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Comparison of proton beam radiotherapy and hyper-fractionated accelerated chemoradiotherapy for locally advanced pancreatic cancer

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ABSTRACT

Objectives: We compared the clinical outcomes of proton beam radiotherapy (PBRT) and those of conventional chemoradiotherapy via hyper-fractionated acceleration radiotherapy (HART) after induction chemotherapy in patients with locally advanced pancreatic cancer (LAPC).
Methods: Twenty-five consecutive patients with LAPC received induction chemotherapy comprising gemcitabine and S-1 before radiotherapy. Of these, 15 and 10 were enrolled in the HART and PBRT groups, respectively.
Results: Moderate hematological toxicities were observed only in the HART group, whereas two patients in the PBRT group developed duodenal ulcers. All patients underwent scheduled radiotherapy, with overall disease control rates of 93% and 80% in the HART and PBRT groups, respectively. Local progression was observed in 60% and 40% of patients in the HART and PBRT groups, respectively. However, there was no statistical significance between the two groups regarding the median time to progression (15.4 months in both) and the median overall survival (23.4 v.s. 22.3 months).
Conclusions: PBRT was feasible and tolerable, and scheduled protocols could be completed with careful attention to gastrointestinal ulcers. Despite the lower incidence of local recurrence, PBRT did not yield obvious progression control and survival benefits relative to conventional chemoradiotherapy.

Introduction

The prognosis of pancreatic cancer remains extremely, with an overall 5-year survival rate of only 1–4% [1]. As the only about 20% of patients with pancreatic cancer can undergo tumor resection due to the late diagnosis, chemotherapy alone and chemoradiotherapy (CRT) are generally accepted as standard treatments for locally advanced pancreatic cancer [2–6]. Distant metastatic lesions complicate the use of radiation therapy. However, the local disease control achieved with radiation could attenuate morbidity and improve the quality of life. Induction chemotherapy is thought to further enhance the clinical benefits of CRT for pancreatic cancer [7–9].

Globally, proton beam radiotherapy (PBRT) is increasingly used for the treatment of various neoplasms, including gastrointestinal tumors [10–12]. The near-total absence of an exit dose allows excellent dose distributions with PBRT, especially in the beam-exit path. This permits the use of a very limited number of treatment fields and further reduces the total whole-body integral dose [11]. Although several studies have indicated that the clinical outcomes of PBRT for pancreatic cancer are feasible and tolerable, no randomized control studies have compared PBRT with conventional radiotherapy, despite the observation of radiation-induced ulcers in the stomach and duodenum in several patients who received concurrent gemcitabine (GEM) chemotherapy and PBRT [12–15].

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Moreover, most previous studies included insufficient numbers of patients to determine the clinical significance of treatment outcomes.

The present study compared the clinical outcomes of patients with unresectable locally advanced pancreatic cancer who had undergone PBRT versus those receiving conventional x-ray radiotherapy via hyper-fractionated accelerated radiotherapy (HART) with concomitant S-1 chemotherapy.

Methods

Patients

This study was conducted in accordance with the guidelines outlined in the Declaration of Helsinki. The prospective protocol for data correction was approved by the Human Studies Group at Kagoshima University hospital (approval number: 25–63). Twenty-five consecutive patients with locally advanced and unresectable pancreatic cancer who received radiotherapy at Kagoshima University Hospital, Kagoshima, Japan, between January 2010 and December 2015 were enrolled in this study. The inclusion criteria were an age older than 20 years, a Karnofsky performance score (KPS) [16] >70, and a lack of prior radiotherapy or chemotherapy for another malignancy within the past 5 years. All patients in the study cohort had histologically or cytologically confirmed adenocarcinoma determined via endoscopic ultrasound-guided fine needle aspiration, as well as acceptable baseline hematological, hepatic, and renal function.

We defined locally advanced and unresectable tumors according to the expert consensus statement reported by Callery et al., in 2009 [17]. The criteria were following: the superior mesenteric artery (SMA) or celiac axis encasement greater than 180°, unreconstructable superior mesenteric vein (SMV)/portal vein (PV) occlusion or aortic invasion or encasement. Computed tomography (CT) and magnetic resonance imaging (MRI) findings were used to classify tumors as inoperable because of vascular encasement.

Treatment strategy

Induction chemotherapy was performed using a combination of GEM and S-1 prior to radiotherapy. Patients received more than two cycles of chemotherapy before HART or PBRT. In each cycle, GEM was administered via 30-min intravenous infusions of 1000 mg/m^2 on days 1 and day 8, and S-1 (Taiho Pharmaceutical Co., Ltd. Tokyo, Japan) was administered orally at a dose of 60 mg/m^2 twice per day from day 1 to day 14.

The treatment protocol for the PBRT was as follows. The gross tumor volume (GTV) was defined as the recognized tumor volume on enhanced CT images. The clinical target volume (CTV) was defined as the GTV plus a 10-mm margin, and included the regional lymphatic area. The planning target volume was defined as the CTV plus a set-up margin (5 mm) and internal margins, which were calculated using 4-dimensional CT data. Patients received either a standard dose of 50 Gy-equivalents (GyE) in 25 fractions via conventional 3-dimensional (3-D) conformal irradiation, or an escalated dose of 67.5 GyE via a field-in-field technique if the dose-planning simulations suggested the patient would benefit from dose escalation (Fig. 1). We prevented the maximum doses from exceeding 56 GyE to the stomach and esophagus, 50 GyE to the duodenum and small intestine, 55 GyE to the colon, and 48 GyE to the spinal cord [18].

Patients were treated with 150–210-MeV proton beams produced using a beam-wobbling system to ensure a flatter irradiation field, and a ridge filter to form a dispersed Bragg peak when using 360° rotating gantries (Mitsubishi Electric Corporation, Tokyo, Japan). The AZ-733V respiratory gating system (Anzai Medical Corporation, Tokyo, Japan) was used to ensure beam irradiation during the exhalation phase. S-1 was administered orally in two daily doses comprising 80 mg/m [2]/day from days 1–21.

Conventional CRT comprising HART with concomitant S-1 was administered for 4 weeks. Conformal 10-MV photon radiotherapy was administered in twice-daily 1.4-Gy fractions to yield a total dose of 56 Gy. S-1 was administered orally in same manner as described for PBRT. The radiation field included the primary tumor and a margin of 1–3 cm to cover the regional lymph nodes.

One month after the completion of HART or PBRT, S-1 chemotherapy was administered for 14 days, followed by a 7-day rest period. This cycle was repeated as a maintenance therapy until disease progression or unacceptable toxicity occurred.

All patients had the guidance of the treatment protocol about HART and PBRT together including chemotherapy. They were allowed to choose one of them of their own accord. However, the national health insurance of Japan can cover the financial cost of only the HART treatment but not PBRT treatment.

Evaluation and statistical analysis

Four weeks after completing radiotherapy, the clinical responses of patients in both groups were assessed by CT or MRI. Tumor responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) [19]. Treatment toxicities were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Following treatment completion, each patient underwent a physical examination and repeated evaluation of the tumor markers carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), as well as surveillance CT or MRI scanning every 3 months until disease progression occurred.

Comparability of the HART and PBRT groups was verified with Student's t tests and chi square statistics. Cross-tabulations were analyzed with chi square or Fisher's exact tests, where appropriate. Data are presented as mean ± standard deviation. Overall survival was estimated from the start of primary chemotherapy using the Kaplan–Meier method, and the time to progression (TTP) at the primary tumor site or distant sites was also estimated. All tests were conducted at an alpha level of 0.05, with a 95% confidence interval (CI), and were performed using IBM SPSS Statistics 24 software (IBM, Chicago, IL, USA).

Results

Patient characteristics

The HART and PBRT group comprised 15 and 10 patients, respectively. The patients' characteristics are summarized in Table 1. Eighteen patients had SMA or celiac axis encasement, and five patients had unreconstructable SMV/PV occlusion. Two patients had encasement of unresectable common hepatic artery due to anatomical aberrant ramification. Age, sex ratio, KPS, tumor size, distribution of the unresectable factor, and preoperative tumor marker levels did not differ significantly between the groups.

Treatment toxicities

The toxicities experienced by patients in both groups during and after treatment are shown in Table 2. The average number of cycles of GEM/S-1 combination induction chemotherapy was 2.4 (range, 1–5 cycles). Five patients ceased GEM treatment after experiencing hematological adverse effects during the first cycle, and continued receiving S-1 for another two or three cycles. One patient developed grade 4 neutropenia, and three developed non-hematological