the PTV (Fig. 5 (c)). DVHs of the PTV, rectum, and bladder were rapidly degraded with MSS plans greater than or equal to 2.0 cm compared with MSS 1.0 cm plan.

Figure 6 (a) shows the HI of the PTV by MSS for the five patients. Average differences between the MSS 1.0 cm and 1.5 cm plans, and the 1.5 cm and 2.0 cm plans were within 0.1% and 9.6%, respectively. HI values were rapidly degraded in the MSS 2.2 cm plan and above, with differences between the 1.0 cm and 2.2 cm, 2.5 cm, and 3.0 cm plans of more than 15%, 32%, and 51%, respectively. With regard to V107 of PTV, the difference between MSS 1.0 cm and 1.5 cm was 2% (Fig. 6 (b)). In contrast, V107 values of the MSS 2.0 cm or greater plans were more than 2.5-fold that of the MSS 1.0 cm plan. The same tendency was also observed with regard to maximum rectal and bladder doses. Although the differences between the MSS 1.0 cm and 1.5 cm or 2.0 cm plans were within 2.5%, these ratios rapidly increased at an MSS of 2.2 cm and greater, and with the MSS 2.5 cm plan were 1.11- and 1.28-fold that of the MSS 1.0 cm plan, respectively (Fig. 6 (c), (d)). The degree of increase in the ratio of these parameters appeared to correlate with a larger seminal vesicle volume.

Table 3 summarizes these dosimetric results and statistical analyses according to various MSS settings. The difference in HI of PTV between the MSS 1.0 cm and 1.5 cm plans was within 0.5%, which was not statistically significant ($p = 0.240$). Although 9.6% difference for the five patients was observed between MSS 1.5 cm and 2.0 cm, this was not significant ($p = 0.155$), with only the difference between the MSS 2.2 cm and 2.5 cm plans being significant. With regard to the V107 of PTV, however, a significant difference was observed between MSS 1.5 cm and 2.0 cm ($p < 0.05$), whereas no significant difference was observed between MSS 1.0 cm and 1.5 cm. The same tendency was observed with regard to maximum rectal dose. For maximum bladder dose, no significant difference was observed between MSS 1.5 cm and 2.0 cm ($p = 0.065$).

Composite plan verification at various MSS plans

Figure 7 shows the results of composite verification of various MSS plans in patient 1. Regions in which the dose difference between the measured and calculated doses was within 5% are colored. The red regions indicate that the measured dose was larger than the planned dose, but that the

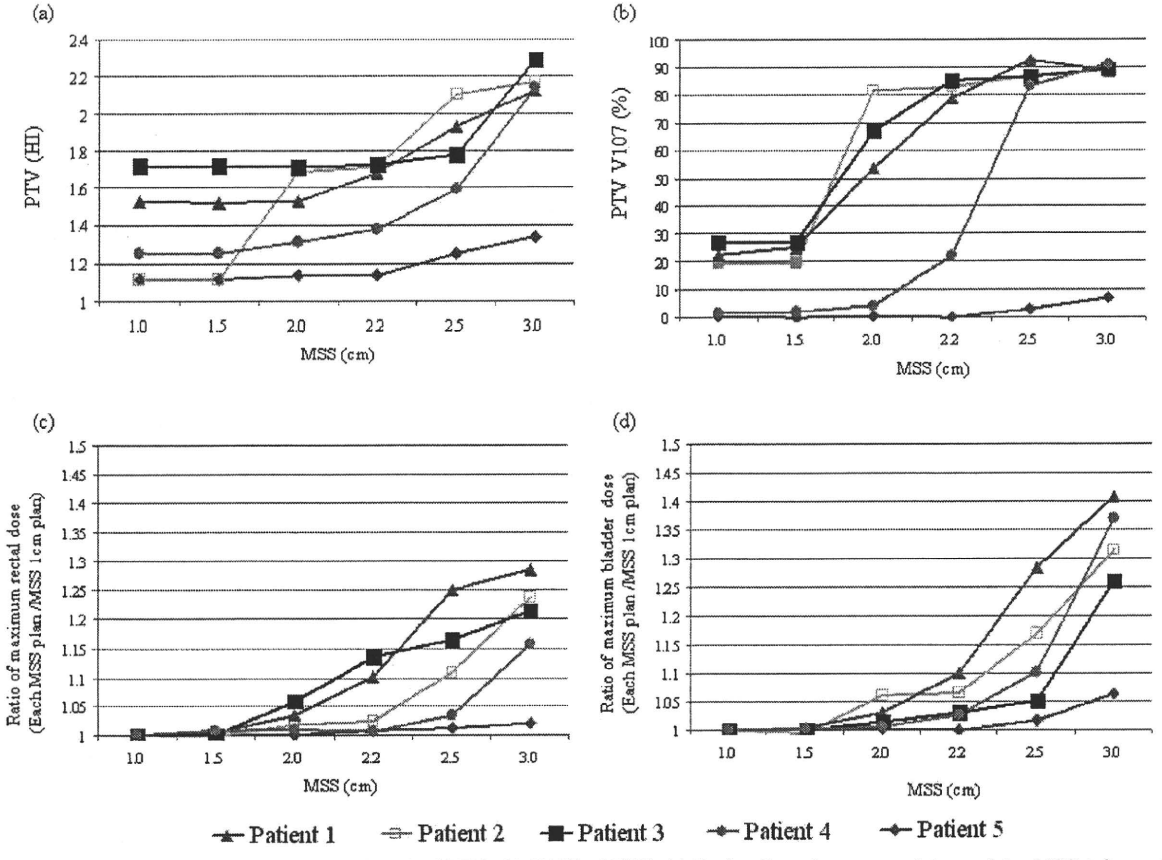

Fig. 6. Effect of MSS on DVH parameters. (a) HI of PTV, (b) V107 of PTV, (c) Ratio of maximum rectal dose of the MSS 1.0 cm plan to those of other MSS plans, and (d) ratio of maximum bladder dose of the MSS 1.0 cm plan to those of the other MSS plans.

Table 3. Summary of dosimetric results by MSS for five patients

MSS (cm)	1.0	1.5	2.0	2.2	2.5	3.0
PTV (HI)	1.345 ± 0.27	1.346 ± 0.154	1.475 ± 0.250	1.525 ± 0.260	1.732 ± 0.328	2.010 ± 0.383
p-value		(0.240)[a]	(0.154)[b]	(0.087)[c]	(< 0.05)[d]	
p-value			(0.155)[e]	(0.075)[f]	(< 0.05)[g]	
PTV (V107 (%))	14.12 ± 12.29	14.73 ± 12.70	41.25 ± 37.05	53.72 ± 39.84	70.54 ± 37.89	72.99 ± 36.90
p-value		(0.101)[a]	(< 0.05)[b]			
p-value			(< 0.05)[e]			
Max. rectal Dose (Gy)	75.8 ± 1.1	75.9 ± 1.0	77.6 ± 2.3	80.0 ± 5.1	84.5 ± 8.3	89.7 ± 8.7
p-value		(0.179)[a]	(< 0.05)[b]			
p-value			(< 0.05)[e]			
Max. bladder Dose (Gy)	79.4 ± 4.4	79.4 ± 4.3	81.2 ± 5.6	83.0 ± 6.3	89.4 ± 10.2	102 ± 12.9
p-value		(0.463)[a]	(0.054)[b]			
p-value			(0.065)[e]	(0.056)[f]	(0.079)[g]	(0.029)[h]

Abbreviation: MSS = minimum segment size. [a] Comparison of MSS of 1.0 cm vs. 1.5 cm. [b] Comparison of MSS of 1.0 cm vs. 2.0 cm. [c] Comparison of MSS of 1.0 cm vs. 2.2 cm. [d] Comparison of MSS of 1.0 cm vs. 2.5 cm. [e] Comparison of MSS of 1.5 cm vs. 2.0 cm. [f] Comparison of MSS of 2.0 cm vs. 2.2 cm. [g] Comparison of MSS of 2.2 cm vs. 2.5 cm. [h] Comparison of MSS of 2.5 cm vs. 3.0 cm.

dose difference was within ± 5%. On the other hand, the blue regions indicate that the measured dose was smaller than the planned dose, but that the dose difference was within ± 5%. The white regions indicate that the difference between the measured and planned dose was greater than ± 5%. Many such regions were observed with the MSS 1.0 cm plan (Fig. 7 (a)) in the PTV, whereas few were seen with the MSS 1.5 cm plan. The white regions in Fig. 7 (b), (c) and (d) around the PTV show high-dose gradient regions in which DTA within 3 mm was confirmed.

DISCUSSION

We investigated the optimum minimum segment size in two-step IMRT optimization with regard to both planning quality and dosimetric accuracy.

Several optimization methods are available in commercial treatment planning systems, including two-step optimization and direct-aperture optimization.[1–6] Several studies have demonstrated the optimal minimum segment size for IMRT planning.[6,9,16] Worthy *et al.* reported that the minimum segment area setting in DMPO should be 8 cm^2, taking into account both planning quality and treatment delivery time.[6] Lydon investigated the calculation accuracy of small segments using Pinanacle[3] and Varian linear accelerator[18] and demonstrated that segments of less than 1 cm in width should not be used for IMRT. Aspradakis *et al.* reported that a minimum segment size of less than 2 cm was not suitable for step and shoot IMRT, considering mechanical limitations such as beam output stability for low MU settings.[9] However, these latter two papers did not investigate the effect of minimum segment size on planning quality. To our knowledge, optimal segment size in two-step optimization with regard to both planning quality and dosimetric accuracy has not been investigated in detail.

In the present study, no significant change was seen between the MSS 1.0 cm and 1.5 cm plans with respect to DVHs of the PTV, bladder and rectum. In contrast, a significant change was seen between the MSS 1.5 cm and 2.0 cm plans for V107 of the PTV and maximum rectal dose, and planning quality rapidly deteriorated with MSS plans greater than 2.2 cm. Interestingly, the degree of degradation of HI or V107 of the PTV and maximum rectal and bladder dose tended to depend on seminal vesicle volume (Fig. 6): as seminal vesicle volume increases, a larger part of the PTV involves the rectum. To compensate for regions overlapping

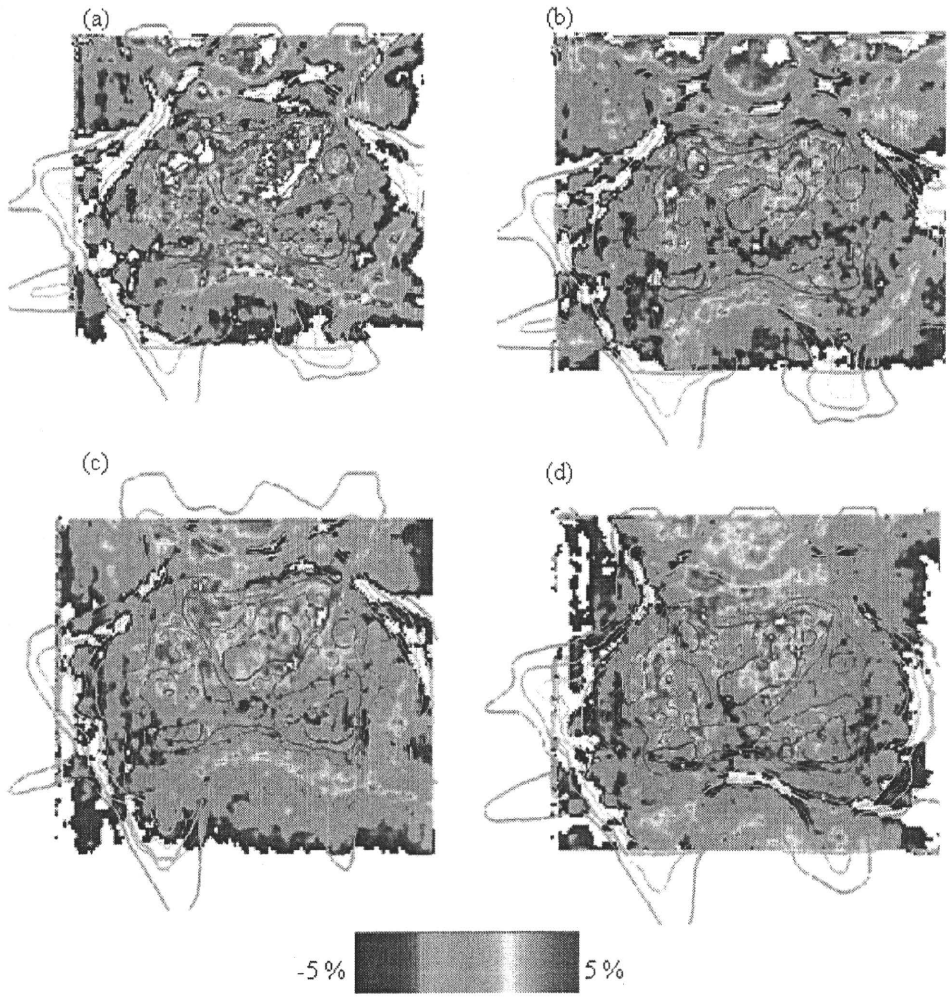

Fig. 7. Results of composite plan verification for Patient 1 by GafChromic film by MSS. Colored regions indicate dose differences between planned and measured values of within 5%. (a) MSS 1.0 cm, (b) MSS 1.5 cm, (c) MSS 2.0 cm, and (d) MSS 2.5 cm.

the PTV and rectum, smaller segments were generated (data not shown). In such situations, a smaller MSS might provide better coverage of the PTV.

On the other hand, the number of total segments and total MU in the MSS 1.5 cm plan were significantly decreased compared with the MSS 1.0 cm plan, indicating that treatment time with the MSS 1.5 cm plan may be shorter than with the 1.0 cm plan, during which intrafractional patient movement may occur. Therefore, with regard to planning quality, we concluded that the optimal minimum segment size setting was MSS 1.5 cm, but that more than 2.2 cm was clinically unacceptable. It also appeared that planning quality tended to be worse when seminal vesicle volume was large (Fig. 6 (a), (b)). In such cases, even MSS of 2.0 cm or greater should be avoided.

Compared to the traditional radiotherapy with fields $> 4 \times 4$ cm^2, small fields or segments used in IMRT can result in significant uncertainty in the accuracy of clinical dosimetry.[7] Thus it becomes difficult to assure the accuracy of beam delivery.[7–11] To examine whether small MSS plans can accurately calculated and delivered, we next conducted composite plan verification for the MSS 1.0 cm, 1.5 cm, 2.0 cm and 2.5 cm plans using GafChromic-type EBT films. We used the plan of patient 1 because the proportion of 1×1 cm^2 subsegment with MSS 1.0 cm plan was the largest of the 5 patients, which is the severe condition in IMRT plan verification. In IMRT, a dose difference of 3% has been commonly used as a tolerance level.[19] Van Battum *et al.* estimated an uncertainty of at least 1.3% (1SD) for GafChromic-type EBT film dosimetry.[19] Our data revealed a 1.4% dose difference (1SD) between calculation by XiO and by film measurement in the flat region of a simple field profile (5.0×5.0 cm^2), which agreed with an ion chamber measurement within 0.5% (data not shown). In addition, there are

other sources of dose uncertainties including film inhomogeneity which was found to be 1.1%.[20] We therefore set a tolerance level of 5% for dose difference analysis. Our data showed that the MSS 1.0 cm plan was not acceptable because the regions where the dose difference between calculated and measured dose was beyond 5% existed around PTV. On the other hand, the MSS 1.5 cm plan was acceptable because only few regions had a dose difference between the calculated and measured dose of more than 5%. Although dose distribution between the MSS 1.0 cm and 1.5 cm plans was similar (Fig. 4), the proportion of segments was found to be different (Fig. 3). In particular, the MSS 1.0 cm plan contained many smaller subsegments, such as 1.0×1.0 cm^2. Previous study has shown that the calculation accuracy of off-axis 1.0×1.0 cm^2 was beyond 5% using Helax Collapsed Cone algorithm.[9] Therefore these subsegments might be related with discrepancies between the calculated and measured dose.

Although many issues in small field dosimetry remain, including beam modeling accuracy and output factors measurement technique,[7,9,21] our composite plan verification contains these components. We therefore concluded that the use of a 1.5 cm MMS setting is appropriate with regard to both planning quality and dosimetric accuracy.

Of note, MLC positioning within 0.6 mm in this study was assured by performing MLC positional calibration at least once a month and checking it weekly. In addition, we used segments of greater than 5 MU only, ensuring stable beam delivery and output. We also assured dose calculation accuracy down to a 1.5×1.5 cm field within the accuracy of 2% dose difference and a 2-mm DTA (data not shown).

With regard to more complicated IMRT, such as for head and neck cancer, the percentage of smaller segments would be larger. Although the results of this study are therefore relevant to prostate IMRT only, the process we used to determine minimum segment size would be useful in studies of other sites of IMRT.

In conclusion, the minimum segment size setting in IMRT optimization impacts dose distribution. Our data showed that an MSS 1.5 cm setting was suitable for prostate IMRT planning with regard to both planning quality and dosimetric accuracy. Although several papers have demonstrated that DMPO is a practical and preferable alternative to two-step optimization,[1,6,22] commercial treatment planning systems that use only two-step optimization remain available. Our findings could therefore be useful in determining or reviewing the validity of MSS settings in clinical practice.

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RADIATION ONCOLOGY

RESEARCH Open Access

Age is not a limiting factor for brachytherapy for carcinoma of the node negative oral tongue in patients aged eighty or older

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Abstract

Background: To examine the role of brachytherapy for aged patients 80 or more in the trend of rapidly increasing number.

Methods: We examined the outcomes for elderly patients with node negative oral tongue cancer (T1-3N0M0) treated with brachytherapy. The 21 patients (2 T1, 14 T2, and 5 T3 cases) ranged in age from 80 to 89 years (median 81), and their cancer was pathologically confirmed. All patients underwent definitive radiation therapy, with low dose rate (LDR) Ra-226 brachytherapy (n = 4; median 70Gy), with Ir-192 (n = 12; 70Gy), with Au-198 (n = 1) or with high dose rate (HDR) Ir-192 brachytherapy (n = 4; 60 Gy). Eight patients also underwent external radiotherapy (median 30 Gy). The period of observation ranged from 13 months to 14 years (median 2.5 years). We selected 226 population matched younger counterpart from our medical chart.

Results: Definitive radiation therapy was completed for all 21 patients (100%), and acute grade 2-3 mucositis related to the therapy was tolerable. Local control (initial complete response) was attained in 19 of 21 patients (90%). The 2-year and 5-year local control rates were 91%, (100% for T1, 83% for T2 and 80% for T3 tumors after 2 years). These figures was not inferior to that of younger counterpart (82% at 5-year, n.s.). The cause-specific survival rate was 83% and the regional control rate 84% at the 2-years follow-up. However, 12 patients died because of intercurrent diseases or senility, resulting in overall survival rates of 55% at 2 years and 34% at 5 years.

Conclusion: Age is not a limiting factor for brachytherapy for appropriately selected elderly patients, and brachytherapy achieved good local control with acceptable morbidity.

Background

Oral tongue carcinoma is a highly curable cancer when treated with radiation therapy, especially interstitial brachytherapy [1]. Iridium-192 (Ir-192) hairpins or cesium-137(Cs-137) needles are usually used for low-dose-rate (LDR) interstitial radiotherapy in Japan. We used a high-dose-rate (HDR) remote-controlled after-loading system, using an Ir-192 microsource, the MicroSelectron-HDR (Nucletron, Veenendaal, The Netherlands) installed in 1991. Since with this system there is no risk of radiation exposure except to the patient, HDR makes it possible to treat patients in a normal ward, so that the quality of life during treatment may be better. We have already reported on the outcome of HDR brachytherapy for early oral tongue cancer which included a prospective Phase III study [2-4]. In addition, we reported that the efficacy of brachytherapy for T3 oral tongue cancer, especially when using HDR, was enhanced by its excellent dose distribution [5]. The number of elderly patients in Japan has been increasing steadily because of advances in both health and medical care and the leading cause of death among the elderly is cancer. The number of people aged 80 or over reached 7,130,000 in Japan in 2007, which counts for more than 5% of the population. The problems involved in treating older patients with cancer are time pressing [6].

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As aging is a highly individualized process, the indication, strategy, and techniques of radiation therapy for the elderly should not be defined exclusively by chronologic landmarks [6]. We studied 21 80-year-old or older patients with oral tongue cancer treated by brachytherapy. Since to the best of our knowledge, there have been no previous reports regarding such patients, we conducted this retrospective review of the feasibility of brachytherapy for elderly patient with T1-3N0 oral tongue cancer.

Methods

Patients

Between 1967 and 2004, 21 patients (9 males and 12 females) with previously untreated mobile tongue cancer were treated with radiotherapy at Osaka University Hospital and Osaka National Hospital. Patients treated with radiotherapy combined with chemotherapy were excluded from the study. All tumors were histologically identified as squamous cell carcinoma. Table 1 lists patient and treatment characteristics. The patients' median age was 81, ranging from 80 to 89. There were 2 T1, 14 T2, and 5 T3 tumors (UICC TNM classification of 1987). During the study period, we also treated about 700 patients with T1-3N0 oral tongue carcinoma [4], with the elderly group accounting for 3% of all patients. The age of the 21 patients ranged from 80 to 89 years (median 81) at the start of radiation therapy, and the male-to-female ratio was 9:12. Performance status (PS) was classified as 0-1, based on the World Health Organization classification. For this study, the clinical records of consecutive these 21 patients from our database were reviewed (Table 1). To compare the result of treatment to younger counterpart, we reviewed population adjusted (sex, T-stage, with external radiotherapy) 226 patients treated during same time period. The background comparison was shown in Table 2.

Radiation therapy

All implantation was done under local anesthesia. For patients in the LDR group, the treatment sources consisted of an Ir-192 pin for 12 patients, a Ra-226 needle for 4 and a ^{198}Au grain for one patient. Each needle was implanted with the Paterson-Parker system using a reference point 5 mm distant from the implant plane. The median dose and range for the LDR group treated with brachytherapy only was 70 Gy (61-84 Gy). Patients in the HDR group received a total dose of 60 Gy in ten fractions during one week at 5 mm distance from the radioactive source. Two fractions were administered per day. The time interval between fractions was more than 6 hours. Dose rates at the reference points for the LDR group were 0.30 to 0.8 Gy/h, and for the HDR group 1.0 to 3.4 Gy/min. Patients were followed up for at least 13 months or until their death, with a median follow-up time of 2.5 years (range: 1.3 - 14 years). Large T2 tumor or more including ulceration or thicker tumor received external irradiation. A total of 8 patients (T2: 3, T3: 5) underwent external radiotherapy using a Co-60 teletherapy unit or a linear accelerator. These patients received 2-3 Gy per fraction for a median dose of 30 Gy (30 - 50 Gy), and were treated with a single lateral field that involved the primary site and the upper jugular lymph nodes. Nutrition support was given by nasal tube feeding during brachytherapy. No patient required tracheostomy. The routine follow-up interval was 1 month for the first year, two months for the second year, and 3 - 6 months thereafter. We examined the outcomes in terms of local control, lymph node control, cause-specific and overall survival. Early toxicities were assessed by Common Toxicity Criteria version 3 (CTC v3). Late toxicities were counted if soft tissue (ulceration lasting 3 months or more) and/or bone (bone exposure and necrosis) reactions occurred.

Statistical Analysis

For a statistical analysis, a Student's t-test for normally distributed data and the Mann Whitney U-test for skewed data were used. The percentage was analyzed using a Chi-square test. Local control and survival data were estimated according to the Kaplan-Meier method, and were examined for significance with a logrank test. All analyses used the conventional $p < 0.05$ levels of significance.

Results

Local control, regional control, cause-specific and overall survival

The 2- and 5-year local control rates for the 21 elderly patients were both 91% (Figure 1). The 2-year (5-year) local control rates for T1, T2, T3 tumors were 100% (100%), 83%, (83%) and 80% (not available), respectively (n.s.). These figures was not inferior to that of younger counterpart (82% at 5-year, Figure 2 n.s.). Two patients showed local recurrence. An 83-year-old female (ID15) received external radiotherapy for lymph node metastasis found just after completion of brachytherapy, but local recurrence appeared and resulted in death. One more local failure occurred in an 80-year-old female with T2N0 oral tongue cancer (ID 19) treated with the Ir-192 source. During the first night of treatment in the RI ward, she tried to brush her teeth and pulled out the guide gutter of the Ir-192, so that the Ir-192 needles were replaced with Au-198, resulting in partial response and recurrence 4 months later. The 2-year and 5-year cause-specific survival (CSS) rates were both 83% (83% and 78% in control group), but the respective overall survival rates were 55% and 34% (83% and 76% in control group). Incidence of lymph-node metastasis was

Table 1 Characteristics and clinical background of the study population

No.	Sex	Age	T	Longest diameter	Short diameter	Thickness	Tumor type	External RT dose	Brachytherapy dose	Radioactive Source	Initial response	Survival	Disease control	Outcome	Complications	Comorbidity
		(year)		(mm)	(mm)	(mm)		(Gy)	(Gy)			(year)		(status)		
1	F	86	2	25	15	5	exo	73	Ir	CR	1.2	NED	DID			
2	F	85	2	25	13	5	sup	30	60	Ra	CR	7	NED	DID		
3	M	82	1	20	11	5	sup	70	Ra	CR	2	NED	DID (senile decay)			
4	F	82	1	20	7	3	exo +ulc	65	Ir	CR	6	NED	DID (senile decay)		Hypertention	
5	M	82	2	35	23	15	ins+ulc	30	60	Ir	CR	3	NED	DID		
6	M	82	2	25	12	10	NA	68	Ir	CR	1	NED	Alive		TIA	
7	F	81	2	25	12	10	ulc	76	Ir	CR	14	nodal failure 4M	Alive (salvaged by surgery)			
8	F	82	2	38	17	10	ind	48	ms	CR	2.5	NED	Alive	Ulcer and bone exposure after biopsy		
9	M	81	2	24	15	12	ind	60	Ir	CR	1.4	nodal failure 8M	Dead (nodal failure)			
10	F	80	2	23	7	5	ind	70	Ir	CR	12	NED	DID (senile decay)		Hypertention	
11	M	80	2	23	18	7	exo	75	Ir	CR	6	NED	Alive		Hypertention	
12	M	80	2	NA	NA	NA	NA	70	Ir	CR	2	NED	DID			
13	M	80	3	42	25	25	ulc	33	60	ms	CR	1.4	NED	DID		
14	M	80	3	42	23	13	ulc+ind	30	85	Ra	CR	3	NED	DID (senile decay)		
15	F	83	3	42	20	20	ulc+ind	30	70	Ra	PR	1	nodal failure 0M	Dead (nodal failure and local failure)		
16	F	89	3	50	30	20	ulc+ind	36	32	ms	CR	1.3	NED	DID		
17	F	83	2	31	24	8	ind +exo	70	Ir	CR	4	NED	DID			
18	M	81	3	35	28	15	ulc+ind	36	54	Ir	CR	0.9	NED	DID		
19	F	80	2	25	20	10	ind	70	Au	PR	1.8	local failure 4M	Dead (local failure)			
20	F	80	2	25	20	6	ind	50	54	Ir	CR	2	NED	Alive		
21	F	82	2	27	22	12	exo		54	ms	CR	2	NED	Alive	Mild ulcer, pain	

Ir; Ir-192, Ra; Ra-226, ms; Ir-192 microSelectron-HDR, Au; Au-198 grain

sup; superficial type, exo;exophytic type, ind; indurative type, ulc; ulcerative type

DID; died for intercurrent disease, DT; death for tongue cancer, NED; no evidence of disease, NA; not avairalble

TIA; transient ischemic attack

Table 2 Background of aged patients and younger conterpart

				Aged (80-) (N = 21)		Control (-79) (N = 226)	
Age	Age	Median (Range)		81 (80-89)		56 (18-79)	
Gender	Male			9	(43%)	101	(45%)
	Female			12	(57%)	125	(55%)
T classification	T1			2	(10%)	30	(13%)
	T2			14	(67%)	146	(65%)
	T3			5	(24%)	50	(22%)
	Long diameter	(mm)		30 ± 8		26 ± 9	
	Short diameter	(mm)		18 ± 7		18 ± 8	
	Thickness	(mm)		11 ± 6		9 ± 6	
Source	Ra-226			4	(19%)	72	(32%)
	Ir-192			12	(71%)	120	(63%)
	Au-198			1	(5%)	0	(0%)
	MS-HDR			4	(19%)	34	(15%)
External radiotherapy	Brachytherapy only			13	(80%)	165	(73%)
	Combined with external radiotherapy			8	(20%)	61	(27%)
Prescribed dose	Brachytherapy	Median (Range)(Gy)	LDR	70 (54-85)		70 (50-112)	
			HDR	54 (32-60)		60 (42-60)	
	External radiotherapy	Median (Range)(Gy)		LDR		30 (12-60)	

HDR; high dose rate, LDR; low dose rate

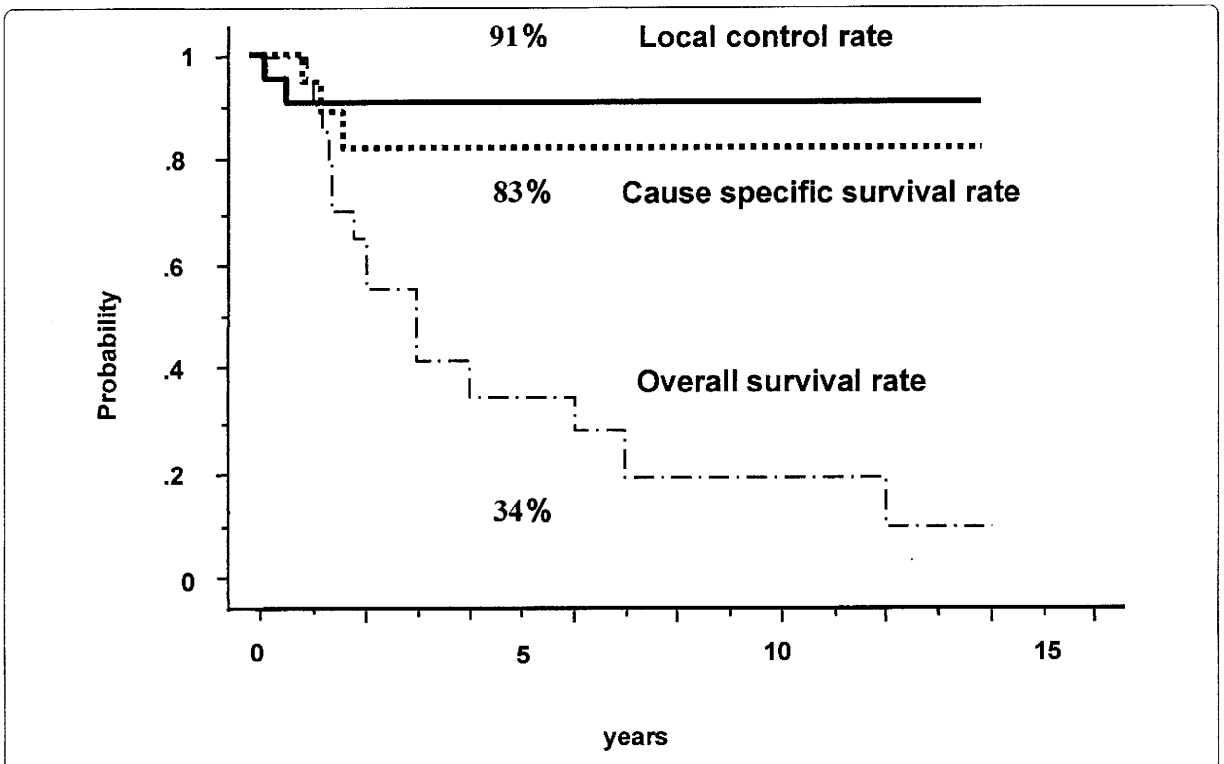

Figure 1 Local control, cause specific survival and overall survival rates for patients 80 or more with oral tongue cancer treated with interstitial radiotherapy. solid line; local control rate, dotted line; cause specific survival rate, dashed line; overall survival rate.

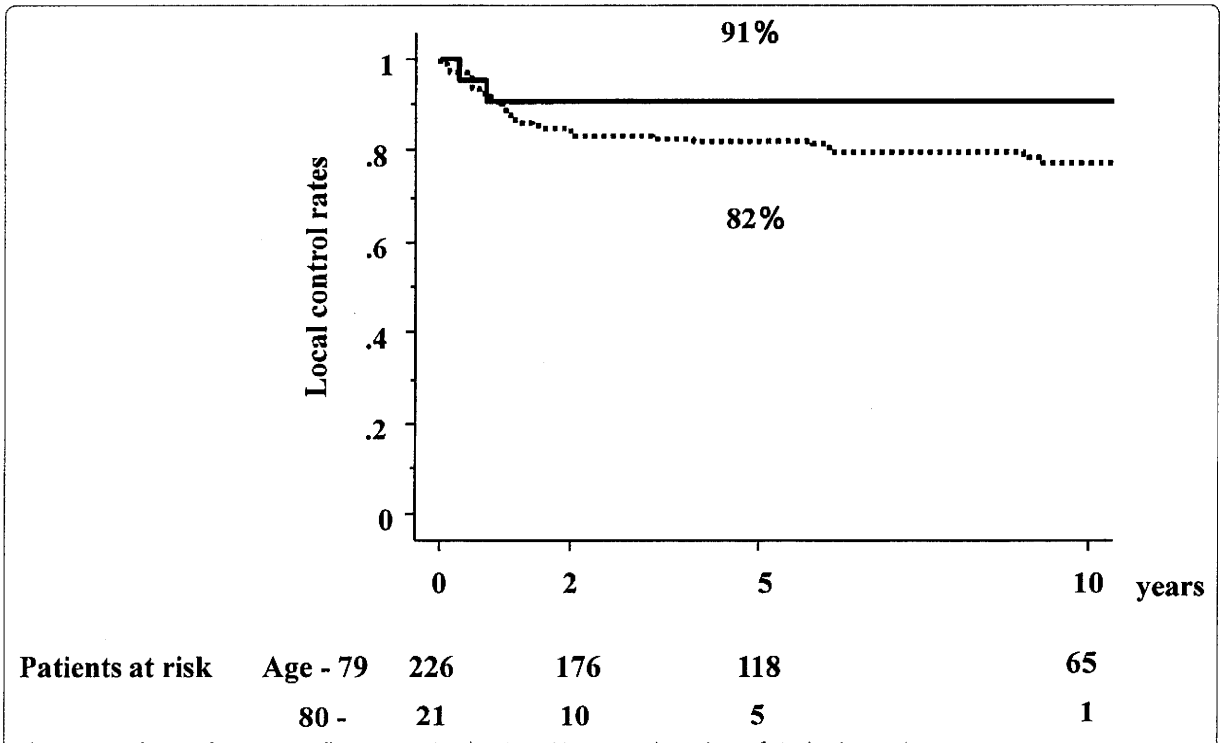

Figure 2 Local control rates according to age. Aged patients 80 or more showed no inferior local control rate to younger counterpart.

21% at 2 years (34% in control group) and all four recurerce appeared at ipsilateral side. Of the 4 patients who showed nodal failure, three underwent surgery, one of whom could be salvaged. Actuarially 12 patients died because of intercurrent disease or old age. The follow-up for 5 patients had to be terminated because the patients or their family requests.

Tolerance and Complications

Grade 2-3 acute mucositis, pharyngitis for combined external radiotherapy and oral mucositis for solely brachytherapy, occurred but were acceptable. No grade-4 skin or mucosal acute reactions were documented. The intensity of acute reactions in the elderly patients was almost the same as that observed in younger patients. Late reactions after brachytherapy comprised one bone exposure and/or two ulcer formations lasting 3 months more (2/21 = 10%; Table 1). One case showed tongue deformation with ulceration scar. In previous cohort [4], 10 to 30% of delayed reaction was found according to treatment volume and addition of external radiotherapy. Aged patients showed similar ratio of delayed reaction.

Discussion

The patients 80 years old or older among those who were treated by brachytherapy accounted for about 3% of our cohort. The incidence of carcinogenesis among this age group is currently unavailable, but oncologists are treating increasing numbers of elderly cancer patients, so that we should be more deeply concerned about treatment strategies for these patients. The deterioration of biological functions associated with aging leads to a diminished reserve capacity and increased vulnerability to age-related diseases and overall forces of mortality [6-8]. As the effects of aging depend on the individual, they manifest themselves with great variability and heterogeneity, thus making it extremely difficult if not impossible to determine a standard therapy for elderly patients based only on chronologic landmarks. When deciding on a personalized mode of treatment for older patients, it is important to assess each patient's quality of life and life expectancy. Prognostic factors related to the tumor (TNM stage, pathology, etc.), physical and/or psychological status (PS, etc.), and social support should be taken into account when estimating the outcome of treatment and life expectancy of elderly patients. However, the major part of prospective trials is carried out with patients younger than 70 so that little evidence regarding elderly patients is available.

Generally, local treatment is more appropriate than systemic therapy for the elderly. Standard chemotherapy, especially combination treatment, is not encouraged

because of elderly patients' physiologically impaired functions and diminished reserve capacity of important organs [9-11]. Unsatisfactory outcomes of combination therapy have been reported [8], although better results with less toxic antineoplastic agents or reduced doses of chemotherapeutic agents especially designed for elderly patients with non-Hodgkin's lymphoma have been reported [12]. Moreover, the rates of acute adverse effects, morbidity, and mortality remain high for the elderly, so that extended radical surgery is not encouraged for the same reasons. It is important for their quality of life and life expectancy to attain local control of symptomatic primary lesions. Carefully planned radiation therapy for the elderly is expected to become increasingly important [13]. A prospective study has also reported the usefulness of radiotherapy for esophageal cancer in elderly patients [14], and found that patients with good PS could tolerate doses that administered according to a standard radiotherapy schedule [9]. Our findings agreed with this study in that the completion rate of radiotherapy and local control rate for elderly patients were not inferior to those for younger patients.

One of the limitations of this study is that its retrospective nature leads to a lack of detailed information about co-morbidity. This is important because cardiovascular and pulmonary diseases as well as diabetes and other diseases are more pronounced in elderly than younger patients. In addition, as mentioned in results, unexpected accidents will occur more frequently in elderly than younger patients. We found four cases of hypertention and a TIA records in patients' charts, however, they were able to be diagnosed as candidates for brachytherapy with local anesthesia and we noted that adverse reactions such as mucositis in HDR brachytherapy were similar for elderly patients: spotted mucositis started to appear three days after the end of brachytherapy while confluent mucositis developed and reached a peak at ten days, but disappeared by the fourth to eighth week without any major complications [2]. Fortunately, we did not encounter the aspiration pneumonia after brachytherapy in current study. Severe deterioration in QOL, such as speech disturbance, swallowing function loss, and frequent short hospital stay were also not a case enhanced than younger counterpart. Although the number of patients in this series was too small to draw definite conclusions regarding efficacy, late toxicity and tolerance, our data suggest the potential benefits of brachytherapy for elderly patients.

Because radiation therapy is considered to be a minimally invasive treatment procedure, it has the advantage of preserving the shape and functions of the tongue. Brachytherapy was historically performed with Ra-226, which involved exposure of the surrounding tissue. To minimize undesirable radiation to normal tissues, an afterloading technique using Ir-192 was implemented. This LDR brachytherapy has been widely used since and become the gold standard in brachytherapy. Many institutes have reported successful results for tongue cancer treated with LDR brachytherapy [2,15]. Since then, HDR brachytherapy using a remote afterloading technique has been introduced in several brachytherapy centers, including ours [2-4]. We previously reported our phase III data and a retrospective review with good results for T1-3 N0 patients to show the comparable outcome of HDR. However, retrospective reviews including ours reported that older patients aged 65 or over showed poorer local control than their younger counterparts [3,4]. In a 648-patient cohort, 5-year local control rates were 87% for T1, 78% for T2, and 68% for T3 in younger patients, but 72% for T1, 67% for T2, and 54% for T3 in elderly patients aged 65 or over ($p < 0.05$) [4]. These findings prompted us to examine the background characteristics of older patients. We found that one possible explanation for poor local control was poor oral hygiene including dental factors in the elderly in previous study [12], which could be modified by careful intervention. In addition, in the study reported here, we found that patients aged 80 or over showed good outcome including four locally controlled HDR patients. Therefore age is not a sole factor on a local control rate by brachytherapy, other confounding factor such as tumor, oral hygiene, PS, co-morbidities have affected outcomes. Although further studies are needed to establish optimum schedules and techniques, elderly patients with good PS may tolerate brachytherapy schedules so that the advisability of definitive radiation therapy should be considered.

In conclusion, patients aged 80 or over showed results comparable to those for their younger counterparts, and an aggressive approach for appropriately selected elderly patients achieved good local control.

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Authors' contributions
HY conceived of this study and drafted manuscript. KY participated in the design of this study. TK and YY participated in the statistical analysis. MK, SF, NK, KS and TN participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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CLINICAL INVESTIGATION **Cervix**

RECTAL DOSE AND SOURCE STRENGTH OF THE HIGH-DOSE-RATE IRIDIUM-192 BOTH AFFECT LATE RECTAL BLEEDING AFTER INTRACAVITARY RADIATION THERAPY FOR UTERINE CERVICAL CARCINOMA

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Purpose: The purpose of this study was to reconfirm our previous findings that the rectal dose and source strength both affect late rectal bleeding after high-dose-rate intracavitary brachytherapy (HDR-ICBT), by using a rectal dose calculated in accordance with the definitions of the International Commission on Radiation Units and Measurements Report 38 ($ICRU_{RP}$) or of dose–volume histogram (DVH) parameters by the Groupe Européen de Curietherapie of the European Society for Therapeutic Radiology and Oncology.

Methods and Materials: Sixty-two patients who underwent HDR-ICBT and were followed up for 1 year or more were studied. The rectal dose for ICBT was calculated by using the $ICRP_{RP}$ based on orthogonal radiographs or the DVH parameters based on computed tomography (CT). The total dose was calculated as the biologically equivalent dose expressed in 2-Gy fractions (EQD_2). The relationship between averaged source strength or the EQD_2 and late rectal bleeding was then analyzed.

Results: When patients were divided into four groups according to rectal EQD_2 (≥ or <median dose) and source strength (≥ or <2.4 $cGy.m^2.h^{-1}$), the group with both a high EQD_2 and a high source strength showed a significantly greater probability of rectal bleeding for $ICRU_{RP}$, D_{2cc}, and D_{1cc}. The patients with a median rectal dose above the threshold level did not show a greater frequency of rectal bleeding unless the source strength exceeded 2.4 $cGy.m^2.h^{-1}$.

Conclusions: Our results obtained with data based on $ICRU_{RP}$ and CT-based DVH parameters indicate that rectal dose and source strength both affect rectal bleeding after HDR-ICBT. © 2010 Elsevier Inc.

High-dose rate, Intracavitary brachytherapy, Late rectal complications, Source strength, ^{192}Ir.

INTRODUCTION

Brachytherapy is essential in radiotherapy for cervical carcinoma and is often combined with external beam radiation therapy (EBRT) for radical treatment. Several studies have suggested that control rates are significantly improved with EBRT and brachytherapy compared with EBRT alone (1, 2). High-dose-rate remote afterloading intracavitary brachytherapy (HDR-ICBT) is widely used throughout Asia and Europe, and its use is steadily increasing in the United States (3). A patterns-of-care study performed in Japan from 1999 to 2001 showed that approximately 90% of patients with cervical cancer who underwent ICBT were treated with HDR and that iridium-192 (^{192}Ir) was used as the ICBT source at almost half of the institutes enrolled in the study (4).

However, rectal complications are a major concern for patients with uterine cervical carcinoma who are treated with a combination of EBRT and ICBT. We previously reported that patients treated not only with a rectal biologically effective dose (BED) ≥100 Gy_3 but also with an average source strength of >2.4 $cGy.m^2.h^{-1}$ had a high incidence of rectal bleeding. To our knowledge, this was the first report to demonstrate the effect of source strength and rectal BED on rectal complications after HDR-ICBT in patients with uterine cervical carcinoma (5). However, we were unable to calculate the rectal dose by using the International Commission on Radiation Units and Measurements Report 38 rectal reference point ($ICRU_{RP}$) because we did not start using radiopaque gauze for vaginal packing until 2003. Instead, the rectal point

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dose for ICBT was calculated by inserting a lead wire into the rectal lumen.

Recently, the working group for gynecologic brachytherapy of the Groupe Européen de Curietherapie of the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) introduced guidelines for contouring the target volumes and organs at risk (OARs) for three-dimensional image-based treatment planning for cervical carcinoma. This group also proposed guidelines for analyzing the dose–volume histogram (DVH) parameters calculated from these volumes (6, 7). A minimum dose for the most irradiated tissue volume of 0.1cc ($D_{0.1cc}$), 1cc (D_{1cc}), and 2cc (D_{2cc}) for, respectively, the rectum, the sigmoid, and the bladder is recommended for routine recording.

Since 2003 we have been using radiopaque gauze for vaginal packing and have obtained computed tomography (CT) during the first session of the HDR-ICBT procedure. The purpose of this study was to reconfirm, by using the retrospectively calculated rectal dose in accordance with the definitions of $ICRU_{RP}$ or GEC-ESTRO DVH parameters obtained by CT, our findings that rectal dose and source strength both affect late rectal bleeding.

METHODS AND MATERIALS

Patient characteristics

A total of 87 patients with histologically proven carcinoma of the uterine cervix were treated at the Department of Radiation Oncology, Osaka University Hospital, Osaka, Japan between February 2003 and May 2007. Patients were staged according to the International Federation of Gynecology and Obstetrics criteria and clinically examined without general anesthesia by a gynecologic oncologist and a radiation oncologist using palpation, cystoscopy, and sigmoidoscopy. Abdominal CT and pelvic magnetic resonance imaging (MRI) were performed to help with appropriate staging. Complete blood counts and liver and renal function tests were also performed. Twenty-five patients were excluded from the study because 3 had received interstitial brachytherapy, 11 were lost to follow-up, 5 died or showed local recurrence within 1 year after radiotherapy, and 6 had for various reasons not undergone CT during the first session of HDR-ICBT. We analyzed the remaining 62 patients, who had been treated with ^{192}Ir HDR-ICBT using a tandem-ovoid or tandem-cylinder applicator and followed up for 1 year or more (median, 42 months; range, 12–62 months). The stage distribution of the patients was as follows: 10 with Stage I disease (16%), 27 with Stage II (44%), 21 with Stage III (34%), and 4 with Stage IV (6%). The median age of the study cohort was 69 years (range, 35–86 years).

Radiotherapy

Both EBRT and HDR-ICBT were performed as previously described (5), with some modifications. The treatment schedules for EBRT and HDR-ICBT are listed in Table 1. A set of Fletcher-type (Fletcher-Williamson Asian-Pacific) metal applicators (Nucletron International B.V., Veenendaal, The Netherlands) was mainly used for ICBT. For patients with vaginal infiltration or with a narrow vagina, a tandem with a vaginal cylinder was used. Anterior and posterior vaginal packing with radiopaque gauze was used to maximize the distance from the source to the bladder wall and the rectal wall. Calculation of the dose profiles was based on orthogonal radiographs taken during each individual application, and the $ICRU_{RP}$ dose was estimated from these films with a treatment planning system (Plato, Nucletron). A series of transverse CT images of the pelvis with the applicators inserted was also obtained in 2.5- or 5-mm steps during the first HDR-ICBT. Concurrent chemoradiotherapy was administered to 25 of the patients (40%). Nedaplatin, an analog of cisplatin developed in Japan, was administered 5 times weekly at 35 mg/m^2 with a concurrent EBRT and ICBT.

Table 1. Treatment schedule for uterine cervical carcinomas

Tumor stage	WP (Gy)	CS (Gy)	ICBT
T1a	0	0	7.2 Gy × 4
T1b	0	40	7.2 Gy × 4
T2	20	30	7.2 Gy × 4
T3	30	20	6.8 Gy × 4
T4	40	10	6.8 Gy × 3

Abbreviations: WP = whole-pelvic irradiation; CS = pelvic irradiation with midline block; ICBT = intracavitary brachytherapy.

Calculation of rectal dose

Cumulative DVH was analyzed according to the recommendations of the GEC-ESTRO Working Group (7). The rectum was contoured from the bottom of the ischial tuberosity to the sigmoid flexure by using the external wall contour. The minimal dose received by the 0.1-cc, 1-cc, and 2-cc volumes with the highest irradiation ($D_{0.1cc}$, D_{1cc}, and D_{2cc}, respectively) was determined. To determine the dose from the combined EBRT (whole pelvic irradiation dose, excluding the fractions with central shielding) and ICBT, the total dose (EBRT + ICRT) was calculated as the biologically equivalent dose in 2-Gy fractions (EQD_2) using the linear quadratic model for incomplete sublethal damage repair (8). The equation used to calculate the EQD_2 was as follows:

$$EQD_{2total} = EQD_{2EBRT} + EQD_{2ICBT} = Nd(d + \alpha/\beta)/(2 + \alpha/\beta) + N_B d_B(d_B + \alpha/\beta)/(2 + \alpha/\beta)$$

where N is the fraction number of EBRT (before central shielding), d is the fractional dose of EBRT, N_B is the fraction number of HDR-ICBT, and d_B is the fractional dose of HDR-ICBT. The values used for late effects on OARs (*i.e.* bladder, rectum, and sigmoid colon) were α/β =3 Gy. For the first HDR-ICRT session, EQD_2 for $ICRU_{RP}$ was estimated from the orthogonal radiographs, and EQD_2 for the respective DVH parameters was estimated from CT images with the applicators inserted. For subsequent HDR-ICRT sessions, only EQD_2 for $ICRU_{RP}$ was estimated each time, whereas the DVH parameters obtained in the first session were reused because no CT scan was performed.

Follow-up and evaluation of late rectal complications

The patients were followed up by gynecologic and radiation oncologists on an outpatient basis every month in the first year, every 2 months in the second year, every 3 months in the third year, every 4 months in the fourth year, every 6 months in the fifth year, and annually thereafter until 10 years after treatment. Each follow-up examination included collection of clinical history; a physical examination comprising abdominal, pelvic bimanual and speculum examinations; and a Pap smear from the vaginal vault or uterine cervix. The method for the grading of rectal complications has been described previously (5). Grade 1 toxicity refers to minor

Table 2. Mean value of $ICRU_{RP}$ or dose–volume parameters according to rectal bleeding

Variable	Mean dose ± SD ($Gy_{\alpha\ \beta\ 3}$) Overall	Bleeding (-)	Bleeding (+)	p*
$ICUR_{RP}$	69 ± 17	64 ± 17	83 ± 20	<0.001
D_{2cc}	72 ± 16	68 ± 15	85 ± 14	<0.001
D_{1cc}	82 ± 2	76 ± 15	98 ± 19	<0.001
$D_{0.1cc}$	117 ± 49	107 ± 47	145 ± 41	0.004

Abbreviation: $ICRU_{RP}$ = International Commission on Radiation Units and Measurements Report 38 rectal reference point; D_{2cc}, D_{1cc}, $D_{0.1cc}$ = minimum dose received by the 2-cm^3, 1-cm^3, and 0.1-cm^3 volumes with the highest irradiation, respectively.

* Student's t test.

symptoms requiring no treatment; Grade 2 to symptoms responding to simple outpatients management; Grade 3 to distressing symptoms requiring hospitalization for diagnosis, minor intervention, or transfusion; and Grade 4 to fistula formation or the need for major surgical intervention.

Source strength

Data for the ^{192}Ir source strength were collected on each day of the HDR-ICBT session, and the average source strength was calculated over three or four ICBT sessions.

Statistical analysis

The actuarial rate of rectal bleeding was estimated using the Kaplan-Meier method, and differences between factors were examined with the log-rank test. Student's t-test was used to compare the mean dose when the rectal bleeding occurred to the mean dose without using the dose–volume parameters (D_{2cc}, D_{1cc}, $D_{0.1cc}$) or $ICRU_{RP}$ data.

RESULTS

Of the 62 patients, 17 (27%) developed late rectal bleeding, including 13 (21%) with Grade 1 toxicity, 2 (3%) with Grade 2, 0 (0%) with Grade 3, and 2 (3%) with Grade 4. The median EQD_2 representing the sum of the EBRT and HDR-ICRT dose was 65 Gy (range, 22-118 Gy) for $ICRU_{RP}$, 71 Gy (range, 29–112 Gy) for D_{2cc}, 80 Gy (range, 32–150 Gy) for D_{1cc}, and 108 Gy (range, 39–285 Gy) for $D_{0.1cc}$. Differences in the mean EQD_2 dose for patients with or without rectal bleeding are shown in Table 2. Patients with rectal bleeding received a significantly greater nominal total dose for $ICRU_{RP}$ ($p < 0.001$), D_{2cc} ($p < 0.001$), D_{1cc} ($p < 0.001$), and $D_{0.1cc}$ ($p = 0.004$). The patients were divided into low-EQD_2 (<median dose) and high-EQD_2 (≥median dose) groups. The actuarial rectal bleeding rate for each group is shown in Fig. 1. The 2-year rectal bleeding rates for the low-EQD_2 and high-EQD_2 groups were, respectively, 12% and 47% for $ICRU_{RP}$, 15% and 44% for D_{2cc}, 12% and 47% for D_{1cc}, and 8% and 51% for $D_{0.1cc}$. The high-EQD_2 group had a significantly greater rectal bleeding risk for all parameters ($ICRU_{RP}$, D_{2cc}, D_{1cc}, and $D_{0.1cc}$).

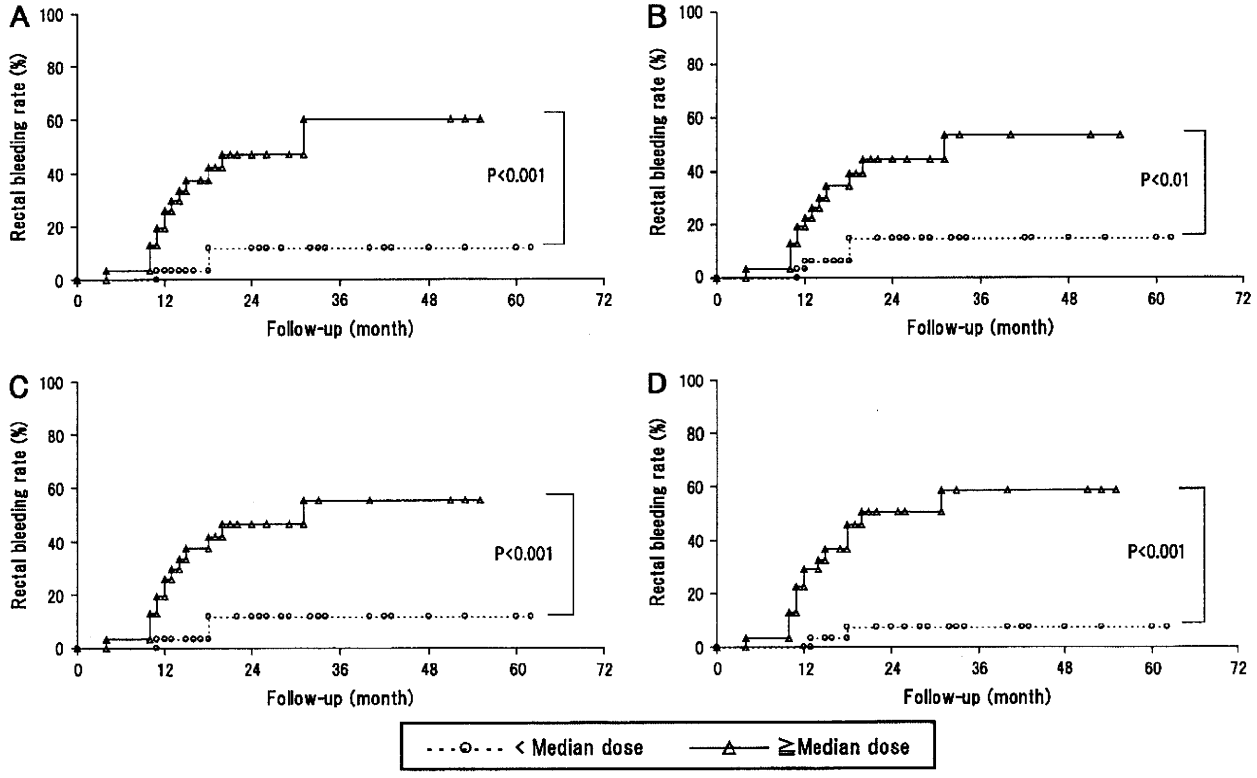

Fig. 1. Actuarial rectal bleeding rates for two groups based on the biologically equivalent dose in 2-Gy fractions (EQD_2) (<median dose vs. ≥median dose for each parameter). (A) International Commission on Radiation Units and Measurements Report 38 rectal reference point ($ICRU_{RP}$) (B) D_{2cc}. (C) D_{1cc}. (D) $D_{0.1cc}$.

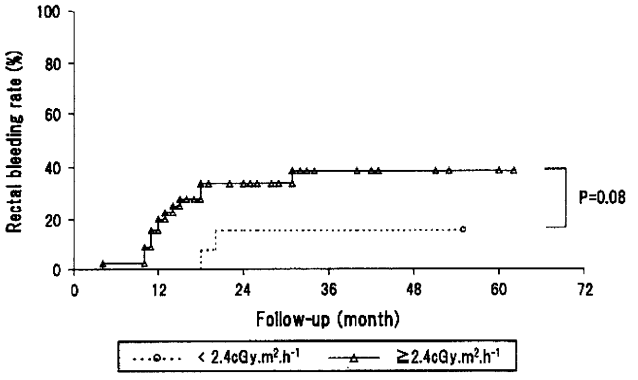

Fig. 2. Actuarial rectal bleeding rates for two groups based on ^{192}Ir source strength threshold values of 2.4 cGy.m^2.h^{-1}.

Patients were also divided into two groups based on the threshold source strength of 2.4 cGy.m^2.h^{-1} (the median source strength was 2.512 cGy.m^2.h^{-1} with a range of 1.904–4.631 cGy.m^2.h^{-1}). The group with the stronger source strength showed greater rectal bleeding, but the difference was not statistically significant (15% vs. 34% at 2 years; $p = 0.08$), as shown in Fig. 2.

Next, the patients were separated into four groups according to the median rectal EQD_2 and the threshold source strength of 2.4 cGy.m^2.h^{-1}; Group 1 (<median dose and <2.4 cGy.m^2.h^{-1}), Group 2 (<median dose and ≥2.4 cGy.m^2.h^{-1}), Group 3 (≥median dose and <2.4 cGy.m^2.h^{-1}), and Group 4 (≥median dose and ≥2.4 cGy.m^2.h^{-1}). The actuarial rectal bleeding rate for each group is shown in Fig. 3. There was a significant difference in rectal bleeding between Group 4 and Groups 1–3 for $ICRU_{RP}$, D_{2cc}, and D_{1cc}. For EQD_2 at $D_{0.1cc}$, there was a significant difference in rectal bleeding between Group 4 and Groups 1 and 2. Group 4 also had greater rectal bleeding than Group 3, but the difference was not statistically significant ($p = 0.1$). The relationship between the rectal dose and source strength for each patient is also shown in Fig. 4. Correlation coefficient analysis showed no significant relationship between rectal dose and source strength. Both patients with Grade 4 rectal bleeding were in Group 4. Clinical parameters of patients who did and did not develop late rectal bleeding were also compared (Table 3), but there was no significant difference between the two groups regarding age (<70 vs. ≥70 years old), stage (Stage I-II vs. Stage III-IV), or concurrent chemotherapy (No vs. Yes).

DISCUSSION

In a previous report, we demonstrated that patients with not only BED ≥100 Gy_3 but also an average source strength of >2.4 cGy.m^2.h^{-1} showed a correlation with a high incidence of rectal bleeding (5). To our knowledge, this was the first report to demonstrate the effect of source strength

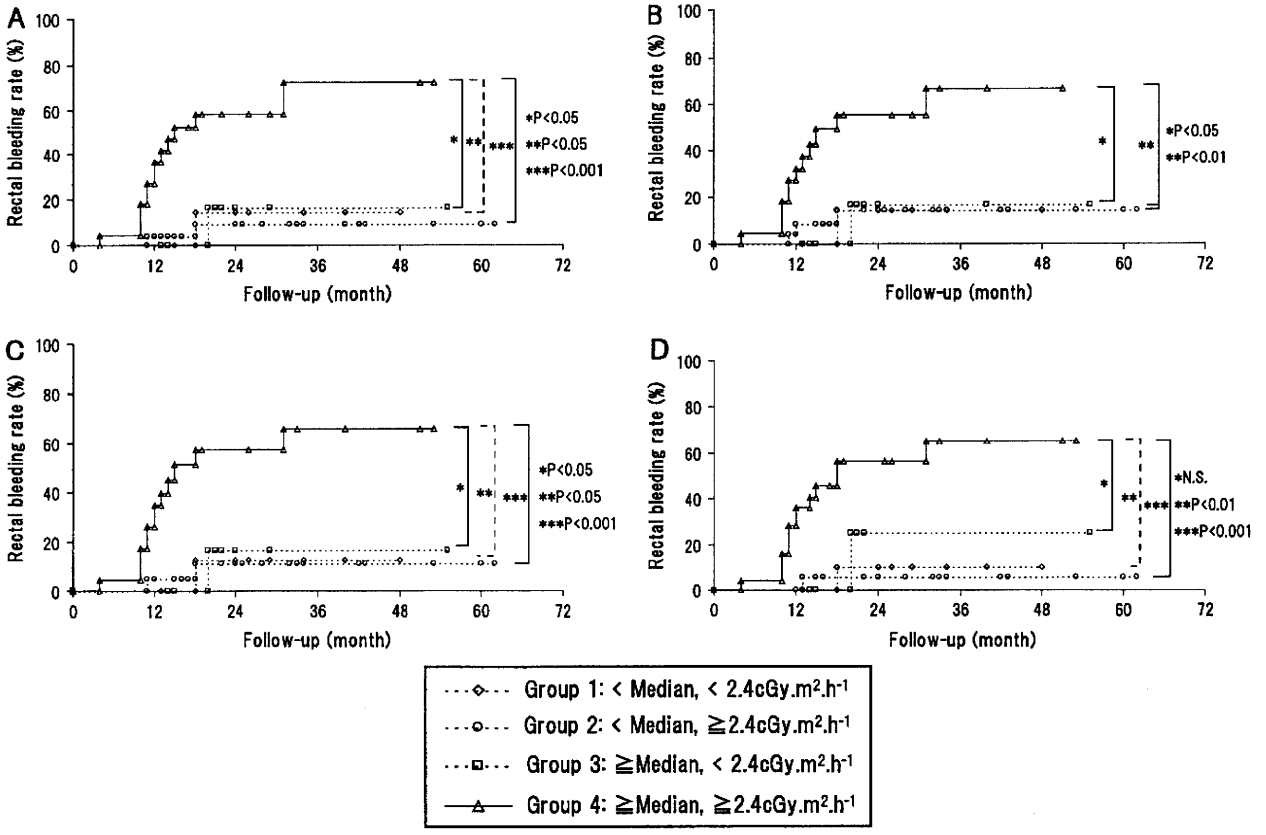

Fig. 3. Actuarial rectal bleeding rates for four groups based on the threshold values of the median dose and the source strength of 2.4 cGy.m^2.h^{-1}. (A) International Commission on Radiation Units and Measurements Report 38 rectal reference point ($ICRU_{RP}$). (B) D_{2cc}. (C) D_{1cc}. (D) $D_{0.1cc}$.

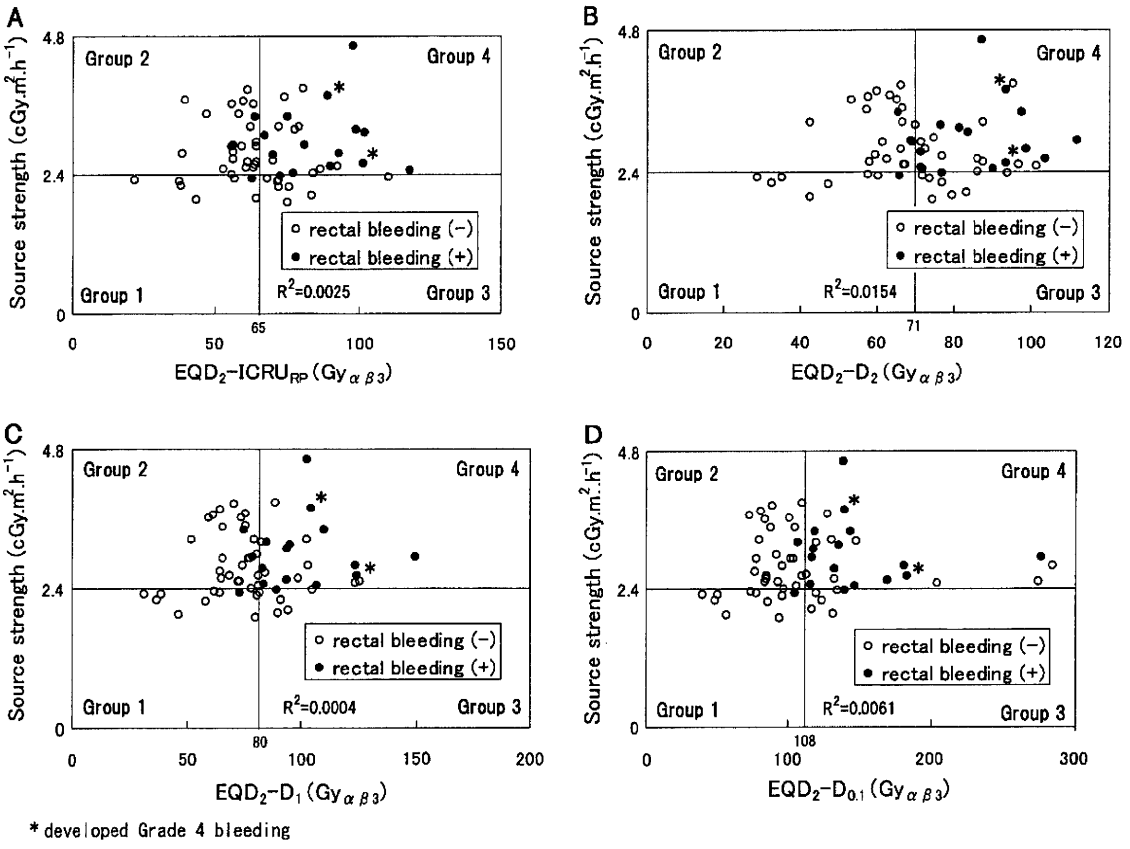

Fig. 4. Relationship of rectal dose and source strength for each patient. (A) International Commission on Radiation Units and Measurements Report 38 rectal reference point ($ICRU_{RP}$). (B) D_{2cc}. (C) D_{1cc}. (D) $D_{0.1cc}$.

and rectal BED on rectal complications after HDR-ICBT in patients with uterine cervical carcinoma. However, the previous study had a limitation in that we had defined the rectal dose as the dose to the lead wire inserted into the rectal lumen, which made it difficult to compare our result with those of other reports. We therefore decided this time to calculate the rectal dose by using the $ICRU_{RP}$ or GEC-ESTRO DVH parameters, which are considered to represent generally accepted dose points or parameters for communicating results among institutions. For the current study, the establishment of four groups of patients by using threshold levels for the rectal dose (≥ or <median dose) and source strength (≥ or <2.4 cGy.m^2.h^{-1}) showed that patients with values above the respective thresholds experienced a significantly greater frequency of rectal bleeding than did other patients. It should be noted that patients with a rectal median dose above the threshold did not show a greater frequency of rectal bleeding unless the source strength exceeded 2.4 cGy.m^2.h^{-1}. These results are in agreement with those reported by the previous study. These findings together suggest that rectal bleeding is affected not only by rectal dose but also by ^{192}Ir source strength during HDR-ICRT.

Table 3. Correlation of clinical factors with rectal bleeding

Factor	Patients, *n*	Rectal bleeding, *n* (%)		*p**
		No	Yes	
Age (y)				0.85
<70	32	24 (75)	8 (25)	
≥70	30	21 (70)	9 (30)	
Local stage				0.89
I–II	37	26 (70)	11 (30)	
III–IV	25	19 (76)	6 (24)	
CCRT				0.17
No	37	29 (78)	8 (22)	
Yes	25	16 (64)	9 (36)	

Abbreviation: CCRT = concurrent chemoradiotherapy.
* Log–rank test.

Figure 2 shows that the source strength is not the only prognostic factor for rectal bleeding (p = 0.08). For $D_{0.1cc}$ (which would correspond to the maximal dose as determined by X-ray–based planning), there was no significant difference in rectal bleeding between Group 4 (≥median dose and ≥2.4 cGy.m^2.h^{-1}) and Group 3 (≥median dose and <2.4 cGy.m^2.h^{-1}) (Fig. 3). These data indicate that the rectal dose is a more powerful prognostic factor for rectal bleeding than is the source strength.

In our previous study, the rectal dose was calculated as the BED by combining the EBRT and the HDR dose. In the current study, rectal dose is shown as the EQD_2 dose for reasons of simplicity and to allow for correlation with standard low-dose-rate (LDR) doses. The median EQD_2 values were 65 Gy

for $ICRU_{RP}$ and 71 Gy for D_{2cc}, which correspond to a BED Gy_3 of 107 Gy and 119 Gy, respectively. These values are a little higher than those of our earlier results using data obtained by inserting a lead wire into the rectal lumen (with a median BED of 101.5 Gy_3), because the lead wire in the lumen tends to separate from the rectal wall and thus to result in underestimation of the rectal wall dose as confirmed in the cohort of the present study (data not shown).

These days, conventional $ICRU_{RP}$ is not always considered to be the best predictor of rectal dose (9). However, there are a few reports of $ICRU_{RP}$ correlating well with D_{2cc} in a CT-based DVH analysis (10, 11). Additionally, GEC-ESTRO has recommended both $ICRU_{RP}$ and DVH parameters for recording and reporting because the correlation between dose–volume relations and dose–volume effect has scarcely been investigated (7). We therefore decided to analyze rectal dose by using both $ICRU_{RP}$ and CT-based DVH parameters. Many studies using $ICRU_{RP}$ (12, 13) or DVH parameters in HDR-ICBT have indicated that a higher rectal dose is significantly related with rectal bleeding. Noda *et al.* (14), using a CT-based rectal mucosal point dose, showed that a rectal BED $\geq$140 Gy_3 was associated with a significantly greater frequency of rectal complications, and Koom *et al.* (15) found that several DVH parameters obtained from three-dimensional CT-based treatment planning or $ICRU_{RP}$ are significantly associated with endoscopic scoring of mucosal changes in the rectum. However, these reports of CT-based DVH analysis results show only the relationship between rectal dose and rectal bleeding but do not deal with the power of the source.

The dose–rate effect has been analyzed in several LDR studies, which have shown that a higher dose–rate is associated with a higher incidence of late morbidity (16, 17). Therefore, we hypothesized that a higher dose–rate is also correlated with a higher incidence of rectal bleeding in ^{192}Ir HDR-ICBT. However, it is difficult to evaluate the dose–rate effect in ^{192}Ir HDR-ICBT compared with LDR-ICBT because the ^{192}Ir source has a short half-life (about 74 days) and attenuates rapidly during the treatment period (intra- or inter-fraction). In as much as the strength of the source is thought to affect the dose–rate, the ^{192}Ir source strength was measured on each day of the HDR-ICBT session, and the average source strength was calculated over three or four sessions as an indicator of the dose–rate.

The dose–rate effect at HDR is thought to be smaller than that at LDR because there is little impact of sublethal damage repair. However, the dose–rate effect at HDR is more complicated than at LDR because fractionation compensates for the relative lack of protection of late-responding normal tissues. An effect of dose–rate in HDR brachytherapy has been found in radiobiologic models (18, 19). Manning *et al.* (18) estimated the dose–rate effect using a single-plane template model, with examination of variability in dose–rate in brachytherapy performed with an HDR stepping source. Different late adverse effects were found between the relatively uniformly irradiated central zone of the template and the heterogeneously irradiated peripheral zone. The model also showed pronounced dependence on source strength, especially in cells of late-responding tissues with short repair times. In HDR treatment of cervical carcinoma using a stepping source, the instant dose–rate at each stepping point (dwell point) changes dramatically during the time course of irradiation. A peripheral location of the applicator, such as the rectal wall, may provide irradiation at an ultra-high dose–rate. Positioning of the source at the ovoid apex is likely to provide a higher dose–rate and a higher source strength, and it is likely to be associated with a late rectal effect.

One weakness of this study is that CT scans after insertion of an applicator were obtained only during the first HDR-ICRT session. However, the occurrence between sessions of substantial changes in the spatial relationship of the applicator relative to target structures and OARs have been demonstrated (20, 21), and these findings indicate the importance of individual treatment planning for each fraction. Examination of pelvic CT images for every ICBT session would allow precise calculation of dose parameters, but this approach would be time consuming and not cost effective in actual practice. The GEC-ESTRO group has provided recommendations for target delineation using MRI-contoured volumes (6, 7). MRI is superior to CT for imaging the normal anatomy of the female pelvis and for identifying the extent of cervical carcinoma, but we were unable to perform MRI scans during ICBT because of the lack of an MRI-specific applicator. Viswanathan *et al.* (22) reported that CT tumor contours can overestimate the tumor volume but that there were no significant differences between CT and MRI in terms of volumes or doses to the OARs. We therefore believe that CT-based contouring is adequate for DVH analysis of OARs.

In conclusion, this is the second report on evaluation of the effect of ^{192}Ir source strength on rectal bleeding in patients undergoing HDR-ICRT. Our results show that both rectal dose and source strength affect rectal bleeding after HDR-ICRT using $ICRU_{RP}$ and CT-based DVH parameters.

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Gastro-intestinal radiotherapy

Details of recurrence sites after elective nodal irradiation (ENI) using 3D-conformal radiotherapy (3D-CRT) combined with chemotherapy for thoracic esophageal squamous cell carcinoma – A retrospective analysis

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ABSTRACT

Purpose: To describe patterns of recurrence of elective nodal irradiation (ENI) in definitive chemoradiotherapy (CRT) for thoracic esophageal squamous cell carcinoma (SqCC) using 3D-conformal radiotherapy.
Methods and materials: One hundred and twenty-six consecutive patients with stages I–IVB thoracic esophageal SqCC newly diagnosed between June 2000 and July 2009 and treated with 3D-CRT in our institution were recruited from our database. Definitive CRT consisted of two cycles of nedaplatin/5FU repeated every 4 weeks, with concurrent radiation therapy of 50–50.4 Gy in 25–28 fractions. Until completion, radiotherapy was delivered to the N1 and M1a lymph nodes as ENI in addition to gross tumor volume.
Results: All 126 patients were included in this analysis, and their tumors were staged as follows: T1/T2/T3/T4, 28/18/54/26; N0/N1, 50/76; M0/M1a/M1b, 91/5/30. The mean follow-up period for the 63 surviving patients was 28.3 (±22.8) months. Eighty-seven patients (69%) achieved complete response (CR) without any residual tumor at least once after completion of CRT. After achieving CR, each of 40 patients experienced failures (local = 20 and distant = 20) and no patient experienced elective nodal failure without having any other site of recurrence. The upper thoracic esophageal carcinoma showed significantly more (34%) relapses at the local site than the middle (9%) or lower thoracic (11%) carcinomas. The 2-year and 3-year overall survival was 56% and 43%, respectively. The 1-year, 2-year and 3-year disease-free survival was 46%, 38% and 33%, respectively.
Conclusions: In CRT for esophageal SqCC, ENI was effective for preventing regional nodal failure. The upper thoracic esophageal carcinomas had significantly more local recurrences than the middle or lower thoracic sites.
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Concurrent chemoradiotherapy (CCRT) is well established as a standard approach to treat locally advanced esophageal cancer [1–3]. It has shown results of a 2-year local control rate of 55% and a 5-year survival rate of 25%, accompanied with severe therapy-induced side effects. Herskovic et al. [1] reported that the rates of severe and life-threatening side effects were 44% and 20%, respectively. A 2% death rate was observed to be iatrogenic as well.

Based on the results of RTOG 85-01 [1], CCRT has been broadly applied as a standard management for patients with inoperable esophageal cancer. In this study, 30 Gy was given to the whole esophagus followed by a cone down of 20 Gy to the primary tumor with 5-cm proximal and distal margins. However, the loco-regional failure and life-threatening side effects were as high as 50% and 20%, respectively. Therefore, the RTOG 94-05 trial was conducted [2], in which 50.4 Gy was administered to the radiation field with superior and inferior borders of 5 cm beyond the primary tumor followed by a cone down of 14.4 Gy to the primary tumor with 2-cm proximal and distal margins. Unfortunately, no apparent benefit was obtained and the treatment related death was even higher. This may be interpreted that the superior and inferior borders of 5 cm beyond the primary tumor did not cover high-risk sub-clinical metastatic areas. Recently, Zhao et al. [4] evaluated the appropriate target volumes in radiotherapy-alone of 68.4 Gy in 41 fractions using late-course accelerated hyperfractionated three-dimensional conformal radiotherapy (3D-CRT) for esophageal squamous cell carcinoma (SqCC) and concluded that the omission of elective nodal irradiation (ENI) was not associated with a significant amount of failure in lymph node (LN) regions not included in the planning target volume (PTV).

Since the early 1980s, Japanese surgeons have practiced 3-field regional LN dissections for esophageal cancer [5,6]. There are some reports indicating that prophylactic 3-field LN dissections for esophageal cancer can lead to an improved survival [7,8]. In

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