Table 1. Patient and disease characteristics

	No. of Patients	%
Age (median: 64 y)		
< 70	143	68.1
≥ 70	67	31.9
Gender		
Female	88	41.9
Male	122	58.1
Primary site		
Head	143	68.1
Body	51	24.3
Tail	14	6.7
Unknown	2	0.9
Maximum tumor size (median: 3 cm)		
< 3.0 cm	92	43.8
≥ 3.0 cm	116	55.2
Unknown	2	0.9
ECOG performance status scale		
0	35	16.7
1	146	69.5
2	23	11.0
3	2	0.9
Unknown	4	1.4
CA19-9 (U/ml) (median: 131.5)		
< 1000	160	76.2
≥ 1000	38	18.1
Unknown	12	5.7
Pathological T stage (UICC 2002)		
Is	1	0.5
1	22	10.5
2	53	25.2
3	98	46.7
4	35	16.7
Unknown	1	0.5
Pathological N stage (UICC 2002)		
0	51	24.3
1	153	72.9
Unknown	6	2.8
Degree of resection		
R0	147	70.0
R1	63	30.0

Abbreviations: ECOG = Eastern Cooperative Oncology Group; CA19-9 = carbohydrate antigen 19-9; UICC = International Union Against Cancer; R0 = gross complete resection with negative margins; R1 = gross complete resection with positive margins.

Table 2. Treatment characteristics

Treatment	No. of Patients/Total	%
RT method		
IORT with EBRT	62/210	29.5
IORT without EBRT	148/210	70.5
IORT doses		
20 Gy	64/210	30.5
25 Gy	90/210	42.9
30 Gy	56/210	26.7
Maximal IORT field size		
3-5	34/210	16.2
6	129/210	61.4
7-9	47/210	22.4
IORT beam energy (MeV)		
(median: 10 MeV)		
< 9	10/210	4.8
9	62/210	29.5
10–11	58/210	27.6
12	49/210	23.3
> 12	31/210	14.8
Radiation field of EBRT		
Primary + LN	42/62	67.7
Primary only	20/62	32.3
EBRT total radiation dose (Gy)		
(median: 45 Gy)		
< 40	15/62	24.2
40-44.9	7/62	11.3
45-49.9	13/62	21.0
50	26/62	42
> 50	1/62	1.6
CT-based treatment planning		
for EBRT		
Yes	60/62	96.8
No	2/62	3.2
Conformal therapy of EBRT		
Yes	59/62	95.2
No	3/62	4.8
Chemotherapy use		
Yes	114/210	54.3
No	96/210	45.7

Abbreviations: EBRT = external beam radiotherapy; IORT = intraoperative radiotherapy; RT = radiotherapy; LN = regional lymph nodes; CT = computed tomography.

shielded from the radiation beam (8). Therefore, IORT allows tissues with residual microscopic disease to be irradiated at high doses while simultaneously reducing the risk of radiation-related toxicity. However, information regarding the results of IORT for resected pancreatic cancer is limited, and the precise role of IORT for resected pancreatic cancer remains to be elucidated.

In the current study, we reviewed a retrospective and multi-institutional series of 210 pancreatic cancer patients who were treated with gross complete resection followed by IORT with or without EBRT, and evaluated the efficacy and safety of IORT for resectable pancreatic cancer.

METHODS AND MATERIALS

The Japanese Radiation Oncology Study Group (JROSG) conducted a nationwide questionnaire survey of radiotherapy for non-metastatic pancreatic cancer patients treated between 2000 and 2006. The questionnaire included detailed information regarding patient characteristics, treatment characteristics, and treatment outcomes. Details of the JROSG survey have been described elsewhere (9). In brief, 34 radiation oncology centers in Japan that belong to the JROSG agreed to participate in this survey, and detailed information on 870 patients was acquired. Of these, 217 patients were treated with gross complete resection and IORT with or withou EBRT. The histology of 210 patients was adenocarcinoma, 5 patients had other histologies, such as anaplastic carcinoma and undifferentiated carcinoma, and 2 patients had no histological information. These latter 7 patients were excluded from this analysis, and the remaining 210 patients with histologically diagnosed adenocarcinoma were included in the current study.

Patient and disease characteristics in all 210 patients are shown in Table 1. The median age of all patients was 64 years (range, 36–88 years) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ranged from 0 to 3 (median: 1). One-hundred fifty-two patients (70.0%) underwent R0 resection, and the remaining 65 patients underwent R1 resection (R0: gross complete

Table 3. Agents and chemotherapy schedules (n = 114)

		No. of Patients administered Timing		
	No of actual Patients (%)	Before RT	During RT	After RT
No. of actual Patients(%)	114 (100%)	23 (20.2%)	40 (35.1%)	97 (85.1%)
Drugs				
GEM	82 (71.9%)	2*	34*	64*
5FU	26 (22.8%)	0	7*	19*
S-1	13 (11.4%)	0	1*	12*
CDDP	10 (8.8%)	0	5*	5*
UFT	10 (8.8%)	0	0	10*

Abbreviations: RT = radiotherapy; GEM = gemcitabine; FU = fluorouracil; CDDP = cisplatin; UFT = tegafur/uracil; S-1 = a combination of tegafur, 5-chloro-2, 4-dihydroxypyridine, and oteracil potassium.

* When combination chemotherapy was used, each drug of combination has been counted.

resection with negative margins; R1 = gross complete resection with positive margins). We used the tumor staging system devised by the Union Internationale Contre le Cancer (10). More than 80% of patients had pathological T0–3 disease, and more than 70% of patients had pathological N1 diseases. The median maximum tumor size was 3.0 cm (range, 1–8.3 cm) and the median serum concentration of carbohydrate antigen 19-9 (CA19-9) was 131.5 U/ml (range: 0–99,999 U/ml). All patients had undergone total or regional pancreatectomy with radical lymph node dissection of the para-aortic area as well as peripancreatic regional nodes. Total pancreatectomy, distal pancreatectomy, pancreaticoduodenectomy, and the Appleby procedure was performed for 4, 48, 152, and 6 patients, respectively.

Treatment characteristics in all 210 patients are shown in Table 2. With respect to radiotherapy method, 62 patients (29.5%) were treated with IORT with EBRT and the remaining 148 patients (70.5%) were treated IORT without EBRT. The IORT was administered using a 6–15 MeV electron beam, and the IORT doses ranged from 20 to 30 Gy (median: 25 Gy). Of the 62 patients treated in conjunction with EBRT, the total doses of EBRT (International Commission on Radiation Units and Measurements 50) ranged from 20 to 60 Gy (median: 45 Gy) with a single fraction of 1.8–2 Gy 5 days per week. The treatment of IORT field was designed to cover the tumor bed with a minimum of 1-cm margins for almost all patients. Treatment cones of 5 × 5 to 7 × 7 cm square, 5- to 7-cm diameter circle were frequently used. The treatment field of EBRT consisted of the primary tumor only in 32.3% (20 of 62 patients) of patients and the primary tumor plus regional lymph nodes in the remaining 67.7% (42 of 62 patients) of patients. Computed tomography–based treatment planning and conformal radiotherapy were both used in more than 95% of patients treated with EBRT.

Chemotherapy was administered to 114 patients (54.3%). Agents and chemotherapy schedules are described in Table 3. When gemicitabine was administered before and during radiotherapy, a dosage of 1,000 mg/m^2 was usually administered weekly for 3 weeks with a 1-week rest, depending on response and toxicity. Some patients received gemcitabine at a dosage of 250–350 mg/m^2 intravenously weekly during radiotherapy for approximately 6 weeks. Gemicitabine maintenance chemotherapy was usually given at 1,000 mg/m^2 weekly for 3 weeks with a 1-week rest until disease progression or unacceptable toxicity. 5-fluorouracil (5FU) was generally administered via continuous infusion at 200–300 mg/m^2/day daily just before each irradiation as part of the chemoradiotherapy protocol. After the completion of chemoradiotherapy, patients continued receiving 300–500 mg/m^2 5FU intravenous bolus infusion until evaluation by computed tomography revealed tumor progression. The S-1 was administered orally twice daily on the day of irradiation during and after radiotherapy, in dosages ranging from 50 to 80 mg/m^2. Patients treated with cisplatin (CDDP) received approximately 5 mg/m^2 during and/or after radiotherapy. Tegafur/uracil (UFT) was administered at 300 mg/m^2 daily during and/or after radiotherapy.

Distributions of patients according to treatment modality, degree of resection, maximum tumor size, and PS were indicated in Table 4. In the current study, there were no definitive treatment policies for pancreatic cancer during the survey period; thus, treatment was determined by the respective physicians at each institution. We assigned 210 patients into 12 treatment modality groups by EBRT use (Yes vs. No), chemotherapy use (GEM vs. Non-GEM–Chemo vs. No), and degree of resection (R0 vs. R1) and analyzed whether the degree of resection influenced IORT dose, EBRT dose, maximum tumor size, and PS (Table 5). There were no significant differences in IORT dose, EBRT dose, maximum tumor size, or PS

Table 4. Distribution of patients according to treatment modality, degree of resection, maximum tumor size, and performance status

		Degree of resection		Maximum tumor size (cm)			Performance status			
Treatment modality	No. of Patients	R0	R1	<3.0	≥3.0	Unknown	0	1	2–3	Unknown
IORT										
20 Gy	64	38	26	22	41	1	6	44	12	2
25 Gy	90	64	26	44	45	1	21	55	13	1
30 Gy	56	45	11	26	30	0	8	47	0	1
EBRT										
No	148	107	41	62	85	1	30	95	19	4
< 40 Gy	15	14	1	13	2	0	3	8	4	0
40–50 Gy	46	25	21	16	29	1	2	42	2	0
> 50 Gy	1	1	0	1	0	0	0	1	0	0
Chemotherapy use										
No	96	74	22	40	56	0	13	77	5	1
Non-GEM	32	21	11	14	17	1	7	22	2	1
GEM	82	52	30	38	43	1	15	47	18	2

Abbreviations: IORT = intraoperative radiotherapy; EBRT = external beam radiotherapy; R0 = gross complete resection with negative margins; R1 = gross complete resection with positive margins; GEM = gemcitabine.

Table 5. Comparisons of IORT dose, EBRT dose, tumor size and PS according to the degree of resection in each treatment modality

Treatment modality group	Degree of resection	No. Patients	IORT dose (Gy)				EBRT dose(Gy)				Maximum tumor size (cm)				PS			
			Median	Mean	Range	*p* Value	Median	Mean	Range	*p* Value	Median	Mean	Range	*p* Value	Median	Mean	Range	*p* Value
IORT	R0	64	30.0	27.3	20–30	0.7952	-	-	-	-	3.0	3.2	1.0–8.3		1	0.9	0–2	0.9956
IORT	R1	16	30.0	27.5	20–30		-	-	-		3.6	4.0	1.5–10.0	0.1665	1	0.9	0–3	
IORT + EBRT	R0	10	20.0	21.5	20–25		49.6	44.9	30–50		2.9	2.7	1.0–3.9		1	1	1–1	0.4000
IORT + EBRT	R1	5	20.0	22.0	20–25	0.7388	50.0	49.0	40–50	0.1332	3.5	3.5	3.0–4.0	0.0709	1	0.8	0–1	
IORT + Non-GEM-Chemo	R0	13	20.0	23.4	20–30		-	-	-		2.8	3.0	1.0–3.9		1	0.8	0–2	0.7793
IORT + Non-GEM-Chemo	R1	8	20.0	22.1	20–30	0.3834	-	-	-	-	3.5	3.3	3.0–4.0	0.3135	0	0.75	0–2	
IORT + EBRT + Non-GEM-Chemo	R0	7	25.0	22.9	20–25		38.0	39.7	20–60		2.8	3.0	2.0–4.5		1	1.1	1–2	0.4000
IORT + EBRT + Non-GEM-Chemo	R1	5	20.0	22.0	20–25	0.2216	50.0	50.0	50–50	0.1030	4.1	4.1	3.0–5.0	0.0848	1	1	1–1	
IORT + GEM	R0	30	25.0	24.7	20–30		-	-	-		3.0	3.1	1.7–5.5		1	0.9	0–3	0.0778
IORT + GEM	R1	17	25.0	23.2	20–30	0.1596	-	-	-		3.0	3.3	2.0–5.0	0.5557	1	1.3	0–2	
IORT + EBRT + GEM	R0	23	25.0	23.6	20–25		40.0	40.4	30–50		2.1	2.7	1.3–7.0		1	1.1	0–2	0.3628
IORT + EBRT + GEM	R1	12	25.0	22.9	20–25	0.3857	45.0	45.1	26–50	0.0787	3.0	3.0	1.0–5.0	0.6158	1	0.9	0–2	

Abbreviations: IORT = intraoperative radiotherapy; EBRT = external beam radiotherapy; PS = performance status; GEM = gemcitabine; Chemo = chemotherapy; R0 = gross complete resection with negative margins; R1 = gross complete resection with positive margins.

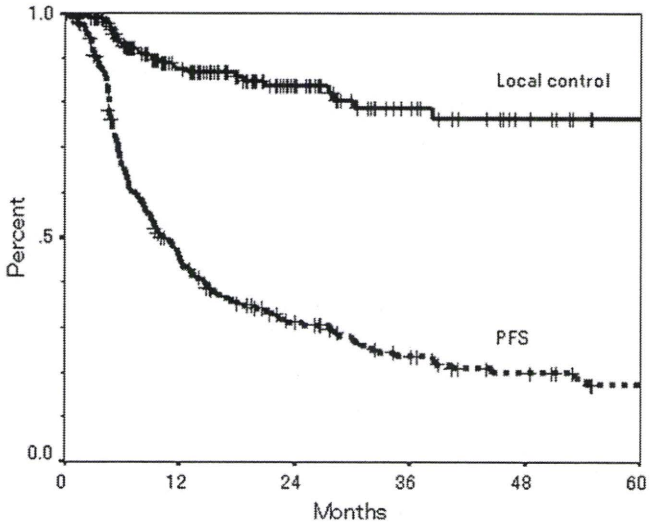

Fig. 1. Local control and progression free survival (PFS) curves for 210 patients with pancreatic cancer who were treated with gross complete resection.

according to the degree of resection in each treatment modality group.

The median follow-up of the surviving 62 patients was 26.3 months (range, 2.7–90.5 months). Overall survival (OS), progression-free survival, metastasis-free rates, and local control rates were calculated actuarially according to the Kaplan-Meier method (11) and were measured starting from the day of initial treatment. Differences between groups were estimated using the chi-square test, Student's *t* test, and the log rank test (12). Multivariate analysis was performed using the Cox regression model (13). A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed using the SPSS software package (version 11.0; SPSS, Inc., Chicago, IL). Late complications were graded in accordance with the National Cancer Institute—Common Terminology Criteria (NCI-CTC) Version 3.0.

RESULTS

At the time of this analysis, 150 patients (70.0%) had disease recurrence (local only in 23 patients; regional lymph nodes only in 7 patients; liver only in 49 patients; peritoneum only in 28 patients; other distant metastases, such as at bone or lung, only in 16 patients; and multiple sites in 43 patients). Among 43 patients with multiple recurrences, 9 patients had a simultaneous local recurrence. Therefore, local recurrence occurred in a total of 31 patients (14.8%). The 2-year actuarial local control rate in all 210 patients after radiotherapy was 83.7% (Fig. 1). Patients who underwent R0 resection had a statistically significantly higher local control than those who underwent R1 resection ($p = 0.0226$), and the 2-year actuarial local control rates in patients who underwent R0 resection and R1 resection were 87.1% and 74.6%, respectively (Table 6). By contrast, other factors, such as CA19-9, the use of chemotherapy, pathological N stage, and IORT dose, did not influence local control (Table 6).

The proportions of patients with locally controlled disease were analyzed with respect to IORT doses, degree of resection, and RT modality (Table 7). In patients treated with R0 resection, the incidence of locally control was highest in patients treated with 25 Gy-IORT + EBRT (96%) in comparison with other subgroups. However, no significant difference in local control was observed in comparison with patients treated with 25 Gy-IORT (93%, $p = 0.6259$). Furthermore, in patients treated with R1 resection, the incidence of local control was highest in patients treated with 25 Gy-IORT + EBRT (90%) compared with that in any other subgroups. Nevertheless, no significant difference in local control was noted between patients treated with 25 Gy-IORT and EBRT and those treated with 25 Gy-IORT alone (69%, $p = 0.2109$).

Table 6. Local control rates and metastasis-free rates according to the degree of resection, CA 19-9 level, chemotherapy use, pathological N stage, and IORT dose

	No. of Patients	2-year LCR (%)	*p* Value	2-year MFR (%)	*p* Value
Degree of resection					
R0	147	87.1	0.0226	44.6	0.0148
R1	63	74.6		25.8	
CA19-9 (U/mL)					
< 1000	160	84.2	0.5217	43.9	0.0030
≥ 1000	38	79.2		21.0	
Chemotherapy use					
Yes	96	88.6	0.2569	47.2	0.0044
No	114	80.5		29	
Pathological N stage					
N0	51	81.9	0.8059	61.9	0.0001
N1	153	85.2		30.2	
IORT dose					
< 25 Gy	64	78.1	0.1225	45.8	0.238
≥ 25 Gy	146	86.4		36.2	

Abbreviations: LCR = local control rate; MFR = metastasis-free rate; CA19-9 = carbohydrate antigen 19-9; R0 = gross complete resection with negative margins; R1 = gross complete resection with positive margins; IORT = intraoperative radiotherapy.

Of the 210 patients, 148 (70.5%) died during the period of this analysis. Of those 148 patients, 134 patients died of pancreatic cancer and the remaining 14 patients died without any sign of clinical recurrence (9 died of intercurrent disease and 5 of unknown cause). The 2-year actuarial progression-free survival rate and the median time to progression for all 210 patients were 31.2% and 10.1 months, respectively (Fig. 1). Table 4 indicates the metastasis-free rates according to the degree of resection, level of CA19-9, use of chemotherapy, and IORT dose. Degree of resection, CA19-9 level, chemotherapy use, and pathological N stage significantly influenced the metastasis-free rates, whereas IORT dose did not influence the metastasis-free rate. Figure 2 indicates the OS curves in all 210 patients. The median survival time and the 2-year actuarial OS rate in all 210 patients were 19.1 months and 42.1%, respectively. Concerning the use of chemotherapy, the 2-year OS rates for patients treated with chemotherapy (48.0%) was significantly higher than for those treated without chemotherapy (34.8%) ($p = 0.0011$, Fig. 3). On univariate analysis, use of chemotherapy, degree of resection, CA 19-9, and pathological N stage had a significant impact on OS and

Table 7. Proportions of patients with locally controlled patients treated with R0 and R1 resection with respect the IORT doses and the combination of EBRT

	No. of Patients	IORT dose			Total
		20 Gy	25 Gy	30 Gy	
R0 resection					
IORT alone	107	16/22 (73%)	39/42 (93%)	38/43 (88%)	93/107 (87%)
IORT + EBRT	40	14/16 (88%)	23/24 (96%)	-	37/40 (93%)
Total	147	30/38 (79%)	100/109 (92%)	38/43 (88%)	130/147 (88%)
R1 resection					
IORT alone	41	11/14 (79%)	11/16 (69%)	9/11 (82%)	31/41 (76%)
IORT + EBRT	22	9/12 (75%)	9/10 (90%)	-	18/22 (82%)
Total	63	20/26 (77%)	20/26 (77%)	9/11 (82%)	49/63 (78%)

Abbreviations: IORT = intraoperative radiotherapy; EBRT = external beam radiotherapy; R0 = gross complete resection with negative margins; R1 = gross complete resection with positive margins.

on multivariate analysis; these four factors also were significant prognostic factors (Tables 8 and 9). Other factors such as tumor size, PS, and radiotherapy modality did not influence OS. At the time of this analysis, 12 of 210 patients (5.7%) had survived for more than 5 years, and all 12 patients had achieved local control.

NCI-CTC Grade 3–4 late gastrointestinal toxicity was observed in 7 patients (3.3%). Four patients experienced Grade 4 toxicity (1 patient with Grade 4 colitis, 2 patients with Grade 4 gastrointestinal bleeding, and 1 patient with Grade 4 ileus). There were no cases of Grade 5 toxicity. Regarding 4 patients who experienced Grade 4 toxicity, 3 of 4 patients (75%) were treated with 30 Gy-IORT

DISCUSSION

The current study indicates that IORT yields an excellent local control rate for resected pancreatic cancer, with a 2-year local control rate of 83.7% in all 210 patients. Several reports have also demonstrated the efficacy of IORT on local control (14–18). Reni *et al.* indicated that for patients with Stage I–II diseases, IORT reduced the local failure rate from 60% to 27% ($p = 0.04$) (14). Alfieri *et al.* noted increased local control with the addition of IORT in resected pancreatic cancer, and they found that local control was 58% in the IORT group vs. 29% in the group that did not receive IORT ($p < 0.01$) (17). Zerbi *et al.* reported that local recurrence was detected in 27.0% of patients treated with surgery and IORT and in 56.4% of patients treated with surgery alone (18). Concerning EBRT, approximately 50% of patients treated with adjuvant EBRT experience local recurrence even after complete resection (4, 7). Considering the low local control rate in patients treated with surgery alone and those treated with adjuvant EBRT, IORT is an attractive treatment modality to achieve local control in patients with resected pancreatic cancer.

Although the efficacy of IORT for local control has been reported, the optimal use of IORT, such as dosing and EBRT combination strategies, remains unclarified. From the previous reports on IORT for pancreatic cancer, doses

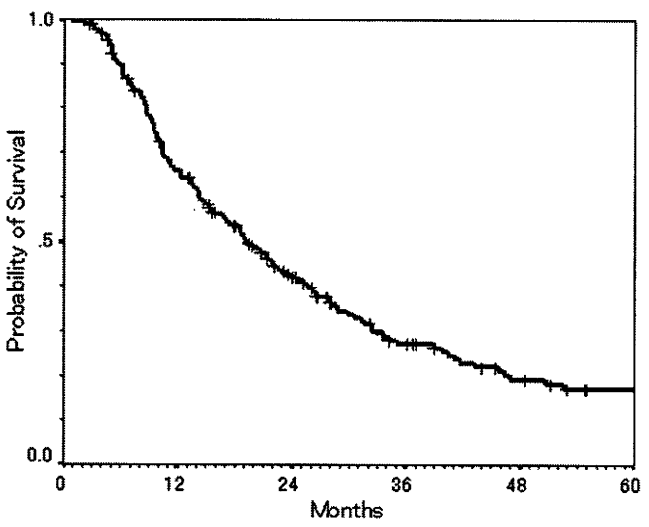

Fig. 2. Actuarial overall survival curves for 210 patients with pancreatic cancer who were treated with gross complete resection.

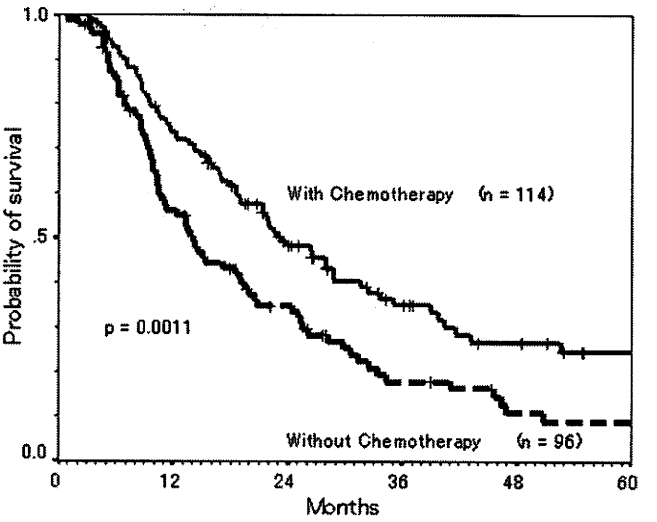

Fig. 3. Actuarial overall survival curves according to chemotherapy administration in patients with pancreatic cancer who were treated with gross complete resection and intraporative radiotherapy. A significant difference was observed between patients who did and did not receive chemotherapy ($p = 0.0011$).

Table 8. Univariate analysis of various potential prognostic factors for overall survival in patients with resected pancreatic cancer treated with IORT

	No. of Patients	Univariate analysis OS, 2- year rate (%)	*p* Value
Degree of resection			
R0	147	50.6	0.0001
R1	63	22.5	
Chemotherapy use			
Yes	114	48.0	0.0011
No	96	34.8	
CA19-9			
< 1000	160	48.2	0.0025
≥ 1000	38	18.9	
Pathological N stage			
N0	51	55.6	0.0038
N1	153	37.8	
Tumor size (cm)			
< 3	92	51.6	0.0550
≥ 3	116	35.0	
RT method			
IORT	148	39.4	0.119
IORT + EBRT	62	48.7	
PS			
0–1	181	43.5	0.2313
2–3	25	33.4	
Gender			
Female	88	41.1	0.5498
Male	122	42.8	
Age (y)			
< 70	143	42.7	0.7161
≥ 70	67	40.9	
Tumor site			
Head/body	197	42.4	0.7593
Tail	13	37.5	
IORT dose (Gy)			
< 25	64	37.1	0.8315
≥ 25	146	44.6	
Pathological T stage			
Tis-2	75	38.9	0.8916
T3–4	134	43.6	

Abbreviations: IORT = intraoperative radiotherapy; R0 = gross complete resection with negative margins; EBRT = external beam radiotherapy; R1 = gross complete resection with positive margins; CA19-9 = carbohydrate antigen; 19-9; PS = performance status.

varied among institutions ranging from 10 to 30 Gy (8, 19), and the optimal dose of EBRT when combined with IORT also has yet to be decided. In the current study, in patients treated with R0 resection, the incidence of locally control in patients treated with 25-Gy IORT (96%) was higher than in other subgroups. Therefore, in patients treated with R0 resection, 25-Gy IORT alone may be sufficient to prevent local recurrence. By contrast, in patients treated with R1 resection, the incidence of locally control in patients treated with 25-Gy IORT + EBRT (90%) was higher than in other subgroups but only 69% in patients treated with 25-Gy IORT alone. These results suggest that in patients treated with R1 resection, 25-Gy IORT alone was insufficient to achieve local control, and 25-Gy IORT + EBRT appears to be most appropriate for these patients. Further studies are required to determine the optimal doses for IORT in this patient population.

Table 9. Multivariate analysis of potential prognostic factors for overall survival in patients with resected pancreatic cancer treated with IORT

Variable	RR (95% CI)	*p* Value
Chemotherapy use (Yes vs. No)	1.795 (1.255–2.569)	0.001
Degree of resection (R0 vs. R1)	0.515 (0.349–0.761)	0.004
CA19-9 (<1000 U/mL vs. ≥ 1000 U/mL)	0.652 (0.430–0.988)	0.044
Pathological N stage (N0 vs. N1)	0.610 (0.388–0.958)	0.032

Abbreviations: IORT = intraoperative radiotherapy; R0 = gross complete resection with negative margins; R1 = gross complete resection with positive margins; RR = relative risk; CI = confidence intervals.

Despite the favorable local control rates in patients treated with IORT, the role of IORT in survival for these patients remains controversial (18–24). Sindelar *et al.* conducted a small randomized trial that compared adjunctive IORT with EBRT in patients with resectable pancreatic cancer and concluded that the survival rate did not differ among patients who received IORT, EBRT, or no EBRT (19). Fossati *et al.* reported that no significant benefit in survival was observed in the IORT group compared with the no-IORT group of 33 patients with resected pancreatic cancer, although the local control rate was significantly better in the IORT group (20). In contrast to these results, however, a survival advantage with IORT was reported by several groups. Ozaki *et al.* (23) suggested that IORT combined with radical resection and extended lymph node dissection may substantially improve survival. Reni *et al.* reported improved median survival with IORT at 18.5 months compared with 13 months in their non-IORT group (14). Therefore, it is important to evaluate possible factors affecting the prognosis of patients who undergo IORT.

Several previous studies have suggested potential prognostic factors associated with OS, such as degree of resection, tumor stage, and tumor size in patients treated with macroscopically gross resection and IORT (24–26). In the current study, chemotherapy use, degree of resection, CA 19-9 level, and pathological N stage were independent prognostic factors for OS. Also, these four factors significantly affected the metastasis-free rate. Therefore, our results indicate that distant metastases remain the major problem affecting survival in these patients. Takamori *et al.* conducted an extended study of radical resection combined with IORT for 41 patients with pancreatic cancer, and local recurrence occurred in only 2 patients (4.9%), but cancer-related death occurred in 32 patients, 18 of whom had liver metastases (16). Furuse *et al.* conducted a study of IORT and EBRT with prolonged 5-FU infusion in patients with locally advanced pancreatic cancer, and the median survival time of patients without metastatic spread in the abdominal cavity was 12.9 months, whereas that of patients with metastatic spread was 5.8 months (27). Several other reports have indicated that the local and distant recurrence rates in these and other studies vary from 12 to 50% and 42 to 94%, respectively, with the use of IORT (14, 17, 28, 29). Therefore, in addition to achieving

local control, preventing distant metastases appears to be necessary for improving the prognosis of these patients.

Our results indicated that IORT combined with chemotherapy confers a survival benefit to pancreatic cancer patients in comparison with IORT alone. The use of chemotherapy also reduced the metastasis-free rate, suggesting that chemotherapy may prevent distant metastasis of these tumors. Recent reports have indicated that adjuvant radiotherapy and chemotherapy improves survival after surgery in comparison with patients with observation (30, 31). Herman *et al.* analyzed 908 patients who were treated with pancreaticoduodenectomy and found that adjuvant concurrent 5-FU–based chemotherapy and radiotherapy significantly improves OS in comparison with patients not receiving chemotherapy and radiotherapy (30). Corsini *et al.* reported the results in 472 patients treated with R0 resection, and OS was better in patients who received adjuvant chemotherapy and radiotherapy than in those not receiving chemotherapy and radiotherapy (31). Regarding drugs for pancreatic cancer, 5-FU, with or without mitomycin-C, has been frequently used for therapy of pancreatic cancer (32, 33). Recently, single-agent gemcitabine was found to be marginally superior in clinical benefit and survival compared with 5-FU, and a single-agent gemcitabine has become the standard first-line agent for the treatment of pancreatic cancer (34). More recent reports have indicated that S-1 and UFT are promising agents for pancreatic cancer (35, 36). Further evaluations of optimal sequencing of radiotherapy and these chemotherapy agents should be performed to maximize treatment outcomes for pancreatic cancer patients.

In the current study, 12 of 210 patients (5.7%) survived for more than 5 years, and all 12 patients had achieved local control. Recent reports have also indicated that achieving local control is associated with improved survival for patients with resected tumors (37–39). Valentini *et al.* indicated that patients achieving local control had significantly more favorable OS (3-year OS: 28.4%) than did patients who did not achieve local control (3-year OS: 11.9%) when treated with IORT (37). These results suggested that although metastasis still remains as the primary challenge for treatment of pancreatic cancer, improvement of local control induced by higher radiotherapy doses may affect the survival of patients who tend to have less disseminated disease. Inasmuch as chemotherapy alone appears to be insufficient for inducing favorable local control (Table 6), IORT represents an important treatment modality for better achievement of this goal.

In the current study, the frequency of severe late toxicity was only 3%, highlighting the safety of IORT treatment. Several other reports have also described the feasibility of IORT for pancreatic cancer (14, 15, 24, 40). Toxicity is different for each tissue type, but doses of approximately 25 Gy are generally well tolerated with IORT (41). In the current study, 3 of 4 patients who experienced Grade 4 toxicity (75%) were treated with 30 Gy-IORT, and 30 Gy-IORT may be associated with higher risk of late complications for these tumors. Therefore, when IORT is used, a dose of 25 Gy appears to be appropriate for these tumors. Further studies are required to determine the optimal timing and dose of EBRT when combined with IORT.

In conclusion, our results indicate that IORT yields an excellent local control rate for resected pancreatic cancer, with few severe late toxicities. Our results also suggest that IORT combined with chemotherapy confers a survival benefit in comparison with IORT alone. Inasmuch as IORT can result in favorable local control and the addition of chemotherapy increases the OS rate, IORT combined with chemotherapy appears to be a promising strategy for patients treated with gross complete resection. However, this study is a retrospective study with various treatment modalities, and further prospective studies are required to confirm our results.

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Predicting the Severity of Acute Urinary Toxicity after Brachytherapy with Iodine-125 for Localized Prostate Cancer

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Prostate cancer is one of the common cancers in the world. In Japan, prostate brachytherapy (PB) with iodine-125 has become a treatment option for localized prostate cancer since 2003. Nevertheless, severe acute urinary toxicity (AUT) remains as one of the intractable side effects. We assessed AUT and the changes in international prostate symptom score (IPSS) before and after PB for localized prostate cancer. IPSS is a questionnaire tool for tracking the subjective urinary symptoms. Between 2006 and 2009, 104 eligible patients underwent PB with iodine-125 were analyzed. AUT was graded with the radiation therapy oncology group (RTOG) scale. Eligible patients filled out IPSS questionnaires before and after PB. Clinical and treatment-related factors were examined for correlation with the severity of AUT and the interval to IPSS resolution. AUT of RTOG Grade 0 (no changes) and Grade 2 was detected in one and 96 patients, respectively, whereas seven patients (6.7%) experienced AUT of Grade 3. Thus, the incidence of severe AUT (Grade 3) after PB was low. A greater number of needles ($p = 0.012$) were associated with AUT of RTOG Grade 3 on the univariate analysis. The median interval to IPSS resolution was 6 months (7 ± 6 months). Greater post-implant maximal IPSS ($p < 0.001$) was associated with slower IPSS resolution, whereas higher pre-implant IPSS ($p < 0.001$) was associated with faster IPSS resolution on the multivariate analysis. In conclusion, reducing the number of needles in PB may be helpful for decreasing the rate of severe AUT.

Keywords: prostate cancer; brachytherapy; iodine-125; acute urinary toxicity; quality of life
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Prostate cancer is one of the common cancers in the world. The spread of prostate-specific antigen (PSA) screening has led to an increase in incidence and an increasing proportion of early, good-prognosis prostate cancers (Ferrer et al. 2008). Prostate brachytherapy (PB) is a standard treatment option for localized prostate cancer (LPC) because of its excellent long-term disease control and ability to conserve a patient's quality of life due to the relative absence of severe long-term side effects (Grimm et al. 2001; Potters et al. 2005). In Japan, PB with iodine-125 has become a treatment option for LPC since 2003. Nevertheless, severe acute urinary toxicity (AUT) such as irritative voiding symptoms and occasional prolonged catheterisation remain as common side effects (Bittner et al. 2007). Therefore, it is important to assess severe AUT and clarify the clinical and treatment factors related to severe AUT (Wallner et al. 2002; Beekman et al. 2005; Niehaus et al. 2006; Bittner et al. 2007). In addition, the inclusion of patient-reported toxicity data was reported to provide more detailed assessment of AUT (Namiki et al. 2006; Ash et al. 2007; Ferrer et al. 2008). Therefore, AUT after PB was examined using the radiation therapy oncology group (RTOG) scale as an objective parameter and the international prostate symptom score (IPSS) as a subjective variable in this study. IPSS was used to screen for diagnosis and tracking the subjective urinary symptoms of the benign prostatic hyperplasia (Bosch et al. 1995). In the present study, we describe the incidence and associated factors for AUT of RTOG Grade 3 and IPSS resolution as a surrogate for recovery from acute subjective urinary symptoms.

Patients and Methods

Eligibility criteria for PB

Eligible patients included those with low-risk disease (clinical stage T2a or lower, initial prostate specific antigen [iPSA] level ≤ 10.0 ng/mL and Gleason score (GS) ≤ 6), and "low-tier" intermedi-

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ate-risk disease (stage T2b or lower, iPSA 10-20 ng/mL, and GS ≤ 7) (Barrett et al. 2009). Patients with low-risk prostate cancer and a prostate volume (PV) of ≤ 40 cm^3 were treated with PB alone. Patients with GS =7 or PV larger than 40 cm^3 received neoadjuvant hormonal therapy (NHT) before PB to reduce PV.

We treated 130 patients with localized prostate cancer with iodine-125 permanent seed implantation at our institution between July 20, 2006 and June 1, 2009. Among the 130 patients, 21 patients who did not have a minimal follow-up of 6 months nor sufficient serial IPSS data at least three subsequent assessments after PB were not included in this analysis. In addition, the other five patients were excluded from the analysis because they did not fulfil one component of our eligibility criteria. Therefore, we analysed 104 patients in this study.

Written informed consent was obtained from each patient before PB. The research ethics board of Tohoku University School of Medicine approved this study.

Implant procedure

The pre-implant treatment planning was performed to assess pre-implant ultrasound PV (PUPV) about 1 month before the implant procedure. The patient was placed in the extended lithotomy position for the procedure. Implants were designed from transrectal ultrasound (TRUS) images of the prostate taken at 5-mm intervals from the base through the apex. The captured images were digitised with a planning computer using the VariSeed 7.1 planning system (Varian Medical Systems, Palo Alto, CA, USA). The clinical target volume was defined as the prostate visualised on the TRUS images. A prescribed dose of 145 Gy was designed to cover ≥ 95% of the planning target volume (PTV) (prostate with 3-5-mm margins). Using a peripheral loading technique, we set the treated volume to include the PTV within the prescribed isodose. The implantation was performed via TRUS guidance with the patient under spinal anaesthesia and in the extended lithotomy position with an aerated jelly in the urethral catheter allowed for identification of the urethra. A Mick applicator (Mick Radionuclear Instruments, Bronx, NY, USA) was used to deposit the seeds. I-125 was the only source used, with a mean activity of 0.34 mCi/seed (range, 0.29-0.40 mCi/seed). To minimise micturition problems, an alpha-blocker (silodosin, 8 mg/day, orally) was routinely prescribed to all patients from the day after implantation, and it was continued until it was no longer required symptomatically.

Computed tomography (CT) scans were obtained 1 day and 1 month after implantation for post-implant dosimetric analysis. Axial CT scan images of the pelvis were taken at 1-mm intervals. The PB radiation oncologist contoured the prostate and urethra carefully for each patient. The urethral dose was defined by doses at the centre of the prostate on CT images acquired 1 month after PB. The calculated dosimetry parameters were the percentage of prostate volume receiving 100%, 150%, and 200% of the prescribed minimal peripheral dose (prostate V_{100}, V_{150}, and V_{200}, respectively) and the minimal dose values received by 90% of the PV (prostate D_{90}). Additionally, the minimal dose values received by 90% of the urethra volume (urethral D_{90}) were recorded.

Outcome measurements

Clinical follow-up was started from the day of implantation. Current eligible patients filled out self-assessment IPSS questionnaires at pre-implant IPSS (as IPSS-baseline), and at 1, 3, 6, 12, and 24 months after treatment. The minimum IPSS follow-up for this study group was 6 months. Post-implant maximal IPSS (IPSS-max) was also recorded as the highest score for acute urinary symptoms within 3 months after PB. IPSS resolution was defined as a return of IPSS-max to within 2 points of the IPSS-baseline score.

Assessment of AUT

AUT was graded using the RTOG scale (Lawton et al. 1991). According to that scale, AUT was defined as morbidity occurring within 3 months after seed implantation. The RTOG scale of AUT is as follows:

RTOG Grade 0: no change.

RTOG Grade 1: frequency of urination or nocturia twice the pre-treatment habit; dysuria; urgency not requiring medication.

RTOG Grade 2: frequency of urination or nocturia less frequent than every hour. Dysuria, urgency, or bladder spasm requiring a local anesthetic (e.g., Pyridium).

RTOG Grade 3: frequency with urgency and nocturia hourly or more frequently; dysuria, pelvic pain, or bladder spasm requiring regular, frequent narcotics; gross hematuria with or without clot passage; obstruction requiring an indwelling catheter or a minor procedure.

RTOG Grade 4: hematuria requiring transfusion; acute bladder obstruction not secondary to clot passage; ulceration or necrosis.

Statistical analyses

Clinical, treatment-related, and dosimetric factors were assessed for univariate and multivariate correlations with acute urinary RTOG Grade 3 or worse toxicities and the interval to IPSS resolution. Clinical and treatment-related factors included patient age, iPSA level, diabetes, hypertension, the utilisation of NHT, presence of acute urinary retention, IPSS-baseline, IPSS-max, PUPV, CT-determined PV 1 day (CTPV1D) and 1 month after implant (CTPV1M), the ratio between CTPV1D and CTPV1M as a surrogate of post-implant oedema, and the number of needles and seeds used. Dosimetric factors included prostate V_{100}, V_{150}, V_{200}, prostate D_{90}, and urethral D_{90}.

The interval to IPSS resolution was examined using Kaplan-Meier curves. We assessed the relationship between the interval to IPSS resolution and those factors using the log-rank test and Mann-Whitney *U*-test for the univariate analysis (UVA) and a Cox proportional hazard regression analysis for the multivariate analysis (MVA). All factors were input to the MVA. Furthermore, the correlation between acute urinary RTOG Grade 3 or worse toxicities and these variables excluding acute urinary retention was evaluated. Because acute urinary retention was considered to be one of the acute urinary Grade 3 or worse toxicities, the chi-square test and Mann-Whitney *U*-test were used in the UVA. The logistic regression test was performed for the MVA. These analyses were conducted using SPSS 11.0 (SPSS, Chicago, IL, USA). Differences were regarded as statistically significant at *P*-values less than 0.05.

Results

The patient characteristics are shown in Table 1. The median follow-up period was 21 months (range, 6-36 months). No patient received supplementary external beam radiotherapy or adjuvant hormonal therapy.

AUT of RTOG Grade 3 and acute urinary retention

AUT of RTOG Grade 0 and AUT of Grade 1-2 were

Table 1. Patient characteristics.

Factors				n = 104 Patients (n) (%)
Clinical stage*	T1c			79 (76)
	T2a			24 (23)
	T2b			1 (1)
Hypertension				38 (36.5)
Diabetes				15 (14.4)
NHT				45 (43.3)
Age (y)	Median	66	Range	50-77
Gleason score	Median	7	Range	4-7
iPSA	Median	5.9	Range	1.5-19.3
PUPV (cm^3)	Median	24.1	Range	9.3-39.8
CTPV1D (cm^3)	Median	25.3	Range	10.8-44.7
CTPV1M (cm^3)	Median	21.3	Range	9.0-37.4
CTPV1D/ CTPV1M ratio	Median	1.2	Range	0.8-1.9
Number of needles	Median	26	Range	17-45
Number of seeds	Median	70	Range	45-89
V_{100} (%)	Median	97.3	Range	78.9-100
V_{150} (%)	Median	64	Range	27.8-92.8
V_{200} (%)	Median	27.7	Range	10.1-64.5
D_{90} (Gy)	Median	172.4	Range	108.1-230.3
UD_{90} (Gy)	Median	149.6	Range	46.0-210.3

NHT, neoadjuvant hormonal therapy; iPSA, initial prostate-specific antigen; PUPV, pre-implant ultrasound prostate volume; CTPV1D, computed tomography determined prostate volume 1 day after implant; CTPV1M, computed tomography determined prostate volume 1 month after implant; V_{100}, V_{150}, V_{200}, percentage of prostate volume receiving 100%, 150%, and 200% of the prescribed minimal peripheral dose, respectively; D_{90}, minimal dose received by 90% of the prostate; UD_{90}, minimal dose received by 90% of the urethra. *2002 TNM staging system.

recorded in one and 96 patients, respectively. AUT of RTOG Grade 3 was recorded in seven patients (6.7%). Of these seven patients, five experienced acute urinary retention, and two had other urinary symptoms. However, they did not need surgical intervention for the symptoms. Thus, none of the patients experienced AUT of RTOG Grade 4. A greater number of needles ($p = 0.012$) were associated with AUT of RTOG Grade 3 on the UVA, but not on the MVA (Table 2).

IPSS resolution

The IPSS increased and peaked by the 3-month visit after PB, but subsequently recovered to the baseline level. The median IPSS-baseline and IPSS-max were 7 (range, 0-23) and 17 (range, 0-34), respectively. The IPSS-max in one patient was 0. Of the 104 patients, IPSS resolution was achieved in 92 patients (88.5%) (Fig. 1). The median interval to IPSS resolution was 6 months (7 ± 6 months). A greater IPSS-max ($p < 0.001$) was associated with a slower IPSS resolution in the MVA. A greater IPSS-baseline ($p < 0.001$) resulted in faster IPSS resolution (Table 3). The relationship between PUPV and IPSS resolution was equivocal.

Discussion

Our incidence of AUT at RTOG Grade 3 was 6.7%, which was comparatively lower than that in other reports. The reason may be due to the difference of PV. Keyes et al. (2009) reported an incidence of AUT at RTOG Grade 3 of 16.2%. Their median of planning ultrasound-determined target volume was 38.0cm^3 (range, 17.0-67.2 cm^3). According to Williams et al. (2004), the incidence of acute urinary retention was 19.7% and the PV in TRUS was 35.1 ± 8.6 cm^3. Salem et al. (2003) reported that 11 among 60 consecutive patients developed AUT at Grade 3 and their median pre-implant prostate ultrasound volume was 30 ml. Wust et al. (2004) found that 14% of their patients required a catheter because of manifest retention and the PV was 34 ± 14 ml. In addition, according to Keyes et al. (2009), a larger pre-implant PV increased the likelihood of acute RTOG Grade 3 toxicity. Our median of PV was 24.1 cm^3 and was smaller compared with previous studies, as summarized in Table 1. Such a difference in PV may account for the lower rate of severe AUT in our patients.

In our study, only the number of needles used was significantly associated with AUT of RTOG Grade 3 in the UVA, although we could not find a relationship between

Table 2. Factors associated with acute urinary RTOG Grade 3 toxicity after prostate brachytherapy.

Factors	UVA	MVA
	p	*p*
Age	0.775	0.855
iPSA	0.312	0.275
Diabetes	0.991	0.187
Hypertension	0.65	0.195
NHT	0.982	0.624
IPSS-baseline	0.219	0.504
IPSS-max	0.071	0.158
PUPV	0.504	0.183
CTPV1D (cm^3)	0.636	0.392
CTPV1M (cm^3)	0.631	0.317
CTPV1D/CTPV1M ratio	0.731	0.431
Number of needles	0.012	0.1
Number of seeds	0.824	0.583
V_{100}	0.496	0.917
V_{150}	0.751	0.212
V_{200}	0.581	0.45
D_{90}	0.82	0.231
UD_{90}	0.086	0.148

IPSS, International Prostate Symptom Score; UVA, univariate analysis; MVA, multivariate analysis; CI, confidence interval; other abbreviations as in Table 1.

AUT of RTOG Grade 3 and the number of seeds. Probably the number of our patients included in the analysis is too low to find the number of seeds as predictor. Several authors also reported a correlation between AUT and number of needles. Wust et al. (2004) demonstrated a relationship between the number of needles and urinary toxicity in the acute phase. According to Keyes et al. (2009), a greater number of needles contributed to acute RTOG Grade 2 or

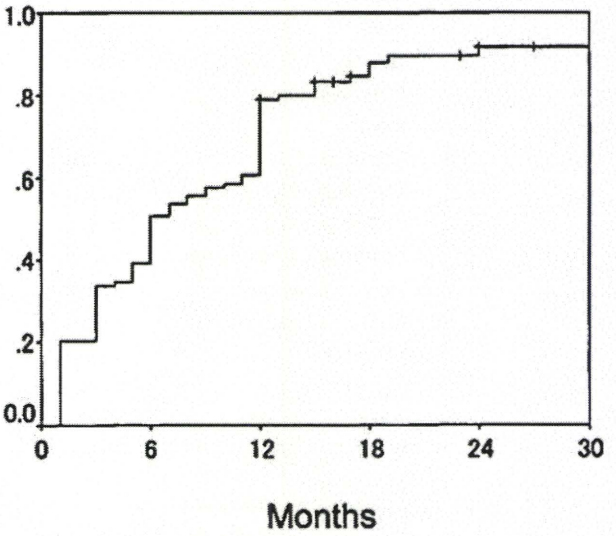

Fig. 1. Kaplan-Meier curve of the interval to international prostate symptom score (IPSS) resolution in 104 patients. IPSS resolution was achieved in 92 patients (88.5%).

Table 3. Factors associated with the interval to IPSS resolution after prostate brachytherapy.

Factors	UVA	MVA	
	p	*P*	Odds ratio (95% CI)
Age	0.173	0.141	—
iPSA	0.649	0.45	—
Diabetes	0.588	0.314	—
Hypertension	0.654	0.967	—
NHT	0.397	0.15	—
AUR	0.594	0.676	—
IPSS-baseline	0.024	< 0.001	1.16 (1.097 - 1.226)
IPSS-max	0.001	< 0.001	0.883 (0.847 - 0.921)
PUPV	0.295	0.019	1.11 (1.02 - 1.211)
CTPV1D (cm^3)	0.11	0.74	—
CTPV1M (cm^3)	0.242	0.93	—
CTPV1D/CTPV1M ratio	0.344	0.823	—
Number of needles	0.789	0.57	—
Number of seeds	0.053	0.054	—
V_{100}	0.776	0.995	—
V_{150}	0.675	0.684	—
V_{200}	0.68	0.653	—
D_{90}	0.534	0.983	—
UD_{90}	0.796	0.957	—

AUR, acute urinary retention; other abbreviations as in Table 1 and Table 2.

worse toxicity, whereas it was not significantly associated with acute RTOG Grade 3 toxicity.

Our median interval to IPSS resolution was 6 months and shorter than several reports (Williams et al. 2004; Keyes et al. 2009), or comparable to others (Ohashi et al. 2006; Bottomley et al. 2007; Anderson et al. 2009). The short interval may be associated with our lower incidence of severe AUT, compared with the findings of other reports (Williams et al. 2004; Keyes et al. 2009). In addition, we revealed that a greater IPSS-baseline was related to a faster IPSS resolution, and a greater IPSS-max was associated with a slower IPSS resolution, consistent with the previous studies (Neill et al. 2007; Keyes et al. 2009). According to Neill et al. (2007), one reason that a higher IPSS-baseline predicts a faster IPSS resolution may be that the higher the IPSS-baseline is, the smaller is the range of IPSS increase required to reach IPSS-max due to the maximal IPSS score of 35 points. Those patients with a higher baseline score may tend to recover to that value faster than those with a lower baseline. According to Keyes et al. (2009), this might be related to patient expectations and/or to the pre-existing urinary symptoms, which might mask any new dysfunction caused by PB.

Although several authors reported relationship between dosimetric variables and IPSS normalization (Wust et al. 2004; Neill et al. 2007), we found no correlation between acute urinary morbidity and prostate V_{100}, V_{150}, V_{200}, or D_{90}. One reason may be that the PV in this analysis is too small to find correlation between dosimetric parameters, AUT at RTOG Grade 3, and IPSS resolution. Compared to our study, PV in their study was greater, and the prostate size difference may have contributed to differences in findings.

We found no relationship between urethral dose and AUT of Grade 3, similar to several reports (Allen et al. 2005; Ohashi et al. 2006; Neill et al. 2007). In contrast, Thomas et al. (2008) reported that a greater urethral dose at the prostate base predicted worse urinary toxicity after PB, and variation in the urethral dose may have had a significant direct effect on toxicity at the prostate base. Wallner et al. (1995) also demonstrated increased urinary RTOG Grade morbidity with exceptionally high urethral doses. They reported that patients with RTOG Grades 0-1 or urinary morbidity Grades 2-3 had average maximum urethral doses of 447 Gy and 592 Gy, respectively (Wallner et al. 1995; Thomas et al. 2008). In the present study, the assessment of urethral catheter placement for collecting dosimetric data was not performed during CT 1 month after PB. We might not have accurately contoured the urethral wall and may have failed to archive adequate urethral dosimetric data in several patients, which may have caused the absence of a statistical relationship between urethral dose and urinary morbidity. This was one of our limitations in this study.

Our study had several limitations, elsewhere. First, we did not analyze a more detailed relationship between urinary dose and urinary morbidity. In contrast, Williams et al. (2004) reported that a heightened IPSS change was correlated to an increased number of seeds implanted above the level of the prostate base. Second, multiple urinary evaluations using measures such as a combination of IPSS, University of California at Los Angeles Prostate Cancer Index, and the Expanded Prostate Index Composite urinary scores, should be considered to provide more objective measurement, whereas we used only the IPSS and the acute RTOG scale to assess acute urinary symptoms in this study (Namiki et al. 2006; Ash et al. 2007). Several authors have demonstrated that patient-reported toxicity data are superior to physician-reported data (Namiki et al. 2006; Ash et al. 2007; Ferrer et al. 2008). Third, this study was limited to acute phase toxicity after PB. A longer follow-up and further study are necessary to estimate long term treatment outcomes and toxicities. Forth, we could not mention the duration of NHT in all patients. Several patients in this study had received NHT at the other hospitals before PB. There was no detailed information of their duration of NHT.

Conclusion

Our incidence of severe AUT after PB was comparatively lower than previous reports. Mostly subjective acute urinary symptom after PB recovered within around 1 year. Worse acute urinary symptom after PB appears to slow the improvement, whereas severer urinary symptom before PB may hasten the recovery. A greater number of needles are associated with severe AUT. Therefore, we may be able to decrease the rate of severe AUT by reducing number of needles in PB.

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RESEARCH ARTICLE Open Access

Focal dose escalation using FDG-PET-guided intensity-modulated radiation therapy boost for postoperative local recurrent rectal cancer: a planning study with comparison of DVH and NTCP

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Abstract

Background: To evaluate the safety of focal dose escalation to regions with standardized uptake value (SUV) >2.0 using intensity-modulated radiation therapy (IMRT) by comparison of radiotherapy plans using dose-volume histograms (DVHs) and normal tissue complication probability (NTCP) for postoperative local recurrent rectal cancer

Methods: First, we performed conventional radiotherapy with 40 Gy/20 fr. (CRT 40 Gy) for 12 patients with postoperative local recurrent rectal cancer, and then we performed FDG-PET/CT radiotherapy planning for those patients. We defined the regions with SUV > 2.0 as biological target volume (BTV) and made three boost plans for each patient: 1) CRT boost plan, 2) IMRT without dose-painting boost plan, and 3) IMRT with dose-painting boost plan. The total boost dose was 20 Gy. In IMRT with dose-painting boost plan, we increased the dose for BTV+5 mm by 30% of the prescribed dose. We added CRT boost plan to CRT 40 Gy (*summed plan 1*), IMRT without dose-painting boost plan to CRT 40 Gy (*summed plan 2*) and IMRT with dose-painting boost plan to CRT 40 Gy (*summed plan 3*), and we compared those plans using DVHs and NTCP.

Results: D_{mean} of PTV-PET and that of PTV-CT were 26.5 Gy and 21.3 Gy, respectively. V_{50} of small bowel PRV in *summed plan 1* was significantly higher than those in other plans ((*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)). There were no significant differences in V_{30}, V_{40}, V_{60}, D_{mean} or NTCP of small bowel PRV.

Conclusions: FDG-PET-guided IMRT can facilitate focal dose-escalation to regions with SUV above 2.0 for postoperative local recurrent rectal cancer.

Background

Although positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) has become widely used for diagnosis of various malignant tumors, the spatial resolution of PET images alone is not high and it is difficult to determine anatomical sites in detail. However, this problem has been solved by the use of a combined PET/CT system, which enables both PET and CT images to be obtained at almost the same time and at the same position.

Local recurrence rates of rectal cancer after surgery including dissection of lateral nodes have been reported to be about 9~12% in Japan [1-3], and the prognosis after local recurrence is poor. In the case of local recurrence, the best salvage treatment for achieving long-term local control and survival is total pelvic exenteration with distal sacrectomy. The 5-year overall

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survival rate in patients after R0 resection has been reported to be 30~40% [4,5]. Since about half of the patients with local recurrent rectal cancer die due to only local lesions without distant metastasis [6], local control would be beneficial for survival. However, extended surgery is not widely used because of high morbidity and mortality rates. Moreover, it has been pointed out that total pelvic exenteration reduces the quality of life of patients. Furthermore, Tepper et al. reported that only 34% of patients with locally or distantly recurrent rectal cancer could receive a potentially curative resection [7]. In Japan, due to the lower rate of local recurrence after surgery alone, induction radiotherapy is not performed in most patients [8]. And, based on SEER, over 30% of patients with advanced-stage rectal cancer in the United States also did not undergo radiation therapy [9]. Therefore, external body radiotherapy is one of the most widely used therapies and provides good palliation of pain in 50~80% of patients with postoperative local recurrence; however, it has a poor survival benefit [10]. We have been performing conventional irradiation for postoperative local recurrent lesions with a total dose of 60 Gy (2 Gy/fraction · 5 fractions/week), but we have considered that dose escalation is necessary to cure patients because rectal cancer has many hypoxic fractions [11]. In fact, some studies have revealed that local failure rate after radiotherapy alone decreased with increasing irradiation dose [12,13]. However, dose escalation with conventional radiotherapy is difficult due to the location of critical organs (e.g, small bowel) around the lesion.

Huebner et al. showed by a meta-analysis that the sensitivity, specificity and accuracy of FDG-PET for local recurrent rectal cancer were 94.5%, 97.7% and 95.9%, respectively [14]. FDG-PET is superior to conventional modalities (e.g, CT and MRI) for distinguishing between local recurrence and postoperative scar. There have been several reports recently on the usefulness of FDG-PET for radiotherapy planning in lung cancer and head and neck cancer. FDG-PET has been reported to be useful for delineation of target gross tumor volume (GTV) or clinical target volume (CTV).

We performed FDG-PET/CT planning in 12 patients with postoperative local recurrent rectal cancer during conventional radiotherapy at 40 Gy.

As a preclinical study, we planned focal dose escalation to high FDG uptake regions in those 12 patients with intensity-modulated radiation therapy (IMRT) in the radiotherapy planning system, and we compared the IMRT plans with conventional radiotherapy plans in dose-volume histograms (DVHs) and normal tissue complication probability (NTCP).

The purpose of the present study is to evaluate the safety of focal dose escalation to regions with standardized uptake value (SUV) above 2.0 using IMRT in DVH and NTCP in patients with postoperative locoregional recurrent rectal cancer

Methods

Criteria for eligibility

Eligibility criteria were as follows: (1) postoperative locoregional recurrent rectal cancer, (2) unresectable, (3) age between 20 and 79 years, (4) Karnofsky Performance Status (KPS) score of > = 60, (4) without distant metastasis, (5) tumor is grossly measurable, and (6) no serious medical or psychologic conditions precluding safe administration of treatment.

Radiotherapy

A linear accelerator (Clinac 23EX (VARIAN Medical Systems, Palo Alto, CA), 6 or 15 MV) was used as the X-ray source.

First, we performed radiotherapy planning using CT with contrast medium for 12 patients with postoperative locoregional recurrent rectal cancer. All target volumes were outlined slice by slice on the treatment-planning CT images. GTV was defined as the gross extent of the tumor shown by imaging as well as physical examination, CTV was defined as GTV plus a 10-mm circular margin for potential microscopic spread, and planning target volume (PTV) was defined as CTV plus a 5-mm circular margin to account for organ motion and patient setup errors. Additionally, we attached a 5-mm leaf margin to PTV. The patients were prescribed 40 Gy in 20 fractions with the dose prescribed to the isocenter (CRT 40 Gy) using a median of 4 (range 3-4) coplanar irradiation fields.

Next, we performed FDG-PET/CT with a carbon graphite flat tabletop in the supine position for radiotherapy planning at 40 Gy in the same 12 patients. The images obtained by CT and PET were sent to the radiation therapy planning system as DICOM data, and the CT and PET images were fused using DICOM information. Residual gross extent of the tumor shown in CT images at 40 Gy was defined as GTV2, CTV-CT was defined as GTV2 plus a 5-mm circular margin, and PTV-CT was defined as CTV-CT plus a 5-mm circular margin. We defined the regions with standardized uptake value (SUV) above 2.0 as biological target volume (BTV) and BTV+5-mm circular margin as PTV-PET. Our radiotherapy planning system could show the degree of FDG accumulation with not SUV but Bq/ml in PET images. If the total dose of FDG administered to the patient and the patient's body weight are known, we can define regions with an arbitrary range of SUVs even in our radiotherapy planning system by adjusting the window level and range. In the present study, we delineated BTV under the condition showing SUV of 2.0 to 20.0.

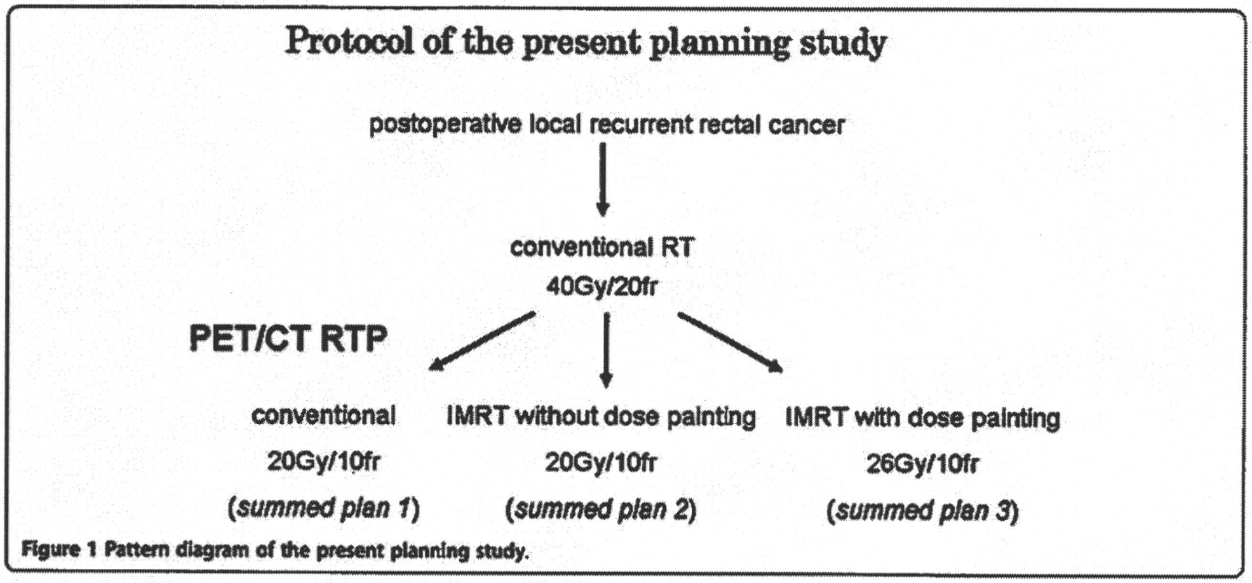

Figure 1 Pattern diagram of the present planning study.

We made three boost plans for each patient: 1) conventional radiotherapy plan (CRT boost plan), 2) IMRT plan not using dose painting (IMRT without dose-painting boost plan), and 3) IMRT plan using dose painting (IMRT with dose-painting boost plan) (Figure 1). The fractional dose of radiotherapy was 2.0 Gy with normalization at 95% of PTV-CT, and the total boost dose was 20.0 Gy. In IMRT dose-painting boost plan, we increased the dose of PTV-PET by 30% of the prescribed dose (2.6 Gy/fraction, total 26.0 Gy) using dose-painting.

We defined the small bowel as the organ at risk (OAR) because the small bowel is the most vulnerable to radiation in pelvic organs, and we carefully delineated the whole small bowel in the abdomen and pelvis, preferably with the colon, bladder or other organs with reference to CT using contrast medium. The planning organ at risk volume (PRV) was margined with 5 mm to the OAR as with the PTV margin.

IMRT plans were generated using Varian Eclipse (Helios IMRT) Workstations. The beam arrangement consisted of seven coplanar non-colinear fields (30°, 80°, 130°, 180°, 230°, 280°, 330°), and delivery of IMRT was carried out using the sliding window technique with a 15 MV linear accelerator equipped with a dynamic multileaf collimator. Our primary inverse planning objectives were as follows: (1) uniform dose of 20 Gy to PTV-CT (relative weight, w = 15), (2) maximal irradiated dose (Dmax) of small bowel PRV <20 Gy (w = 20) (total Dmax of small bowel PRV <60 Gy), (3) dose received by 5% (D5) of small bowel PRV <15 Gy (w = 8) (total D5 of small bowel PRV <55 Gy), and in the IMRT with dose-painting boost plan, we added (4) dose received by 95% (D95) of PTV-PET >26 Gy (w = 10) (total D95 of PTV-PET >66 Gy, which means normalized 2-Gy-equivalent biologically effective dose, 67.3 Gy, calculated using an alpha/beta value of 10).

IMRT planning for this study was theoretical and was not used for treatment. All of the patients underwent conformal radiation therapy to a total dose of 60~66 Gy (2.0 Gy/fraction/day).

We added each boost plan to CRT 40 Gy (*summed plan 1*: CRT 40 Gy + CRT boost plan, *summed plan 2*: CRT 40 Gy + IMRT without dose-painting boost plan, *summed plan 3*: CRT 40 Gy + IMRT with dose-painting boost plan) (Figure 2) and we compared those plans using DVHs and NTCP of small bowel PRV.

The differences in dose distribution between IMRT without dose-painting boost plan and IMRT with dose-painting boost plan were evaluated by the conformity index (C.I.), which we defined as the ratio of the volume irradiated with 95% of the prescribed dose to PTV-CT.

NTCP

NTCP was calculated using the Lyman-Kutcher-Burman model.

$$NTCP = 1 / \sqrt{2\pi} \int_{-\infty}^{t} \exp(-\chi^2 / 2)dx, \quad (1)$$

$$t = (D - TD_{50}(v)) / (m\, TD_{50}(v)). \quad (2)$$

Irradiation of fractional volume $v = V/V_{ref}$ corresponds to parameter TD50 (v) for 50% complication probability, given by the following power law:

$$TD_{50}(v) = v^{-n}\, TD_{50}. \quad (3)$$

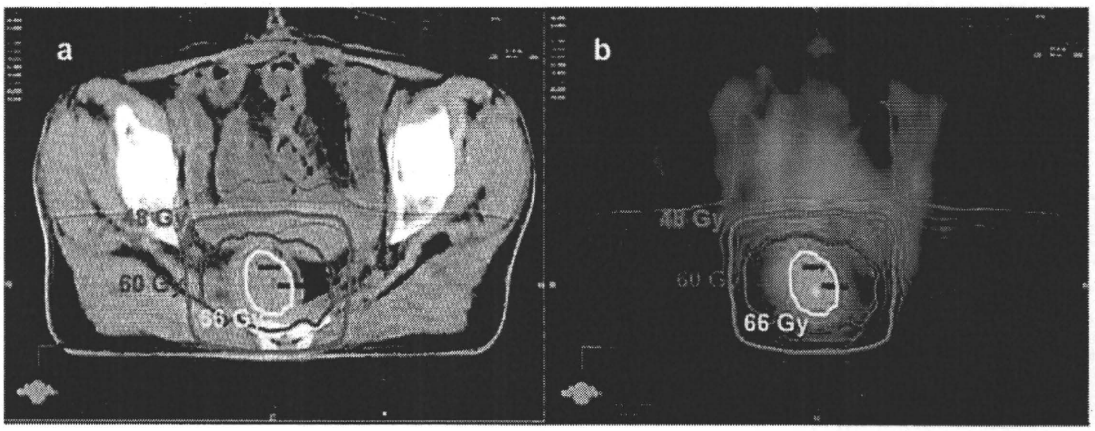

Figure 2 Dose distribution of *summed plan 3* (summed plan of CRT 40Gy and IMRT with dose-painting boost plan) in a patient. a): dose distribution in CT, b): dose distribution in FDG-PET.

V_{ref} is the total volume of the organ.

With inhomogeneous irradiation, there are multiple partial volume irradiations to different doses. The effects of partial volume irradiations are computed according to the Kutcher-Burman (K-B) effective-volume dose-volume histogram reduction scheme [15]. The K-B method satisfies the consistency requirement that partitioning a uniform irradiation of the entire volume into multiple partial volume irradiations to the same dose results in the same NTCP. The organ dose is described as independent fractional volume elements v_j, (j = 1,... k), $\sum_{j=1}^{k} v_j = 1$, irradiated to doses d_j. Then, with the K-B algorithm, an effective fractional volume $V_{eff(j)}$ defined as follows is computed for each v_j. The effective fractional volume is the volume that, when irradiated to reference dose d_{ref}, would give the same complication probability in the Lyman model as the actual fractional volume v_j irradiated to dose d_j. If v_j were the only fractional volume irradiated, then from equality of effect and Eq. (B), it would follow that

$$V_{eff(j)} = v_j (d_j / d_{ref})^{1/n}. \quad (4)$$

In the K-B method, Eq. (D) is applied to all fractional subvolumes. In the present study, d_{ref} was chosen to be the maximum dose D_{max}. The total effective fractional volume receiving the reference dose is calculated as follows:

$$V_{eff} = \sum_{j=1}^{k} V_{eff(j)}, \quad (5)$$

using $v = V_{eff}$ in Eq. (C) and $D = d_{ref} = D_{max}$ in Eq. (B)

The parameters used to calculate small bowel obstruction and perforation were n = 0.15, m = 0.16, and TD_{50} = 55 [16,17].

Chemotherapy

For all of the 12 patients, S-1 60 mg/m^2 was given orally twice daily (within 30 minutes after morning and evening meals) for 2 weeks, followed by a drug-free interval of one week (one cycle) concomitant with radiation therapy. Chemotherapy was not performed for a period of at least 4 weeks before initiation of radiation therapy in any of the patients.

FDG-PET

PET scans were performed 1 hour after administration of ^{18}F-fluorodeoxyglucose at a dose of 3.1 MBq/kg using a Biograph PET/CT scanner (Siemens, Hoffman Estates, IL) under the condition of more than 4 hours of fasting. A transmission scan was performed for attenuation correction before the emission scans (using a computed tomography scan). Seven bed positions were used for emission scans, with an acquisition time of 2 minutes per position. For radiotherapy planning, PET/CT scans were performed in the same posture as that for treatment on a flat carbon-fiber table top. The PET images were reconstructed with an ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm.

For semiquantitative analysis of increased FDG uptake lesions, SUV based on body weight (g) was calculated and converted into a value based on lean body mass:

SUV = [tissue activity concentration (Bq/ml)]/[administered activity (Bq)/weight (g)].

The blood glucose levels of all patients before scans were less than 150 mg/dl.

Statistical analysis

Statistical significance was defined as a value of $p < 0.05$ in the present study. SPSS software for Windows version 11.0 (SPSS Inc, Chicago, IL) was used for all calculations. Multiple pairwise comparisons were performed by

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

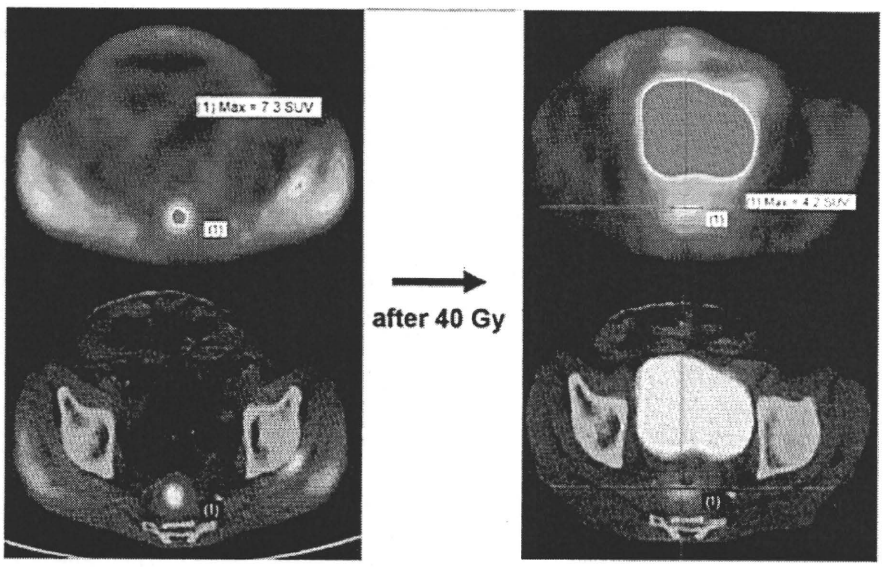

Figure 3 Change in FDG accumulation. This patient had anastomatic recurrence with 7.3 SUVmax before radiation therapy. After 40 Gy, the accumulation was decreased by 3.1 SUVmax.

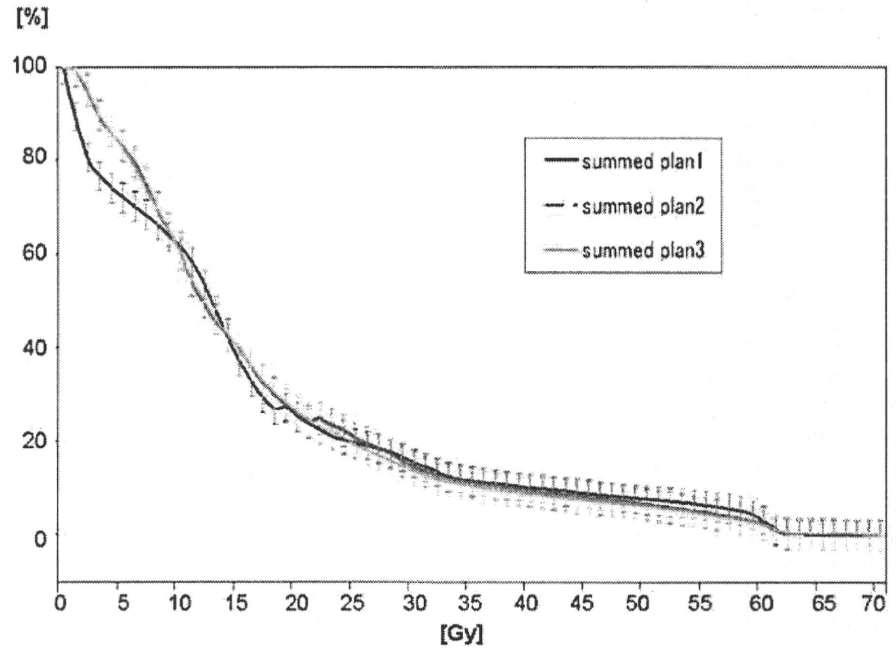

Figure 4 Mean DVH (whole curve) of small bowel PRV in each summed plan.

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