progressed after treatment in the other patient. In 85 evaluable patients, 83 (98%) achieved CR and residual cancer cells were confirmed in 2 patients. Failures were observed in 33: locoregional failures in 30, distant metastasis (malignant pleural effusion) in 1 and unspecified in 2. Among the 30 patients with locoregional failures, one had failure at the primary esophageal site and regional LN metastasis concurrently. Esophageal failures were observed in 25 patients: 13 were primary tumor failures and 12 were metachronous esophageal cancers. There were no differences according to tumor depth in the occurrence rate of all esophageal failures, primary site failures and metachronous esophageal cancers. Regional LN metastases were observed in 6 patients. Although submucosal cancer patients showed a high rate of regional LN metastasis compared with mucosal cancer patients, the difference lacked significance (2% in mucosal and 12% in submucosal cancer, $p = 0.10$). Furthermore, 5 failures were not in the EBRT field and one was in the EBRT field.

Among the 33 patients with failures, an early stage failure detected as a superficial esophageal lesion was observed in 15 patients and an advanced stage failure was observed in 18. According to the depth of tumor, the occurrence rate of advanced stage failures was significantly higher in submucosal cancer patients (7% in mucosal and 37% in submucosal cancer, $p < 0.01$). Regarding salvage treatments for 15 patients with early stage failures, 14 patients were salvaged by esophagectomy or endoscopic resection. For 18 patients with advanced stage failures, only one patient who received lymphadenectomy with adjuvant CRT for LN metastasis out of the EBRT field was salvaged.

Survival rates and prognostic factor

At the time of last follow-up, 49 of 87 patients had died. Seventeen patients had esophageal cancer deaths including one treatment-related death; 2 in mucosal and 15 in submucosal cancer patients. Submucosal cancer patients showed a higher rate of esophageal cancer deaths compared with mucosal cancer patients ($p < 0.01$). Eleven patients died of other malignancies: lung cancer in 3, hepatocellular carcinoma in 3, head and neck cancer in 2, and single cases each of malignant lymphoma, bile duct carcinoma and bladder sarcoma. Among these 11 patients, 3 had esophageal metachronous cancers and 1 had LN recurrence, however, all of them were controlled by salvage treatments. Twenty-one patients died of intercurrent diseases: pulmonary infection in 9, heart disease in 4, hepatic failure in 2, unknown cause in 2 and single cases each of renal failure, suicide, senility and cerebral thrombosis.

The 5-year OS, CSS and LRC for all patients were 58% [95% confidence intervals (CI) 48–69%], 78% (95% CI 69–88%) and 63% (95% CI 52–75%), respectively (Fig. 1). According to the depth of tumors, the 5-year OS, CSS and LRC for mucosal and submucosal cancers were 84% (95% CI 73–95%) and 31% (95% CI 17–46%), 97% (95% CI 92–100%) and 55% (95% CI 38–73%), and 75% (95% CI 62–89%) and 49% (95% CI 36–67%), respectively (Fig. 2a–c). There were significant differences in OS, CSS and LRC between mucosal and submucosal cancer ($p < 0.01$, $p < 0.01$ and $p = 0.02$, respectively). Prognostic factors according to UVA are summarized in Table 3. The significant factors for LRC were tumor depth ($p = 0.02$) and tumor length ($p = 0.01$), those for CSS were tumor depth ($p < 0.01$) and tumor length ($p = 0.02$), and those for OS were KPS ($p = 0.04$), operability ($p = 0.02$), double cancer within 5 years ($p < 0.01$) and tumor depth ($p < 0.01$). MVA for OS revealed that tumor depth was the only significant prognostic factor ($p < 0.01$).

Toxicity

Toxicities are summarized in Table 4. Grade ≥3 acute toxicities of esophagitis, leucopenia and thrombocytopenia occurred in 2, 1 and 0 patients, respectively. Grade ≥3 late toxicities of esophageal ulcers, pneumonitis, pleural effusion and pericardial effusion were observed in 5, 0, 0 and 1 patients, respectively. Details of Grade ≥3 late toxicities of the esophageal ulcers are shown in Table 5. All of them received IBT boost following EBRT and 3 patients developed esophago-mediastinal fistulas concurrently. One needed bypass surgery (Grade 4) and another died of mediastinitis (Grade 5). The other 3 patients recovered by conservative treatment. The lone patient with Grade 3 pericardial effusion, who was the same patient with Grade 3 esophago-mediastinal fistula, developed Grade 2 pleural effusion concurrently. Both pericardial and pleural effusion decreased after recovery from the fistula. Regarding

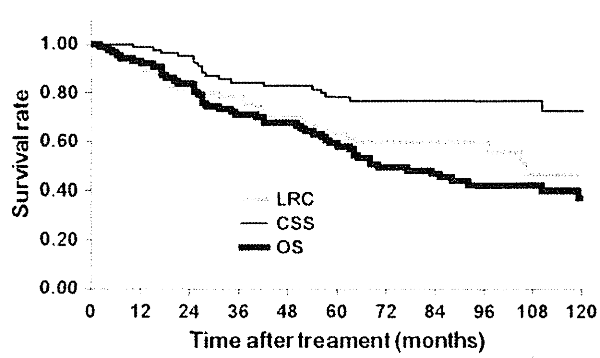

Fig. 1 Curves for overall survival (*OS*), cause-specific survival (*CSS*) and locoregional control (*LRC*) rates for all patients. The 5-year OS, CSS and LRC were 58% (95% CI 48–69%), 78% (95% CI 69–88%) and 63% (95% CI 52–75%), respectively

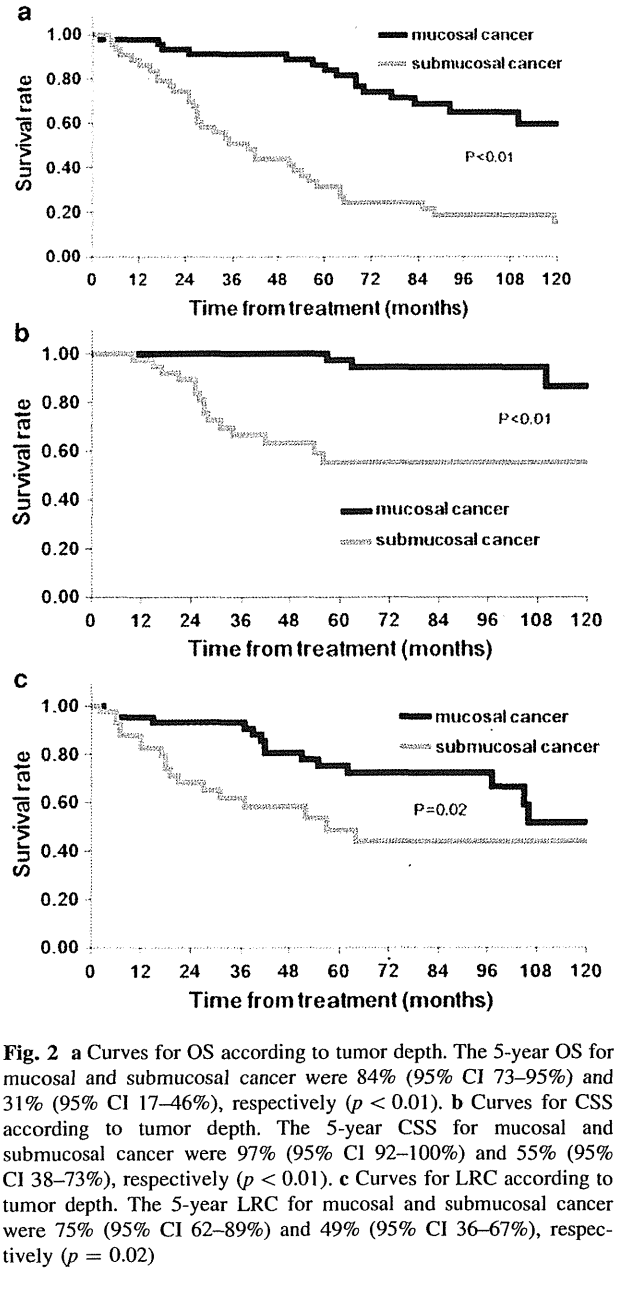

Fig. 2 **a** Curves for OS according to tumor depth. The 5-year OS for mucosal and submucosal cancer were 84% (95% CI 73–95%) and 31% (95% CI 17–46%), respectively ($p < 0.01$). **b** Curves for CSS according to tumor depth. The 5-year CSS for mucosal and submucosal cancer were 97% (95% CI 92–100%) and 55% (95% CI 38–73%), respectively ($p < 0.01$). **c** Curves for LRC according to tumor depth. The 5-year LRC for mucosal and submucosal cancer were 75% (95% CI 62–89%) and 49% (95% CI 36–67%), respectively ($p = 0.02$)

occurrence of Grade ≥3 esophageal ulcers, no significant factor emerged.

We also investigated cardiac ischemia and heart failure after RT (Grade ≥3 according to CTCAE v3.0) (Table 6). Cardiac ischemia occurred in 5 patients. Two patients died of acute myocardial infarction, at 2 and 6 months after RT. One had a history of angina and the other patient had a history of brain infarction and KPS of 60. The time to onset of the other 3 patients was 22, 76 and 151 months after RT. They received stent placement and were alive 65, 24 and 13 months later, respectively. Four patients suffered heart failure. One died of heart failure at 64 months after RT; he had a history of dilated cardiomyopathy. The time to onset of the other 3 patients was 42, 46 and 124 months. They received pacemaker placement; one of them died of malignant lymphoma 9 months later; the other 2 patients were alive 18 and 47 months later. Investigation of significant factors associated with cardiac ischemia and heart failure revealed that a history of heart disease before RT was the only significant factor ($p = 0.002$) (Table 7).

Discussion

With advances in endoscopic equipment, the number of SECs treated has increased. According to the report of the Registry of Esophageal Carcinomas in Japan, SEC accounted for 8.5% of esophageal cancer patients treated in 1979–1982 and 28% in 1998–1999 [1, 2]. In the data of the Japanese Patterns of Care Study, 21% of the esophageal cancer patients who were treated with RT in 1999–2001 had SEC [3].

In our study, there was a clear difference in treatment results depending on the depth of tumor invasion. Tumor depth was a significant factor for OS, CSS and LRC by UVA. Furthermore, tumor depth was the only significant factor for OS by MVA. Favorable treatment outcomes in mucosal cancer were achieved in this study. The CR rate was 98% and the 5-year OS, CSS and LRC were 84, 97 and 75%, respectively. These results were almost equivalent to that reported for surgery [4–9]. Most of the mucosal cancers in this study were large or multiple lesions that were difficult to completely resect by EMR or had margin-positive lesions after EMR. In the 1990s, surgery or radiotherapy was often considered for these lesions. However, remarkable progress in endoscopic techniques has resulted in significant changes. Recently, endoscopic submucosal dissection (ESD) has been increasingly used as a new technique of endoscopic resection. ESD facilitates en-bloc resection even in large lesions where piecemeal resection was needed by EMR. Takahashi et al. [20] reported that ESD reduced the local recurrence rate (0.9% in the ESD group and 9.8% in the EMR group) significantly and that the disease-free survival rate was significantly better with ESD than with EMR. Most mucosal cancers can now be cured by endoscopic treatment alone due to advances in the technique of endoscopic resection. Thus, surgery and RT in the treatment of mucosal cancer have been relegated to a limited role.

Initial response for submucosal cancer was considered equally good as that achieved for mucosal cancer. CR rate was 98% and high long-term LRC and survival rates were anticipated. However, the 5-year OS, CSS and LRC were 31, 55 and 49%, respectively. These results were obviously inferior to those of mucosal cancer, and little difference

Table 3 Prognostic factors

Patient characteristics	n	LRC		CSS		OS		
		5-year rate (%)	UVA	5-year rate (%)	UVA	5-year rate (%)	UVA	MVA
Age (years)								
≤70	49	61	n.s.	84	n.s.	65	n.s.	–
>70	38	67		72		51		
Gender								
Male	80	62	n.s.	77	n.s.	58	n.s.	–
Female	7	86		100		57		
KPS								
90–100	71	61	n.s.	79	n.s.	64	0.04	0.222
60–80	16	74		73		37		
Operability								
Operable	33	63	n.s.	86	n.s.	72	0.010	0.076
Inoperable	54	63		73		50		
Double cancer within 5 years								
Yes	16	69	n.s.	90	n.s.	64	0.007	0.485
No	71	63		77		31		
Tumor depth								
Mucosal	44	75	0.023	97	<0.001	84	<0.001	0.003
Submucosal	43	49		55		31		
Tumor length (cm)								
≤3.0	63	72	0.012	85	0.026	63	n.s.	–
>3.0	24	38		63		45		
Circumferential extent								
≤1/2	70	65	n.s.	79	n.s.	60	n.s.	–
>1/2	17	57		78		51		
Multiple Lugol-voiding regions								
Yes	59	58	n.s.	78	n.s.	58	n.s.	–
No	28	74		81		60		
Multiple cancer in esophagus								
Yes	21	69	n.s.	81	n.s.	52	n.s.	–
No	66	62		78		60		

KPS Karnofsky performance status, *LRC* locoregional control rate, *CSS* cause-specific survival rate, *OS* overall survival rate, *UVA* univariate analysis, *MVA* multivariate analysis, *n.s.* not significant

Table 4 Toxicity

	G2	G3	G4	G5	≥G3 (%)
Acute					
Esophagitis	22	2	0	0	2 (2%)
Leukopenia	3	1	0	0	1 (1%)
Thrombocytopenia	1	0	0	0	0 (0%)
Late					
Esophagus	3	3	1	1	5 (6%)
Pneumonitis	2	0	0	0	0 (0%)
Pleural effusion	3	0	0	0	0 (0%)
Pericardial effusion	–	1	0	0	1 (1%)

G grade

was seen when compared with previous reports of RT alone [10–16]. The main pattern of failures was locoregional failures (18 of 19 patients with failures). These outcomes suggest that treatment needs to be intensified to improve the locoregional control rate for submucosal cancer patients.

Table 5 Details of patients with esophageal ulcer (≥Grade 3)

	Depth	Treatment	Complication	Grade	Support
1	Mucosal	EBRT + IBT	Ulcer + perforation	3	TPN
2	Submucosal	EBRT + IBT	Ulcer	3	TPN
3	Submucosal	EBRT + IBT	Ulcer	3	TPN
4	Submucosal	EBRT + IBT	Ulcer + perforation	4	Bypass surgery
5	Submucosal	EBRT + IBT	Ulcer + perforation	5	Death

EBRT external beam radiotherapy, *IBT* intraluminal brachytherapy, *TPN* total parental nutrition

Table 6 Details of patients with heart disease (≥Grade 3)

	Sex	Age	History of HD	Tumor site	Treatment	Complication	Onset (months)	Outcome (months)	
1	Male	69	Angina	Mt	IBT	CI	2	Dead with AMI	2
2	Male	78	–	Mt	EBRT + IBT	CI	5	Dead with AMI	6
3	Male	61	–	Mt	EBRT + IBT	CI	22	Alive	87
4	Male	70	–	Mt	EBRT + IBT	CI	76	Alive	100
5	Male	73	AR	Mt	EBRT + IBT	CI	151	Alive	164
6	Male	84	–	Lt	EBRT + IBT	HF	42	Dead with ML	51
7	Male	65	DCM	Lt	EBRT + IBT	HF	50	Dead with HD	64
8	Male	71	OMI	Mt	EBRT + IBT	HF	46	Alive	64
9	Male	55	AF	Mt	EBRT + IBT	HF	124	Alive	171

HD heart disease, *EBRT* external beam radiotherapy, *IBT* intraluminal brachytherapy, *CI* cardiac ischemia, *HF* heart failure, *AR* aortic regurgitation, *DCM* dilated cardiomyopathy, *OMI* old myocardial infarction, *AF* atrial fibrillation, *AMI* acute myocardial infarction, *ML* malignant lymphoma, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus

Intraluminal brachytherapy is a RT method that can deliver an isolated high dose to local tumors while sparing the surrounding normal tissues. Its efficacy for SEC has been reported by several authors [13–19]. However, a significant advantage of IBT in the treatment of esophageal cancer remains to be demonstrated. The Study Group of the Japanese Society of Therapeutic Radiology and Oncology reported no advantage when IBT was compared with EBRT alone [11]. Recently, some promising results of IBT combined with EBRT for submucosal cancer were reported by Ishikawa et al. [19] from Gunma University. Their study showed a significant difference in the 5-year CSS between the IBT + EBRT group and EBRT alone (86 vs. 62%, $p = 0.04$). However, there were no significant differences in LRC, OS and recurrence-free survival. Furthermore, according to the Japanese Patterns of Care Study, the performance rate of IBT in the treatment of esophageal cancer in Japan has been decreasing [3]. Concurrent CRT has become the standard therapy as a non-surgical treatment for locally advanced esophageal cancer, because randomized controlled trials revealed the efficacy of CRT [21–23]. Recently, the efficacy of CRT for SEC has been studied. Yamada et al. [24] reported that the 5-year OS of CRT for stage I esophageal cancer was 66.4%. Kato et al. reported the outcome of a phase II trial of CRT in patients with stage I esophageal cancer. In their study, the 4-year OS was 80.5% [25]. The survival rates from these studies were equivalent to those of surgery. There has thus been a shift from RT alone to CRT in the RT methods for SEC.

In this study, 13 primary site recurrences and 12 metachronous esophageal cancers were observed. Fifteen of these 25 lesions were detected as superficial lesions and 14 of these were successfully salvaged. Meanwhile, most of the patients who developed advanced recurrences died of esophageal cancer. This suggests that detection of esophageal failures or metachronous cancers as a superficial lesion by periodic endoscopy is very important.

In treating with IBT, avoiding the toxicity of treatment-related esophageal ulcer is of critical importance. Nemoto et al. [10] recommended that the IBT fractional dose should not exceed 5 Gy to prevent esophageal ulcers. Akagi et al. [26] have also recommended a small fractional dose of 2.0 or 2.5 Gy in high-dose-rate IBT to minimize esophageal complications. In our study, Grade ≥3 esophageal ulcer occurred in 5 patients (6%). This incidence rate was comparatively low; however, Grade 4 and 5 ulcers

Table 7 Late toxicities: heart disease

Characteristics	n	Heart disease	
		n (%)	p value
Age (years)			
≤70	49	5 (10)	n.s.
>70	38	6 (16)	
Gender			
Male	80	9 (11)	n.s.
Female	7	2 (29)	
KPS			
90–100	71	7 (10)	n.s.
60–80	16	4 (25)	
Operability			
Operable	33	2 (6)	n.s.
Inoperable	54	9 (17)	
Tumor depth			
Mucosal	44	6 (14)	n.s.
Submucosal	43	5 (12)	
Tumor length (cm)			
≤3.0	63	7 (11)	n.s.
>3.0	24	4 (17)	
Treatment			
IBT alone	27	2 (7)	n.s.
IBT + EBRT	60	9 (15)	
Diabetes mellitus			
Yes	14	2 (14)	n.s.
No	73	9 (12)	
Heart disease history			
Yes	14	6 (43)	0.002
No	73	5 (7)	
Hypertension			
Yes	15	2 (13)	n.s.
No	72	9 (13)	
Alcoholic drinking			
Yes	64	7 (11)	n.s.
No	23	4 (17)	
Tobacco smoking			
Yes	66	7 (11)	n.s.
No	21	4 (19)	

KPS Karnofsky performance status, *n.s.* not significant

occurred in patients treated with IBT fractional doses of 2.0 and 2.5 Gy. We need to be aware of the occurrence of severe esophageal ulcer even when we perform IBT with a low fractional dose.

In our study, Grade ≥3 pneumonitis, pleural effusion and pericardial effusion developed in 0, 0 and one patient, respectively. This result suggests that RT without chemotherapy was safe regarding these toxicities. We also investigated cardiac ischemia and heart failure after treatment. Nine patients suffered Grade ≥3 events. Two died of AMI and one died of heart failure. Five of them had a history of heart disease, and a history of heart disease was the only significant factor associated with developing events of cardiac ischemia and heart failure after RT ($p = 0.002$). Radiation-induced heart disease is one of the complications after thoracic RT. The effects on various portions of heart, such as pericardium, myocardium or coronary artery, due to RT have been reported [27–29]. In CRT of esophageal cancer, cardiopulmonary toxicities became problems to be solved after the report by Ishikura et al. [30]. We are not sure whether all events of cardiac ischemia and heart failure in this study occurred due to irradiation. However, in the RT for esophageal cancer, irradiation to the heart cannot be avoided. Therefore, efforts should be made to decrease the irradiation dose to the heart as much as possible using the newest technique. Furthermore, follow-up with attention to development of heart disease is important.

As mentioned previously, the role of IBT has been limited in the treatment of SEC. However, we consider that IBT can be a treatment option for mucosal cancer patients who have multiple or large legions that have a risk of severe esophageal stenosis by endoscopic resection and for submucosal cancer patients who have difficulties in receiving surgery or concurrent chemotherapy because of high age or concurrent illnesses.

In conclusion, there was a clear difference in treatment results depending on tumor depth. The outcomes of IBT combined with EBRT for submucosal cancer were not satisfactory and more intensive treatment should be considered. In our institution, CRT was introduced for submucosal cancer after 2002 and the efficacy and safety of CRT are currently under investigation.

Conflict of interest No author has any conflict of interest.

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Clinical Investigation: Thoracic Cancer

Dose–Volume Metrics Associated With Radiation Pneumonitis After Stereotactic Body Radiation Therapy for Lung Cancer

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Summary

To identify dose–volume factors associated with radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT) for lung cancer, this study analyzed 74 patients who underwent SBRT for primary lung cancer. RP grade 2 or worse was observed in 15 patients (20.3%). Lung V25 and PTV volume were significant factors. SBRT with PTV ≥37.7 ml and lung V25 ≥4.2% indicated a 50% risk of RP grade 2 or worse.

Purpose: To identify dose–volume factors associated with radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT) for lung cancer.

Methods and Materials: This study analyzed 74 patients who underwent SBRT for primary lung cancer. The prescribed dose for SBRT was uniformly 48 Gy in four fractions at the isocenter. RP was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.3. Symptomatic RP was defined as grade 2 or worse. Optimal cut-offs dividing the patient population into two subgroups based on the incidence of symptomatic RP were sought using the following dose–volume metrics: PTV volume (ml), mean lung dose (Gy), and V5, V10, V15, V20, V25, V30, V35, and V40 (%) of both lungs excluding the PTV.

Results: With a median follow-up duration of 31.4 months, symptomatic RP was observed in 15 patients (20.3%), including 1 patient with grade 3. Optimal cut-offs for pulmonary dose–volume metrics were V25 and V20. These two factors were highly correlated with each other, and V25 was more significant. Symptomatic RP was observed in 14.8% of the patients with V25 <4.2%, and the rate was 46.2% in the remainder ($p = 0.019$). PTV volume was another significant factor. The symptomatic RP rate was significantly lower in the group with PTV <37.7 ml compared with the larger PTV group (11.1% vs. 34.5%, $p = 0.020$). The patients were divided into three subgroups (patients with PTV <37.7 ml; patients with, PTV ≥37.7 ml and V25 <4.2%; and patients with PTV ≥37.7 ml and V25 ≥4.2%); the incidence of RP grade 2 or worse was 11.1%, 23.5%, and 50.0%, respectively ($p = 0.013$).

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Conclusions: Lung V25 and PTV volume were significant factors associated with RP after SBRT.

Keywords: Radiation pneumonitis, Stereotactic body radiation therapy, Dose—volume analysis

Introduction

Stereotactic body radiation therapy (SBRT) consists of two key features. One is its high degree of accuracy, which allows delivery of a high dose to a very limited volume while limiting the dose to normal tissues. The other key feature is hypofractionation. With conventional radiotherapy, schedules of 30 to 40 fractions are commonly used, with a total dose of 60 to 74 Gy for lung cancer. SBRT is usually performed in a single fraction or two to five fractions with a much higher fractional dose (6—20 Gy). These key features of SBRT lead to high control rates of local tumors (1, 2). Use of SBRT should improve the prognosis for inoperable or elderly patients with early stage non-small-cell lung cancer (NSCLC) (3).

The safety of SBRT is being confirmed in multi-institutional Phase II trials for peripheral lung cancer in both inoperable patients (1, 4) and operable patients (2). In the Radiation Therapy Oncology Group (RTOG) trial 0236 (1), protocol-specified treatment-related grade 3 and 4 adverse events occurred in 12.7% and 3.6%, respectively; no grade 5 adverse events were reported. In the Nordic Phase II study of SBRT (4), grade 3 toxicity was seen in 21%; no grade 4 or 5 toxicity was reported. Nagata *et al.* reported grade 3 toxicity in 6.2% of operable patients in the Japan Clinical Oncology Group (JCOG) 0403 (2).

Radiation pneumonitis (RP) is one of the most common toxicities after SBRT, as well as after conventional radiotherapy to the lung. The reported rates of symptomatic RP after SBRT range from 9% to 28% (5—11). Although most of the RP was grade 2 and manageable, a few cases were severe, and there is a potential risk of mortality (5). It is very important to develop a method to predict the risk of RP after SBRT for the lung.

The dose—volume metrics from a treatment plan might be a predictor for RP. In conventional radiotherapy for the lung, many dose—volume data are available, and dose constraints have been proposed to reduce the risk of pneumonitis. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) recommended a lung V20 $\leq$30% to 35% and mean lung dose (MLD) $\leq$20 to 23 Gy to limit the risk of RP to $\leq$20% in definitive radiotherapy for NSCLC with conventional fractionation (12). However, there are no established criteria regarding dose—volume factors in hypofractionated SBRT. Therefore, we searched for dose—volume factors associated with RP after SBRT for lung cancer.

Methods and Materials

This study analyzed consecutive 74 patients who underwent SBRT for pathology-proven NSCLC from September 2003 to March 2008. All patients were diagnosed with Stage I lung cancer based on CT. The eligibility criteria for SBRT for Stage I lung cancer were as follows: surgery was contraindicated or refused; maximal tumor diameter was 40 mm or less; the tumor was not adjacent to mediastinal organs (spinal cord, esophagus, heart, and main bronchus); the patient could remain stable for longer than 30 min with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; the patient had no active interstitial pneumonitis; and written informed consent was obtained. Patient characteristics are shown in Table 1. For these patients, the prescribed dose of SBRT was uniformly 48 Gy in four fractions at the isocenter. A median in overall treatment time was 5 days (range, 4—12 days). Chemotherapy was not administered unless disease progression was confirmed.

SBRT procedure

Details of our SBRT procedure have been described in our previous reports (13, 14). The patient was immobilized with a stereotactic body frame (Elekta AB, Stockholm, Sweden). Irradiation was performed with 6-MV x-ray beams from a linear accelerator (Clinac 2300 C/D; Varian Medical Systems, Palo Alto, CA) with multiple non-coplanar static ports (range, five to eight ports). The beams were shaped into a planning target volume (PTV) plus 5-mm margins using multi leaf collimators.

The SBRT was planned with the Eclipse (Varian Medical Systems) treatment planning system. An internal target volume (ITV) was determined using computed tomography (CT) with a slow-scan technique, considering tumor motion assessed by x-ray fluoroscopy. The PTV was defined as the ITV with a 5-mm margin for setup uncertainty. To delineate lung volumes, the segmentation wizard in Eclipse was applied to the slow-scan CT images with a threshold value of −300 Hounsfield units (HU). The lung

Table 1 Patient characteristics

Sex	
Male	55
Female	19
Age (y)	
Median (range)	77 (63—88)
ECOG performance status	
0	37
1	30
2	7
Operability	
Operable	24
Inoperable	50
Histology	
Adenocarcinoma	36
Squamous cell carcinoma	30
Other*	8
T-stage (7th UICC staging)	
T1a	26
T1b	27
T2a	21

Abbreviation: UICC = Union for International Cancer Control.

* Other included three large-cell carcinomas and five non-small-cell carcinomas not otherwise specified.

volumes were then trimmed manually to remove overlapping regions involving the PTV and bronchi.

RP grading

The patients were followed up 1, 2, 4, 6, 9, and 12 months after the SBRT, then every 3 months for Years 2 to 5, and then every 6 months thereafter. CT was performed every 2 to 4 months in the first year, every 6 months between Years 1 and 5 after the treatment, and annually thereafter.

Radiation pneumonitis was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v.3 for pneumonitis, which consists of the following grades: grade 1, asymptomatic with radiographic findings only; grade 2, symptomatic and not interfering with the activities of daily living (ADL); grade 3, symptomatic, interfering with the ADL and O_2 indicated; and grade 4, life-threatening, ventilatory support indicated. We defined symptomatic RP as grade 2 or worse.

Statistical analysis

The dose–volume metrics were re-calculated using the Analytical Anisotropic Algorithm (AAA) with the same monitor units as used in the clinical setting. The grid size for the calculation was $2.5 \times 2.5 \times 2.5$ mm^3.

The following dose–volume metrics were evaluated in this study: PTV volume (ml), MLD (Gy), and V5, V10, V15, V20, V25, V30, V35, and V40, where V*d* is the relative volume of normal lung (%) that received more than a threshold dose of *d* Gy. We defined normal lung as both lungs excluding the PTV.

The optimal cut-offs dividing the patient population into two subgroups based on the incidence of symptomatic RP were searched using the recursive partitioning method. After dividing the groups, the occurrence rates for symptomatic RP were compared using Fisher's exact test. R version 2.13.1 with the rpart package (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses. Statistical significance was defined as $p < 0.05$.

Results

With a median follow-up duration of 31.4 months (range, 4.2–65.0 months), symptomatic RP was observed in 15 patients (20.3%), consisting of 14 patients with grade 2 and 1 patient with grade 3. RP was diagnosed based on symptoms with radiologic findings. The median time to symptomatic RP was 4.5 months (range, 1.1–16.1 months).

Table 2 summarizes the dose–volume metrics of the PTV and normal lung. The PTV ranged from 9.9 to 86.6 ml (median, 32.5 ml). The median MLD was 3.2 Gy (range, 1.6–7.6 Gy). The median lung V20 and V25 were 4.4% and 2.9%, respectively. The lung metrics (MLD and V5–40) were highly correlated with each other, with correlation coefficients (R) of 0.61 to 0.99. In contrast, the correlations between the PTV volume and lung metrics were weak ($R = 0.37–0.59$). The PTV volume, MLD, V20, and V25 were respectively 42.1 ml, 3.7 Gy, 5.4%, and 3.8% in mean for patients with grade 2 RP. Those values were respectively 38.1 ml, 4.0 Gy, 5.0%, and 3.3% for a patient with grade 3 RP.

The optimal cut-offs for the dose–volume metrics are shown in Table 3. Lung V25 and V20 were significant factors, and V25 was more significant. The rate of symptomatic RP was 14.8% in the patients with V25 <4.2%, whereas the rate was 46.2% in the remainder ($p = 0.019$). The PTV volume was another significant factor. The symptomatic RP rate was significantly lower in the group with PTV <37.7 ml compared with the larger PTV group (11.1% vs. 34.5%, $p = 0.020$). On classifying the patient population into three subgroups (patients with PTV <37.7 ml, $n = 45$; patients with PTV ≥37.7 ml and V25 <4.2%, $n = 17$; and patients with PTV ≥37.7 ml and V25 ≥4.2%, $n = 12$), the incidence of symptomatic RP was 11.1%, 23.5%, and 50.0%, respectively ($p = 0.013$).

Table 2 Dose–volume metrics

		Median (range)
PTV	Volume (ml)	32.5 (9.9–86.6)
Lung	Mean dose (Gy)	3.2 (1.6–7.6)
	V40 (%)	0.7 (0–2.9)
	V35 (%)	1.4 (0.2–4.8)
	V30 (%)	2.0 (0.5–6.6)
	V25 (%)	2.9 (0.9–9.5)
	V20 (%)	4.4 (1.7–13.1)
	V15 (%)	6.7 (2.6–18.2)
	V10 (%)	10.3 (4.4–25.1)
	V5 (%)	16.7 (7.1–37.3)

Abbreviation: PTV = planning target volume.

Discussion

We investigated the dosimetric factors associated with symptomatic RP (≥grade 2) after SBRT, and found that PTV and lung V25 were significant factors. The optimal cut-offs for these factors (PTV <37.7 ml and V25 <4.2%) were much lower than prespecified constraints that other SBRT trials used to mainly limit the risk of grade 3 toxicities (*e.g.*, MLD <18 Gy, lung V40 <100 ml, V15 <25%, and V20 <20% for the JCOG 0403 trial; and lung V20 <10% for RTOG 0236). As only 1 patient in our cohort had grade 3 RP, it was difficult to build a model for predicting severe RP (*e.g.*, grade 3 or worse). Severe RP is uncommon after SBRT for the lung. Grade 3 RP was observed in 3.6% of the patients in RTOG

Table 3 Optimal cut-off values and crude rates of symptomatic RP

	Cut-off values	Symptomatic RP <Cut-off	Symptomatic RP ≥Cut-off	p values
PTV (ml)	37.7	11.1%	34.5%	0.020*
MLD (Gy)	4.7	17.2%	40.0%	0.110
V40 (%)	1.6	17.6%	50.0%	0.093
V35 (%)	1.9	15.3%	40.0%	0.066
V30 (%)	2.8	15.3%	40.0%	0.066
V25 (%)	4.2	14.8%	46.2%	0.019*
V20 (%)	5.8	15.0%	42.9%	0.030*
V15 (%)	4.9	5.3%	25.5%	0.096
V10 (%)	10.1	11.4%	28.2%	0.089
V5 (%)	26.8	17.9%	42.9%	0.143

Abbreviations: MLD = mean lung dose; PTV = planning target volume; RP = radiation pneumonitis.

* Statistically significant.

Table 4 Summary of reports on dose–volume factors associated with radiation pneumonitis grade 2 or worse after stereotactic body radiation therapy

First author, reference	Year	n	Dose fractionation (total dose/fractions)	Heterogeneity correction algorithm	PTV volume (ml), median (range)	RP grade 2 or worse (crude rate)	Scoring system	Suggested factors
Yamashita (5)	2007	25	48 Gy/4–6 fr	CC	43.9 (7.5–239.4)	28.0%	CTCAE v3	CI
Ricardi (6)	2009	60	45 Gy/3 fr or 26 Gy/1 fr	CC	*NA*	14.3%	RTOG	MLD† (ipsilateral lung-CTV)
Borst (7)	2009	128	35–60 Gy/4–8 fr	CS	9.6 (0.2–106.9) in GTV	10.9%	CTC v2	MLD† (bilateral lung-GTV)
Guckenberger (8)	2010	59	26 Gy/1 fr or 37.5 Gy/3 fr	AAA	33 (2–236)	18.6%	SWOG	MLD† and V2.5–50 (ipsilateral lung-CTV)
Ong (9)	2010	18	55 Gy/5 fr or 60 Gy/8 fr	AAA	137 (87–286)	27.8%	CTCAE v4	V5 (contra-lateral lung)
Barriger (10)	2010	251	24–66 Gy/3–5 fr	*NA**	48.3 (8–401)	9.4%	CTC v2	MLD and V20 (bilateral lung-GTV)
Stauder (11)	2011	84	32–60 Gy/3–5 fr	*NA**	42.9 (5.3–321.5)	12.5%	CTCAE v3	PTV maximal dose
Present study		74	48 Gy/4 fr	AAA	32.5 (9.9–86.6)	20.3%	CTCAE v3	PTV volume and V25 (bilateral lung-PTV)

Abbreviations: AAA = analytical anisotropic algorithm; CC = collapsed cone convolution superposition; CI = conformity index; CS = convolution–superposition; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; fr = fractions; MLD = mean lung dose; NA = not available; RP = radiation pneumonitis; RTOG = Radiation Therapy Oncology Group; SWOG = Southwest Oncology Group.

* Authors reported that tissue heterogeneity was corrected in some patients, but information on heterogeneity correction algorithm was not available.

† MLD was evaluated using normalized total dose, which is the equivalent dose in 2-Gy fractions.

0236 (1) and in 3.1% of the operable patients in JCOG 0403 (2). Baumann *et al.* reported that no one developed grade 3 pneumonitis in their Phase II trial of SBRT (4).

Table 4 summarizes published reports that focused on the dose–volume metrics associated with RP grade 2 or worse after SBRT. The RP rates varied from 9.4% to 28.0%, and the suggested dose–volume factors for RP differed among the reports. This variation might be caused by differences in the PTV volume, dose fractionation schedule, and RP scoring system.

The scoring criteria for RP differ among toxicity grading systems. Steroid use for pneumonitis is scored as grade 3 in the RTOG system, whereas the Common Toxicity Criteria (CTC) v.2 scores symptomatic patients requiring steroids as grade 2. CTCAE v.3 removed steroid use from the pneumonitis scoring system. From CTCAE v.3 to v.4, the pneumonitis score was modified slightly. Grade 2 pneumonitis in CTCAE v.4 was defined as "symptomatic, medical intervention indicated or limiting instrumental ADL." The number of patients considered to have RP depends on which system is used to evaluate RP. Tucker *et al.* retrospectively evaluated 442 patients who received definitive radiotherapy for NSCLC using the three RP grading systems: RP grade 2 or worse was observed in 129 (29%), 109 (25%), and 195 (44%) patients according to RTOG, CTC v.2, and CTCAE v.3, respectively (15). The rate of grade 2 to 3 RP according to CTCAE v.3 seemed to be slightly higher (20.3%) in our study compared with other studies that evaluated it using CTC v.2 or the RTOG system. Nevertheless, we administered steroids to 6 patients (8.1%) only. Scoring systems should be considered when interpreting the results regarding RP.

This study indicated that a large PTV is a significant risk factor for symptomatic RP after SBRT. Ong *et al.* treated large tumors in 18 patients with a PTV >80 ml (median, 137 ml) with SBRT using volumetric modulated arc therapy (9). The investigators reported 5 patients (27.8%) with RP grade 2 to 3. We speculate that the large PTV volume was one of the reasons for their relatively high risk of pneumonitis. From our results, minimizing the PTV is one way to limit the RP risk. When a lung tumor has large respiratory motion, respiration management will contribute to the prevention of RP by reducing the PTV.

To correct for differences in dose fractionation, three reports (6–8) in Table 4 used normalized total doses (NTD), which were equivalent doses in 2-Gy fractions in terms of pulmonary toxicity. Borst *et al.* evaluated the relationship between the MLD and the incidence of RP after SBRT (7). They calculated the MLD in the NTD form using the linear-quadratic model with an α/β ratio of 3 Gy. A significant dose–response relationship was found between RP and MLD. We used a uniform dose fractionation of 48 Gy in four fractions for all of our patients, and we evaluated dosimetric factors in the form of a nominal dose. Although we cannot apply normalization to our data exactly, the median MLD was roughly estimated to be 3.7 Gy in NTD. The usefulness of NTD evaluation for pulmonary toxicity after SBRT should be validated in future studies.

Heterogeneity correction and the definition of lung volume may influence the dose–volume factors of the lung. De Jaeger *et al.* evaluated differences between the equivalent–pathlength and convolution–superposition algorithms in MLD and V20 for 68 patients treated with conformal radiotherapy for NSCLC (16). MLD and V20 differed between the two algorithms by 16.9% and 12.0% on average, respectively. The TD_{50} for RP grade 2 or worse in MLD was estimated to be 34.1 Gy with the equivalent-pathlength algorithm, whereas the value was 29.2 Gy with the convolution—superposition algorithm. Because most related reports have used convolution—superposition algorithms, we applied the AAA, which is a convolution—superposition algorithm, to recalculate the dose—volume data so as to limit the influences of heterogeneity correction.

Our definition of lung volume was both lungs segmented with a threshold value of −300 HU on slow-scan CT from which PTV was excluded. Lung volume can vary depending on which lung is evaluated (ipsilateral, contralateral, or bilateral), exclusion of tumor volume (GTV or PTV), type of planning CT (slow-scan CT, 4D CT, or breath-hold CT), and the threshold HU for segmentation. When the PTV is subtracted from the lung volume, a high-dose volume within the PTV margin is not evaluated as dose—volume factors for the lung. These conditions were not always stated in the previous papers, and future articles should include this information.

Factors other than the dose—volume metrics also affect the occurrence of pneumonitis after SBRT. The serum level of Krebs von den Lungen-6 (KL-6) is a predictor of RP. Hara *et al.* evaluated 16 patients who received single-fraction SBRT with 20 to 35 Gy (17). The relative increase in the serum KL-6 between before and at 2 months after SBRT was significantly correlated with the occurrence of grade 3 RP by the RTOG criteria. Iwata *et al.* reported that the pretreatment serum KL-6 levels, gender, and PTV volume were correlated with symptomatic RP in a univariate analysis, and the pretreatment KL-6 levels remained significant in a multivariate analysis (18). They concluded that patients with a pretreatment KL-6 level ≥300 U/ml should be followed carefully for the occurrence of RP. CT or x-ray imaging before and after SBRT should help to predict severe RP. Yamashita *et al.* recommended prescreening of interstitial pneumonitis on CT, in addition to checking the serum KL-6 and surfactant protein-D (SP-D) levels to limit the risks of severe RP (19). They reported that after introducing the prescreening, the occurrence rate of RP grade 4 to 5 decreased from 18.8% to 3.5%. Takeda *et al.* reported that the early appearance of RP on chest x-ray after SBRT was correlated with the severity of RP (20). The radiographic appearance of RP during the initial 2 months indicated a 40% risk for grade 3 RP, whereas the risk was only 1.2% when the radiologic change appeared 3 months after SBRT. Considering biomarkers (KL-6 and SP-D) and radiologic imaging as well as dose—volume factors helps us to limit the risks for severe pneumonitis after SBRT.

Our study has several limitations. First, this study was based on a retrospective review; thus, it was prone to selection bias. Second, the number of RP events was limited in the present study. Third, that clinical factors other than dose—volume metrics were not taken into consideration. Prospective data are awaited to investigate a correlation between pulmonary toxicities and dosimetric factors.

Conclusion

In conclusion, this study found that the lung V25 and PTV volumes were significant factors associated with RP after SBRT. Use of SBRT with PTV ≥37.7 ml and lung V25 ≥4.2% indicated a 50% risk of RP grade 2 or worse.

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Clinical Investigation: Gynecologic Cancer

Treatment Outcome of Medium-Dose-Rate Intracavitary Brachytherapy for Carcinoma of the Uterine Cervix: Comparison With Low-Dose-Rate Intracavitary Brachytherapy

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Summary

We evaluated and compared the efficacy of medium-dose-rate (MDR) and low-dose-rate (LDR) intracavitary brachytherapy (ICBT) for uterine cervical cancer. No significant statistical differences were seen in overall survival and the actuarial rates of late complications grade 2 or greater at 5 years between the two groups. These data suggest that MDR ICBT is effective, useful, and equally good as LDR ICBT in daytime (about 5 hours) treatments of patients with cervical cancer. These data suggest that MDR ICBT is effective, useful, and equally as

Purpose: To evaluate and compare the efficacy of medium-dose-rate (MDR) and low-dose-rate (LDR) intracavitary brachytherapy (ICBT) for uterine cervical cancer.

Methods and Materials: We evaluated 419 patients with squamous cell carcinoma of the cervix who were treated by radical radiotherapy with curative intent at Tokyo Women's Medical University from 1969 to 1999. LDR was used from 1969 to 1986, and MDR has been used since July 1987. When compared with LDR, fraction dose was decreased and fraction size was increased (1 or 2 fractions) for MDR to make the total dose of MDR equal to that of LDR. In general, the patients received a total dose of 60 to 70 Gy at Point A with external beam radiotherapy combined with brachytherapy according to the International Federation of Gynecology and Obstetrics stage. In the LDR group, 32 patients had Stage I disease, 81 had Stage II, 182 had Stage III, and 29 had Stage IVA; in the MDR group, 9 patients had Stage I disease, 19 had Stage II, 55 had Stage III, and 12 had Stage IVA.

Results: The 5-year overall survival rates for Stages I, II, III, and IVA in the LDR group were 78%, 72%, 55%, and 34%, respectively. In the MDR group, the 5-year overall survival rates were 100%, 68%, 52%, and 42%, respectively. No significant statistical differences were seen between the two groups. The actuarial rates of late complications Grade 2 or greater at 5 years for the rectum, bladder, and small intestine in the LDR group were 11.1%, 5.8%, and 2.0%, respectively. The rates for the MDR group were 11.7%, 4.2%, and 2.6%, respectively, all of which were without statistical differences.

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good as LDR ICBT in daytime treatments of patients with cervical cancer.

Conclusion: These data suggest that MDR ICBT is effective, useful, and equally as good as LDR ICBT in daytime (about 5 hours) treatments of patients with cervical cancer.

Keywords: Cervical cancer, Radiotherapy, Intracavitary brachytherapy, Medium-dose-rate

Introduction

Radiotherapy (RT) has been established and recognized as one of the most effective treatment modalities for all stages of uterine cervical cancer, and treatment of early-stage diseases has shown results that are comparable to those of surgery (1). In Japan, however, early-stage cervical cancer is usually treated by radical hysterectomy. About 90% of patients with Stage I disease and 53% with Stage II disease (49% received postoperative RT) received surgery. Only 9% and 46% of patients with Stage I and Stage II, respectively, received radical RT (2). In most institutions in Japan, the gynecologist who believes surgical treatment is superior to RT determines the treatment policy, and the majority of patients in Stages I through IIB are subjected to radical hysterectomy (3). Radiation oncologists generally have been relegated to treating advanced cancer patients and medically inoperable patients with early-stage cancers.

There are three modalities for brachytherapy according to dose rate, namely, low-dose-rate (LDR), medium-dose-rate (MDR), and high-dose-rate (HDR). According to the International Commission on Radiation Units & Measurements (ICRU) Report 38 (4), brachytherapy dose rates are thought to be between 0.4 and 2 Gy/h for LDR, between 2 and 12 Gy/h for MDR, and more than 12 Gy/h for HDR. In Japan, LDR intracavitary brachytherapy (ICBT) has been used for many years. However, because of problems regarding the physical and psychological burden imposed on patients with long treatment times, as well as occupational radiation exposure to the medical staff, LDR ICBT has gradually been replaced by HDR ICBT, which was developed by Henschke *et al.* (5).

We have used LDR ICBT with the T.A.O. manual afterloading applicator by Tazaki E, Arai T and Oryu S (6) from 1969 to 1986, and treatment results have been reported (7). In 1986 the Selectron MDR (^{137}Cs) machine with a remote afterloading system (RALS) (Nucletron, Veenendaal, The Netherlands) for MDR ICBT was first introduced in Japan at Tokyo Women's Medical University (8−11). MDR ICBT has not had a long history of use in cervical cancer, and only a moderate number of articles have been published (8−18). The usefulness of MDR ICBT for cervical cancer was evaluated and compared with LDR by analyzing our treatment results.

Methods and Materials

Patients

There were 419 patients with pathologically proven squamous cell carcinoma of the uterine cervix who were treated with RT by use of brachytherapy with curative intent at the Clinical Oncology Division of the Department of Radiology, Tokyo Women's Medical University Hospital, from 1969 to 1999. Patients were initially evaluated and staged without general anesthesia by physical and pelvic examination by both gynecologists and radiation oncologists. All patients underwent chest radiography, intravenous pyelogram (IP), cystoscopy, proctoscopy, renogram, and routine blood work. Lymphangiography, venography, and chest—to—pelvis computed tomography (CT) scan were performed in selected patients. Because CT became available after the 1980s, it was performed only in about one-quarter of the patients with advanced disease for the LDR group, as opposed to half of the patients in the MDR group. Lymphangiography was performed in one-third of the patients in the LDR group with advanced disease. It was rarely performed for the patients in the MDR group and was replaced by CT scans after the 1990s. Besides observation of direct invasion of the tumor, it was important that examination of the bladder and rectal mucosa and bladder capacity by cystoscopy and proctoscopy established a baseline before the treatment.

Table 1 shows the characteristics of the 419 patients: 324 were treated with LDR and 95 with MDR. In the LDR group, 32 patients had International Federation of Gynecology and Obstetrics Stage I disease, 81 had Stage II, 182 had Stage III, and 29 had Stage IVA. In the MDR group, 9 patients had Stage I disease, 19 had Stage II, 55 had Stage III, and 12 had Stage IVA. Stage III tumors were classified into three types depending on the extent of tumor lesions: small tumor (S), tumor slightly extending to the unilateral pelvic wall; medium tumor (M), tumor massively extending to the unilateral pelvic wall; and large tumor (L), barrel-type tumor extending to the pelvic wall or tumor extending to the bilateral pelvic walls (7−11). In Stage III tumors, there were many more large (L) tumors in the MDR group than in the LDR group ($p = 0.0016$). Patients treated with palliative intent and patients with active double cancers were excluded from this study. Patients in the MDR group were older than those in the LDR group ($p = 0.0039$). No statistically significant differences were detected between the LDR and MDR groups for performance status (PS), pretreatment hemoglobin (Hb), ureteral stenosis on IP, coexisting illness, and previous abdominal surgery.

Treatment policies

RT was administered via a combination of external beam radiotherapy (EBRT) to the pelvic cavity and intracavitary irradiation. Treatment policies for RT according to stages of cervical cancer at our institution are shown in Table 2. In Stage I and Stage II disease, the described treatment protocol was chosen for the older or medically inoperable patients. LDR ICBT and MDR ICBT were administered in accordance with the guidelines for RT included in *The General Rules for Clinical and Pathological Management of Uterine Cervical Cancer in Japan* (19). When MDR ICBT was performed, the total dose at Point A was always equal to that of LDR ICBT. That is, the dose per fraction was set lower and 1 or 2 more fractions were used in cases receiving MDR ICBT compared with LDR ICBT.

Radiotherapy

The methods for EBRT have been reported previously (7). Between 1969 and June 1986, LDR ICBT was administered by use of the

Table 1 Patient characteristics

	LDR (1969 to June 1986)	MDR (July 1986 to 1999)	*p* Value (chi-square test)
No. of patients	324	95	
Age [range (mean)] (yr)	28–85 (60)	30–89 (64)	$p = 0.0039$
Stage I	32	9	
Stage II	81	19	
Stage III	182	55	
Small (S)*	50	9	
Medium (M)*	77	21	
Large (M)*	55	25	$p = 0.0016$
Stage IVA	29	12	
PS 0	151	78	
PS 1	129	11	
PS 2	25	6	NS
PS 3	6	0	
PS 4	2	0	
Pretreatment Hb [range (mean)] (g/dl)	5.4–15.9 (11.7)	7.4–14.5 (11.1)	NS
IP stenosis			
Yes	36	18	
No	288	77	NS ($p = 0.067$)
Coexisting illness†			
Yes	117	40	
No	207	55	NS
Previous abdominal surgery‡			
Yes	79	21	
No	245	74	NS
Follow–up [range (median)]	4 mo to 27 yr (9 yr)	4 mo to 16 yr (6 yr 3 mo)	

Abbreviations: Hb = hemoglobin; IP = intravenous pyelogram; NS = not significant; PS = performance status.

Data are given as numbers of patients except where noted.

* Small tumor (S), tumor slightly extending to pelvic wall; medium tumor (M), tumor massively extending to one pelvic wall; and large tumor (L), tumor extending to both pelvic walls.

† For example, diabetes mellitus and hypertension.

‡ For example, appendectomy.

Manchester technique, with ^{137}Cs tubes as the radiation source. The T.A.O. applicator was used for this purpose (7). Starting in July 1986, MDR ICBT was performed (8). Typical application and dose distribution with Manchester type applicator and Selectron medium-dose-rate machine are shown in Fig. 1. In patients receiving LDR ICBT, the dose rate at Point A was 0.8 to 1 Gy/h, 10 to 12 Gy per fraction, once a week, for 3 or 4 fractions. In patients receiving MDR ICBT, the total dose at Point A was the same as that for LDR with a dose rate of 1.6 to 2 Gy/h (approximately twice that for LDR). The fraction dose was set lower (8–10 Gy), whereas the number of fractions was increased to 4 or 5 and administration was performed once a week. EBRT was not administered on the same day when ICBT was performed. Additional EBRT was given to bring the total dose to 55 to 60 Gy if there was still a suspicion of remaining tumor. To avoid prolongation of overall treatment time (OTT), the brachytherapy that was administered concurrently during the period of EBRT was started as soon as possible after the patient's condition allowed insertion of a tandem into the uterine cavity (9).

Table 2 Radiotherapy treatment policies for cervical cancer at Tokyo Women's Medical University

		External irradiation (Gy)		Intracavitary irradiation (Point A [Gy]/fractions)	
Stage	Tumor size	Whole pelvis	Central shield	Low-dose-rate	Medium-dose-rate
I		0	45–50	50/4–5	50/5–6
II	Small	0	45–50	50/4–5	50/5–6
	Large	20	30	40/3	40/4–5
III	Small* to medium*	25–30	25–30	30–40/2–3	30–40/4–5
	Large*	30–40	20–25	30–40/2–3	30–40/4–5
IVA†		30–50	10–20	20–40/2–3	20–40/2–5
IVB		Palliative		Palliative	

* Small tumor, tumor slightly extending to pelvic wall; medium tumor, tumor massively extending to one pelvic wall; and large tumor, tumor extending to both pelvic walls.

† Chemotherapy (including intra-arterial infusion chemotherapy) where possible.

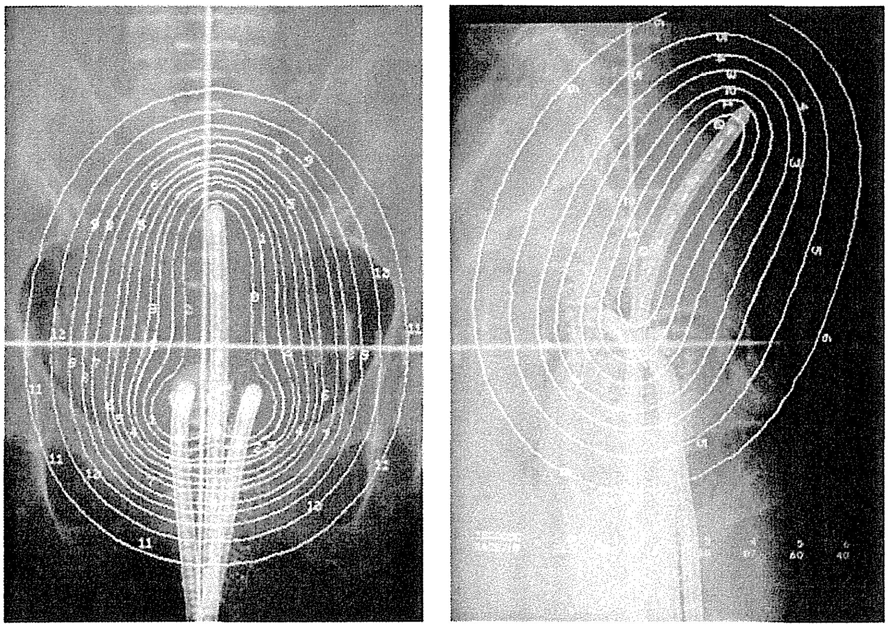

Fig. 1. Typical application and dose distribution with Selectron medium-dose-rate machine.

Determination of bladder and rectal dose

In MDR ICBT the reference dose points of the bladder and rectum were defined according to the recommendations of ICRU Report 38 (4). However, the dose to the bladder and rectum could not be evaluated in LDR ICBT because LDR ICBT was performed too long ago.

Chemotherapy

Chemotherapy generally was not combined for the patients in Stages I and II. Intra-arterial infusion chemotherapy or systemic chemotherapy mainly consisted of cisplatin, and 5-fluorouracil was administered to only a few patients in Stages III and IVA if general conditions such as renal function and other clinical factors were good enough to tolerate chemotherapy since 1980 (11). There were several schedules, and although the regimen was not unified, there was no significant difference in the outcome.

Follow-up

Complete response rates of primary tumors were evaluated at 1 month after the completion of RT by pelvic examinations by both gynecologists and radiation oncologists.

After completion of RT, most patients were followed up once a month for the first year, every 2 months for the second year, every 3 or 4 months in the third to fifth years, and twice a year thereafter. At the time of each consultation, patients were evaluated by physical and pelvic examinations. As a rule, during the first 5 years, routine blood and urine studies plus cystoscopy and proctoscopy were performed every year to evaluate for late complications before complaints, such as hematuria or rectal bleeding, were registered by patients and to be able to follow them up carefully. To evaluate disease status and recurrence, patients underwent chest radiography and abdominal CT scan (since 1980) every 6 months for 2 years and then once a year for 5 years after RT. Suspected persistent or recurrent disease was confirmed with a biopsy wherever possible. Treatment failures were classified as pelvic recurrences or distant metastases.

Late radiation complications were graded according to the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer late radiation morbidity scoring criteria (20).

Statistical analysis

Survival was measured from the date of initiation of therapy to the date of death or the most recent follow-up by use of the Kaplan-Meier method, with significance determined by the Wilcoxon test. Overall survival (OS) rates were used to assess the mortality rates due to cervical cancer. The time to disease recurrence in the pelvis was measured from the date of initiation of therapy to the date of first disease recurrence or progression in the primary cervical tumor or vagina. Deaths due to cervical cancer, deaths resulting directly from treatment-related complications, and deaths from unknown causes less than 5 years after treatment were scored as events.

Table 3 Complete response rate and stage

	LDR	MDR	Total
Stage I	32/32 (100)	9/9 (100)	41/41 (100)
Stage II	81/81 (100)	18/19 (95)	99/100 (99)
Stage III	139/182 (76)	41/55 (75)	180/237 (76)
Stage IVA	19/29 (66)	4/12 (33)	23/41 (56)
Total	271/324 (84)	72/95 (76)	343/419 (82)

Abbreviations: LDR = low-dose-rate; MDR = medium-dose-rate. Date are given as number of patients (percentage).

Table 4 Status at the time of last follow-up

Status and cause of death	LDR	MDR
Dead	239 (74)	50 (53)
Cervical carcinoma	118	33
Complications of radiotherapy	4	1
Second primary tumor	24	4
Unrelated or other disease	92	12
Unknown causes	2	0
Alive	85 (26)	44 (46)
Lost to follow-up	0	1 (1)
Total	324	95

Abbreviations: LDR = low-dose-rate; MDR = medium-dose-rate.
Date are given as number of patients (percentage).

Results

Outcomes

The median OTT was 44 days for the LDR group (41 days for Stages I and II and 47 days for Stages III and IVA) and 50 days for the MDR group (43 days for Stages I and II and 51 days for Stages III and IVA). Complete response rates of primary tumors by stage at 1 month after the completion of RT by pelvic examination are shown in Table 3. There were no statistical differences between the LDR and MDR groups ($p = 0.081$). Status at the time of last follow-up for all patients is listed in Table 4. In the LDR group, 118 patients (36%) died of cervical cancer. In the MDR group, 33 patients (35%) died of cervical cancer.

Patterns of recurrence by stage and treatment including patients with local uncontrolled disease are shown in Table 5. There were 13 patients with local uncontrolled disease in the LDR group (Stage III in 8 and Stage IVA in 5) and 7 patients in the MDR group (Stage II in 1, Stage III in 5, and Stage IVA in 1). No statistical difference was seen in patterns of recurrence between the two groups. Distant metastasis rates with advanced disease were higher than local recurrence rates in both groups.

The OS rates for the LDR and MDR groups are shown in Figs. 2a and 2b. There was no significant difference between the two groups. For patients in Stage III treated by LDR, the difference in OS rates for the small-medium (SM) and large (L) tumor groups was statistically significant ($p = 0.000104$). For the MDR group in Stage III, the difference in OS rates for the small-medium (SM) and large (L) tumor groups was not statistically significant ($p = 0.07$). There were no significant differences in the 5- and 10-year OS rates between the LDR and MDR groups (Fig. 2c).

Regarding the 5- and 10-year cause-specific survival for the LDR and MDR groups, there was no statistically significant difference between the two groups.

Pretreatment Hb levels were classified into the following four groups: A, 11.0 g/dl or less; B, 11.1 to 12.0 g/dl; C, 12.1 to 13.0 g/dl; and D, greater than 13.0 g/dl. In the LDR group, the A group had a significantly poorer prognosis for OS than the B, C, or D group. In the MDR group, the A group had a significantly poorer prognosis than the B or C group but not the D group because of the small number of cases.

The 5- and 10-year OS rates for the MDR group were 67% and 54%, respectively, for patients without IP stenosis ($n = 77$) compared with 17% and 0%, respectively, for patients with IP stenosis ($n = 18$) ($p = 0.000132$). The 5- and 10-year OS rates for the LDR group were 63% and 49%, respectively, for patients without IP stenosis ($n = 288$) and 36% and 25%, respectively, for patients with IP stenosis ($n = 36$). The difference between the two groups was also statistically significant ($p = 0.00074$). Age did not influence the prognosis for both groups.

Late complications

Late complications greater than Grade 2 are shown in Figs. 3a and 3b and Table 6. Sixty-seven percent of the rectal complications for the LDR group occurred within 3 years after treatment. On the other hand, 39% to 72% of the bladder complications occurred during the first 2 to 4 years, and their occurrence continued to increase gradually thereafter for more than 7 years. With regard to major complications (Grade 3 or greater), the 5- and 10-year actuarial rectal complication rates were 3.2% and 3.2%,

Table 5 Patterns of initial recurrence* by treatment and stage

Stage	L	PAN	V	DM	L+DM	Total
Low-dose-rate						
I	1	1	0	1	0	3/32 (9)
II	7	2	0	5	2	16/81 (20)
III	29	12	3	30	4	78/182 (43)
IVA	8	2	2	7	0	19/29 (65)
Total	45 (14)	17 (5)	5 (1)	43 (13)	6 (2)	116/324 (36)
Medium-dose-rate						
I	0	0	0	0	0	0/9 (0)
II	2	0	0	1	1	4/19 (21)
III	8	3	2	6	1	20/55 (36)
IVA	2	2	1	0	1	6/12 (50)
Total	12 (13)	5 (5)	3 (3)	7 (7)	3 (3)	30/95 (32)

Abbreviations: DM = distant metastasis; L = local (central or peripheral) recurrence; L+DM = local recurrence and distant metastasis; PAN = para-aortic lymph node; V = Virchow lymph node.
Date are given as number of patients (percentage).
* Including 20 patients with local uncontrolled disease (13 patients in LDR group [8 Stage III and 5 Stage IVA] and 7 patients in MDR group [1 Stage II, 5 Stage III, and 1 Stage IVA]).

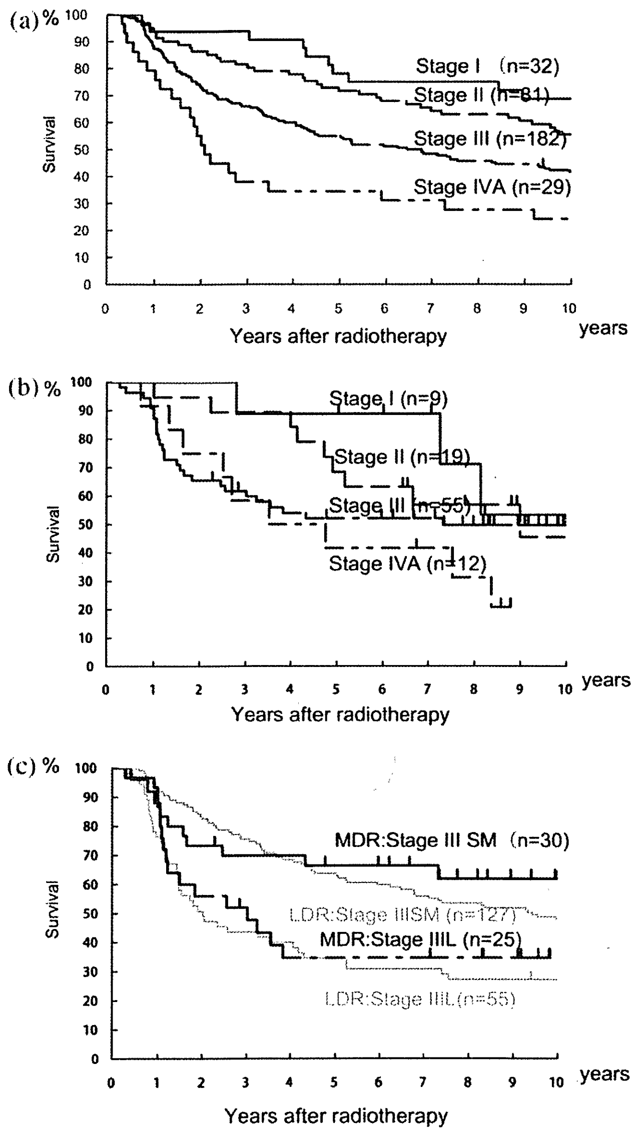

Fig. 2. (a) Overall survival for low-dose-rate (LDR) brachytherapy. (b) Overall survival for medium-dose-rate (MDR) brachytherapy. (c) Overall survival for Stage III patients by tumor size.

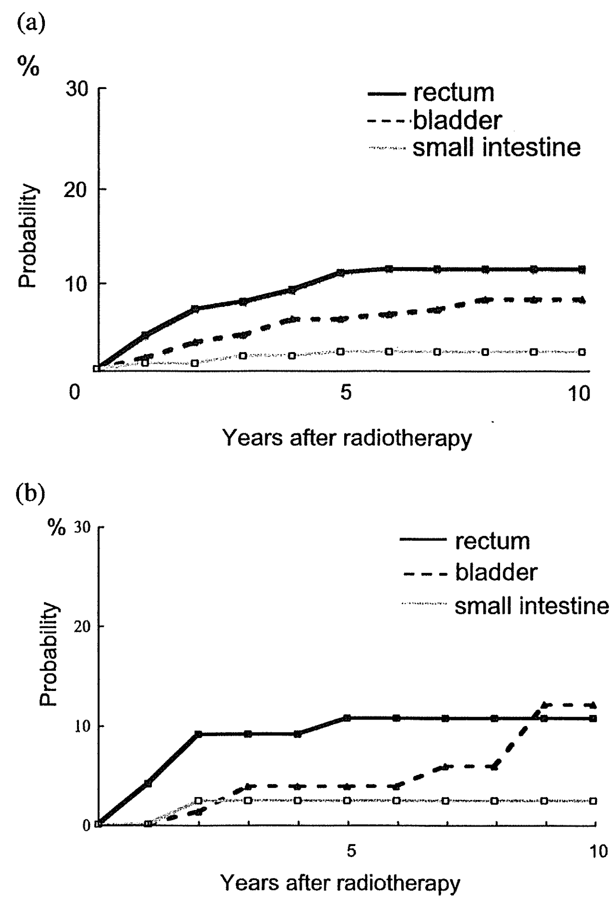

Fig. 3. (a) Cumulative rates of late complications (Grade 2 [G2] or greater) for low-dose-rate (LDR) intracavitary brachytherapy. (b) Cumulative rates of late complications (Grade 2 or greater) for medium-dose-rate (MDR) intracavitary brachytherapy.

respectively. The rates for bladder and small intestine complications were 1.2% and 2.9%, respectively, and 2% and 2%, respectively.

Eighty-five percent of the rectal complications for the MDR group occurred within the first 2 years after treatment. On the other hand, 49% to 100% of bladder complications occurred during the first 7 to 9 years, and their occurrence continued to increase markedly after 8 years. With regard to major complications (Grade 3 or greater), rectum and bladder complications occurred within the first 3 years (2.8% and 1.1%, respectively). There were no major complications of the small intestine. Late complications in the LDR and MDR groups tended to be similar, and no significant differences were seen. There were no statistical differences between history of previous abdominal surgery and late complications for the LDR group, as well as for the MDR group. Of the 4 patients in the LDR group, 2 died of bladder complications. The remainder died of rectum and ileum complications. One patient died of bladder complications in the MDR group.

For the MDR group, Grade 3 rectal complications were not observed in any of the patients with a total rectal dose of less than 60 Gy. No bladder complications of Grade 3 or 4 were observed in any of the patients in the MDR group who received a total bladder dose of less than 69 Gy.

Discussion

For a long time, LDR ICBT with ^{226}Ra or ^{137}Cs was generally used for ICBT, and satisfactory treatment results had been obtained. However, certain aspects of LDR ICBT were troublesome, such as (*1*) the long treatment time because of the LDR for ICBT, (*2*) the high physical and psychological burdens for the patients because of the long treatment time, and (*3*) the difficulty of maintaining the precise position of applicators during the long treatment time. In addition, preloaded applicators had to be manually inserted, resulting in what are now regarded as unacceptably high radiation exposures to the medical staff. In addressing these problems, RALS was developed by Henschke *et al.* (5) and has been gradually used by various treatment centers. In Japan HDR has seen widespread successful use for the treatment of carcinoma of the uterine cervix for the past 37 years. The merits of HDR ICBT over LDR ICBT lie in the short treatment time, low burden on the patient, and minimum exposure for the medical staff. On the other

Table 6 Late complications* (Grade 2 or greater) by treatment and stage

	Bladder		Rectum		Small intestine		
	Grade 2	Grade 3 or greater	Grade 2	Grade 3 or greater	Grade 2	Grade 3 or greater	Total
Low-dose-rate							
Stage I	1	0	0	0	0	1[†]	2/32 (6)
Stage II	7	1	7	2	2	1	20/81 (25)
Stage III	8	6[‡]	19	7[†]	1	3	44/182 (24)
Stage IVA	0	2	1	1	1	1	6/29 (21)
Total	16	9	27	10	4	6	72/324 (22)
Medium-dose-rate							
Stage I	0	0	0	0	1	0	1/9 (1)
Stage II	3	0	2	0	1	0	6/19 (32)
Stage III	1	2	1	4	2	0	9/55 (16)
Stage IVA	0	0	2	0	0	0	2/12 (17)
Total	4	2	8	2	2	0	18/95 (19)

Date are given as number of patients (percentage).

* According to Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer scoring criteria for late radiation morbidity.

† One patient.

‡ Two patients: death (Grade 5) resulting directly or indirectly from complications.

hand, HDR ICBT requires added shielding for the treatment room and entails equipment maintenance problems. Because of some concerns about the late toxicity of HDR ICBT, LDR ICBT still prevails in Western countries. Treatment results of LDR and HDR ICBT have been reported to be equal in Japan (21−24).

According to the ICRU definition, MDR treatment in our study would be classified as LDR. However, Hunter (25) and Patel *et al.* (16) noted that, considering the results and clinical trials of cervical cancer, a separation between LDR and MDR at a dose rate of less than 1 Gy/h might be more appropriate than at 2 Gy/h. Tanaka *et al.* (18) classified 1.7 Gy/h as the mean dose rate at Point A in MDR. We classified 1.6 to 2 Gy/h (1.8 Gy/h) as the mean dose rate at Point A in MDR. We performed MDR ICBT as follows: The total dose at Point A was always equal to that of LDR ICBT. The dose per fraction was set lower, and the number of fractions was increased by 1 or 2 in cases receiving MDR ICBT compared with LDR ICBT. When compared with other countries, our dose rate is slightly higher and the total dose at Point A is slightly lower.

Recently, MDR ICBT has developed from LDR ICBT with an RALS (12). The dose rate of MDR ICBT is 2 or 3 times higher than that of LDR ICBT. The treatment time of MDR is about 5 hours, and it is convenient for outpatient. On the other hand, it took overnight for LDR, and hospitalization treatment is necessary. The treatment time for MDR is reduced while maintaining the biologic dose effectiveness of LDR. This resulted in enabling daytime treatments and reduced the exposure dose to the medical stuff to zero. It has been reported that the optimal dose of MDR ICBT was reduced to 10% to 20% of the prescribed dose of LDR ICBT (12,13,16). Newman (14) noted that the dose rate to Point A had increased from 0.75 to 1.5 Gy/h and the dose prescribed for ICBT was reduced by 20% after the introduction of remote afterloading. There was no significant difference between the MDR and LDR groups in OS. The increase in late complications may be because of the increase in dose rate. The rate of late Grade 3 complications in the LDR group was 4% compared with 22% in the MDR group. Patel *et al.* (16) suggested that at a dose rate of 2.2 ± 0.1 Gy, the brachytherapy dose reduction factor should be around 30% to keep the morbidity as low as possible without compromising the local control rates. Jones *et al.* (15) mentioned that the mean intracavitary dose was reduced by 25% when the dose rate was increased from 0.55 Gy/h to 1.2 to 1.4 Gy/h. However, more Grade 3 complications occurred in Selectron patients. Leborgne *et al.* (17) reported that the MDR5 (an optimized new medium-dose-rate brachytherapy schedule) schedule (1.54 Gy/h) must include an increased fractionation and reduction of the total dose of about 20% when compared with LDR. There were no significant differences between the LDR and MDR groups in the 3-year actuarial central recurrence−free rates and for late Grade 2 to 3 complications. In addition, the mean OTT was 10 days shorter for MDR than that for LDR. They mentioned that this was an additional advantage for the patients in the MDR group. On the basis of these articles, MDR ICBT should be used with about a 20% to 30% reduction of the total dose when compared with LDR.

It has occasionally been pointed out that Japanese patients were treated with a lower total dose of EBRT than patients in Western countries (31). Japanese guidelines for RT for cervical cancer have been used for a long time (19), and treatment results have been good. It is thought that this result was because of the following: First, the sharp dose gradient of ICBT should be taken into account when one is evaluating the dose response in cervical carcinoma (26). Because of this gradient, a higher dose is delivered to the central tumor inside Point A (24). After administration of 20 Gy or 30 Gy of EBRT, the tumor will shrink, and the tumor outside Point A receives a lower dose with ICBT but also receives an additional dose of 50 Gy or greater with EBRT. Second, OTT was shorter than in Western countries.

OTT is one of the important prognostic factors for patients with cervical carcinoma treated with RT (9). In our study, during the period of EBRT, the first brachytherapy administration was initiated as soon as possible after the patient's condition allowed insertion of a tandem into the uterine cavity for both LDR and MDR ICBT to avoid prolongation of OTT. The median OTT was 44 days for LDR and 50 days for MDR. The reason for this difference may be aging, acute complications such as diarrhea, and additional RT for residual pelvic or para-aortic tumor in the MDR group. An excellent treatment result with RT alone for early cervical cancer in a prospective multi-institutional study was recently reported in Japan (27). In that study the median OTT was 43 days. That is similar to our OTT in the early stages (41 days for LDR and 43 days for MDR). As Nakano *et al.* (24) also mentioned, taking into account the biologic effect of radiation on the OTT, our treatment may be more intensive than others, even though the Point A doses were relatively lower.

In this study OS and recurrence rates for both the MDR and LDR groups showed no statistically significant differences for all stages (Stages I–IVA). For Stage III, the small and medium tumor groups showed better survival than the large tumor group. In this study the incidence rate of late complications in the LDR group was slightly higher than that in the MDR group but without a significant difference. Regarding the possible cause, the MDR group had a shorter follow-up period than the LDR group. Another possibility is that when the treatment plan for MDR was made, bladder and rectum doses were evaluated for each case, and changes were made in the position and in the number of the source depending on the case and individual treatment was performed. Our data for survival and late complications in the LDR and MDR groups were not different from those in other reports. No statistical differences were seen between history of previous abdominal surgery and late complications in LDR and MDR ICBT patients.

It has been reported that late radiation complications generally occur within the first 2 to 4 years after treatment. However, late complications occurring after more than 10 years of treatment have been observed (24). In our series rectal complications occurred most frequently during the first 2 years in the LDR and MDR groups, and thereafter the incidence decreased gradually in the LDR group and markedly in the MDR group. On the other hand, bladder complications continued to occur for more than 5 years after RT in the LDR and MDR groups, with the incidence increasing markedly after 8 years after RT in the MDR group (Fig. 3). Eifel *et al.* (28) reported similar results in their study. Thus it appears clear that follow-up should be conducted for a long time after RT for appropriate evaluation and management of late complications.

The mean age was significantly higher in the MDR group than in the LDR group, but this was regarded as resulting from aging of the recent patients. The level of pretreatment Hb was a prognostic factor in the LDR and MDR groups. In our study the patients with operable Stages I and II had a high age (mean, 61 years for LDR and 70 years for MDR). The Hb levels of aged patients are usually low compared with young patients. Moreover, the Hb levels of patients with advanced stages are usually low because of a high amount of tumor bleeding. Teshima *et al.* (29) similarly reported that the 5-year OS rate of patients in Stage III decreased significantly according to the level of Hb, from 67% (Hb level >13.0 g/dl) to 16% (Hb level >10.0 g/dl and <12.0 g/dl). In our study IP stenosis was also a significant prognostic factor for LDR and MDR ICBT. Similarly, Rose *et al.* (30) reported that hydronephrosis was a significant but not independent prognostic factor.

In conclusion, our data suggest that MDR ICBT is an effective therapy that is as good as LDR ICBT at the point of the dose distribution and in daytime treatments of patients with cervical carcinoma.

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