients with tumor volume exceeding 109.2 cm^3, dose escalation to GTVin can significantly increase OS rate as shown in Fig. 4c (*P*= 0.004), while dose escalation to GTVin had no significant impact on the OS of the patients with tumor volume less than 109.2 cm^3 (*P*= 0.510).

When treatment response was included in the multivariate analysis, it was the most significant prognostic factor for OS as shown in Table 2 (Multivariate analysis 1). When only the pretreatment clinical factors and treatment related factors were included in the multivariate analysis, age and tumor status were the significant prognostic factors for OS as shown in Table 2 (Multivariate analysis 2), favoring younger patients and LRPC.

Comparison of toxicities

In the whole cohort, 15 and 4 patients had grade 1-2 and grade 3 digestive adverse events, respectively. Grade 1-2 and 3-4 hematological adverse events were observed in 20 and 16 patients; 8 patients had grade 1-2 hepatotoxicity while 1 patients had grade 4. The toxicities between two group (BED_{10} > 72 Gy vs. ≤ 72 Gy) had no difference (*P*= 0.509).

Discussion

As a gordian knot, pancreatic cancer is the fourth leading cause of cancer-related death throughout the world. [4] More than 80% of pancreatic cancer patients lost surgical resection probability, at initial diagnosis due to difficulty in early diagnosis. The 5-year OS rate was less than 5%.[5] CRT is an optional scheme for locally advanced and recurrent pancreatic cancer patients.[6]

Here we analyzed 65 patients with locally advanced or recurrent pancreatic cancer after CRT. In our study, we purposefully delineate a GTVin for dose escalation, other than using dose constraints to give higher dose to area away from normal tissues as suggested by ASTRO 2019 guideline. Our method also achieved satisfactory results. Purposefully delineating a GTVin may help radiation oncologists to avoid the temptation to “under-contour” the GTV which lends itself to poor plan evaluation and coverage. Our results suggested dose escalation for tumor on the premise of normal tissue dose tolerance may bring

more survival benefit for patients with large tumor volumes, especially when tumor is quite near to small intestine.

Nicholas G. Zaorsky et al. meta analysis show that BED_{10}= 70 Gy was not significantly associated with one-year local control rate, but the criteria of studies in this meta analysis were not consistent.[7] Data regarding the benefits of dose-escalation in pancreatic ductal adenocarcinoma are emerging.[8] Soumon Rudra et al. analyzed 44 unresectable local advanced pancreatic cancer patients with comprehensive treatment combined radiation and chemotherapy.[9] In their research, hypofractionated IMRT and SBRT were used to elevate radiation dose. They contrasted patients' clinical outcomes in terms of $BED_{10} \geq$ 70 Gy and< 70 Gy. It appeared higher dose group had a better 2-year OS (49% vs 30%, *P*= 0.03) and a better trend of 2-year free from local failure rate (77% vs 57%, *P*= 0.15). Grade 3 and over toxicities did not appeared in higher dose group. Although evidence level is low, ASTRO guideline suggest dose escalation for LAPC with high consensus in panel (85%).[10] Technical innovations and the relatively low toxicity observed thus far with SMART, has led to new initiatives to attempt local dose-escalation for LAPC. Advanced techniques and higher radiation doses are currently being evaluated in a prospective clinical trials (Clinical Trials.gov: NCT03621644, CT003340974).[11]

Our analysis showed LRPC without distant metastasis after radical resection had longer mOS than those with primary unresectable LAPC, which may be due to the smaller tumor volume in the LRPC group and CRT could yield better tumor control. Local recurrence without distant metastasis may be a manifestation of good tumor biological behavior. At present, there is a lack of research on the difference between LRPC and LAPC, which warrant further exploration to explain this phenomenon.

Univariate and multivariate analysis showed that the short-term symptom relief was a significant prognostic factor for OS, including relief of jaundice, pain, diarrhea and/or other symptoms. Pancreatic cancer is generally considered to be radiation resistant and those patients without response to CRT had poor survival results. Prediction of tumor response to standard treatment strategy is of vital importance. Vipin Dalal et al reviewed studies using radiomics to predict the short-term efficacy, local control, DFS and OS of pancreatic cancer patients with different stages to antitumor therapy.[12] Allen Li's team used daily CT image extraction parameters to predict tumor withdrawal after CRT,[13] which we can consider to apply in further study, to stratify patients before treatment and try to optimize treatment in clinical studies.

CA199 as that significant biomarker to diagnosis of pancreatic cancer, has a high specificity and sensitivity even up to 80%.[14]The level of serum CA199 is negatively correlated with patients' better prognosis. Our study indicated patients with CA199 > 115 U/mL before radiation therapy had a relative shorter survival time, which had a consensus of previous studies. However, we failed to prove CA199 as a negative prognostic factor probably due to the long span of these patients. And it was one of our study's limitation. Also, radiation techniques were various, resulting the discrepancy in tumor dose when it comes to tumor with the same size. Limited patients may cause biases when analyzing. We do hope larger and

more powerful prospective study and randomized controlled trials will be developed in the future to strengthen what we found in this study.

Conclusion

In conclusion, LAPC/LRPC patients with larger tumor volume may get survival benefit from CRT with simultaneous integrated boost of radiation dose, with acceptable toxicities. Short term treatment response, especially symptom relief is the most significant prognostic factor for LAPC/LRPC patients after comprehensive CRT, thus prediction of treatment response before start of treatment is in urgent need.

Abbreviations

LAPC/LRPC: local advanced and recurrent pancreatic cancer

CRT: chemoradiotherapy

OS: overall survival

BED: biological effective dose

GTV: gross tumor volume

SMV: superior mesenteric vein

SMA: superior mesenteric artery

GTVin: internal GTV

PR: partial response

SD: stable disease

PD: progressive disease

BMI: body mass index

PNI: prognostic nutritional index

Declarations

Ethical Approval and Consent to participate

This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All procedures performed in the present study involving human participants were in accordance with the

ethical standards of institutional and/or national research committees and the 1964 Helsinki Declaration and its later amendments or similar ethical standards. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of supporting data

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are no competing interests.

Funding

Not applicable

Authors' contributions

JT , SJX and LS contributed to this work equally. WWX and ZYJ are responsible for conceptualization, design and quality control of this study. JT, LS and WWX performed the study selection, data curation, statistical analyses, and writing the manuscript. SJX and WWX re-evaluated all images. LQ supervised statistical analyzing of this study. WWX and ZYJ reviewed and edited the manuscript respectively. All authors reviewed the manuscript and approved the final version.

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Tables

Table 1. Clinical characteristics of 65 patients

Characteristic	Total number	Percentage (%)	mOS(months)
Total number	n=65	100	23.6
Age (years)			
≤ 61	40	61.5	25.4
> 61	25	38.5	19.0
Gender			
male	39	60.0	23.2
female	26	40.0	23.9
Diabetes			
Yes	12	18.5	24.1
No	53	81.5	23.6
HBP			
Yes	17	26.2	16.2
No	48	73.8	24.4
BMI			
< 31	16	24.6	24.5
≥ 31	49	75.4	23.2
PNI			
< 41	11	16.9	29.1
≥ 41	54	83.1	23.4
CA199 (U/mL)			
< 115	20	30.8	32.8
≥ 115	45	69.2	18
Tumor status			
LAPC	47	72.3	17.2
LRPC	18	27.7	40.7
Con-chemotherapy			
Yes	37	56.9	27.5
No	28	43.1	16.9

Radiation tech			
3D-CRT/CT-sim	17	26.2	20.2
VMAT/IMRT	42	64.6	23.9
SBRT	6	9.2	20.8
BED_{10} (Gy)			
≤ 72	54	83.1	21.9
> 72	11	16.9	31.8
GTV volume (cm^3)			
< 109.2	55	84.6	24.0
≥ 109.2	10	15.4	17.3
GTVin dose escalation			
Yes	23	35.4	25.1
No	42	64.6	20.0
Symptom relief			
Yes	49	75.4	25.7
No	16	24.6	13.2

Table 1. Clinical characteristics of 65 patients. mOS: median overall survival; HBP: high blood pressure; BMI: body mass index; PNI: prognostic nutritional index, PNI values were calculated with the formula' albumin (g/L) + (0.005 × total lymphocyte count)';[15] CA199: carbohydrate antigen 199; Con-chemotherapy: concurrent chemotherapy; Radiation tech: radiation technology; BED_{10} equals to $nd\times[1+d/(\alpha/\beta)]$. (n refers to fraction times, d refers to fraction dose, and nd refers to total dose. The α/β was assigned as 10; GTVin: internal GTV.

Table 2. Summary of univariate and multivariate analysis of 65 patients

	Univariate analysis HR(95% CI)	*P*	Multivariate analysis 1 HR(95% CI)	*P*	Multivariate analysis 2 HR(95% CI)	*P*
Age (> 61y vs. ≤ 61y)	1.60(0.93-2.90)	0.09	1.82(0.31-1.93)	0.05	2.04(0.31-2.29)	0.02*
Gender (female vs. male)	0.98(0.55-1.70)	0.95				
Diabetes (Yes vs. No)	1.00(0.53-2.10)	0.89				
HBP (Yes vs. No)	1.50(0.79-2.80)	0.22				
BMI (> 31 vs. ≤ 31)	1.40(0.72-2.90)	0.30				
PNI (< 41 vs. ≥ 41)	1.40(0.66-3.00)	0.38				
CA199 (≥ 115 U/mL vs. < 115 U/mL)	2.30(1.20-4.40)	0.01*	1.90(0.35-1.84)	0.07	1.98(0.35-2.00)	0.05
Tumor status (LRPC vs. LAPC)	0.48(0.25-0.91)	0.02*	0.54(0.36-1.73)	0.08	0.49(0.35-2.06)	0.04*
Con-chemotherapy (Yes vs. No)	0.58(0.34-1.00)	0.05	0.71(0.29-1.16)	0.25	0.62(0.28-1.68)	0.09
Radiation tech (3D-CRT/CT-sim vs.VMAT/IMRT vs SBRT)	0.87(0.53-1.40)	0.59				
BED_{10} (> 72 Gy vs ≤ 72 Gy)	0.58(0.25-1.40)	0.20	0.39(0.47-2.00)	0.05	0.46(0.47-1.67)	0.10
GTV volume (≥ 109.2 cm^3 vs < 109.2 cm^3)	1.80(0.92-3.70)	0.08	1.53(0.37-1.14)	0.25	1.58(0.37-1.25)	0.21
GTVin dose	0.71(0.40-	0.25				

escalation (Yes vs No)	1.30)			
Symptom relief (Yes vs No)	0.42(0.23-0.78)	<0.01*	0.44(0.35-2.36)	0.02*

Table 2. Summary of univariate and multivariate analysis of 65 patients. Univariate analysis and two multivariate analysis of 65 PC patients. Multivariate analysis 1 included symptom relief to Cox proportional hazards model. Multivariate analysis 2 only considered pretreatment clinical factors and treatment related factors.

HR: hazard ratio; CI: confidence interval.

P values were calculated by Cox proportional hazards model. *P< 0.05

Figures

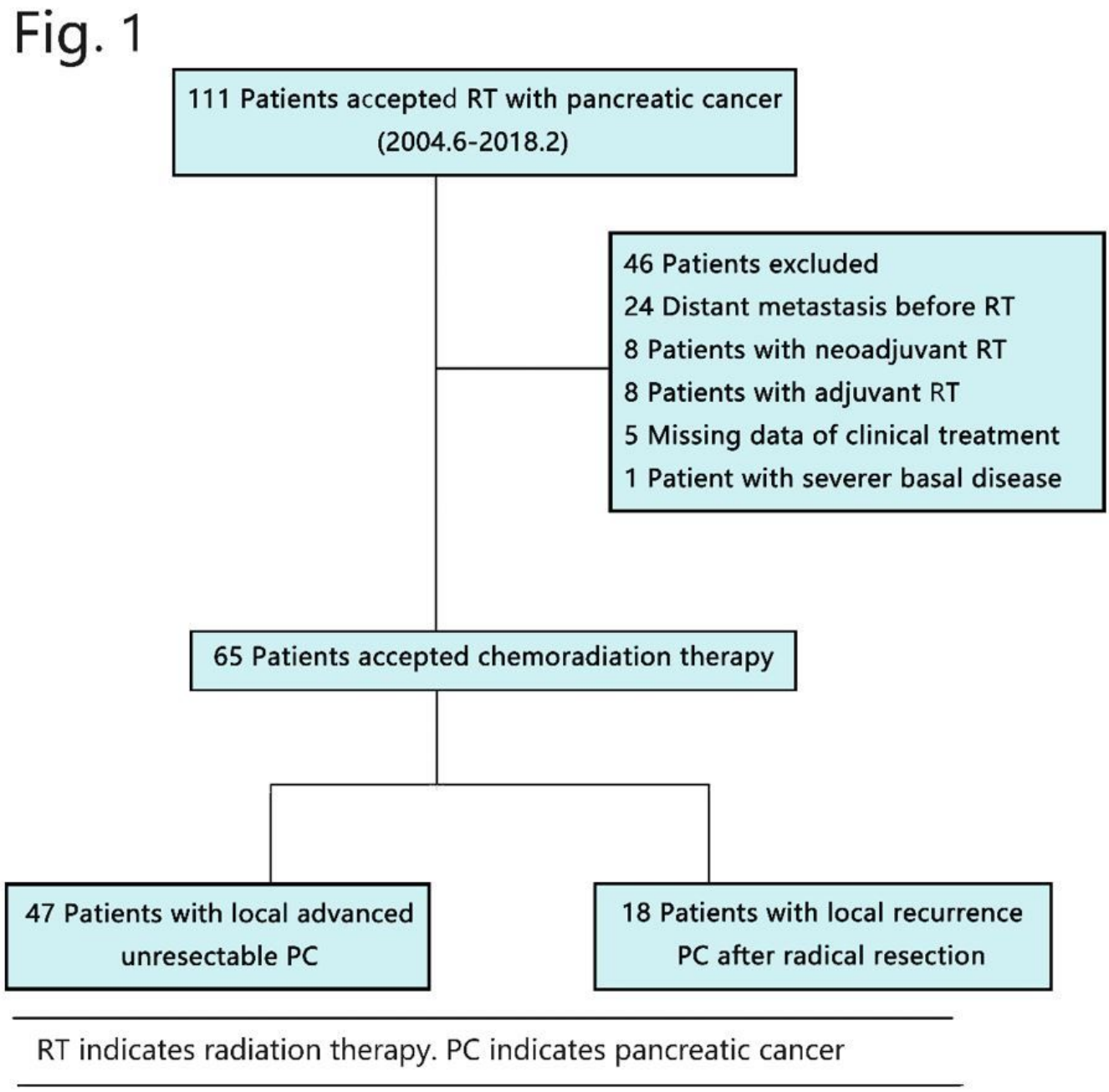

Figure 1

Patient flowchart

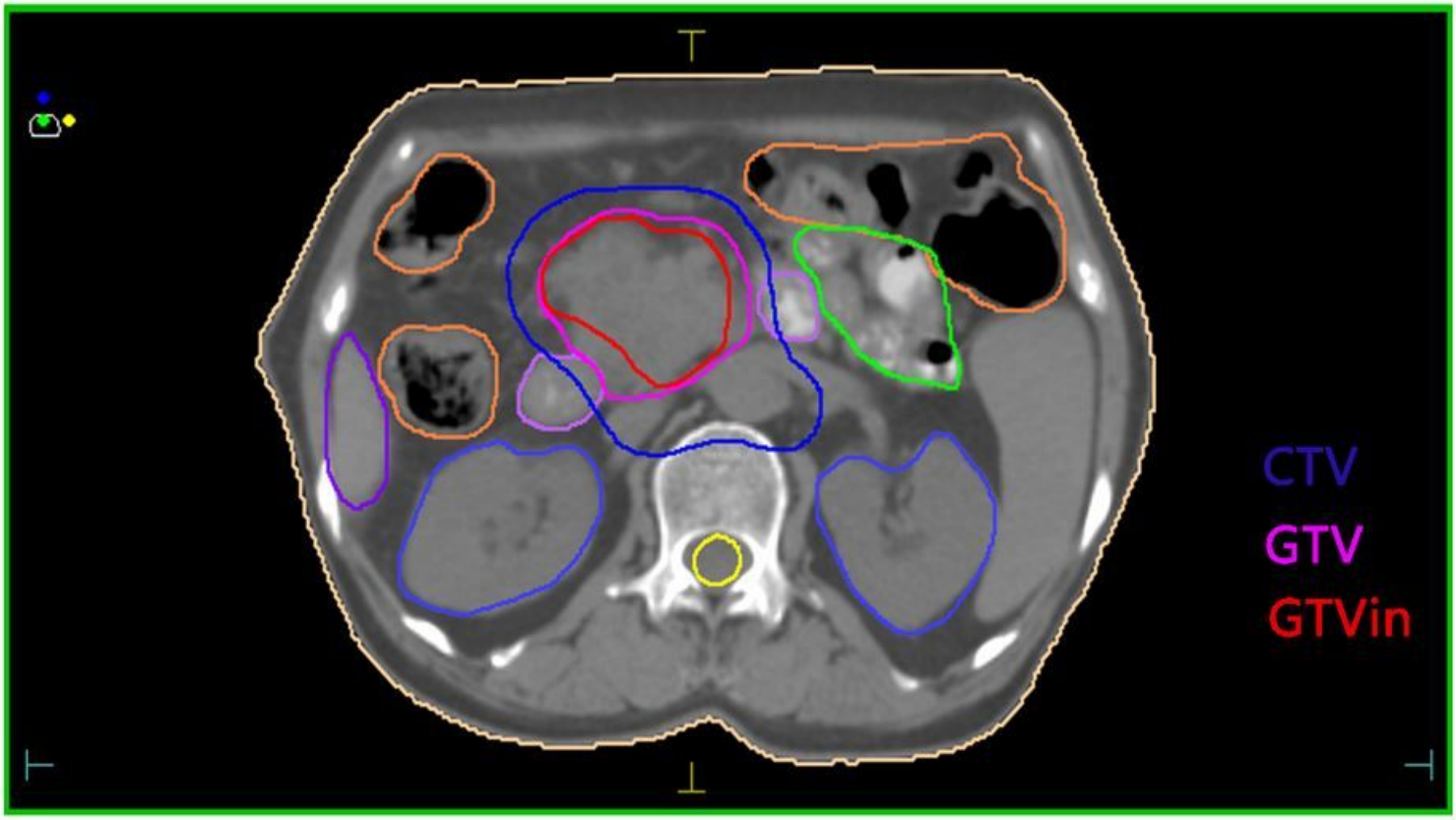

Figure 2

Details of the target delineation of pancreatic cancer in radiation planning. Medium blue, magenta and red lines refer to CTV, GTV and GTVin, respectively.

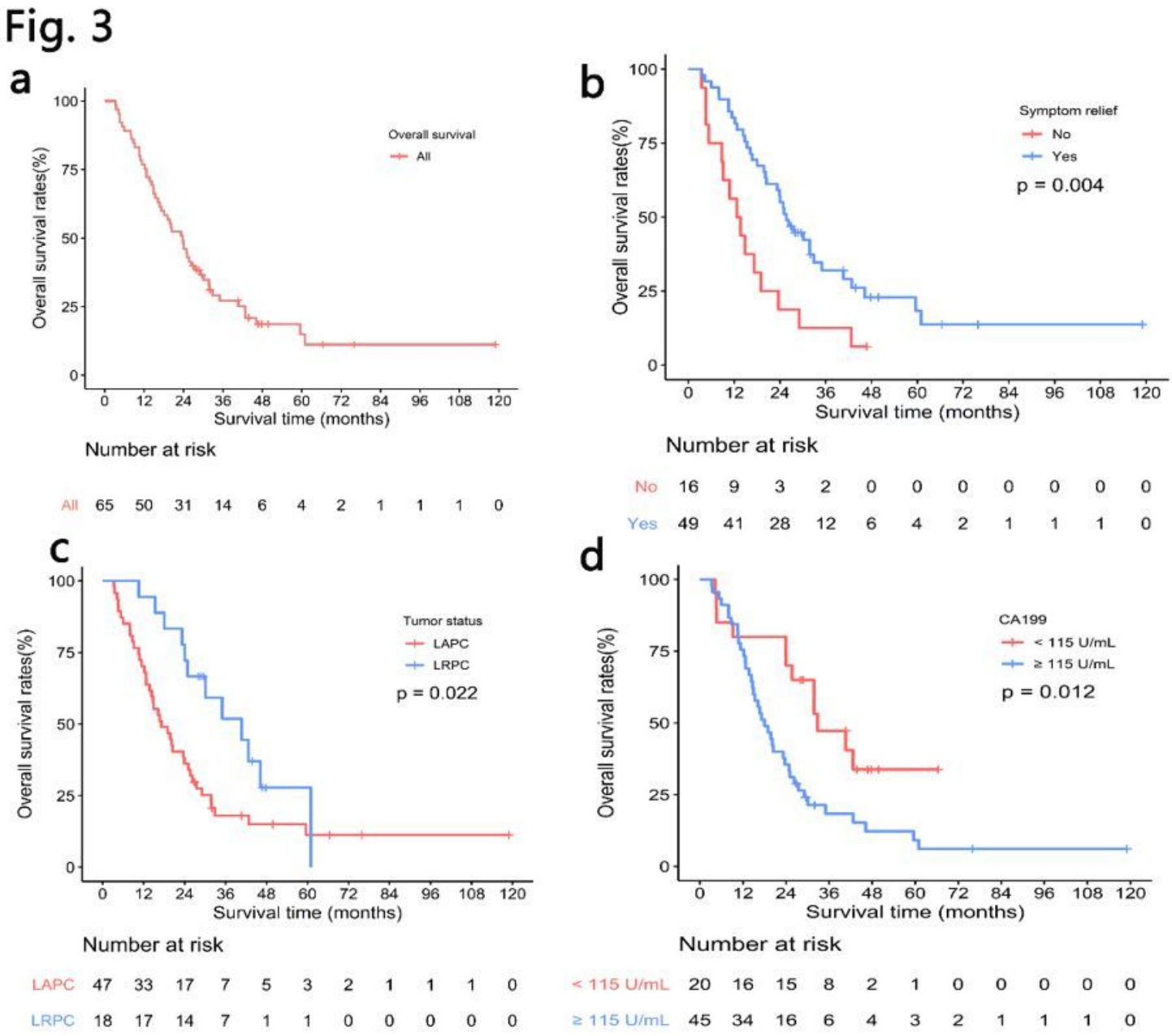

Figure 3

The Kaplan-Meier survival curves. (a). curves of 65 patients overall survival. (b), (c), (d) curves for patients stratified by Symptom relief, primary or not and CA199. P values were calculated using Log-rank test.

Fig. 4

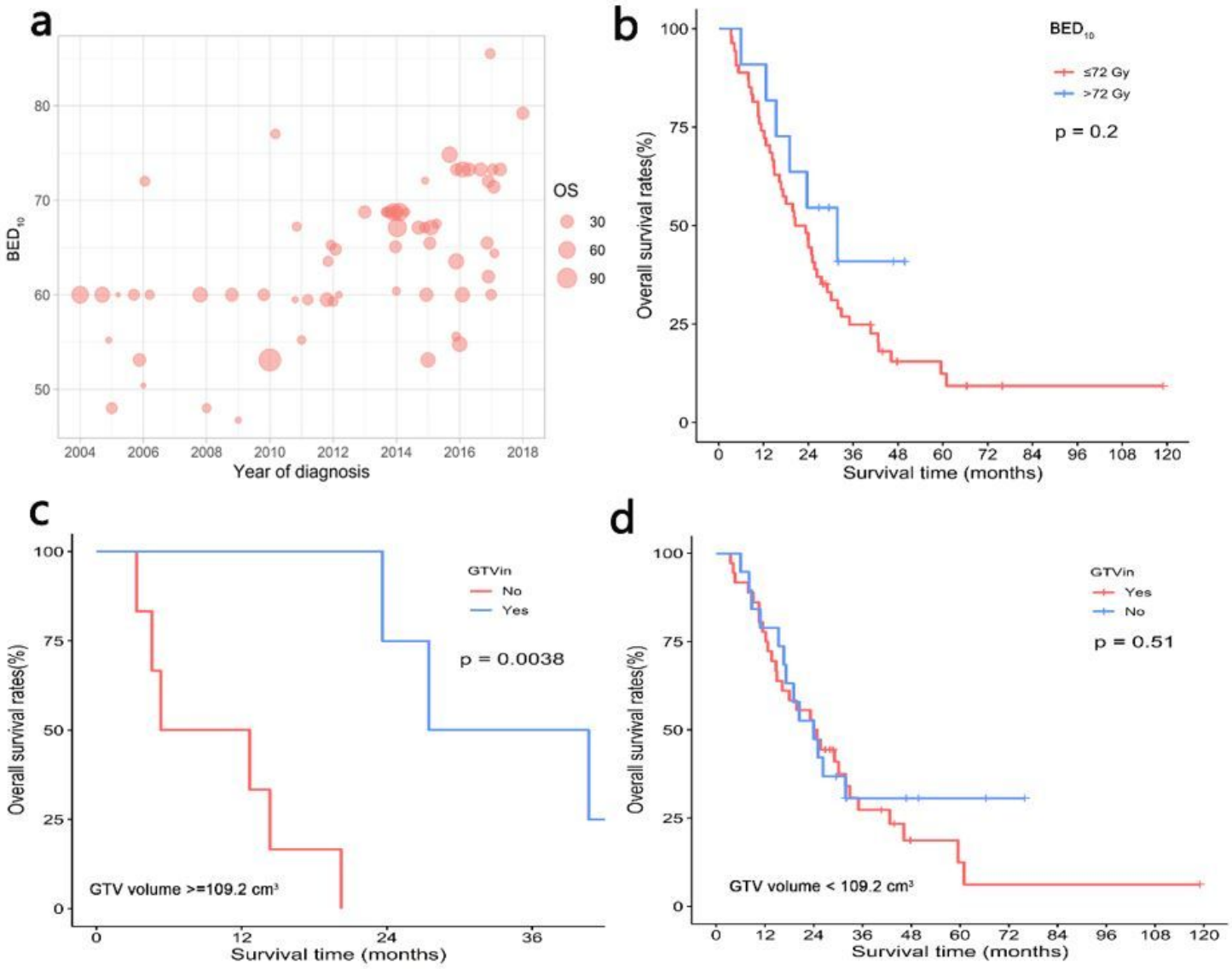

Figure 4

(a). The distribution of BED10. The size of the circle presents individual OS. The picture shows three typical OS with their unique size of circle. (b) Kaplan-Meier survival curves for BED10. (c), (d) curves of overall survival for PC patients with GTV volume≥ 109.2 cm3 and GTV volume< 109.2 cm3 classified into different GTVin groups. OS: overall survival time.