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Original article

Dosimetric analysis of upper gastrointestinal ulcer after carbon-ion radiotherapy for pancreatic cancer

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ABSTRACT

Purpose: The aim of this study was to clarify the incidence, clinical risk factors, and dose–volume relationship of upper gastrointestinal (GI) ulcer after carbon-ion radiotherapy (C-ion RT) for pancreatic cancer.

Materials and methods: Fifty-eight pancreatic cancer patients were treated with C-ion RT from April 2014 to December 2015. The total dose was 55.2 Gy (RBE) in 12 fractions. D_{2cm3} of GI tracts were restricted under 46 Gy (RBE); RBE-weighted absorbed dose. The association between dosimetric parameters ($V_{10–50}$, D_{max}, D_{1cm3}, D_{2cm3}) and GI ulcer was examined using Spearman's correlation. The incidence of GI ulcer was compared between the two groups divided by the cutoff value.

Results: Twelve patients (21%) experienced gastric ulcer including only one (2%) grade 3 ulcer. There was no grade 4/5 toxicity or duodenal ulcer. $V_{10–30}$ was significantly associated with gastric ulcer. The 1-year estimated risk of gastric ulcer for the determined cutoff values were 51% vs. 10% (V_{10}, $\geqslant$102 cm^3 or less), 42% vs. 9% (V_{20}, $\geqslant$24 cm^3 or less), 34% vs. 4% (V_{30}, $\geqslant$6 cm^3 or less).

Conclusions: The incidence of GI ulcer after C-ion RT was very low with the dose constraint of D_{2cm3} <46 Gy (RBE). To further minimize the risk of GI ulcer, $V_{10–30}$ should also be reduced.

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The role of radiotherapy for pancreatic cancer is controversial. Two recent randomized studies to evaluate the role of chemoradiotherapy (CRT) compared with chemotherapy alone in locally advanced pancreatic cancer showed conflicting results [1,2]. Preliminary data from the LAP 07 trial revealed no clear benefit from consolidative CRT following chemotherapy [3]. This is partly because pancreatic cancer is radioresistant; meanwhile, the sensitivity of the organs in the upper abdomen has limited radiation doses to levels that are ineffective against pancreatic cancer [4].

A dose escalation trial of carbon-ion radiotherapy (C-ion RT) with concurrent gemcitabine for locally advanced pancreatic cancer was previously conducted in National Institute of Radiological Sciences in Japan and achieved improved survival, with a median survival time of 23.9 months and a 2-year survival rate of 48% [5]. Carbon-ion beams offer improved dose distribution and provide greater biological effectiveness than photons or protons [6,7]. C-ion RT can administer a high-intensity dose to the target, which exceeds the tolerance dose of normal tissue, especially the gastrointestinal (GI) tract. In a previous C-ion RT dose escalation trial, the incidence of GI toxicity was very low, so the maximum tolerated dose could not be identified [5]. Only one patient (1%) experienced late grade 3 gastric ulcer, and about half of the patients who were prescribed 55.2 Gy (RBE), which is the relative biologic effectiveness (RBE)-weighted absorbed dose defined in ICRU report 78 [8], experienced acute grade 1 or 2 GI ulcers. Based on these data, the maximal absolute dose that covered 2 cm^3 (D_{2cm3}) of the GI tract was indicated to be restricted under 46 Gy (RBE). The identification of reliable predictors for GI ulcer will be important for future dose escalation studies. However, no prior study to our knowledge has investigated the dose–toxicity relationship for the treatment of pancreatic cancer with C-ion RT.

Our aim in this study was to verify the assurance of the dose constraint of D_{2cm3} <46 Gy (RBE), and to explore the predictive factors of risk for upper GI ulcer from the dose–volume histogram (DVH) of the organs at risk in pancreatic cancer patients treated with C-ion RT.

Materials and methods

Patients and treatment

We retrospectively analyzed 58 consecutive pancreatic cancer patients who were treated with curative intent by C-ion RT at

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our institution from April 2014 to December 2015. Fifty-three patients were treated with concurrent chemotherapy, namely gemcitabine or S-1 based chemotherapy. Forty-five patients underwent chemotherapy before the initiation of C-ion RT. Most patients were recommended to undergo adjuvant chemotherapy. In all patients, gastroduodenal-protective drugs were administered prophylactically at the beginning of C-ion RT.

Carbon-ion radiotherapy

The details of the C-ion RT technique were approximately same as those reported previously [5]. In our institution, a set of 2-mm-thick non-contrast-enhanced computed tomography (CT) images was taken under respiratory gating for treatment planning purposes. Three-dimensional treatment planning of C-ion RT was performed using the XiO-N (ELEKTA, Stockholm, Kingdom of Sweden and Mitsubishi Electric, Tokyo, Japan) software program.

The gross tumor volume (GTV) was determined mainly by contrast-enhanced dynamic CT. Magnetic resonance imaging or 18 fluoro-2-deoxyglucose positron emission tomography was also taken into account. The clinical target volume (CTV) was defined as a GTV with a 5-mm margin and a locoregional elective nodal and neuroplexus region. The locoregional elective nodal regions, which are classified as N2 stations according to the General Rules for Cancer of the Pancreas published by the Japan Pancreas Society [9], included the celiac, superior mesenteric, peri-pancreatic, portal, and para-aortic region for pancreatic head cancer and the splenic region for pancreatic body and tail cancer. The planning target volume (PTV) was defined as the clinical target volume with a 5-mm margin for possible positioning errors, respecting anatomical boundaries such as the stomach, duodenum, and small intestine. In cases in which the tumor was located close to critical organs, the margin was reduced accordingly.

The planned total dose was 55.2 Gy (RBE) in 12 fractions. The RBE value was estimated to be 3.0 at the distal part of the spread-out Bragg peak and the biological model was reported in reference [6]. The D_{2cm3} of the GI tracts was restricted to under 46 Gy (RBE). At least 90% of the PTV received at least 95% of the prescribed dose. The beam arrangements were a four-field plan.

Dosimetric analysis and evaluation of upper gastrointestinal ulcer

The external surfaces of the critical organs including stomach, duodenum and small intestine were contoured on each axial slice of the planning CT images. A dose–volume histogram (DVH) was calculated using a 3-dimensional planning computer (XiO-N). The following dosimetric parameters were generated from the DVH: the maximal absolute dose, covering 1 cm^3 of the organ (D_{1cm3}), D_{2cm3}, and the absolute volume of the organ receiving more than a threshold dose, with a dose of 10–50 Gy (RBE) in increments of 10 Gy (RBE) (V_{10}–V_{50}). Additionally, the absolute PTV was also acquired.

GI ulcer was evaluated according to the Common Terminology Criteria of Adverse Events, version 4.0. Acute toxicity was defined as toxicity that occurred within 3 months from the start of C-ion RT. Late toxicity was defined as toxicity that occurred after 3 months. In all patients, upper GI endoscopy was performed before and 1 month after C-ion RT. Subsequent endoscopic explorations were performed at the time of any sign of upper GI pain or discomfort or anemia, or bloody stool, or at least every six months when there were no signs or symptoms.

Statistical analysis

The study analyzed clinical and dosimetric parameters affecting the development of GI ulcer. Gender, age, chemotherapy, tumor size, tumor location, clinical stage, PTV, and chemotherapy were considered binary variables. Furthermore, Spearman's correlation was used to examine the strength of association between V_{10}–V_{50}, D_{max}, D_{1cm3}, and D_{2cm3} of the GI ulcers. As we describe below, GI ulcers appeared only in the stomach, so that the DVH parameter of the stomach was analyzed in this study. A receiver operating characteristic (ROC) curve was also generated to assess the predictability of dosimetric parameters related to GI ulcer and to determine the optimal cutoff value for each dosimetric parameter. Each dosimetric parameter was divided into two groups using the optimal cutoff value obtained from ROC analysis, and the estimated incidence of GI ulcer was compared between the two groups with the log-rank test. Statistical significance was defined as a p value <0.05. Analyses were performed with the JMP 8.0 software (SAS Institute, Inc., Cary, NC).

Results

Patient characteristics

The median follow-up time was 9.3 months (range, 3.1–21.3). One-year overall survival was 84%. At the time of analysis, 51 patients (88%) were alive. The patient characteristics and treatment details are summarized in Table 1.

Incidence of upper GI ulcer

Among the 58 patients, gastric ulcers were observed in 12 patients (21%), and only one patient (5%) experienced grade 3 ulcer at 1.1 month from the C-ion RT. She was administered a one-time transfusion because of anemia, but active bleeding was not observed. Grade 2 ulcer was observed in 9 patients and grade 1 ulcer in 2 patients. These grade 1/2 ulcers were relieved with proton pump inhibitor and rest without any intensive endoscopic or surgical treatment. Ten (83%) of 12 ulcers occurred within the acute phase, and the median time of ulcer occurrence was 2.0 months (range, 1.1–8.1). The estimated cumulative incidence

Table 1
Patient characteristics.

Characteristic	Value
Patients (n)	58
Age (y)	
Median (range)	66 (42–92)
Gender	
Male	29
Female	29
Clinical stage (UICC 7th)	
IIA	8
IIB	3
III	43
IV	4
Tumor location	
Head	24
Body/tail	34
Tumor size (mm)	
Median (range)	35 (15–70)
PTV (cm^3)	
Median (range)	197 (83–412)
Chemotherapy	
Induction chemotherapy	45
Concurrent chemotherapy	53
Gemcitabine	27
S-1	22
Gemcitabine and S-1	4

Abbreviation: PTV = planning target volume.

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