Clinical and Translational Radiation Oncology 21 (2020) 19–24

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

Influence of dose-averaged linear energy transfer on tumour control after carbon-ion radiation therapy for pancreatic cancer ☆

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ARTICLE INFO

Article history:
Received 20 November 2019
Accepted 24 November 2019
Available online 27 November 2019

Keywords:
Pancreatic cancer
Carbon ion radiotherapy
Linear energy transfer

ABSTRACT

Background and purpose: High linear energy transfer (LET) radiation carbon-ion radiotherapy (C-ion RT) is one of the most promising modalities for treating unresectable primary pancreatic cancers. However, how LET contributes to a therapeutic effect is not clear. To assess whether there is an enhanced effect of high LET radiation on tumour control, we aimed to determine the impact of dose-averaged LET on local control (LC) of primary pancreatic tumours.

Materials and methods: A retrospective analysis of 18 patients with primary pancreatic carcinomas treated with definitive C-ion RT with concurrent chemotherapy in 2013 was conducted. The dose of irradiation was 55.2 Gy (RBE). The relationship between dose-averaged LET and LC of primary tumours was evaluated.

Results: All patients had histologically confirmed adenocarcinoma. The median follow-up duration was 22 months. The actuarial LC and overall survival (OS) at 18 months were 62.5% and 70.1%, respectively. There were no cases of grade ≥3 late toxicities observed. Local recurrences developed in four patients (22%), all of which were infield central recurrences. Although there were no significant differences in gross tumour volume (GTV) dose coverage, patients with higher minimum dose-averaged LET (LETmin) values within the GTV had better LC (dose-averaged LETmin ≥44 keV/microm; 18-months LC 100.0% vs 34.3%; p = 0.0366).

Conclusion: Dose-averaged LETmin within the GTV was significantly associated with LC of primary pancreatic cancers. Our data suggest that outcomes for patients with unresectable primary pancreatic cancers receiving C-ion RT can be improved by modulating the dose-averaged LET within the GTV.

1. Introduction

Pancreatic cancer is one of the most lethal cancers and a leading cause of cancer-related deaths, especially in developed countries, with a five-year relative survival rate of only 7% [1]. The only curative treatment for pancreatic cancer is surgical resection; however, because of the lack of early symptoms, only 36% of patients with pancreatic adenocarcinoma are diagnosed at resectable stages of

☆ Linear energy transfer (LET), carbon-ion radiotherapy (C-ion RT), local control (LC), overall survival (OS), gross tumour volume (GTV), locally advanced pancreatic cancer (LAPC), radiation therapy (RT), intensity-modulated RT (IMRT), stereotactic body RT (SBRT), and proton beam therapy (PBT), relative biological effectiveness (RBE), spread out Bragg peak (SOBP), planning target volume (PTV), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (18F-FDG-PET), clinical target volume (CTV), organ at risk (OARs), National Institute of Radiological Sciences' National Institutes for Quantum and Radiological Science and Technology (QST-NIRS), tumour, nodes, and metastases (TNM), hazard ratio (HR).

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https://doi.org/10.1016/j.ctro.2019.11.002

the cancer [2]. Even when surgical resection is performed, the local recurrence rate is 23–32% [3]. Management of locally advanced pancreatic cancer (LAPC) is controversial and has been extensively discussed in the last decade. A major proportion of LAPC patients develop local recurrences as well as distant metastases and the median progression-free survival of chemoradiation is 6.0 months [4]; hence, chemoradiation or chemotherapy alone are both widely-accepted treatments [4–6].

Delivering tumoricidal doses to a radioresistant tumour surrounded by radiosensitive upper-abdominal organs had been a major obstacle to radiation therapy (RT). However, with recent advances in the field of high-precision, radiotherapy techniques, such as intensity-modulated RT (IMRT), stereotactic body RT (SBRT), and proton beam therapy (PBT), can deliver high doses to the tumour while sparing the surrounding tissues [7–9].

Pancreatic cancers are hypoxic and resistant to low linear energy transfer (LET) radiation, such as photon- or proton-based RT [10,11]. Carbon ions, because of their unique physical characteristics and enhanced biological effectiveness, offer a more conformal dose distribution and increased biological effect due to higher LET and higher relative biological effectiveness (RBE) compared with photon- or proton-based RT, which should theoretically overcome radioresistance of hypoxic pancreatic cancers [11,12]; however, the LC rates are not promising. Kawashiro et al. [13] evaluated the efficacy and safety of C-ion RT in LAPC and reported a median overall survival (OS) of 21.5 months with a two-year cumulative local recurrence of 24%.

Carbon ions have an energy-dependent range and only deposit high LET radiation within their narrow Bragg peak; lower LET is deposited in the entrance region. A modulated or spread-out Bragg peak (SOBP) is a weighted function of several Bragg peaks at various energies where higher LET becomes diluted as an increasing number of secondary low LET fragments from inflight nuclear reactions are created along increasing depth. Bassler et al. [14] showed that even equal dose distributions within the target volume can produce very different LET distributions and the high LET region was confined within the edge of the PTV. Thus, the efficacy of C-ion RT can be improved not only with dose escalation in distinct target compartments but also with increased dose-averaged LET and RBE around the central region of the target volume where hypoxia and radioresistance are predominant. The relationship between dose-averaged LET and RBE in vivo is unclear and the relationship is only established in vitro under normoxic conditions, regardless of the oxygen enhancement ratio effect, using cell lines, such as human salivary glands [12].

LET painting attempts to restrict high LET radiation to hypoxic compartments while applying lower LET radiation to normoxic tissues, enabling better tumour control and minimal toxicities [15,16]. Here, we aimed to determine the impact of dose-averaged LET on LC of primary pancreatic tumours because of the unique location and hypoxic environment of pancreatic adenocarcinoma.

2. Materials and methods

A single centre, retrospective analysis of 18 patients with primary pancreatic cancers who were treated with C-ion RT between April and November 2013 at our institute was conducted. Patients provided informed consent authorizing the use of their personal information for research purposes. This study was approved by the appropriate institutional review board and was carried out in accordance with the Declaration of Helsinki. The inclusion criteria were as follows: 1) histologically confirmed pancreatic adenocarcinoma, 2) unresectable or medically inoperable cases, 3) treated with 55.2 Gy (RBE) in 12 fractions in definitive intent, 4) treated with concurrent chemotherapy, 5) non-metastatic disease, and 6) Eastern Cooperative Oncology Group performance status 0–1. Patients who had received RT previously for pancreatic cancer were excluded from this study.

2.1. Study endpoints

The primary endpoint was to determine the impact of dose-averaged LET within GTV on LC of the primary tumour. LC was defined as no evidence of tumour regrowth within the planning target volume (PTV). Local recurrence was defined as infield central if it appeared within the 90% isodose line of the PTV and marginal if it was beyond the 90% isodose line of the PTV. Secondary endpoints were OS as well as acute and late toxicities. Toxicities were defined according to the National Cancer Institute's Common Terminology Criteria for adverse events version 4.0 [17].

2.2. Treatment protocol

As rotating gantry was not available at our institution in 2013, patients were immobilized in both the supine and prone positions in customized cradles (Moldcare, Alcare; Tokyo, Japan) using thermoplastic shells (Shellfitter, Kuraray; Osaka, Japan). A respiratory gating system was used for obtaining planning computed tomography (CT) images and during delivery of C-ion RT. The peak exhalation phase was used for planning CT scans and treatment execution to mitigate movement of the tumour and surrounding organs due to respiration. A set of non-contrast CT images with 2-mm slice thicknesses were obtained for treatment planning. Planning CT images were fused with contrast-enhanced CT, gadolinium-enhanced magnetic resonance imaging (MRI) images, and positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (18F-FDG-PET) images for accurate GTV delineation. Clinical target volume (CTV) encompassed GTV plus 5 mm margins, the neural plexus region, and elective nodal regions around the pancreas, which included the celiac, superior mesenteric, peripancreatic, portal, and para-aortic regions for pancreatic head cancer and the splenic hilar region for pancreatic body and tail cancers. CTV was trimmed from the organ at risk (OARs) in consideration of the natural history and biology of the disease. A 5 mm margin for set-up error was added around the CTV to create the PTV. Patients were treated with 55.2 Gy (RBE) in 12 fractions over three weeks with four fractions per week. The goals for target volume coverage were that 95% of the GTV and 90% of the PTV should be covered by 95% of the prescribed dose.

For dose constraints of OARs, we followed our institutional protocol of D2 cc of $\leq$46 Gy for the tubular gastrointestinal tract, a spinal cord maximum point dose (Dmax) of $\leq$30 Gy (RBE), and less than 30% of the volume of each kidney receiving $\geq$15 Gy (RBE). Three-dimensional treatment planning was performed with Xio-N (ELEKTA, Stockholm, Sweden; Mitsubishi Electric, Tokyo, Japan) planning software. Four beam angles, that is, 0°, 90°, 180°, and 270° were used. The posterior port or 180° beam was delivered to patients in the prone position and all other ports were delivered to patients in the supine position. Treatment planning was performed with biological treatment plan optimization, which took a clinical RBE value of 3 at the distal part of the Bragg Peak into account [13,18].

Twelve patients received concurrent chemotherapy with a dose of gemcitabine 1000 mg/m^2 day 1, 8, 15. Six patients receive 80 mg of S-1(a combination of tegafur, gimeracil, and oteracil) per square meter of body surface area twice a day for 2 weeks, followed by 1 weeks of rest as one course.

2.3. Dose-averaged LET calculation

For carbon ions, the primary charged particles may produce secondary fragments due to nuclear interactions and the contribu-

tions of different ion types need to be added. Importantly, averaging over fluence or dose will lead to different numerical values for the LET at the same position in the SOBP [19]. The biological effect in tumour is the total effect of the different LET components and dose components that building up the radiation field. Dose-averaged LET is a variable which can be included in different LET components and dose components. In this study, dose-averaged LET was obtained using in-house software developed at the National Institute of Radiological Sciences' National Institutes for Quantum and Radiological Science and Technology (QST-NIRS) [20]. A potential semiautomatic method was used to derive dose-averaged LET distributions. Dose-averaged LET is expressed as L_D: $[L_D = \sum_i L_i D_i / \sum_i D_i \approx \sum_i S_i^2 / \sum_i S_i]$, where L_i is the LET from ion track i, D_i is its dose contribution ($\propto L_i$), and S_i is the stopping power of water for the ion. The spatial distribution of LET within the target volume for each C-ion RT plan was analysed.

GTV-targeted, rigid image registration was performed when combining supine and prone images. Each voxel of GTV provided information on quantity of physical doses delivered for each LET value. It was difficult to obtain accurate doses and LET values for the upper gastrointestinal tract, which was strongly influenced by the patients' positions. Although evaluation of dose coverage and dose-averaged LET within GTV were of prime importance in this analysis, we could not nullify the influence of patient position on mild changes in the shape of the GTV.

2.4. Follow-up

Clinical follow-ups were scheduled every three months. Most patients underwent contrast-enhanced CT, 18F-FDG-PET, and/or pancreatic region MRI every three months to assess tumour response. After two years of follow-ups, intervals were prolonged to every six months. Toxicities were also recorded during these follow-ups.

2.5. Statistical analysis

For this pilot study. The follow-up time was calculated from the start date of C-ion RT to the date of the last follow-up. LC, OS, and progression-free survival were calculated using the Kaplan Meier method. Univariate analysis using log-rank test was performed to compare a number of parameters among different subgroups based on patient- and treatment-related factors, such as age, GTV volume, minimum-dose (Dmin) within the GTV, and the minimum-value of dose-averaged LET (dose-averaged LETmin) within the GTV. Multivariate analysis was not performed due to the limited number of patients. P values < 0.05 were considered statistically significant. All statistical analyses were performed using R software, version 3.4.4.

3. Results

3.1. Baseline characteristics

The patients' baseline characteristics are shown in Table 1. The median age of patients was 58 years. The most common primary tumour location was in the pancreatic body. All patients presented with locally-advanced stage T4 cancer. Four patients (22%) had postoperative local recurrences.

3.2. Treatment outcome

The median follow-up period was 22 months (range 4–61). The actuarial LC at 12, 18, and 24 months was 93.8% (95% confidence interval [CI]: 63.2–99.1), 62.5% (95% CI: 27.2–84.4), and 62.5% (95% CI: 27.2–84.4), respectively. OS at 12, 18, and 24 months was 76.5% (95% CI: 48.8–90.4), 70.1% (95% CI: 42.3–86.3), and 50.2% (95% CI: 24.3–71.4), respectively. The disease-free survival at 12, 18, and 24 months was 24.2% (95% CI: 7.6–45.9), 12.1% (95% CI: 2.0–31.9), and 6.1% (95% CI: 0.4–24.1), respectively. LC and OS are shown in Fig. 1. In all, 16 patients developed recurrences. The pattern of recurrence is shown in Table 2. Of the four patients with local recurrences, all had in-field central recurrences. No local recurrence occurred in close margin patients in which CTV was trimmed according to OARs. Median time to local recurrence and distant metastasis was 13 and 8 months, respectively.

Table 1
Baseline Characteristics.

Characteristics		Number (%)
Number of patients		18 (1 0 0)
Sex	male/female	13 (72)/5 (28)
Age (years)	median/range	58/43–71
Performance status	0/1	18 (1 0 0)/0 (0)
Histologic type	Adenocarcinoma	18 (1 0 0)
TNM staging	T4N0M0	18 (1 0 0)
Gross tumour volume (cc)	median/range	28.7/5.9–62.8
Tumour location in pancreas	head/body/tail	4 (22)/13 (72)/1(6)
Carbon-ion radiotherapy		
Fractionation	12 fractions/3 weeks	25 (1 0 0)
Total dose	55.2 Gy (RBE)	25 (1 0 0)
Beam delivery	Passive	25 (1 0 0)
Chemotherapy		
Concurrent chemotherapy	GEM/S-1	12 (67)/6 (33)
Adjuvant chemotherapy	GEM/S-1/GEM + S-1	10 (56)/5 (28)/2 (11)

Abbreviations: TNM = tumour, nodes, and metastases; RBE = Relative Biological Effectiveness; GEM = gemcitabine; S-1 = tegafur, gimeracil, and oteracil potassium.

3.3. Analysis of factors affecting LC

Univariate analysis was used to compare LC and OS among different variables age, post-operative recurrence or not, GTV volume, GTV D98, GTV Dmin, dose-averaged LET98, and dose-averaged LETmin (Table 3). Patients with high dose-averaged LETmin had a better LC (18-months LC 100.0% vs 34.3%; p = 0.0366). There were no significant differences in dose distribution between patients with LC and patients with local failure. GTV dose coverage was similar in patients with LC and local failure and there were no statistically significant differences in GTV D98 and Dmin. Box-and whisker plot of dose-averaged LETmin and Dmin within GTV are shown in Fig. 2. Patients with local failure had significantly lower dose-averaged LETmin within GTV compared with the LC group (median: 40.1 keV/microm vs 45.0 keV/microm, p = 0.006 in *t*-test). A representative case showing dose distribution and dose-averaged LET is shown in Fig. 3.

3.4. Acute and late toxicities

All patients complied with their prescribed treatment. One patient (6%) experienced grade 3 leukopenia related to concurrent chemotherapy with gemcitabine. No other grade $\geq$3 severe late toxicities were observed.

4. Discussion

This is the first clinical study evaluating LET coverage within GTV on LC of unresectable LAPC. We found the dose-averaged LET within GTV was 35–75 keV/microm in all patients. All four local recurrences were found to be central recurrences, despite that in all patients the GTV D98 received was at least 90% of the full prescribed dose of 55.2 Gy RBE in 12 fractions. This prompted us to determine the association between dose-averaged LET distribution

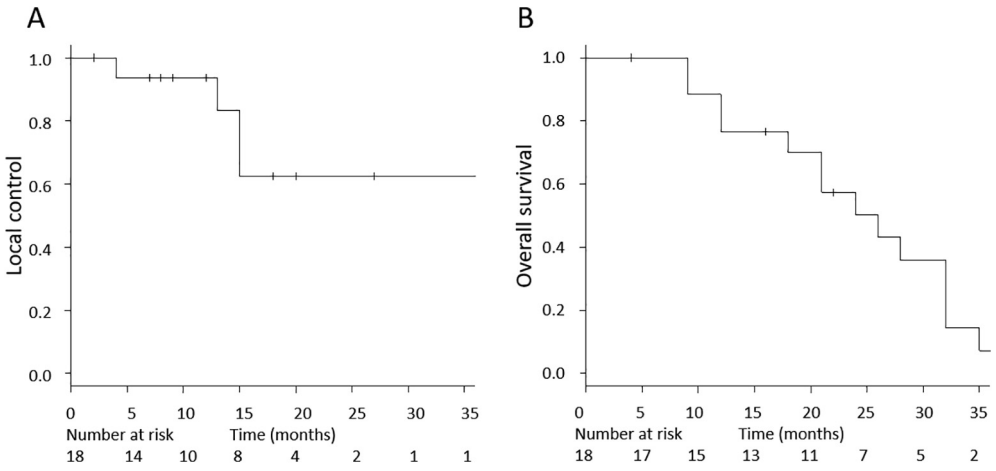

Fig. 1. Kaplan-Meier's curves of local control (A) and overall survival (B) of the entire cohort (number of patients = 18).

Table 2
Pattern of tumour recurrence.

Failure	Number (%) 18 (1 0 0)
Local failure alone	1 (6)
Local failure + Distant metastasis*	3 (17)
Distant metastasis alone	12 (67)

* One was simultaneous, one had local failure 2 months prior, and one had distant metastasis 9 months prior.

within GTV and tumour control/clinical outcome. We found that median values of all dose-averaged LET parameters within GTV were below 50 keV/microm in all patients; this is far from the optimum LET of ≥80–100 keV/microm. This might be one factor contributing to higher local recurrences.

One possible strategy to improve LC is to increase dose to the radioresistant tumour without increasing exposure to other organs, which is difficult due to proximity of the pancreas to surrounding radiosensitive organs. IMRT, SBRT, and proton beams have been explored to accomplish this goal; however, long-term LC rates are not encouraging [7–9]. Compared with IMRT, SBRT, and PBT, C-ion RT provides a more uniform dose distribution to the target due to its unique physical profile with sharp lateral penumbra and better biological effects due to its higher LET. Shinoto et al. [21] showed a trend toward better outcome with C-ion RT dose higher than 45.6 Gy (RBE), the two-year freedom from local progression rate for a 18F-FDG-PET of <45.6 Gy (RBE) was 9%, and of ≥45.6 Gy (RBE) was 40%. They also found that there were no dose limiting toxicities observed at 55.2 Gy (RBE) in 12 fractions over three weeks, along with full dose gemcitabine-based chemotherapy. Kawashiro et al. [13] reported no significant difference in LC between the 52.8 Gy (RBE) and 55.2 Gy (RBE) groups with a one- and two-year cumulative recurrence rate of 16% and 24%, respectively. Currently, it is unclear whether the enhanced biological effectiveness of further increasing the dose or LET will boost efficacy of carbon ions in pancreatic cancer treatment.

In the current study, patients with local failure had significantly lower dose-averaged LETmin within GTV. To eliminate the influence of cold spots within GTV on dose coverage, we evaluated the GTV D98 and Dmin; we did not find any significant association with LC. This finding suggests that the cold LET region within a tumour, in addition to the dose coverage, is strongly associated with local failure. Furthermore, LETmin was found to be an independent prognostic factor related to local failure. Although dose distribution is highly uniform in conventional carbon ion planning, LET distribution is not; the central portion of the target volume is encompassed by lower LET regions. To overcome such problems, we aim to shift to higher LET regions within the central compartment of the target volume and keep the lower LET regions in the periphery to spare critical OARs as much as possible. For QST-NIRS, we are trying to introduce intensity-modulated C-ion RT integrated with LET painting as well as explore the effects of using

Table 3
Univariate analysis of prognostic variables.

Prognostic variables	Category	No. of patients	18-months LC (%)	p-value	18-months OS (%)	p-value
Age (years)	<58	9	40.0	0.326	64.8	0.410
	≥58	9	87.5		75.0	
Post-operative recurrence	No	14	65.5	0.707	60.6	0.931
	Yes	4	50.0		NA	
GTV volume (cc)	<29	8	65.6	0.954	85.7	0.647
	≥29	10	60.0		60.0	
GTV D98 (Gy [RBE])	<54	8	50.0	0.843	75.0	0.775
	≥54	10	64.3		64.8	
GTV Dmin (Gy [RBE])	<46	9	66.7	0.761	66.7	0.479
	≥46	9	59.3		72.9	
Dose-averaged LET98 (keV/microm)	<45	8	43.8	0.0903	68.6	0.651
	≥45	10	100.0		70.0	
Dose-averaged LETmin (keV/microm)	<44	7	34.3	0.0366	62.5	0.614
	≥44	11	100.0		72.7	

Abbreviations: GTV, Gross tumour volume; RBE, Relative Biological Effectiveness; Dmin, minimum-dose; D98, the dose covering 98% volume; LETmin, minimum-value of LET; LET98, LET value covering 98% volume.

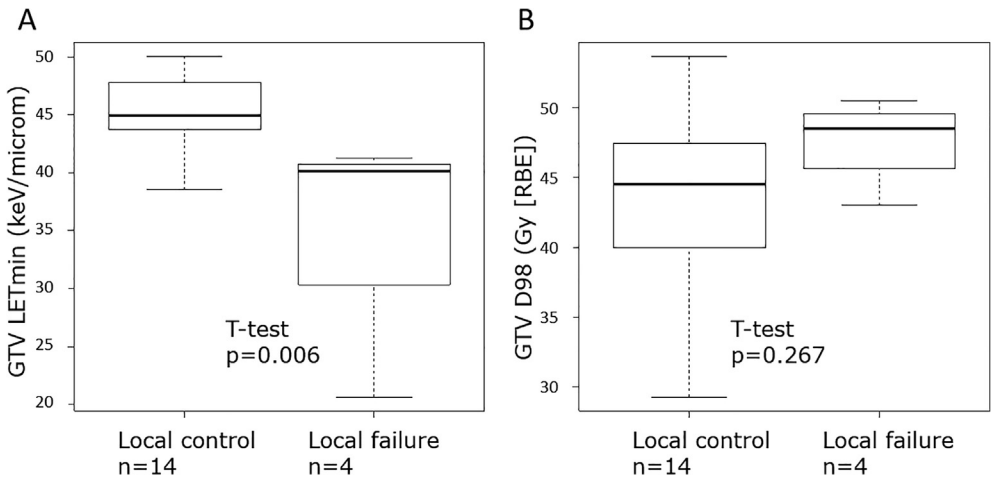

Fig. 2. Box-and-whisker plot showing comparison of dose-averaged minimum-value of linear energy transfer (LETmin) (A) and minimum-dose (Dmin) (B) within the gross tumour volume (GTV) of patients with local control or local failure. RBE, relative biological effectiveness.

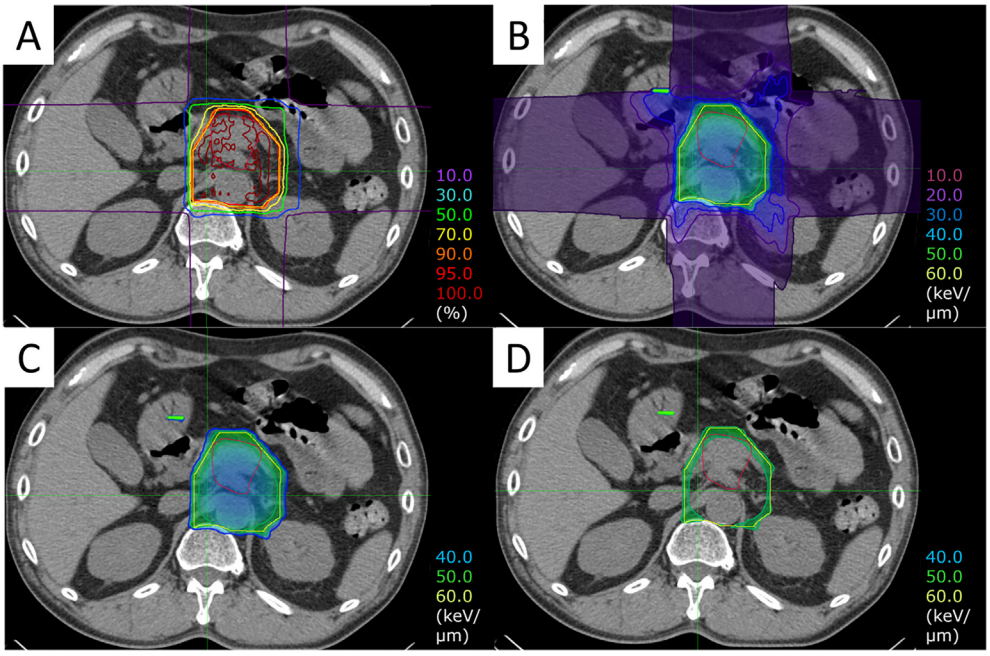

Fig. 3. A representative case of cT4N0M0 pancreatic body cancer with tumour invading the superior mesenteric artery (SMA). A total dose of 55.2 Gy (RBE) was delivered in 12 fractions over three weeks. As bridging, concurrent, and adjuvant chemotherapy, gemcitabine (1000 mg/m^2) was administered every week for three consecutive weeks with a one-week rest period. There was no evidence of local recurrence after 27 months of carbon-ion radiotherapy before the patient died due to pancreatic cancer. The patient developed liver metastasis 12 months after carbon-ion radiotherapy. There were no grade ≥3 severe acute and late toxicities. (A) Dose distribution of carbon-ion radiotherapy. (B) Dose-averaged LET distribution of carbon-ion radiotherapy. (C) Dose-averaged LET distribution of ≥40 keV/microm. (D) Dose-averaged LET distribution of ≥50 keV/microm. Gross tumour volume (GTV) was 31.6 cc. The mean dose within GTV was 55.3 Gy (RBE) (range: 47.4–56.3). The mean dose-averaged LET within GTV was 46.0 keV/microm (range: 41.8–56.0).

multiple ions in the clinical setting. Multi-ion composite particle delivery is an ongoing research project at QST-NIRS. A possible future strategy will involve LET painting with intensity-modulated composite particle therapy using multi-ions beams where high LET radiation will be delivered to the central compartment with lower LET in the subclinical, microscopic disease. This strategy would optimize dose and LET distribution, which would maximize the potential of C-ion RT.

In this study, 15 of 18 patients ultimately developed distant metastasis even though most received systemic concurrent and adjuvant chemotherapies. This implies systemic treatment options could also be improved and that combining robust, systemic treatment with immune checkpoint inhibitors and intensity-modulated composite particle therapy with optimal dose and LET could be the most promising therapy to achieve optimal clinical outcome in unresectable LAPC.

This study has several limitations. It is a retrospective analysis with a small sample size. The two subsets of patients were not well-balanced because of the study's retrospective nature. Fusion uncertainties existed between images acquired in supine and prone positions. Additionally, virtual composite dose distribution was not accurate due to lack of a well-developed, deformable image registration strategy.

5. Conclusion

Dose-averaged LETmin within GTV had a significant association with LC of primary pancreatic cancers. Thus, LC could be improved

with the delivery of optimal dose-averaged LET through C-ion RT in unresectable LAPC. Our results suggest that C-ion RT could be improved by utilizing intensity-modulated, multi-ion particle therapy with optimal dose and dose-averaged LET within the target volume.

Funding

This study was supported by the Research Project with Heavy Ions at the National Institute of Radiological Sciences-Heavy Ion Medical Accelerator in Chiba. The funders had no role in the current study other than providing financial support.

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.

Acknowledgement

We would like to thank Editage for English language editing.

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