using one-way analysis of variance *t*-test with the Bonferroni method.

Ethics

The present study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine (approval number, 2007-418), and informed consent was obtained from all patients before radiation therapy.

Results

The results of comparison of the plans in all 12 patients are shown in Additional file 1; Table S1. Even with the fusion method using DICOM information, there were no significant displacements between PET images and CT images. We did not need to fuse them manually again. The locations of the highest level of FDG accumulation after 40 Gy in local recurrent regions were almost the same as those before radiation therapy in the 12 patients, but maximal SUV decreased significantly from 6.84 ± 3.25 before radiation therapy to 5.14 ± 2.81 at 40 Gy ($p = 0.035$, Wilcoxon's test). Figure 3 shows change in FDG accumulation caused by irradiation of 40 Gy in a patient with anastomotic recurrence. In the present study, although there was no significant difference between GTV and GTV2 (GTV vs. GTV2: 87.52 ± 63.06 cm^3 vs. 79.66 ± 57.80 cm^3, $p = 0.141$), there was a significant difference between GTV2 and BTV (GTV2 vs. BTV: 79.66 ± 57.80 cm^3 vs. 11.12 ± 21.92 cm^3, $p < 0.001$) (Additional file 1; Table S2). In the IMRT with dose-painting boost plan, mean irradiated dose (D_{mean}) of PTV-PET and that of PTV-CT were 26.5 ± 0.8 Gy and 21.3 ± 0.8 Gy, respectively.

With regard to the volume of small bowel PRV receiving 50 Gy or more (V_{50}), there were significant differences between *summed plan 1* and *summed plan 2* and between *summed plan 1* and *summed plan 3* (*summed plan 1* vs. *summed plan 2* vs. *summed plan 3*: 47.11 ± 45.33 cm^3 vs. 40.63 ± 39.13 cm^3 vs. 41.25 ± 39.96 cm^3 ($p < 0.01$, respectively)) (Additional file 1; Table S2).

With regard to the volume of small bowel PRV receiving 60 Gy or more (V_{60}), 40 Gy or more (V_{40}), 30 Gy or more (V_{30}) and D_{mean} of small bowel PRV, there were no significant differences (*summed plan 1* vs. *summed plan 2* vs. *summed plan 3*: V_{60}, 19.76 ± 23.67 cm^3 vs. 13.65 ± 18.88 cm^3 vs. 14.52 ± 19.18 cm^3; V_{40}, 77.32 ± 64.21 cm^3 vs. 71.33 ± 60.20 cm^3 vs. 72.55 ± 61.59 cm^3; V_{30}, 121.18 ± 119.6 cm^3 vs. 113.62 ± 99.69 cm^3 vs. 116.88 ± 104.94 cm^3; D_{mean}, 16.1 ± 5.8 Gy vs. 16.4 ± 5.6 Gy vs. 16.6 ± 5.8 Gy (n.s.)) (Figure 4 and 5, Additional file 1; Table S2).

Focal dose escalation using dose-painting slightly but significantly increased maximal irradiated dose (D_{max}) of small bowel PRV(*summed plan 1* vs. *summed plan 2* vs. *summed plan 3*: 55.0 ± 16.0 Gy vs. 54.9 ± 15.3 Gy vs. 57.4 ± 16.3 Gy ($p < 0.01$, respectively)); however NTCP of small bowel PRV was not significantly increased even using focal dose escalation (*summed plan 1* vs. *summed plan 2* vs. *summed plan 3*: 5.10 ± 5.66% vs. 3.78 ± 4.19% vs. 4.09 ± 4.62%) (Additional file 1; Table S2). In the 4 patients with lateral pelvic lymph node metastasis or perineum recurrence, there were no significant

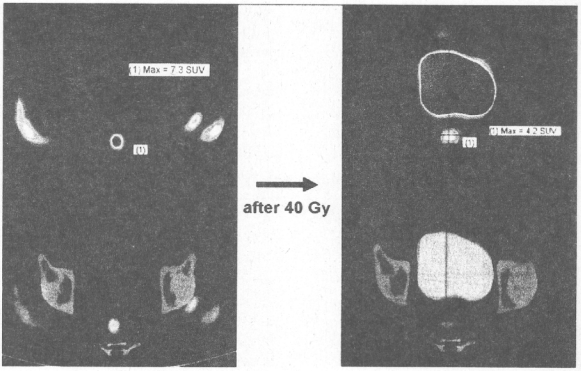

Figure 3 Change in FDG accumulation. This patient had anastomatic recurrence with 7.3 SUVmax before radiation therapy. After 40 Gy, the accumulation was decreased by 3.1 SUVmax.

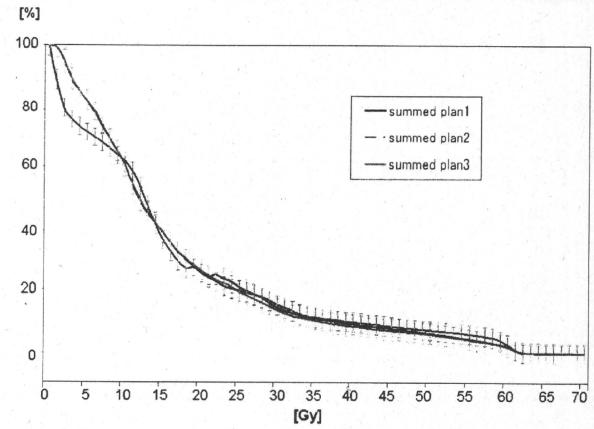

Figure 4 Mean DVH (whole curve) of small bowel PRV in each summed plan.

differences in D_{max} or NTCP of small bowel PRV (*summed plan 1* vs. *summed plan 2* vs. *summed plan 3*: D_{max}, 41.5 ± 23.9 Gy vs. 42.5 ± 23.4 Gy vs. 43.8 ± 24.2 Gy; NTCP, 4.45 ± 8.84% vs. 2.95 ± 5.87% vs. 3.30 ± 6.57%). In 8 patients with presacral or anastomostic recurrence, D_{max} of small bowel PRV of *summed plan 3* was significantly higher than that of *summed plan 2* ($p = 0.006$) but was not significantly higher than that of *summed plan 1* (n.s.) (*summed plan 1* vs. *summed plan 2* vs. *summed plan 3*: 61.8 ± 0.6 Gy vs. 61.1 ± 1.1 Gy vs. 64.2 ± 3.0 Gy); however, IMRT could significantly decrease NTCP of small bowel PRV. There was no significant difference in NTCP of small bowel PRV between *summed plan 2* and *summed plan 3* (*summed plan 1* vs. *summed plan 2* vs. *summed plan 3:* 5.42 ± 4.05% vs. 4.19 ± 3.56% vs. 4.49 ± 3.82%, $p < 0.005$, respectively). The mean DVH of small bowel PRV of *summed plan 3* in patients with lateral pelvic lymph node metastasis or perineum recurrence and that in patients with presacral or anastomostic recurrence are shown in Figure 6.

In the present study, although D_{max} of small bowel PRV of *summed plan 3* was slightly higher than that of *summed plan 1* or *summed plan 2*, V_{50} of small bowel PRV could be reduced by IMRT, and V_{30}, V_{40}, V_{60}, D_{mean} and NTCP were not increased even using focal dose escalation.

There was also no significant difference in C.I. between IMRT without dose-painting and IMRT with dose-painting (IMRT without dose-painting boost plan vs. IMRT with dose-painting boost plan: 1.33 ± 0.10 vs. 1.29 ± 0.61 ($p = 0.115$)).

Discussion

To our knowledge, there are few reports on PET-guided IMRT for lower gastrointestinal cancer. The reasons why we used this planning method for patients with local recurrent rectal cancer were 1) FDG-PET enabled a recurrent tumor to be distinguished from postoperative scar, 2) FDG-PET could reveal the region with higher malignancy activity and 3) it was not necessary to consider large inter- and intra-fractional motions because of adhesion due to the operation.

There have been several reports on PET/CT radiotherapy planning in lung cancer and in head and neck carcinoma. This planning method has been reported to be useful for radiotherapy to delineate target volume. With regard to FDG, there is evidence that FDG-avid regions of a tumor show increased radioresistance in vitro [18,19] and hypoxia in vivo [20]. Therefore, FDG-PET/CT is also useful for radiotherapy planning to detect the region with high residual potency in GTV to be given priority for treatment with a high dose.

It is difficult to clearly show threshold accumulation between malignancy and non-malignancy by FDG-PET because there is usually inflammation around a malignant tumor, there is penumbra of high accumulation and the normal gut tube has slightly high uptake of

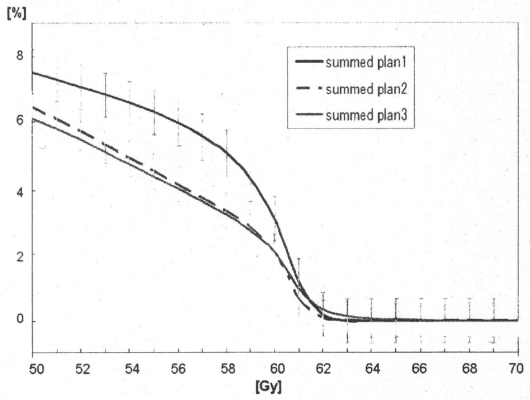

Figure 5 Mean DVH (focused on high dose area (50 to 70 Gy)) of small bowel PRV in each summed plan.

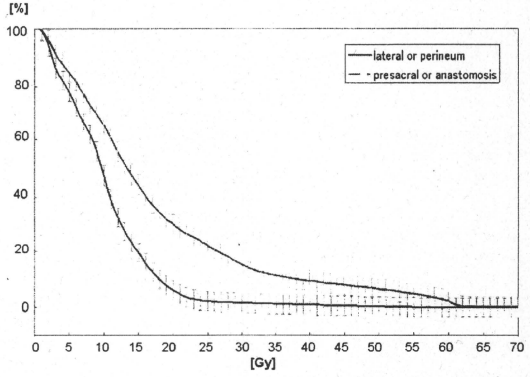

Figure 6 Mean DVH of small bowel PRV of *summed plan 3* in patients with lateral pelvic lymph node metastasis or perineum recurrence and that in patients with presacral or anastomostic recurrence. In patients with lateral pelvic lymph node metastasis or perineum recurrence, the mean DVH of small bowel PRV of *summed plan 3* was significantly lower than that in patients with presacral or anastomostic recurrence.

FDG. There have been many reports on contouring target volume according to 40~50% of maximal SUV value, source-background ratio, and arbitrary SUV value in some malignant tumors [21-25]; however, it remains inconclusive. Bayne et al. pointed out that SUV value had problems with accuracy and reproducibility [26]. In the present study, although we used an arbitrary SUV of 2.0, we consider that it is not a clear border between malignancy and non-malignancy but a region with relatively high malignant potency and with resistance to radiation at 40 Gy including a subclinical margin like CTV margin. Although SUV of 2.5~3.0 was used as a threshold value between malignancy and non-malignancy in many previous studies, we used SUV of 2.0 as

the threshold value for BTV based on the fact that patients in the present study had already been irradiated with 40 Gy and based on the fact that Haberkorn et al. reported the mean SUV of recurrent rectal cancer after radiotherapy with 40 Gy to be 1.8 [27].

Furthermore, in the present study, since normal tissues around the GTV were also irradiated with 40 Gy, the possibility that radiation-induced inflammation masked a residual malignant tumor must also be considered. For other tumors such as head and neck cancer and lymphoma [28,29], chemoradiation-induced inflammatory response causes sufficient numbers of false-positive results limiting PET being performed less than 2 months after chemoradiation. It may be inappropriate to use FDG-PET for radiation planning during radiation therapy. Recently, chemotherapy consisting of 5-FU or Capecitabine with or without the addition of Oxaliplatinum has commonly been performed for recurrent rectal cancer. Also, in the present study, all patients underwent concomitant and/or previous chemotherapy with radiation therapy. Findlay et al. mentioned the so-called flare phenomenon that occurs at 1~2 weeks after the initiation of chemotherapy and that can be observed as a marked increase in FDG metabolism in lesions that show response later [30]. We may also have to investigate the appropriate thresholds of FDG accumulation for BTV for each type of chemotherapy. However, in rectal cancer, many investigators revealed that the positive predictive value of FDG-PET assessment of therapy response during or soon after chemoradiation was very high and was not significantly limited by post-chemoradiation changes [31]. The timing of FDG-PET after chemoradiation for the most accurate assessment of tumor response in rectal cancer is controversial. Further larger prospective surveys of the time courses of tumor FDG uptake during and after chemoradiation in rectal cancer are required.

There are other major problems regarding the use of PET/CT for radiation therapy planning: misalignment of the fusion of PET and CT images due to body movement, bowel peristalsis and difference in volume of urine between the transmission scan and emission scan as well as artifacts due to FDG in urine, so-called "hot urine". These problems can be resolved to a large extent by overnight fasting before PET/CT and by starting the emission scan from the position of the pelvis. Moreover, in the present study, a 5-mm circular margin was attached to each target volume and OAR; however, it might not be sufficient to cover such misalignment. It is necessary to investigate such misalignment using on-line imaging (e.g., cone-beam CT) before clinical application.

In the present study, since V_{30}, V_{40}, V_{60}, D_{mean} and NTCP of small bowel PRV were not increased and V_{50} of small bowel PRV could be reduced due to the differences between GTV2 and BTV, focal dose escalation by 6 Gy to regions with SUV above 2.0 using IMRT with dose-painting boost for postoperative local recurrent rectal cancer is considered to be safe. FDG-PET-guided IMRT has the possibility of improving local control of postoperative local recurrent rectal cancer without increasing the risk of radiation injury of small bowel PRV. However, although NTCP which reflects account all the DVH data was not increased, D_{max} of small bowel PRV in the summed plan using focal dose escalation was significantly higher than that in other summed plans. While the differences in mean D_{max} of small bowel PRV between *summed plan 3* and the other plans were only about 2.5 Gy in the present study, D_{max} of small bowel PRV in *summed plan 3* was more than 65.0 Gy in 4 of the 8 patients with anastomotic or presacral recurrence, and NTCP in *summed plan 3* in 2 of the 4 patients was more than 10%. Since it is known that the small bowel is a "serial organ" and that the dose at which probability of obstruction or perforation is 50% within 5 years after treatment (TD50/5) of the small bowel is 55 Gy [32], although NTCP shows that focal dose escalation is acceptable, dose escalation by only 6 Gy from 60 Gy even using PET-guided IMRT is relatively risky. Therefore, if the region of high FDG accumulation is near the OARs, it might be necessary to reduce the degree of dose escalation and/or reduce the volume to increase irradiation dose (e.g., lesion with SUV > 2.5). Alternatively, using IMRT from the beginning of radiotherapy, using a belly board, and inserting a spacer between the recurrent tumor and OARs may further facilitate dose escalation without increasing the risk of radiation injury. When PTV-PET overlaps PRV, we may have to further modify the irradiation dose setting of the overlapping part.

Rectal cancer is known to have many hypoxic fractions [11]. Some studies have provided evidence that hypoxia has a negative impact on tumor response to radiation and other methods of therapy [33-36]. Although we used FDG for radiotherapy planning in this study to determine the region with high tumor cell density, it may be more important for improving the effect of radiotherapy for rectal cancer to determine the hypoxic regions. There are some tracers for detecting a hypoxic region (e.g., [^{18}F]Fluoromisonidazole-3-fluoro-1-(2'-nitro-1'-imidazolyl)-2-propanol ([^{18}F]FMISO), Cu-diacetyl-bis(N4-methylthiosemicarbazone (Cu-ATSM) and 1-(2-fluoro-1-[hydroxymethyl] ethoxy)methyl-2-nitroimidazole ([^{18}F]FRP170)) [37-39]. Although Lin et al. have already reported the effectiveness in head and neck cancer [40], increasing the irradiation dose with IMRT to the hypoxic region may also be effective for treating postoperative recurrent rectal cancer.

Conclusions

Our findings suggest that FDG-PET/CT-guided IMRT can facilitate focal dose escalation to regions with SUV above 2.0 while providing normal tissue protection in patients with postoperative local recurrent rectal cancer. However, we do not recommend routine clinical use of focal dose escalation using FDG-PET/CT-guided IMRT. In cases in which the region of high FDG accumulation is near the OARs, careful radiotherapy planning is necessary. Based on the results of this planning study, we will start a clinical phase I/II study of focal dose escalation using PET-guided IMRT for patients with postoperative local recurrent rectal cancer in our institution.

Additional file 1: Supplementary tables.

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Authors' contributions

KJ, ST, YO, KN, HA and SY participated in the design of the study. KJ and YT performed the statistical analysis. KJ, TK, TM and LK conceived of the study and participated in its design and coordination. RU and YO helped to draft the manuscript. HA, KT, KN, KF and MK acquired data. MM and NM verified and calculated DVH and NTCP. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

^{18}F-fluorodeoxyglucose positron emission tomography immediately after chemoradiotherapy predicts prognosis in patients with locoregional postoperative recurrent esophageal cancer

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Abstract
Objectives The objectives of this study were to reveal the utility of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) within 7 days after chemoradiotherapy to predict prognosis in patients with postoperative recurrent esophageal cancer.
Materials and methods Patients scheduled to undergo concurrent chemoradiotherapy for postoperative locoregional recurrence of esophageal cancer were recruited. Selection criteria were: (1) locoregional recurrence, (2) no previous radiation therapy, (3) planning treatment with concurrent chemoradiotherapy, (4) FDG-PET performed <2 weeks before chemoradiotherapy, and (5) no serious diabetes. FDG-PET was performed <7 days after chemoradiotherapy. No more treatment after chemoradiotherapy was given until disease progression was diagnosed according to the Response Evaluation Criteria in Solid Tumors (RECIST). Correlations of FDG-PET findings with cause-specific survival and local control rates were investigated prospectively.
Results Twenty patients were enrolled. Median observation period of patients who survived was 45.0 months. Median maximum standardized uptake value (SUV_{max}) after chemoradiotherapy was 2.4, and median SUV_{max} before chemoradiotherapy was 8.4. Cause-specific survival and local control rates were significantly better for patients with $SUV_{max} \leq 2.4$ after chemoradiotherapy (log-rank test, $P = 0.033$ and 0.010, respectively). SUV_{max} before chemoradiotherapy tended to be correlated only with cause-specific survival rate (log-rank test, $P = 0.076$). Change in metabolic activity of FDG was significantly correlated with local control rate (log-rank test, $P = 0.042$).
Conclusions FDG-PET performed even <7 days after chemoradiotherapy predicts prognosis in patients with postoperative recurrent esophageal cancer.

Keywords FDG-PET · Recurrent esophageal cancer · Prognosis · Radiotherapy · SUV_{max}

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Introduction

The usefulness of positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) in patients with esophageal cancer, particularly for staging and detecting recurrence, has been reported [1–3]. There are also reports of the usefulness of pre- or posttreatment FDG-PET for predicting prognosis of primary esophageal cancer [3–9]. However, there is no report on the usefulness of FDG-PET for predicting prognosis of postoperative recurrent esophageal cancer. Recently, chemoradiotherapy (CRT) has been shown to improve the prognosis of patients with postoperative recurrent esophageal cancer [10–16]. At our institution, CRT including prospective study is actively performed for postoperative locoregional recurrent esophageal cancer.

CRT generally causes local inflammatory reactions in normal tissue. FDG uptake in inflammatory lesions is a

well-known phenomenon [17]. Increased FDG uptake caused by radiation-induced inflammation may limit the use of FDG-PET for metabolic measurement in esophageal cancer soon after CRT. Therefore, it has been recommended that FDG-PET be performed several weeks or even months after completion of radiotherapy to assess tumor response [18, 19]. However, we often experienced significant reduction or loss of FDG accumulation even <1 month after irradiation in patients with squamous cell carcinoma. In this study, we prospectively investigated the potential of FDG-PET performed <7 days after CRT completion to predict prognosis and local control of postoperative recurrent esophageal cancer.

Materials and methods

We recruited patients scheduled for CRT in our institution for locoregional recurrence (including para-aortic lymph node metastasis) of esophageal cancer without distant metastasis after no residual tumor (R0) resection that involved extended radical esophagectomy with two- or three-field lymph-node dissection. Although squamous cell carcinoma was histologically proven in all patients before the operation, recurrences were diagnosed comprehensively by upper gastrointestinal endoscopy, ultrasonography, computed tomography (CT), FDG-PET, physical findings, and/or cytology.

Study design

Patient selection criteria were: (1) locoregional recurrence (including para-aortic lymph node metastasis) without distant metastasis after no residual tumor (R0) resection and extended radical esophagectomy with two- or three-field lymph node dissection, (2) no previous radiation therapy, (3) planning for concurrent CRT, (4) FDG-PET performed <2 weeks before CRT, and (5) no serious diabetes. Patients underwent FDG-PET <7 days after CRT completion. They had no more treatment after CRT until progressive disease (PD) was diagnosed according to the Response Evaluation Criteria in Solid Tumors (RECIST). There were no particular rules for treating patients with recurring relapse.

Follow-up

Follow-up evaluations were performed every 1–3 months for the first 2 years and every 6 or 12 months thereafter by endoscopy and enhanced CT. Cause-specific survival and local control rates were calculated from the first day of radiotherapy. We defined PD according to RECIST as failure (recurring relapse) and PD in the irradiated area as local failure.

Endpoints

The primary endpoint of the study was to reveal correlations between maximum standardized uptake value (SUV_{max}) in FDG-PET after CRT and cause-specific survival rate or local control rate. The secondary endpoints were to reveal correlations between SUV_{max} before CRT or changes in metabolic activity of FDG and cause-specific survival rate or local control rate.

Analysis

When patients were divided into two groups, each median value was used as a threshold value. Survival estimates were calculated using the Kaplan–Meier method, and differences were evaluated by the log-rank test. A paired sample t test or Kruskal–Wallis test was then performed to calculate significance of differences. Statistical significance was defined as $P < 0.05$. SPSS software for Windows version 11.0 was used for all calculations.

Ethics

Written informed consent was obtained from all patients, and the study was performed according to the principles of the Declaration of Helsinki and approved by the local ethics committee.

FDG-PET

PET scans were performed 1 h after FDG administration at 3.1 MBq/kg with either a Biograph PET/CT scanner or an ECAT EXACT HR^+ PET scanner (Siemens, Hoffman Estates, IL, USA) after >4 h of fasting. PET was performed in each patient using the same scanner. A transmission scan was performed for attenuation correction before emission scans (using a CT scan with the Biograph PET/CT scanner or ^{68}Ge rod sources with the ECAT EXACT HR^+ PET scanner). Seven bed positions were used for emission scans, with an acquisition time of 2 min per position. All scans were reconstructed using an attenuation-weighted, ordered subset expectation maximization algorithm (OZEM). For semiquantitative analysis of increased FDG uptake lesions, SUV_{max} based on body weight (g) was calculated and converted into a value based on lean body mass:

$$SUV = \text{tissue activity concentration (Bq/ml)/}[\text{administered activity (Bq)/weight (g)}].$$

In cases with multiple recurrence sites, the highest SUV_{max} of all lesions was used for analysis. The percentage changes in FDG metabolic activity ($SUV_{\Delta\%}$) between SUV_{max}

before CRT (pre-SUV) and SUV_{max} after CRT (post-SUV) were calculated using the following formula: $SUV_{\Delta\%}$ = [(pre-SUV − post-SUV)/pre-SUV] × 100 (%).

Treatment

All patients underwent the following concurrent CRT without interruption.

Radiotherapy

A linear accelerator (4 or 10 MV) was used as the X-ray source. The target volume was localized for radiotherapy in all patients in CT planning. The daily fractional radiotherapy dose was 2.0 Gy, administered 5 days a week, and the total dose was 60.0 Gy. For patients who had lymph node metastasis in some regions or metastasis of many lymph nodes in one region, a T-shaped field (including the bilateral supraclavicular, mediastinal, and abdominal regions) was used. For the other patients, local fields with a margin of 1–2 cm from the macroscopic tumor were used. After a total dose of 40.0 Gy, the field was changed for all patients to avoid the spinal cord, and only macroscopic lesions were irradiated, with a margin of 1–1.5 cm.

Chemotherapy

A platinum-based combination regimen, at the very least, was used concurrently with radiotherapy for all patients. Most patients underwent chemotherapy consisting of two cycles of nedaplatin (70 mg/m^2/2 h) and 5-fluorouracil (5-FU) (500 mg/m^2/24 h for 5 days) according to our institutional protocol.

Results

From January 2002 to December 2007, we enrolled 20 patients. Patient characteristics are shown in Table 1. The last observation date was 30 September 2009. At that date, 14 of the 20 patients had relapsed: 9 had recurrence inside the irradiation field, 2 had lymph node metastasis out of the irradiation field, and 5 had distant organ metastasis (2 patients with both lymph node and distant organ metastasis). Fourteen of the 20 patients died: 11 patients died due to progression of disease, 2 due to intercurrent diseases, and one due to an iatrogenic cause. No patient was lost to follow-up. The median observation period was 23.8 (range 4.0–75.0) months for all patients and 45.0 (range 24.0–75.0) months for patients who survived. CRT was completed in all patients, and FDG-PET was performed <7 days after CRT. Blood glucose levels were <150 mg/dl in all patients before FDG administration.

Table 1 Patient characteristics

Characteristics	Number
Gender	
Male	16
Female	4
Age (years)	
Median (range)	63 (54–77)
ECOG PS	
Median (range)	1 (0–1)
Site of recurrence (number of patients)	
Anastomosis site	2
Supraclavicular lymph node	4
Mediastinal lymph node	15
Abdominal lymph node	5
Baseline sum longest diameter (cm)	
Median (range)	4.5 (2.0–11.5)
SUV_{max} before CRT	
Median (range)	8.4 (3.0–20.0)
SUV max after CRT	
Median (range)	2.4 (1.2–5.2)
Chemotherapy (number of patients)	
CDGP + 5-FU	16
CDGP + DOC	3
CDDP + 5-FU + DOC	1
Tumor response (RECIST) (number of patients)	
Complete regression (CR)	7
Partial regression (PR)	10
Stable disease (SD)	3
Progressive disease (PD)	0

ECOG PS Eastern Cooperative Oncology Group Performance Status, *CRT* chemoradiotherapy, *CDGP* nedaplatin, *5-FU* 5-fluorouracil, *DOC* docetaxel, *CDDP* cisplatin, *RECIST* Response Evaluation Criteria in Solid Tumors

Median SUV_{max} in the 20 patients after CRT was 2.4 (range 1.2–5.2), and median SUV_{max} before CRT was 8.4 (range 3.0–20.0). CRT significantly decreased SUV_{max} of in all 20 patients (paired sample t test, $P < 0.001$). The best overall response rate, including complete responses (CR) in 7 patients and partial responses (PR) in 10 was 85.0%. The 1-year and 3-year cause-specific survival rates in the 20 patients were 80.0% [95% confidence interval (CI), 62.5–97.5%] and 48.0% (95%CI 25.6–70.4%), respectively, with a median cause-specific survival period of 24.0 months (95% CI 3.0–45.0). The 1-year and 3-year local control rates in the 20 patients were 69.1% (95% CI 48.4–89.7%) and 51.8% (95% CI 28.9–74.7%), respectively. The median local control period could not be calculated. There was a significant difference between cause-specific survival rates in patients with SUV_{max} >2.4 (n = 10) and patients with SUV_{max} ≤2.4 (n = 10) after CRT (3 years, 20% vs.

77.8%; $P = 0.033$, Fig. 1), and there was also a significant difference between local control rates in patients with SUV_{max} >2.4 ($n = 10$) and patients with SUV_{max} ≤2.4 ($n = 10$) after CRT (3 years, 23.3% vs. 78.8%; $P = 0.01$, Fig. 2). Furthermore, there tended to be a significant difference between cause-specific survival rates in patients with SUV_{max} <8.4 ($n = 10$) and patients with SUV_{max} ≥8.4 ($n = 10$) before CRT (3 years, 67.5% vs. 30.0%; $P = 0.076$, Fig. 3), but there was no significant difference between local control rates in patients with SUV_{max} <8.4 ($n = 10$) and patients with SUV_{max} ≥8.4 ($n = 10$) before CRT (3 years, 46.7% vs. 58.3%; $P = 0.98$).

The median $SUV_{\Delta\%}$ was 68.5% (range 40.2–92.9%). The local control rate in patients with decreases of >68.5% ($n = 10$) was significantly higher than in patients with decreases ≤68.5% ($n = 10$) (3 years, 77.1% vs. 30.0%; $P = 0.042$, Fig. 4). However, there was no significant difference in cause-specific survival rate (3 years, 57.1% vs. 40.0%; $P = 0.89$).

Table 2 shows median (range) SUV_{max} before and after CRT and $SUV_{\Delta\%}$ in patients who showed tumor response. There were no differences among patients who showed tumor response.

Other clinical prognostic factors [Eastern Cooperative Oncology Gropup Performance Status (ECOG PS) and age], as reported previously [16], and baseline sum longest diameter were not correlated with cause-specific survival, local control, or overall survival. Results of univariate

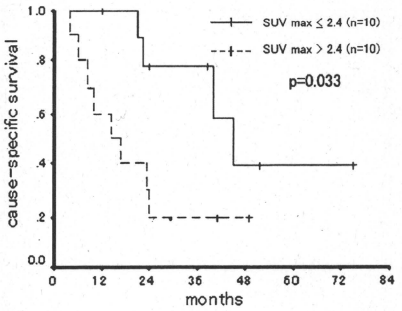

Fig. 1 Cause-specific survival curve for patients with low SUV_{max} after chemoradiotherapy and that for patients with high SUV_{max} after chemoradiotherapy

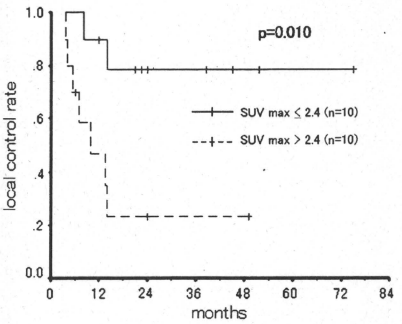

Fig. 2 Local control survival curve for patients with low SUV_{max} after chemoradiotherapy and that for patients with high SUV_{max} after chemoradiotherapy

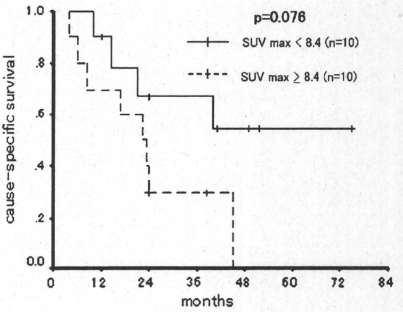

Fig. 3 Cause-specific survival curve for patients with low SUV_{max} before chemoradiotherapy and that for patients with high SUV_{max} before chemoradiotherapy

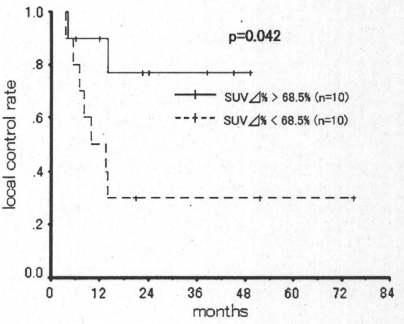

Fig. 4 Local control survival curve for responder patients and that for non-responder patients

Table 2 Median (range) maximum standardized uptake value (SUV_{max}) before and after chemoradiotherapy (CRT) and $SUV_{\Delta\%}$ of each tumor response

	Tumor response (RECIST)			Kruskal–Wallis test
	CR ($n = 7$)	PR ($n = 10$)	SD ($n = 3$)	P value
SUV_{max} before CRT	9.5 (3.0–20.0)	8.25 (3.8–16.1)	8.7 (8.3–10.0)	0.62
SUV_{max} after CRT	1.2 (1.2–3.5)	2.6 (1.5–4.0)	3.2 (1.9–5.2)	0.13
$SUV_{\Delta\%}$	84.8 (42.5–92.9)	65.75 (42.1–82.0)	68.0 (40.2–36.9)	0.34

RECIST Response Evaluation Criteria in Solid Tumors, *CR* complete regression, *PR* partial regression, $SUV_{\Delta\%}$ percentage changes in ^{18}F-fluorodeoxyglucose positron emission tomography (FDG) metabolic activity

Table 3 Univariate analysis of predictive factors for cause-specific survival and local control

	Cause-specific survival (months)			Local control (months)		
Predictive factor	Median	95% CI	Log-rank test	Median	95% CI	Log-rank test
FDG-PET after CRT						
$SUV_{max} \leq 2.4$	45.0	34.6–55.4	0.033	NA	NA	0.010
$SUV_{max} > 2.4$	14.5	3.7–25.3		10.0	0.9–19.1	
FDG-PET before CRT						
$SUV_{max} \leq 8.4$	NA	NA	0.076	14.0	NA	0.98
$SUV_{max} > 8.4$	22.5	12.4–32.6		NA	NA	
$SUV_{\Delta\%}$						
<68.5%	21.0	10.9–31.1	0.89	10.0	1.5–18.5	0.042
≥68.5%	40	8.7–71.3		NA	NA	
Age						
<63	40.0	0–82.7	0.76	NA	NA	0.97
≥63	24.0	19.5–28.5		NA	NA	
ECOG PS						
0	45.0	0.9–89.1	0.40	NA	NA	0.22
1	24.0	12.5–35.5		14.0	8.2–19.8	
Baseline sum longest diameter						
<4.5 cm	40.0	8.3–71.7	0.66	NA	NA	0.60
≥4.5 cm	23.5	13.9–33.1		13.5	NA	

ECOG PS Eastern Cooperative Oncology Group Performance Status, *CRT* chemoradiotherapy, $SUV_{\Delta\%}$ percentage changes in ^{18}F-fluorodeoxyglucose positron emission tomography (FDG) metabolic activity, *CI* confidence interval, *NA* not available

analysis of the above predictive factors for cause-specific survival and local control are summarized in Table 3.

The 1- and 3-year overall survival rates in the 20 patients were 75.0% (95% CI 56.0–94.0%) and 40.0% (95% CI 18.5–61.5%), respectively, with a median overall survival period of 23.5 months (95% CI 21.3–25.7). SUV_{max} before and after CRT and $SUV_{\Delta\%}$ had no significant correlation with overall survival ($P = 0.236$, 0.11, and 0.858, respectively).

Discussion

Although there have been some reports on the possibility of FDG-PET predicting prognosis in patients with primary esophageal cancer [3–9], to our knowledge, this is the first report on FDG-PET in patients with postoperative recurrent esophageal cancer. The reason we used cause-specific rather than overall survival as the endpoint was that some patients were expected to die due to intercurrent diseases or treatment complications [16]. In fact, three patients died from causes other than esophageal cancer. We found that SUV_{max} even <7 days after CRT was correlated with local control and cause-specific survival. This may mean that low FDG uptake after CRT indicates not only loss of activity at the lesion but also metastatic ability of malignant cells. This result also agrees with results obtained by Swisher et al. [7], showing that post-CRT SUV_{max} of primary esophageal cancer was correlated with percentage of viable cells in pathologic specimens at the time of esophagectomy.

In patients with primary esophageal cancer or other malignant tumors, a high false-positive rate due to radiation-induced inflammatory changes has been reported. Therefore, so far, there has been no consensus concerning the timing of FDG-PET after CRT for the most accurate assessment of tumor response. Early determination of residual disease would enable the next salvage therapy (e.g., adjuvant chemotherapy, molecular-targeted therapy, additional irradiation) to be started earlier, but many investigators have reported that FDG-PET should be performed 4–6 weeks after CRT. The best timing for FDG-PET after CRT for primary esophageal cancer is unknown; however, there was, at least, a low false-positive rate for postoperative recurrent esophageal cancer in this study, despite the fact that FDG-PET was performed <7 days after CRT. There were no patients with SUV >3.0 during the first 7 days after CRT among 11 patients who were controlled in the irradiated field at the last observation date. Most patients had recurrences in lymph nodes, not in the anastomotic region. The reason findings of FDG-PET performed even <7 days after CRT might be accurate could be because performing FDG-PET so early avoids radiation-induced mucositis, which is known to result in a relatively high and prolonged FDG accumulation. However, SUV_{max} after CRT in two anastomotic recurrent lesions were 2.2 and 2.0, respectively (SUV_{max} before CRT: 5.4 and 7.7, respectively). FDG accumulation in squamous cell carcinoma is known to be decreased by CRT more than that in adenocarcinoma [20]. All patients in our study had squamous cell carcinoma, which might also have had some effect on the results.

According to RECIST, accurate confirmation of response requires a waiting period of at least 4 weeks after response criteria are first met. In fact, although 7 patients in our study showed CR as the best response record, the recurrent tumor vanished on CT immediately after CRT in only one patienty. From our results, it appears that the FDG-PET modality might provide the earliest possible assessment of treatment response and survival prognosis after CRT in patients with locoregional postoperative recurrent esophageal cancer. Furthermore, the results could be used commonly in squamous cell carcinoma lymph node metastasis from other primary sites (e.g., head and neck, lung, uterus).

Although some studies have shown that a comparison of FDG uptake in the early phase and that in the delayed phase is useful for distinguishing malignancy from inflammation [18, 21–26], from results of our study, a one-phase scan might be sufficient to predict cause-specific survival and local control rates in patients who receive CRT for postoperative locoregional recurrent esophageal cancer. Furthermore, we showed that SUV_{max} in FDG-PET before CRT tended to be correlated with cause-specific survival but not with local control rate. This might mean that FDG uptake before therapy closely reflects the overall malignancy of recurrent tumors, including metastatic ability. However, it might not reflect tumor radiation sensitivity. Thus, high SUV levels before treatment may be indicative of the need for more aggressive systematic therapy. We found no significant correlations between SUV_{max} before CRT and other pretreatment prognostic factors (performance status, age, recurrent pattern), as reported previously [16]. FDG-PET has the possibility of being used as an independent prognostic survival estimation tool before CRT in patients with locoregional postoperative recurrent esophageal cancer.

Several studies have shown that changes in metabolic activity were correlated with tumor response and patient survival [27–29]. In our study, there was a significant correlation between $SUV_{\Delta\%}$ and local control rate, but greater $SUV_{\Delta\%}$ did not prolong survival. Similar observations have been reported previously [7, 20, 27–30]. The observed metabolic change in our study is similar to the time course of tumor FDG uptake during CRT shown by Wieder et al. [30]. However, they showed that the metabolic change was correlated significantly not only with tumor response but also with survival. In our study, we could not determine why $SUV_{\Delta\%}$ was not correlated with survival. In most similar studies, patients underwent esophagectomy with lymph node dissection after CRT, and FDG-PET was performed >4 weeks after CRT. These differences in the procedure may have caused the different results. As described above, FDG accumulation before CRT is considered to reflect overall tumor malignancy, not radiation sensitivity. It is therefore reasonable that $SUV_{\Delta\%}$ is not correlated with survival.

Our study results suggest that a single FDG-PET within 7 days of CRT may be sufficient to predict tumor response and survival prognosis. This issue is controversial. It is thus necessary to perform a multicenter study with multivariate analysis and a much larger number of patients to determine which factor, including SUV_{max} before and after CRT and/or changes in metabolic activity, is the most important for patients with locoregional postoperative recurrent esophageal cancer.

Conclusions

This prospective study showed that FDG-PET after CRT predicts survival prognosis in patients with locoregional postoperative recurrent esophageal cancer. We particularly emphasize that FDG-PET performed even <7 days after CRT enables prognosis prediction. FDG-PET could be the earliest diagnostic modality for local control and survival

prognosis in patients with locoregional postoperative recurrent esophageal cancer.

Conflicts of interest statement There is no conflict of interest in relation to this study.

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CLINICAL INVESTIGATION **Pancreas**

PATTERNS OF RADIOTHERAPY PRACTICE FOR PANCREATIC CANCER IN JAPAN: RESULTS OF THE JAPANESE RADIATION ONCOLOGY STUDY GROUP (JROSG) SURVEY

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Purpose: To determine the patterns of radiotherapy practice for pancreatic cancer in Japan.

Methods and Materials: A questionnaire-based national survey of radiotherapy for pancreatic cancer treated between 2000 and 2006 was conducted by the Japanese Radiation Oncology Study Group (JROSG). Detailed information on 870 patients from 34 radiation oncology institutions was accumulated.

Results: The median age of all patients was 64 years (range, 36–88), and 80.2% of the patients had good performance status. More than 85% of patients had clinical Stage T3-T4 disease, and 68.9% of patients had unresectable disease at diagnosis. Concerning radiotherapy (RT), 49.8% of patients were treated with radical external beam RT (EBRT) (median dose, 50.4 Gy), 44.4% of patients were treated with intraoperative RT (median dose, 25 Gy) with or without EBRT (median dose, 45 Gy), and 5.9% of patients were treated with postoperative radiotherapy (median dose, 50 Gy). The treatment field consisted of the primary tumor (bed) only in 55.6% of the patients. Computed tomography-based treatment planning and conformal RT was used in 93.1% and 83.1% of the patients treated with EBRT, respectively. Chemotherapy was used for 691 patients (79.4%; before RT for 66 patients; during RT for 531; and after RT for 364). Gemcitabine was the most frequently used drug, followed by 5-fluorouracil.

Conclusion: This study describes the general patterns of RT practice for pancreatic cancer in Japan. Most patients had advanced unresectable disease, and radical EBRT, as well as intraoperative RT with or without EBRT, was frequently used. Chemotherapy with gemcitabine was commonly used in conjunction with RT during the survey period. © 2010 Elsevier Inc.

Radiotherapy, pancreatic neoplasm, patterns of radiotherapy, chemotherapy.

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INTRODUCTION

Pancreatic cancer is one of the leading causes of cancer death worldwide. The prognosis of patients with this disease remains extremely poor, with a 5-year survival rate after diagnosis of <5% (1, 2). Most patients present with locally advanced or metastatic disease. The median life expectancy is 3–6 months for those with metastatic disease and 6–10 months for those with nonmetastatic disease (3, 4).

In Japan, the number of patients with pancreatic cancer has been rapidly increasing,, and the number of yearly pancreatic cancer deaths in Japan has increased from approximately 2,000 in 1960 to 20,000 in 2000 (5). Moreover, radiotherapy (RT) has become much more common because a significant number of new methods, as well as technology, for treatment planning has become available (6, 7). Therefore, the optimal management of RT for pancreatic cancer patients has become a major concern in Japan.

Patterns of care studies, initially developed in the United States in the mid-1970s, represent a reliable retrospective study design for establishing the national practice for cancer patients during a specific study period (8–10). A patterns of care study was designed as a national survey to document and analyze the current practice characteristics for cancers in the radiation oncology department. The results of the study could aid in improving healthcare for cancer patients and could also provide data that will allow comparison with other countries. Although several reports have been published on the patterns of RT in Japan for lung, breast, and prostate cancer (11–13), scant information is available on the patterns of RT for pancreatic cancer.

In the present study, the Japanese Radiation Oncology Study Group (JROSG) conducted a nationwide survey of the patterns of RT practice for pancreatic cancer. This study was intended to evaluate the patterns of RT for pancreatic cancer in Japanese radiation oncology centers. To our knowledge, this is the first report to establish how RT is used nationally to treat pancreatic cancer in Japan.

METHODS AND MATERIALS

Between 2008 and 2009, the JROSG conducted a national survey of RT for pancreatic cancer treated between 2000 and 2006 using a questionnaire that requested detailed information regarding patient and treatment characteristics. The following eligibility criteria were used in this survey. The patients were required to have been diagnosed with pancreatic cancer without evidence of distant metastasis; they must have been treated with RT between 2000 and 2006; and they must not have been diagnosed with any other malignancy or have been previously undergone RT. Patients without pathologic verification were diagnosed as having pancreatic cancer according to the clinical and radiographic findings. The clinical findings included serum carbohydrate antigen 19-9 measurements. The radiographic findings included contrast-enhanced computed tomography (CT), ultrasonography, endoscopic ultrasonography, and endoscopic retrograde/magnetic resonance cholangiopancreatography. Of 71 radiation oncology centers in Japan belonging to the JROSG, 34 (48%) agreed to participate in our survey. The other radiation oncology centers did not agree to participate in the present study mostly because too few pancreatic cancer patients were treated with RT between 2000 and 2006. Each center agreeing to participate in the present study provided a database of the patients with pancreatic cancer treated with RT between 2000 and 2006. The study was performed according to the guidelines approved by the institutional review board of each institution whenever necessary.

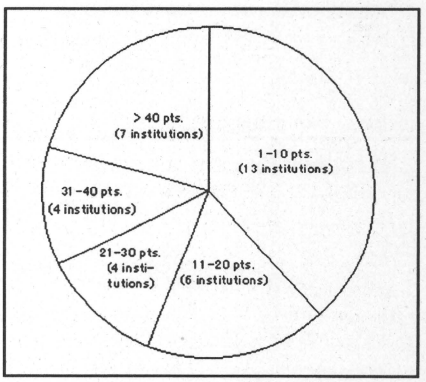

Fig. 1. Distribution of institutions according to number of patients treated between 2000 and 2006. Variations concerning number of patients among institutions.

Statistical analysis was performed using the Statistical Package for Social Sciences, version 11.0 (SPSS, Chicago, IL). The chi-square test and Student's t test were used to investigate the relationship between variables. A probability level of .05 was chosen for statistical significance.

RESULTS

Data registration

Detailed information on 870 patients from 34 radiation oncology institutions (median, 15.5 patients/institution) was accumulated. Figure 1 shows the distribution of the number of institutions according to the number of patients treated during the 7-year period. Variations concerning the number of patients treated during the period were found among the institutions. For example, in 13 (38.2%) of the 34 institutions, 1–10 patients were treated during the 7 years, and in 7 (20.6%), >40 patients were treated during the 7-year period.

Patient and disease characteristics

The patient and disease characteristics of all 870 patients are listed in Table 1. The median patient age was 64 years (range, 36–88), and 42.5% of patients were women. The pretherapeutic evaluations included CT, ultrasonography, and endoscopic retrograde/magnetic resonance cholangiopancreatography for 96.2%, 98.2%, and 61.4% of the patients, respectively. More than 80% of the patients had an Eastern Cooperative Oncology Group performance status of 0-1. Of the 870 patients, 85.2% had Stage T3-T4 disease and 68.9% had unresectable disease. The median maximal tumor

Table 1. Patient and disease characteristics (n = 870)

Characteristic	Patients (n)
Age (median, 64 y)	
<70 y	626 (72.0)
≥70 y	244 (28.0)
Gender	
Female	370 (42.5)
Male	500 (57.5)
Pathologic type verified	
Yes, adenocarcinoma	659 (75.7)
Yes, other	15 (1.8)
No	196 (22.5)
Ultrasonography (before RT)	
Yes	837 (96.2)
No	13 (1.5)
Unknown	20 (2.3)
CT (before RT)	
Yes	854 (98.2)
No	14 (1.6)
Unknown	2 (0.2)
ERCP/MRCP (before RT)	
Yes	534 (61.4)
No	155 (17.8)
Unknown	181 (20.8)
Primary site	
Head	554 (63.7)
Body	277 (31.8)
Tail	33 (3.8)
Unknown	6 (0.7)
Maximal tumor size (median, 4.0 cm)	
<4.0 cm	386 (44.4)
≥4.0 cm	409 (47.0)
Unknown	75 (8.6)
ECOG performance status	
0	166 (19.1)
1	532 (61.1)
2	115 (13.2)
3	10 (1.1)
4	1 (0.2)
Unknown	46 (5.3)
Jaundice	
Yes	276 (31.7)
No	521 (59.9)
Unknown	73 (8.4)
CA19-9 (median, 240 U/mL)	
<1,000 U/mL	565 (64.9)
≥1,000 U/mL	206 (23.7)
Unknown	99 (11.4)
Alcohol consumption	
Yes	253 (29.1)
No	304 (34.9)
Unknown	313 (36.0)
Smoking	
Yes	306 (35.2)
No	314 (36.1)
Unknown	250 (28.7)
Diabetes mellitus	
Yes	237 (27.2)
No	483 (55.6)
Unknown	150 (17.2)
Clinical T stage (UICC 2002)	
Tis	2 (0.2)
T1	30 (3.4)
T2	95 (10.9)
T3	252 (29.0)
T4	488 (56.2)
Unknown	3 (0.3)
Clinical N stage (UICC 2002)	
N0	453 (52.1)
N1	373 (42.9)
Unknown	44 (5.0)
Resectable at diagnosis	
Yes	268 (30.8)
No	599 (68.9)
Unknown	3 (0.3)

Abbreviations: RT = radiotherapy; CT = computed tomography; ERCP/MRCP = endoscopic retrograde cholangiopancreatography/ magnetic retrograde cholangiopancreatography; ECOG = Eastern Cooperative Oncology Group; CA19-9 = carbohydrate antigen 19-9; UICC = International Union Against Cancer.

Data in parentheses are percentages.

size was 4.0 cm (range, 0.9–11.0), and the median serum concentration of carbohydrate antigen 19-9 was 240 U/mL. Approximately 30% of patients each drank, smoked, or had diabetes mellitus.

Treatment characteristics

The treatment characteristics for all 870 patients are listed in Table 2. Approximately 20% of the patients were treated with an investigational protocol. The treatment modality used was radical external beam RT (EBRT) for 49.8% of patients (33 of 34 institutions), intraoperative RT (IORT) with or without EBRT for 44.3% of patients (10 of 34 institutions), and postoperative RT (PORT) for 5.9% of patients (14 of 34 institutions). IORT was administered using a 6–18-MeV electron beam. The treatment field consisted of the primary tumor only in 484 (55.6%) of 870 patients and the primary tumor plus regional lymph nodes in 386 (44.4%. CT-based treatment planning and conformal RT was used in >90% and >80% of patients treated with external beam RT, respectively. Chemotherapy was administered to approximately 80% of patients.

Total radiation dose and radiation field

The total radiation dose was analyzed according to the treatment modality. The median dose of the EBRT group, IORT with or without EBRT group, and PORT group was 50.4 Gy (range, 6–60.8), 25 Gy (range, 12–30; IORT) with or without 45 Gy (range, 6–50; EBRT), and 50 Gy (range, 12–60), respectively. For the EBRT group, most of the patients were treated with a total dose of 50–54.9 Gy (Fig. 2). For the PORT group, most of the patients were treated with a total dose of 50–54.9 Gy (Fig. 3). Moreover, the total radiation doses of the EBRT and PORT groups were not significantly different (p = .40). Therefore, almost uniform total doses were used for the EBRT and PORT groups. The median total dose for patients with negative surgical margins and those with positive surgical margins in the PORT group was 50 Gy (range, 12–56) and 50 Gy (range, 39.6–60), respectively (p = .29). However, for the IORT with or without

Table 2. Treatment characteristics (n = 870)

Characteristic	Patients/total (*n*)
Investigational protocol	
Yes	181/870 (20.8)
No	689/870 (79.2)
Treatment modality	
Radical EBRT	434/870 (49.8)
IORT with or without EBRT	385/870 (44.3)
With EBRT	184
Without EBRT	201
PORT	51/870 (5.9)
Radiation field	
Primary only	484/870 (55.6)
Primary plus regional lymph nodes	386/870 (44.4)
Radiation portals	
2 portals	43/669 (6.4)
≥3 portals	626/669 (93.6)
EBRT beam energy (MV)	
<10	39/669 (5.8)
≥10	630/669 (94.2)
EBRT dose/fraction (Gy)	
<1.8	3/669 (4.5)
1.8	266/669 (39.8)
2.0	338/669 (50.5)
>2.0	62/669 (5.2)
EBRT total radiation dose (Gy)	
<40	84/669 (12.6)
≥40	585/669 (87.4)
CT-based treatment planning	
Yes	616/669 (92.1)
No	53/669 (7.9)
Conformal therapy	
Yes	545/669 (81.5)
No	124/669 (18.5)
IORT dose (Gy)	
<25	104/385 (27.0)
≥25	281/385 (73.0)
Chemotherapy	
Yes	691/870 (79.4)
No	179/870 (20.6)

Abbreviations: EBRT = external beam radiotherapy; IORT = intraoperative radiotherapy; PORT = postoperative radiotherapy.
Data in parentheses are percentages.

EBRT group, significant variations in the IORT and EBRT doses were found. For IORT, the dose was 20–35 Gy (Fig. 4a). For EBRT, 79 (42.9%) of 184 patients were treated with EBRT with a dose of 50–54.9 Gy, and 83 (45.1%) received EBRT with a dose of <45 Gy (Fig. 4b). Significant differences were found in the total dose between the EBRT group and the IORT with or without EBRT group (p <.0001) and between the PORT group and the IORT with or without EBRT group (p <.0001).

Table 3 lists the radiation field according to the treatment modality and clinical N stage. Approximately 45% of patients received RT to the primary tumor (bed) only, irrespective of the treatment modality. The radiation field of the patients with Stage N0 was more frequently the primary tumor (bed) only, and for those with Stage N1, it was more frequently the primary tumor (bed) plus the regional lymph nodes. However, some patients with clinical Stage N1 also underwent RT to the primary tumor (bed) only.

Chemotherapy

Chemotherapy was used in combination with RT for 691 patients (79%). Table 4 lists the drugs and timing of chemotherapy for 691 patients treated with chemotherapy. Of the 691 patients, 66 (9.6%) were treated with chemotherapy before RT, 531 (76.8%) during RT, and 364 (52.7%) after RT. Gemcitabine was the most frequently used drug (n = 515, 74.5%), followed by 5-fluorouracil (5-FU) (n = 211, 30.5%), cisplatin (n = 72, 10.4%), a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and oteracil potassium (TS-1; n = 60, 8.7%), tegafur/uracil (UFT; n = 3, 4.5%), and others (n = 9, 1.3%).

DISCUSSION

Although the results of nationwide surveys of surgical management of pancreatic cancer have been reported (14–18), little information is available regarding the nationwide patterns of RT practice for pancreatic cancer. The National Cancer Database reports and the Surveillance, Epidemiology, and End Results registry have provide data on the proportions of patients treated with RT, but detailed information on RT use has not been described (19, 20). In the present study, we have reported in detail on the patterns of RT practice for pancreatic cancer in Japan between 2000 and 2006. From national surveys of structural characteristics of radiation oncology in Japan, approximately 700 radiation oncology centers were in Japan during the survey period (6, 7). In the present study, although only 34 radiation oncology centers in Japan participated and the patients were not randomly selected, we believe these results, at least roughly, represent the national averages in Japan of the patterns of RT for pancreatic cancer.

Concerning the patient characteristics, our results indicated that >80% of Japanese patients treated with RT had advanced disease, with approximately 70% of patients presenting with unresectable disease, in accordance with previous reports that approximately 80% of patients present with unresectable disease (16, 21). Our results also indicated that the patient performance status was generally good and that >80% of patients were <70 years old. These results indicate that although most of the patients referred for RT had advanced disease, many patients appeared to be good candidates for intensive treatment. In the present study, approximately 30% of patients each were alcohol drinkers, smokers, or had diabetes mellitus. In the United States, 60–81% of patients with pancreatic cancer had diabetes mellitus (22). However, it is not known whether these differences between patients living in Japan and in the United States resulted from differences in access to medical care or biologic differences within the tumors themselves. Additional investigation of the different disease characteristics of the patients in the two countries would be informative.

The present study also showed the treatment characteristics for pancreatic cancer in Japan. No definite treatment guidelines are available for radical and adjuvant RT for pancreatic cancer. Therefore, the National Comprehensive

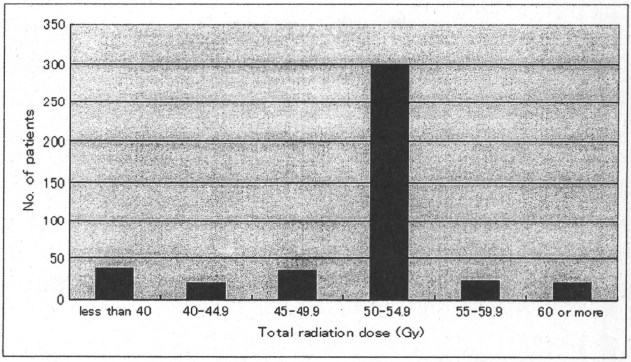

Fig. 2. Distribution of patients treated with radical external beam radiotherapy (EBRT) according to total radiation dose.

Cancer Network (NCCN) panel has recommended that investigational options should be considered for all stages of disease management (23). In the present study, 20.8% of patients were treated with an investigational protocol. Because many patients have relatively good performance status and are relatively young, investigational protocols should be encouraged for a greater number of patients.

With regard to the treatment modality, not only radical EBRT, but also IORT with or without EBRT, was used frequently in Japan. This high rate of IORT using an electron beam might be a unique characteristic of treatment in Japan, although not many institutions (10 of 34 institutions) had instituted IORT. Routine use of IORT combined with EBRT and/or chemotherapy began in Japanese hospitals in the 1980s (24, 25). The results of the present study have indicated that IORT combined with EBRT has continued to be commonly used into the 21st century. IORT is a specialized RT technique that can increase the radiation dose to the primary tumor volume and has been used to improve local tumor control without increasing normal tissue morbidity. A lower incidence of local failure in most series and improved median survival in some patients have been reported with these techniques when combined with conventional EBRT; however, it is uncertain whether this resulted from superior treatment or case selection (4, 26). Therefore, additional prospective studies are needed to assess the efficacy of IORT.

The results of the present study have indicated that CT-based treatment planning and conformal RT were used for >90% and >80% of patients, respectively. The NCCN guidelines strongly recommend the use of CT-based treatment planning and three-dimensional treatment planning (23). From national surveys of the structural characteristics of

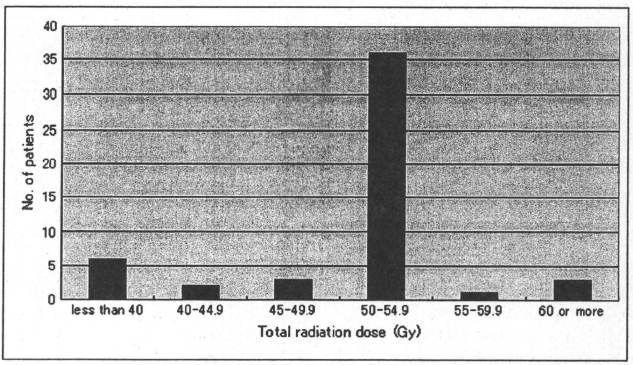

Fig. 3. Distribution of patients treated with postoperative radiotherapy (PORT) according to total radiation dose.

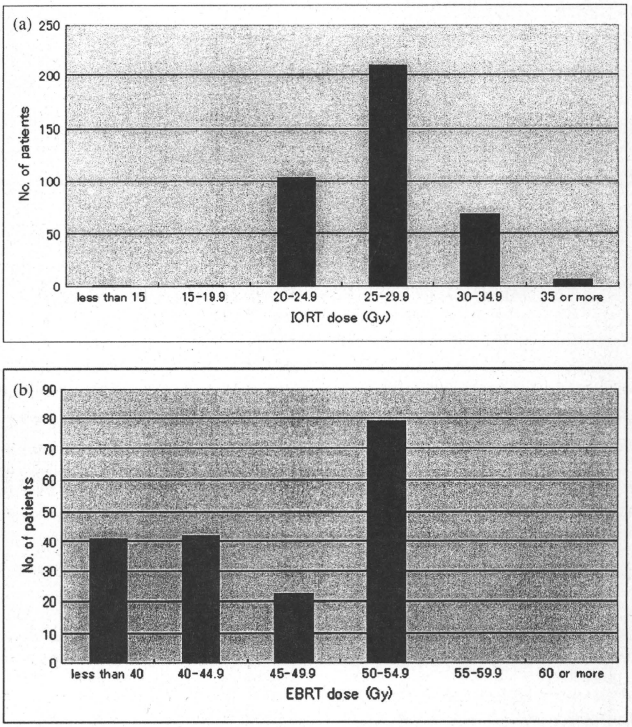

Fig. 4. Distribution of patients treated with (a) intraoperative radiotherapy (IORT) and (b) those treated with IORT plus external beam radiotherapy (EBRT) according to total radiation dose.

radiation oncology in Japan, only 329 (45.3%) of 726 facilities in 2003 and 407 (57.2%) of 712 facilities in 2005 have used CT-based treatment planning (6, 7). These results suggest that patients with pancreatic cancer have undergone RT more often in the facilities with advanced equipment than in facilities without advanced equipment.

Although the optimal radiation dose has yet to be defined, the NCCN guidelines have recommended that for primary definitive chemoradiotherapy, a dose of 50–60 Gy (1.8–2.0 Gy/d) should be administered (23). The NCCN guidelines have also recommended that PORT should be administered at a dose of 45–54 Gy (1.8–2.0 Gy/d). In the present study, most patients were treated with a total dose of 50–54.9 Gy in both the EBRT and the PORT groups. Therefore, almost uniform total doses were used for the EBRT and PORT groups, and the NCCN guideline recommendations appear to have been properly adopted by the Japanese radiation oncology centers. In contrast, for the IORT with or without EBRT group, significant variations in the total doses of IORT and EBRT were found. Concerning IORT, almost all patients were treated with a total dose of 20–35 Gy, and for EBRT, many patients were treated with a total dose of $\leq$50–54.9 Gy; however, a total dose <45 Gy was also given to some patients. From the previous reports of IORT for pancreatic cancer, the doses have varied among institutions from 10 to 30 Gy (24, 25). These results indicate that the optimal doses of IORT and EBRT have yet to be determined. Additional studies are required to determine the optimal doses when IORT is used.

Concerning the radiation field, our results have indicated that for approximately 45% of patients, the primary tumor (bed) only was treated with RT, irrespective of the treatment modality. Also, for each group analyzed, patients with clinical Stage N0 were more likely to receive treatment covering the primary tumor (bed) only, although some patients with clinical Stage N1 were also treated with the radiation field

Table 3. Radiation field according to treatment modality and clinical N stage

Group	Patients (*n*)	Radiation field		*p*
		PT only	PT plus LNs	
Radical EBRT				<.0001
Total	434	208 (47.9)	226 (52.1)	
N0	263	171	92	
N1	167	33	134	
Unknown	4	4	0	
IORT				<.0001
Total	385	152 (39.5)	233 (60.5)	
N0	162	111	52	
N1	184	36	147	
Unknown	39	5	34	
PORT				.002
Total	51	24 (47.1)	27 (52.9)	
N0	28	16	12	
N1	22	7	15	
Unknown	1	1	0	
Total	870	386 (44.4)	484 (55.6)	

Abbreviations: PT = primary tumor (bed); LNs = regional lymph nodes; other abbreviations as in Table 2.
Data in parentheses are percentages.

covering the primary tumor (bed) only. Although the optimal radiation field for pancreatic cancer remains to be defined, the NCCN practice guidelines have recommended that when 5-FU–based chemoradiotherapy is used, the treatment volumes should include the primary tumor location and the regional lymph nodes (23). Several reports have indicated that the rate of severe toxicity is greater in patients treated with gemcitabine-based chemoradiotherapy than in those treated with 5-FU–based chemoradiotherapy (27). Additional studies investigating the optimal radiation field when using chemotherapy drugs, such as gemcitabine, should be conducted.

The present study revealed that chemotherapy was routinely administered with RT. In the United States, a trend has occurred from using RT alone to the more frequent use of combined RT and chemotherapy (16). Regarding the drugs used for pancreatic cancer, 5-FU, with or without mitomycin-C, has been frequently used for pancreatic cancer (28, 29). In 1997, Burris *et al.* (30) indicated that single-agent gemcitabine was marginally superior in clinical benefit and survival compared with 5-FU. Therefore, single-agent gemcitabine has become the standard first-line agent for the treatment of pancreatic cancer. In the present study, gemcitabine was commonly used in conjunction with RT during the survey period. These results indicate that the use of gemcitabine combined with RT has been rapidly adopted in Japan.

Table 4. Drugs used and timing of chemotherapy (n = 691)

Variable	Actual patients (*n*)	Chemotherapy timing* (*n*)		
		Before RT	During RT	After RT
Actual patients (*n*)	691 (100)	66 (9.6)	531 (76.8)	364 (52.7)
Drugs				
GEM	515 (74.5)	59	341	283
5-FU	211 (30.5)	2	173	47
Cisplatin	72 (10.4)	5	60	19
T-1	60 (8.7)	5	29	39
UFT	31 (4.5)	2	13	19
Other	9 (1.3)	0	4	2

Abbreviations: RT = radiotherapy; GEM = gemcitabine; FU = fluorouracil; T-1 = combination of tegafur, 5-chloro-2, 4-dihydroxypyridine, and oteracil potassium; UFT = tegafur/uracil.
Data in parentheses are percentages.
* For combination chemotherapy, each drug of combination was counted.

In the present study, the results have shown that chemotherapy was most often administered during RT and next often after RT. These results indicate that chemotherapy during RT (concurrent chemoradiotherapy) has been the more frequent practice in Japan. Many investigators also administer chemoradiotherapy initially and then follow with chemotherapy until disease progression (31–34). Recently, several reports have indicated that a period of chemotherapy followed by consolidated chemoradiotherapy might be preferable to upfront chemoradiotherapy (35, 36). Additional studies investigating the optimal sequencing of RT and chemotherapy should be undertaken.

CONCLUSION

The present report has described the general patterns of RT practice for pancreatic cancer in Japan. Most patients had advanced unresectable disease, and not only radical EBRT, but also IORT with or without EBRT, was frequently used. Concerning chemotherapy, gemcitabine was commonly used in conjunction with RT in Japan. Our study has also shown extensive variation exists with regard to treatment strategies and the patterns of RT. Therefore, patients with pancreatic cancer should continue to be enrolled in prospective studies investigating novel combinations of chemotherapy and/or biologic agents with RT. In the future, repeat surveys and point-by-point comparisons with the results from other countries will demonstrate how RT for pancreatic cancer has been developed and optimized for patients in Japan.

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