Table 2
Postoperative high–dose rate brachytherapy for soft tissue sarcomas

Characteristics	Number
Interval between OP and BT (days)	
Mean	5.3 (range, 1–7)
<5	2
>5	24
Median number of applicators	7 (range, 2–15)
Fractional dose	
4.5 Gy	1
6 Gy	25
Number of fractions	
5	1
6	25
Total dose (EQD2 for tumor control)	
27 Gy (32.6 Gy)	1
30 Gy (40 Gy)	1
36 Gy (48 Gy)	24
Mean volume encircled by the prescribed dose	74.9 cc (range, 18.5–173)

OP = operation; BT = brachytherapy; EQD2 = equivalent dose with 2 Gy fraction.

between the operation and the HDRBT was 5.3 days in a mean, and 24 HDRBTs were commenced between 5 and 7 days after the operation. Number of implanted tube applicators ranged from two to 15 with a median of seven. The treated volume encircled by the prescribed dose ranged from 18.5 to 173 cc with a mean of 74.9 cc. Chemotherapy was delivered in 12 lesions.

Median followup length was 49.7 months ranging from 4.7 to 187 months. Local recurrence-free survival (LRFS) was calculated in the 26 lesions, and overall survival (OS) in all the 25 patients. Local recurrence was defined as a regrowth of the STS within 5 cm from the operation scars. LRFS and OS were calculated by Kaplan–Meier method (11) with a difference between the survival curves evaluated by a logrank test. Acute morbidities seen within 6 months after HDRBT were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, whereas Radiation Therapy Oncology Group/European Organization for Research and Treatment for Cancer criteria were used for late morbidities (12).

Results

Local recurrence was observed in five lesions. All the local recurrences occurred outside of the treated volume of HDRBT. These local recurrences were within the treated volume, if postoperative EBRT were administered encompassing all the surgical scars with 5 cm margins. LRFS of all 26 lesions was 78.2% in 5 years. According to the surgical margin status, 5-year LRFSs of positive and negative margins were 90.9% and 64.6%, respectively, without

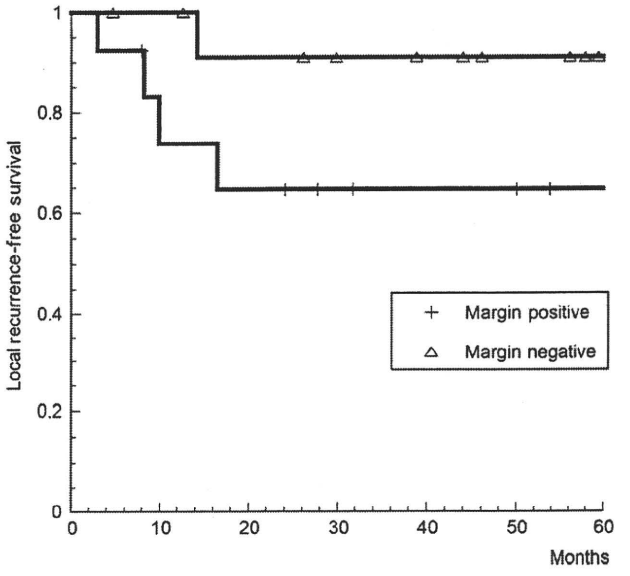

Fig. 1. Local recurrence-free survivals according to surgical margin status.

a statistically significant difference ($p = 0.11$) (Fig. 1). In the lesions treated as a primary therapy, LRFS is 90.9% in 5 years, whereas the recurrent lesions after previous operations showed 5-year LRFS rate of 66.5% ($p = 0.15$) (Fig. 2). The lesions were classified into two groups according to the surgical margin status and number of foregoing operations. Group 1 was defined as recurrent lesions, which were resected with positive surgical margins. All other lesions were classified into Group 2. There were eight lesions in Group 1 and 18 in Group 2. Five-year LRFS was 43.8% and 93.3% in Group 1 and Group 2, respectively

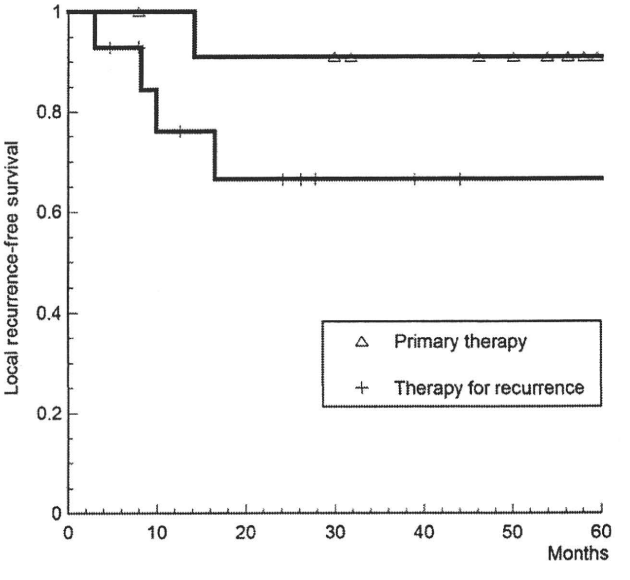

Fig. 2. Local recurrence-free survivals according to number of previous operations.

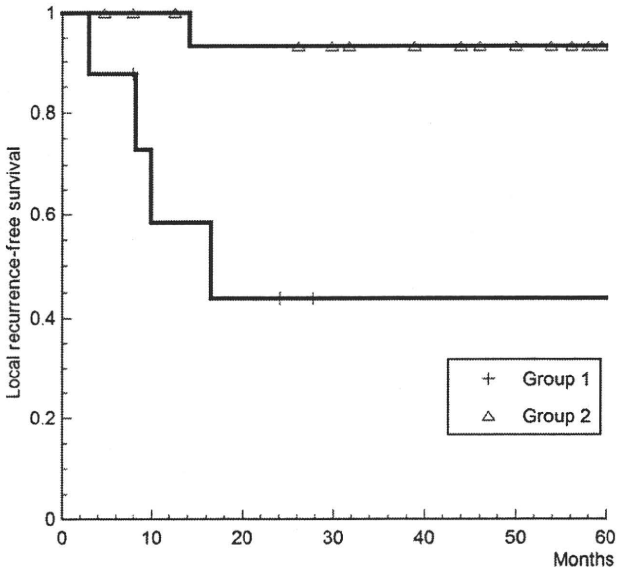

Fig. 3. Local recurrence-free survivals according to the group classification by surgical margin status and number of previous operations (for details refer to the text).

(Fig. 3). The difference reached a statistical significance with $p = 0.004$. Sex, malignant grade, tumor size, number of applicators, and treated volume were found to have no statistically significant influences on LRFS. In the 23 lesions of the extremity STSs, only one amputation was required to control recurrence.

OS of 25 patients was 75.6% in 5 years. There were only 2 patients with Grade 1 malignancy and both of them were alive without recurrence. The patients with Grade 2 and 3 lesions showed similar OSs and 71.6% of them were alive for 5 years.

Acute morbidities were seen in 7 patients with Grade 1 morbidities in 6 patients and Grade 2 in 1 patient (Table 3). Grade 1 morbidities were a slight bleeding from the scar at the time of applicator removal, slight erosion of skin, and seroma formation requiring aspiration only once or twice. Grade 2 morbidity was wound dehiscence, which healed with conservative measures. Chronic morbidities were seen in 4 patients. The Grade 3 and 4 morbidity were seen each in 1 patient. Grade 4 morbidity was bone exposure at the HDRBT site requiring surgical removal of the sequester and repair with bone transplantation. The Grade 3 morbidity was fistula formation with an ensuing infection managed by debridement. Both morbidities occurred within 24 months after HDRBT. Five-year rate of chronic morbidities equal to or greater than Grade 2 was 14.6%.

Table 3
Number of morbidities of postoperative high–dose rate brachytherapy

Morbidities	Morbidity grade	Number of morbidities
Acute morbidity		
Wound complication	1	4
	2	2
Paresthesia	1	1
Seroma formation	1	1
Late morbidity		
Wound complication	2	1
Seroma formation	1	1
Bone exposure	4	1
Infectious fistula	3	1

Discussions

In the management of STS, limb-sparing operation with perioperative radiation therapy has been established as a standard (13). With that combination, LRFS rate is reported to be 75–100% (1–4, 14). However, local recurrence rate is strongly influenced by the surgical margin status, number of previous operations, grade of malignancy, and primary site of STS (1, 2). In the present study, operative margins were microscopically positive in 50% of the patients and the remaining patients had very close margins less than 5 mm. Furthermore, 54% of the lesions were classified as Grade 3 malignancies. Considering the adverse features of this series, LRFS rate of 78.2% in 5 years is relatively favorable. The marginal status, number of the previous operations, and the grade of malignancy did not have an influence on LRFS with a statistical significance, probably because of the small number of the patients in this series. However, the recurrent lesions resected with positive surgical margins showed a poor 5-year LRFS of 43.8% in comparison to the other lesions with 93.3% LRFS in 5 years.

Brachytherapy has an advantage of concentrating dose distribution onto the tumor region with a simultaneous sparing of normal tissues (15), whereas EBRT with wide fields encompassing tumor as well as surgical beds sometimes causes bone fracture, subcutaneous fibrosis, and lymphedema distal to the irradiated site (16). According to Memorial Sloan-Kettering Cancer Center studies, postoperative LDRBT as a single modality reduces local recurrence in margin-negative high-grade STS (1, 3). The LDRBT did not include operative scars and drainage scars in the treated volume. In contrary, local recurrence was not reduced by LDRBT alone in postoperative low-grade STSs (17). They also suggested that high-grade STSs with positive surgical margins are better treated by combination of EBRT and LDRBT (5). Although HDRBT has advantages that radiation dose distribution can be optimized by the manipulation of dwell positions and dwell times of ^{192}Ir source, and radiation exposure to the medical personnel is negligible, the paucity of reported series makes it difficult to establish the optimal fractionation and total dose of HDRBT (6–10). Retrospective analyses revealed that combined EBRT and HDRBT is well tolerated and reduce local recurrence. Chun *et al.* (6) showed that local recurrence was not seen in 17 patients treated with 12–18 Gy

of 6 fractions of HDRBT combined with EBRT of 36–60 Gy. Pohar *et al.* (9) demonstrated that 2-year local control of 94% could be obtained with HDRBT of 13.5 Gy in three fractions with EBRT. Koizumi *et al.* (7) showed somehow poorer local control rate of 48% in 2 years because of the adverse features of their patients with macroscopic residual disease in 31%. In the present study, HDRBT was used without EBRT. HDRBT was delivered to the tumor bed without including surgical and drainage scars. At the launch of the postoperative HDRBT, radiation was planned to be confined to the tumor bed based on the reports from Memorial Sloan-Kettering Cancer Center. Because most of the patients in this series underwent resections reaching to the major neurovascular bundles and the high-dose radiation to them could cause serious morbidities, the total dose of HDRBT was determined by tolerance dose of peripheral nerve assumed as about 60 Gy in a conventional fractionation. The corresponding biologically equivalent dose by 2 Gy fractionation was calculated by linear quadratic model assuming $\alpha/\beta = 10$ Gy and 3 Gy for tumor control and late toxicity, including nerve damage, respectively (18). The equivalent dose by 2 Gy fractionation for HDRBT of 36 Gy was 48 Gy and 64.8 Gy, respectively, for tumor control and late toxicity. Because of the favorable results, this field setup and fractionation regimen of HDRBT have been continued to the present time.

Despite the retrospective nature of this study and the small number of patients, HDRBT alone with the fractionation regimens used in this study seems to be satisfactory to sterilize lesions in the treated volume. However, poor LRFS of 43.8% in 5 years demonstrates that in lesions treated for recurrence and whose surgical margins are positive, STSs tended to recur outside of the treated volume of HDRBT but within 5 cm from the surgical scars. It seems that they had better been treated with combination of HDRBT and wide field EBRT encompassing surgical beds as well as scars and drainage sites.

Serious late morbidity was seen in 2 patients, both of which could be repaired by surgical procedures. Although it is recommended to begin brachytherapy no sooner than 5 days after the operation (1, 15), 2 patients irradiated with a shorter interval did not have any serious morbidities. There were no patients who underwent limb amputation because of morbidities.

Conclusions

In summary, HDRBT alone to the tumor bed without including surgical scars and drainage sites with 36 Gy/6 fractions/3 d seems to be adequate and tolerable as a postoperative treatment for patients initially operated and/or negative for surgical margins. If the lesion is operated for recurrence and surgical margins are positive, administration of wide fields EBRT is recommended.

Acknowledgment

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CLINICAL INVESTIGATION **Head and Neck**

OUTCOMES IN PATIENTS WITH EARLY-STAGE HYPOPHARYNGEAL CANCER TREATED WITH RADIOTHERAPY

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Purpose: To analyze the outcome in patients with early-stage hypopharyngeal cancer (HPC) who were treated with radiotherapy (RT).

Methods and Materials: Between February 1988 and February 2007, 77 patients with Stage I or Stage II HPC underwent definitive RT in the Division of Radiation Oncology at the National Cancer Center Hospital. Eleven of the patients received local irradiation, and the other 66 patients received elective bilateral neck irradiation and booster irradiation to the primary lesion. The median follow-up period for all the patients was 33 months from the start of RT, ranging from 3 to 229 months.

Results: The rates of overall survival, HPC-specific survival, HPC recurrence-free survival, and local control with laryngeal voice preservation for the 77 patients at 5 years were 47%, 74%, 57%, and 70%, respectively. The survival rates were not affected by the patient characteristics or treatment factors, but the RT field was significantly correlated with local control in a multivariate analysis. Seven of the patients had Grade 3 or greater complications, but these complications occurred after salvage surgery in 6 of the patients. Of the 77 patients, 83% had synchronous or metachronous malignancies, but these malignancies did not influence the survival of the patients if the malignancies were detected at an early stage.

Conclusion: RT is an appropriate treatment method for early-stage HPC. However, because synchronous or metachronous malignancies occur at a relatively high frequency, careful follow-up and the early detection of such malignancies are critical. © **2010 Elsevier Inc.**

Hypopharyngeal cancer, Radiotherapy, Synchronous malignancy, Metachronous malignancy.

INTRODUCTION

Patients with hypopharyngeal cancer (HPC) are often first diagnosed at an advanced stage. Because the diagnosis of early-stage HPC is relatively rare, few reports have analyzed the treatment results of early-stage HPC; thus, the optimal treatment for this condition remains uncertain (1).

Foote (2) reported that treatment options for early-stage HPC included endoscopic removal, open function-sparing partial laryngopharyngectomy, total laryngectomy with partial pharyngectomy, and radiotherapy (RT); factors in treatment selection were reported to be the extent and volume of the tumor (including anterior commissure involvement), patient preference (including occupational considerations), patient age, comorbid illnesses, patient compliance, voice quality, physician experience and skill, previous head-and-neck malignancy, risk of a second head-and-neck primary cancer, treatment cost, and physician and institutional biases.

At the National Cancer Center Hospital, patients with Stage I or II HPC are often treated with RT alone. In this study, we reviewed the data on patients who were treated with RT for early-stage HPC and analyzed the outcomes in these patients.

METHODS AND MATERIALS

Patient characteristics

Between February 1988 and February 2007, 77 patients with Stage I (T1N0M0) or Stage II (T2N0M0) HPC underwent RT in the Division of Radiation Oncology at the National Cancer Center Hospital. These patients consisted of 6 women and 71 men, ranging in age from 42 to 80 years (median, 63 years) (Table 1). All the tumors were diagnosed as squamous cell carcinoma by histopathologic examination of the biopsy specimens, and each tumor was staged retrospectively according to the 2002 UICC TNM classification system based on a complete patient history and physical

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Table 1. Patient characteristics

Characteristic	Stage I (n = 42)	Stage II (n = 35)
Sex		
F	2	4
M	40	31
Age (y)		
Range (median)	42–80 (63)	48–79 (63)
HPC site		
Postcricoid region	6	6
Pyriform fossa	30	20
Posterior wall	6	9
Radiotherapy field and dose		
Local	6	5
Dose range (median) (Gy)	60–66 (60)	60–70 (61)
Locoregional	36	30
Primary dose range (median) (Gy)	58–70 (66)	60–70 (66)
Subclinical dose range (median) (Gy)	32–46 (40)	20–50 (40)
Concurrent chemotherapy		
CDDP + 5-FU	10	5
TS-1	1	0

Abbreviations: HPC = hypopharyngeal cancer; CDDP = cisplatin; 5-FU = 5-fluorouracil; TS-1 = tegafur-gimeracil-oteracil potassium.

examination record. The primary sites were the pyriform fossa (PS) in 50 patients (65%), the posterior wall (PW) in 15 (19%), and the postcricoid region (PC) in 12 (16%). At the time when the HPC was found, 21 patients (27%) had symptoms: 12 patients experienced pain in their pharynx, 9 experienced discomfort in their pharynx, and 1 patient experienced a change in his voice (hemilarynx fixation was not observed). Fifty-two patients (68%) were asymptomatic; their HPCs were found by gastrointestinal endoscopy performed as part of a follow-up examination for metachronous malignancies treated before to the diagnosis of HPC in 38 patients (49%: esophageal cancer in 31, gastric cancer in 2, oropharyngeal cancer in 2, oral cancer in 2, and esophageal and gastric cancer in 1), an examination performed before the treatment of some other disease in 10 patients (13%: esophageal cancer in 7, oral cancer in 1, gastric ulcer in 1, and pneumonia in 1), and as part of a general health examination in 4 patients. The symptoms of the remaining 3 patients were not documented.

Treatment

All the patients underwent definitive RT. Either a 4-MV or a 6-MV linac X-ray was used to administer a daily dose of 2 Gy 5 days a week, with a total dosage of 58–70 Gy (median, 66 Gy). A shell was used to immobilize the patient's head, and simulation X-ray radiographs or computed tomography simulation were used to determine the radiation portals and techniques. Local irradiation of the primary site was performed using parallel-opposed lateral fields in 11 patients with a total radiation dose of 60–70 Gy (median, 60 Gy). Elective bilateral neck irradiation was performed in 66 patients using parallel-opposed lateral fields with or without a matched anterior lower neck field or anterior and lateral wedge fields, with a total radiation dose of 20–50 Gy (median, 40 Gy). After the neck irradiation, the radiation to the primary lesion was boosted using a reduced parallel-opposed lateral field, with a total radiation dose of 10–40 Gy (median, 22 Gy).

Chemotherapy was administered concurrently with the RT in 16 patients for the treatment of synchronous cancers (esophageal cancer in 15, and oropharyngeal and laryngeal cancer in 1). Continuous infusions of 5-fluorouracil (5-FU; 600–1,250 mg/day; median, 1,100 mg/day) were given on the first 4 days of weeks 1 and 5 in combination with cisplatin (60–125 mg; median, 110 mg) on the first day of weeks 1 and 5 in the 15 patients with esophageal cancer, and TS-1 (100 mg/day) was successively used for 3 weeks in the 1 patient with oropharyngeal and laryngeal cancers.

Analysis

The median follow-up period was 33 months from the start of RT, ranging between 3 and 229 months. Fifteen patients were observed for less than 12 months: 3 patients died of HPC, 9 died of other cancers, 2 died of unknown reasons, and 1 was alive with another cancer. The median follow-up period for the 35 surviving patients who did not experience a recurrence was 48 months (range,10–229 months.

The overall, HPC-specific, and HPC recurrence-free survival rates and local control rate were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed using the log-rank test and the Cox proportional hazards test. A p value of <0.05 and <0.007 was considered statistically significant in the univariate analyses and the multivariate analysis, respectively, resulting in an overall significance level of 5% (3).

Complications were assessed according to the Common Terminology Criteria for Adverse Events v3.0

RESULTS

Survival

The 5-year overall and HPC-specific survival rates for all 77 patients were 47% and 74%, respectively (Fig. 1). Thirty-nine patients died between 3.1 and 191 months (median, 15 months) after the start of RT; the causes of death were HPC in 13 patients who died 11–50 months (median, 15 months) after the start of RT, other malignancies in 16 patients (esophageal cancer in 9, lung cancer in 2, laryngeal

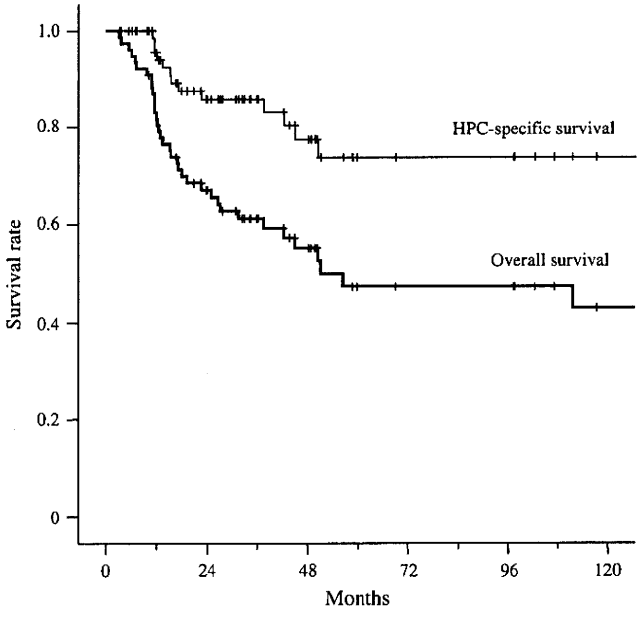

Fig. 1. Overall and hypopharyngeal cancer (HPC)–specific survival for all 77 patients.

Table 2. Overall and HPC-specific survival rates according to patient and clinical factors

Factors		*n*	Overall survival			HPC-specific survival		
			5-year (%)	Univariate *p*	Multivariate *p*	5-year (%)	Univariate *p*	Multivariate *p*
Total		77	47			74		
Sex	F	6	33			40		
	M	71	48	0.27	0.90	76	0.009	0.39
Age (y)	≤65	44	57			72		
	>65	33	34	0.12	0.042	77	0.96	0.60
HPC stage	I	42	52			85		
	II	35	43	0.43	0.18	62	0.024	0.032
HPC site	PC	12	52			59		
	PS	50	53			87		
	PW	15	27	0.052	0.058	43	0.005	0.064
RT field	Local	11	46			56		
	Locoregional	66	48	0.47	0.09	80	0.24	0.18
RT dose:	≤65	35	38			67		
primary (Gy)	>65	42	58	0.12	0.56	83	0.57	0.62
Concurrent CRT	Yes	16	23			69		
	No	61	53	0.085	0.029	74	0.92	0.22

Abbreviations: HPC = hypopharyngeal cancer; RT = radiotherapy; PC = postcricoid region; PS = pyriform fossa; PW = posterior wall; CRT = chemoradiotherapy.

cancer in 1, oropharyngeal cancer in 1, oral cancer in 1, renal cancer in 1, and malignant lymphoma in 1) who died 3.1–191 months (median, 12 months) after the start of RT, and other reasons in 10 patients (infectious pneumonia in 2, heart failure in 1, rupture of an abdominal aortic aneurysm in 1, suicide in 1, and unknown in 5) who died 3.5–57 months (median, 15 months) after the start of RT.

The relations between clinical factors and the overall and HPC-specific survival rates are shown in Table 2. Overall survival was not affected by any patient characteristics or treatment factors. Disease stage and primary site were significant factors for HPC-specific survival in the univariate analysis (disease stage, $p = 0.024$; primary site, $p = 0.005$), and the HPC-specific survival rate in patients with Stage II HPC or a primary site of PC or PW was much lower than that in patients with Stage I or a primary site of PS, but no factors were significant in the multivariate analysis.

Course of HPC

The 5-year HPC recurrence-free survival rate and local control rate with laryngeal voice preservation for all 77 patients were 57% and 70%, respectively (Fig. 2). One patient's tumor remained after RT, 1 patient was diagnosed with lymph node recurrence during RT, and 22 patients experienced disease recurrence 4–51 months (median, 10 months) after the start of RT. Thirteen (54%) of the 24 patients had local recurrences, 8 (33%) had lymph node recurrences, and 3 (13%) had local and lymph node recurrences. Distant metastases were observed in 6 patients (lung in 3, mediastinum in 2, and bone in 1) 11–49 months (median, 19 months) after the start of RT for HPC, but none of these metastases were found before local or lymph node recurrence. The relations between the clinical factors and the HPC recurrence-free survival rate and local control rate with laryngeal voice preservation are shown in Table 3. The HPC recurrence-free survival rate in patients with Stage I HPC or a locoregional RT field was significantly higher than that in patients with Stage II HPC ($p = 0.026$) or a local RT field ($p = 0.036$) in the univariate analysis, but no factors were significantly associated with HPC recurrence-free survival in the multivariate analysis. The primary site and RT field significantly affected the rate of local control with laryngeal voice preservation in the univariate analysis (primary site, $p = 0.036$; RT field, $p = 0.018$), and the local control rate in patients with irradiation of a locoregional field was significantly higher than that in patients with irradiation of a local field in the multivariate analysis ($p = 0.006$).

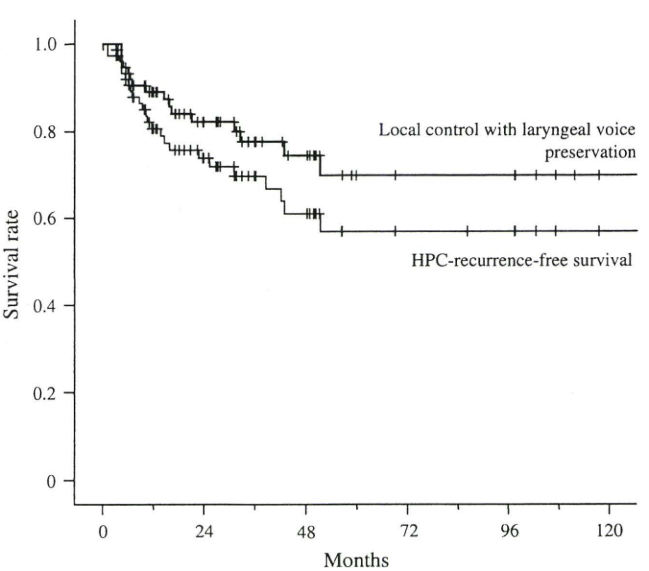

Fig. 2. Hypopharngeal cancer (HPC) recurrence-free survival and local control with laryngeal voice preservation for all 77 patients.

Table 3. HPC recurrence-free survival rate and local control rate with laryngeal voice preservation according to patient and clinical factors

Factors		n	HPC recurrence-free survival			Local control with voice preservation		
			5-year (%)	Univariate p	Multivariate p	5-year (%)	Univariate p	Multivariate p
Total		77	57			74		
Sex	F	6	50			67		
	M	71	57	0.28	0.90	70	0.35	0.98
Age (y)	≤65	44	49			65		
	>65	33	69	0.36	0.42	79	0.41	0.52
HPC stage	I	42	75			84		
	II	35	41	0.026	0.044	56	0.055	0.048
HPC site	PC	12	47			63		
	PS	50	62			76		
	PW	15	52	0.06	0.18	60	0.039	0.056
RT field	Local	11	38			42		
	Locoregional	66	59	0.036	0.10	73	0.018	0.006
RT dose: primary (Gy)	≤65	35	53			68		
	≥66	42	60	0.78	0.81	72	0.99	0.91
Concurrent CRT	Yes	16	56			83		
	No	61	56	0.4	0.96	68	0.5	0.52

Abbreviations: HPC = hypopharyngeal cancer; RT = radiotherapy; PC = postcricoid region; PS = pyriform fossa; PW = posterior wall; CRT = chemoradiotherapy.

Of 16 patients with local recurrence or local and lymph node recurrence, 12 underwent salvage surgery (total laryngopharyngectomy with or without neck resection in 11 and partial pharyngectomy in 1). One patient underwent chemotherapy, 2 received no treatment, and 1 patient was lost to follow-up after a local recurrence was detected. Of the 8 patients with lymph node recurrence, 6 underwent neck dissection, 1 patient underwent RT, and 1 patient received no treatment. All 3 patients who did not undergo salvage surgery died within 15 months. Only 5 patients with local recurrence and 3 patients with lymph node recurrence responded after surgery, and the 5-year overall survival rate for the 12 patients who were treated with salvage surgery was 39 % (Fig. 3). The difference in overall survival according to salvage therapy was significant ($p = 0.003$).

Of the total of 77 patients, 7 (9%) had Grade 3 or greater complications related to the treatment for HPC, and 6 of these patients experienced their complications after salvage surgery: 2 patients died as a result of arterial injury (Grade 5), 1 had a life-threatening arterial injury (Grade 4), 1 had an arterial injury requiring repair or revision (Grade 3), and 2 developed pharyngeal fistulas requiring operative intervention (Grade 3). One patient who did not have a recurrence developed otitis media with discharge (Grade 3).

Synchronous and metachronous malignancy

Of the 77 patients, 64 (83%) had synchronous or metachronous malignancies; the distribution of these malignancies is shown in Fig. 4. Forty-two had metachronous malignancies diagnosed before they underwent treatment for HPC, and 33 (79%) had esophageal cancer. These malignancies were under control at the start of treatment for HPC, but 19 of these patients had synchronous malignancies and/or metachronous malignancies after RT for HPC.

Overall, 23 patients had synchronous malignancies, 26 had metachronous malignancies after RT for HPC, and 8 had both synchronous and metachronous malignancies. The overall survival rate in the patients whose synchronous and/or metachronous malignancies were detected at an early stage (59% at 5 years) was not different from that in patients without synchronous or metachronous malignancies (48% at 5 years), but the survival rate in the patients whose synchronous or metachronous malignancies were detected at an advanced stage (17% at 5 years) was much lower than that in the patients without synchronous or metachronous malignancies

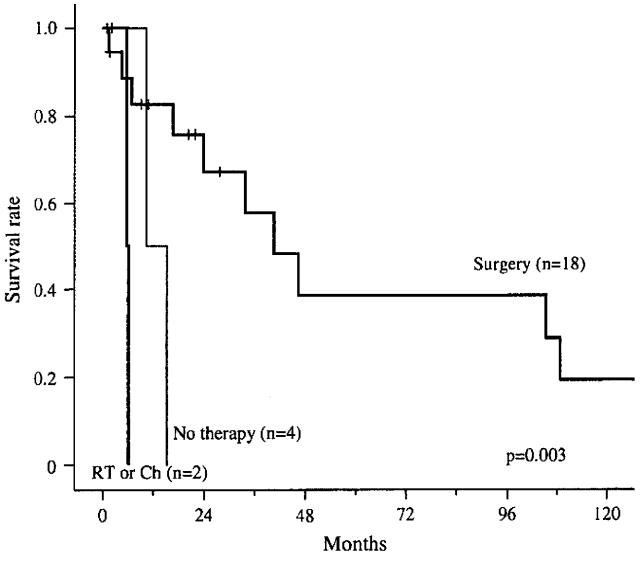

Fig. 3. Overall survival after hypopharyngeal cancer (HPC) recurrence according to salvage therapies (RT = radiotherapy; Ch = chemotherapy).

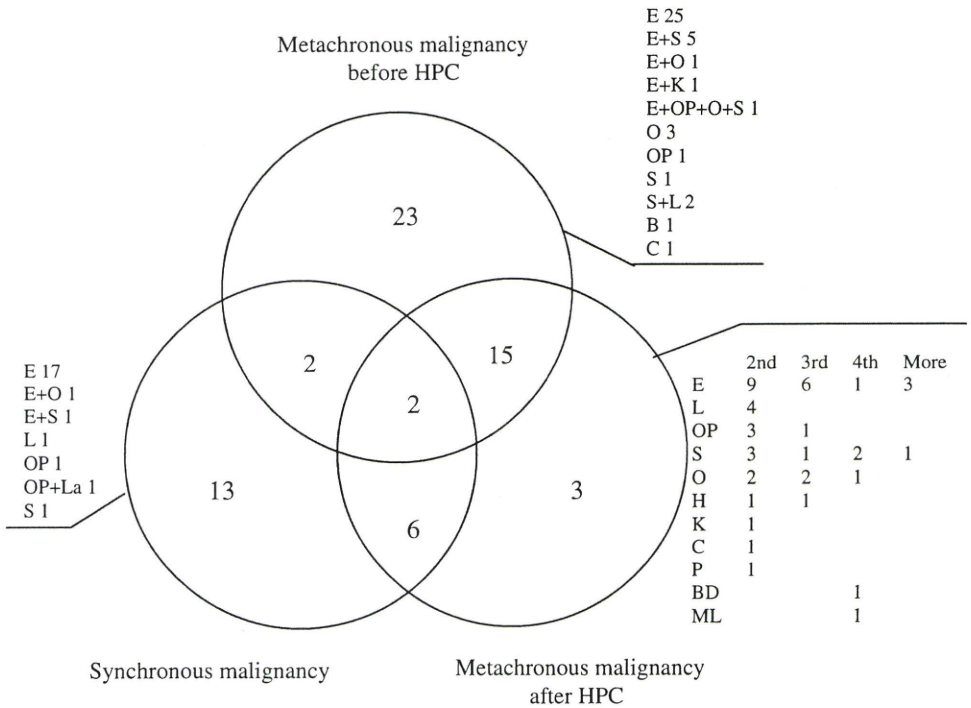

Fig. 4. Number of hypopharyngeal cancer (HPC) patients with synchronous and metachronous malignancy (E = esophagus; S = stomach; O = oral cavity; K = kidney; OP = oropharynx; B = bladder; C = colon; La = larynx; H = liver; P = prostate; BD = bile duct; ML = malignant lymphoma).

or the patients with early-stage synchronous or metachronous malignancies (Fig. 5). Advanced-stage synchronous malignancies were seen in 5 patients with esophageal cancer. All 5 patients received concurrent chemoradiotherapy, but died of their synchronous malignancies 5–13 months (median, 11 months) after the start of RT. Advanced-stage metachronous malignancies were seen in 7 of the 26 patients (lung cancer in 2, oropharyngeal cancer in 2, esophageal cancer in 1, renal cancer in 1, and prostate cancer in 1) 7.5–153 months (median, 12 months) after the start of RT for HPC. Five of these patients died of their advanced-stage metachronous malignancies (lung cancer in 2, oropharyngeal cancer in 1, esophageal cancer in 1, and renal cancer in 1).

The rates of metachronous malignancy after RT for HPC and HPC recurrence after RT, as calculated using the Kaplan-Meier method, are shown in Fig. 6. The rate of HPC recurrence increased rapidly for 2 years after RT and reached a plateau at 4 years. The rate of metachronous malignancy increased year by year after RT. The rate of second primary malignancy was 32% at 5 years and 56% at 10 years, that of third

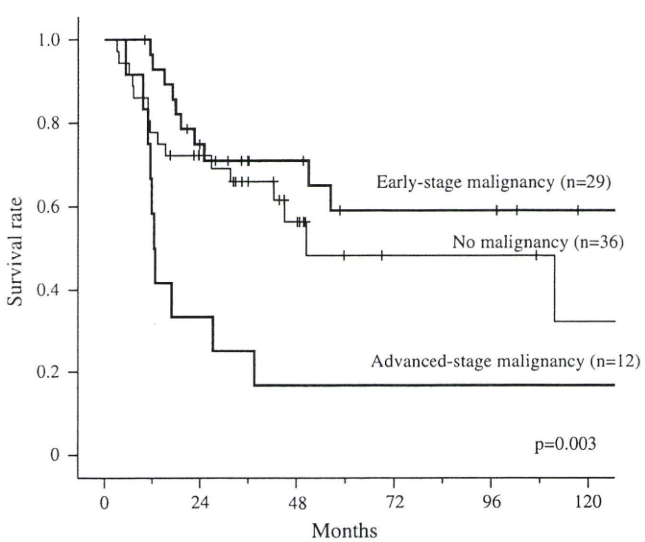

Fig. 5. Overall survival for patients with or without synchronous or metachronous malignancy after radiotherapy for hypopharyngeal cancer (HPC).

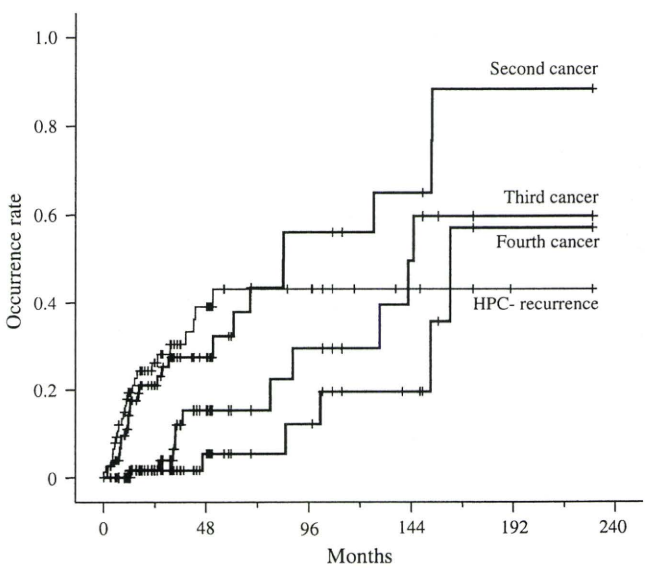

Fig. 6. Rates of hypopharyngeal recurrence and metachronous malignancy after radiotherapy.

malignancy was 15% at 5 years and 29% at 10 years, and that of fourth malignancy was 5% at 5 years and 19% at 10 years.

DISCUSSION

Radiotherapy has long been recognized as effective for early-stage squamous cell carcinoma of the hypopharynx (1, 2). However, few reports have analyzed large numbers of patients undergoing RT for early-stage HPC without lymph node metastasis, and to our knowledge, no reports have statistically analyzed predictors of survival. Concurrent chemoradiotherapy and the computed tomography–based tumor volume have been reported to be strong predictors of local control in HPC patients, including patients with advanced-stage HPC, but whether these factors affect local control or overall survival in patients with early-stage HPC remains unclear (1, 4). In our study, only the RT field significantly affected the local control rate with laryngeal voice preservation in the multivariate analysis, and a locoregional radiation field was appropriate for patients with early-stage HPC. Although disease stage affected the HPC-specific survival rate and the HPC recurrence-free survival rate and the primary site affected the HPC-specific survival rate and the local control rate in univariate analyses, these factors were not significant in a multivariate analysis. The patient and tumor characteristics had no effect on the treatment outcome of RT for early-stage HPC.

Nakamura *et al.* (1) reported the results of an analysis of 115 patients who underwent definitive RT for Stage I and Stage II HPC in a multi-institution study. Their overall and disease-specific survival rates at 5 years were 66% and 77.4%, respectively, and the progression-free survival and local control rates were 67.6% and 76.5% for patients with Stage I, and 51.5% and 62.6% for patients with Stage II at 5 years. Nakamura *et al.* (5) also reported an analysis of 43 other patients who underwent RT with or without salvage surgery for Stage I and II HPC in a single-institution study; the 5-year overall and disease-specific survival rates were 70.4% and 89.5%, respectively. Rabbani et al. (6) analyzed 123 patients with Stage T1–T2N0–N3M0 of the pyriform sinus; the 5-year overall survival, cause-specific survival, and local regional control rate for the 26 patients with T1N0M0 or T2N0M0 HPC were 58%, 85%, and 86%, respectively. In our study, the 5-year HPC-specific survival rate (74%), the HPC recurrence-free survival rate (57%), and the local control rate with laryngeal voice preservation (70%) were similar to these previously reported values, but the 5-year overall survival rate (47%) in our study was lower than the previously reported values (1, 5, 6). We suspect that the larger number of patients with synchronous and metachronous malignancies in the present study may be related to the lower rate of overall survival, compared with the results of previous reports.

The incidence of synchronous and metachronous malignancy in HPC patients has been reported to be approximately 20%, and the most common sites were the lung, the esophagus, and the urinary tract (7, 8). However, patients with early-stage primary tumors have a higher risk of developing a second primary tumor than do patients with advanced tumors because of their longer survival period (7); Nakamura et al. (1, 5) reported that the incidence of synchronous or metachronous malignancy in patients with early-stage HPC was 46.5–56.5%. In our study, 83% (64/77) of the patients had synchronous and/or metachronous malignancy and 53% (41/77) had synchronous malignancy and/or metachronous malignancy after RT for HPC; most of these malignancies were esophageal cancer. Because 54% (42/77) of these patients had a history of treatment for malignancy before the diagnosis of HPC, individual and/or environmental factors might have contributed to the formation of the multiple primary tumors in many of these patients (7). However, the overall survival rate for patients with early-stage synchronous malignancy and/or metachronous malignancy after RT for HPC was similar to that for patients without these malignancies, but the overall survival rate for patients with advanced-stage synchronous malignancy or metachronous malignancy after RT for HPC was significantly poorer. A more careful follow-up for detection of early-stage metachronous malignancy might have improved the overall survival rate in the present study.

The detection of early-stage HPC is as difficult as the detection of early-stage esophageal cancer, but the development of endoscopy has made both of these conditions detectable (9). In our study, HPC was diagnosed during gastrointestinal endoscopy examinations performed as pretreatment or follow-up examinations for other malignancies in 62% (48/77) of the patients. Recently, narrow band imaging has been reported to improve the diagnostic accuracy and sensitivity at which early-stage HPC can be detected (10). However, endoscopy techniques (*i.e.*, endoscopic laser resection) have been used only in a few institutions, and the indication for these treatments is unclear (9, 11). Although Shimizu *et al.* (9) performed endoscopic submucosal dissection in 4 patients with early-stage HPC and reported no local recurrences, no distant metastasis, and no early or late complications, Bernal-Sprekelsen *et al.* (11) performed endoscopic resection using a CO_2 laser and reported the need for a nasogastric feeding tube in 23.2% of the patients with small tumors, postoperative pneumonia in 5.7%, temporary postoperative coughing during oral intake in 28.1%, and severe swallowing difficulties in 3.8%. Thus, the factors associated with the occurrence and severity of various complications after endoscopic resection remain to be clarified (9).

In the present study, because we retrospectively analyzed the data of patients who underwent RT for early-stage HPC, we could not exclude some potential biases and study limitations from our results. However, we believe that RT is an appropriate treatment method for early-stage HPC, compared with surgical resection, because the outcome of RT was not affected by the patient or tumor characteristics in the present study, and cosmetic defects, swallowing disorders, aspiration pneumonia, and speech defects were avoided. Patients with early-stage HPC have a high risk of synchronous and metachronous malignancy, and their prognosis heavily depends on the development of such malignancies. However, if such malignancies are detected at an early

stage, patients whose HPC was treated using RT are often able to receive sufficient treatment for those malignancies, and their overall survival rate is as high as that in patients without these malignancies (1, 5, 6, 9). Patients with early-stage HPC should be carefully examined before and after the start of treatment and should be closely followed up at frequent intervals to ensure the early detection of synchronous and metachronous malignancies (7).

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CLINICAL INVESTIGATION

INTERNATIONAL BRACHYTHERAPY PRACTICE PATTERNS: A SURVEY OF THE GYNECOLOGIC CANCER INTERGROUP (GCIG)

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Purpose: To determine current practice patterns with regard to gynecologic high-dose-rate (HDR) brachytherapy among international members of the Gynecologic Cancer Intergroup (GCIG) in Japan/Korea (Asia), Australia/New Zealand (ANZ), Europe (E), and North America (NAm).

Methods and Materials: A 32-item survey was developed requesting information on brachytherapy practice patterns and standard management for Stage IB–IVA cervical cancer. The chair of each GCIG member cooperative group selected radiation oncology members to receive the survey.

Results: A total of 72 responses were analyzed; 61 respondents (85%) used HDR. The three most common HDR brachytherapy fractionation regimens for Stage IB–IIA patients were 6 Gy for five fractions (18%), 6 Gy for four fractions (15%), and 7 Gy for three fractions (11%); for Stage IIB–IVA patients they were 6 Gy for five fractions (19%), 7 Gy for four fractions (8%), and 7 Gy for three fractions (8%). Overall, the mean combined external-beam and brachytherapy equivalent dose (EQD2) was 81.1 (standard deviation [SD] 10.16). The mean EQD2 recommended for Stage IB–IIA patients was 78.9 Gy (SD 10.7) and for Stage IIB–IVA was 83.3 Gy (SD 11.2) ($p = 0.02$). By region, the mean combined EQD2 was as follows: Asia, 71.2 Gy (SD 12.65); ANZ, 81.18 (SD 4.96); E, 83.24 (SD 10.75); and NAm, 81.66 (SD, 6.05; $p = 0.02$ for Asia vs. other regions).The ratio of brachytherapy to total prescribed dose was significantly higher for Japan ($p = 0.0002$).

Conclusion: Although fractionation patterns may vary, the overall mean doses administered for cervical cancer are similar in Australia/New Zealand, Europe, and North America, with practitioners in Japan administering a significantly lower external-beam dose but higher brachytherapy dose to the cervix. Given common goals, standardization should be possible in future clinical trials. © 2011 Elsevier Inc.

Brachytherapy, Cervical cancer, Radiation dose.

INTRODUCTION

Globally, cervical cancer represents the most common gynecologic malignancy (1). Patients with locally advanced cervical cancer (Stage IB2–IVA) require treatment with external-beam radiation (EBRT) with concurrent chemotherapy administered as a radiation sensitizer followed by brachytherapy (2). The recommended cumulative dose of EBRT and brachytherapy to cure locally advanced disease

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ranges from 80 to 90 Gy recorded at point A using low-dose-rate (LDR) brachytherapy (2).

Over the past 20 years, high-dose-rate (HDR) brachytherapy has increased and replaced LDR in many practices (3). The Patterns of Care for cervical cancer radiation practice in the United States reported a 16% HDR utilization rate in 1999 (4), whereas 85% of surveyed physician members of the American Brachytherapy Society (ABS) reported having HDR at their institution in 2007 (3). Overall, randomized studies indicate that outcomes with HDR resemble those with LDR, though many issues exist regarding the methodology of randomization and the follow-up duration across the studies (5). However, caution regarding large fractions given to normal tissues and adequate tumor coverage have increased awareness and recommendations for the use of computed tomography (CT) or magnetic resonance imaging (MRI) to determine doses to the tumor and the organs at risk (6).

The biologic equivalent dose formulas allow calculation of the brachytherapy dose (7, 8). However, these formulas require an assumption that the α/β ratio for tumor is 10, which may be an underestimation for squamous cell carcinoma. Furthermore, concerns regarding the validity of the linear quadratic model exist for very low or very high doses per fraction (9). Publication of standard fractionation regimens for HDR cervical cancer brachytherapy with point A–based standard loading (10, 11) led to widespread adoption in the United States of the regimen 6 Gy for five fractions over approximately 2.5 weeks. Preliminary results demonstrate a 2-year Grades 3 and 4 bowel toxicity rate of 11% with this HDR regimen (12). By contrast, with 2-year follow-up, only three (5%) Grade 3 or greater gastrointestinal complications occurred in a group of 65 patients treated with 6 Gy for five fractions in one report (13). It remains unknown whether 6 Gy for five fractions has a higher toxicity rate than 5.5 Gy per fraction or than LDR brachytherapy.

The Gynecologic Cancer Intergroup (GCIG) strives to forge collaborations between cooperative groups to move the development of oncologic clinical trials forward in a highly constructive and cost-effective manner. Randomized trials with international participation will accrue cervical cancer patients rapidly and result in advances on a global stage. To determine brachytherapy practice patterns and the HDR brachytherapy regimens most frequently prescribed by GCIG members, a survey of GCIG members was conducted. The goal is to clarify which regimen would be acceptable for future international collaborative clinical trials.

METHODS AND MATERIALS

The GCIG represents an international association of member cooperative groups conducting large clinical trials for gynecologic malignancies. Since its inception in 1997, 18 cooperative groups have joined, including the AGO-Austria (Austria), AGO-OVAR (Germany), ACRIN (USA), ANZOG (Australia, New Zealand), DGOG (the Netherlands), EORTC (Europe), GEICO (Spain), GINECO (France), GOG (USA), JGOG (Japan), MANGO (Italy), MITO (Italy), MRC/NCRI (Great Britain), NCIC (Canada), NSGO (Scandinavia), RTOG (USA), SGCTC (Scotland), and SWOG (USA).

A 32-question survey was designed to address questions regarding standard practice patterns for locally advanced cervical cancer management, such as routine doses of external beam and the use of concurrent chemotherapy, and also to determine baseline brachytherapy practice patterns, including both HDR and LDR utilization, at the time of the survey (Appendix EI available online at at www.redjournal.org). An e-mail providing background information, the purpose of the survey, and a link to a web page for easy retrieval of the survey was sent electronically to the chair of each GCIG member cooperative group in December 2008. Each cooperative group chair could choose to forward the email to six radiation oncology members from separate representative centers that had a large volume of cervical cancer cases. Respondents could complete only one survey on a computer, and entered their names and e-mail addresses to avoid duplicate submissions. The survey website closed in May 2009. Appendix E1 (available online at at www.redjournal.org) lists the specific items queried.

The biologically equivalent doses were calculated in 2-Gy equivalents using the EQD2 equation. For respondents that used a midline block, the total dose to the nodes and the dose to the cervix were summed separately. The EBRT and brachytherapy EQD2 doses were calculated at point A for patients with Stage IB–IIA and those with Stage IIB-IVA disease; then the average was taken for a cumulative sum for all stages. Analysis of reported HDR fractionation regimens was divided by country and by region, including Asia (Japan/Korea); Australia/New Zealand; Europe (Austria, Denmark, England, Finland, Germany, Italy, Ireland, the Netherlands, Scotland, Spain); and North America (USA, Canada). Quartiles of dose were evaluated to determine whether any particular region or country grouped into the highest or lowest dose ranges. The *t*-test statistic was performed to determine whether any significant differences in dose existed by region.

RESULTS

Respondent characteristics

A total of 16 cooperative groups gave member responses to this survey. Of 74 respondents, two were excluded: one non-GCIG member and one GCIG member who did not answer questions regarding brachytherapy, yielding a final study population of 72 respondents. Cooperation was received from the AGO-Austria (n = 3), ABO-Germany (n = 2), ACRIN (n = 1), ANZGOG (n = 6), DGOG (n = 6), EORTC (n = 5), GEICO (n = 1), GOG (n = 5), JGOG (n = 6), KGOG (n = 4), MANGO (n = 3), MITO (n = 2), MRC/NCRI (n = 9), NCIC (n = 10), NSGO (n = 3), and the RTOG (n = 6). Regions of the world represented were Japan/Korea (n = 10), Australia/New Zealand (n = 6), Europe (n = 34), and North America (n = 22).

Of the 72 respondents, 63 (88%) practice radiation oncology; 8 (11%), both medical and radiation oncology; and one (1%), gynecologic oncology. Regarding the average number of cervical cancer patients treated per year, 7 (10%) treat 1 to 9, 18 (25%) treat 10 to 19, 11 (15%) treat 20 to 29, 9 (13%) treat 30 to 39, 6 (8%) treat 40 to 49, 10 (14%) treat 50 to 59, 6

(8%) treat 60 to 69, 4 (6%) treat 70 to 79, and 1 (1%) treats more than 140.

External-beam radiation to the cervix

Physicians were queried regarding the standard EBRT dose prescribed for treating cervical cancer. For those who reported administering a parametrial boost dose, the parametrial doses were excluded from the EBRT cumulative cervical dose calculation, since the goal of a midline block is to avoid significant radiation to the cervix during these fractions. After averaging all respondents' reported dose to the cervix, the mean EBRT dose was 44.2 Gy (range, 19.8–50.4) for Stage IB–IIA patients and 47.2 Gy (range, 30.6–54) for Stage IIB–IVA patients. The average cervical dose for the Japanese respondents (not including the parametrial boost dose) was 23.3 Gy (range, 19.8–30) for Stage IB-IIA patients and 36.7 Gy (range, 30.9–40) for Stage IIB–IVA patients. All Japanese respondents commented that after insertion of a midline block, the total dose to the parametria and pelvic nodes equals 50 Gy (30 Gy to the cervix plus 20 Gy after insertion of the midline block). By contrast, all other countries reported a mean EBRT dose of 46.11 Gy (range, 40–50.4) for Stage IB–IIA patients and 48.2 Gy (range, 40–54) for Stage IIB–IVA patients. The most commonly added parametrial boost dose is 5.4 Gy after 45 Gy to the entire pelvis. For Stage IB–IIA patients, the most common EBRT doses are 45 Gy (n = 41, 57%) and 50.4 Gy (n = 15, 21%). For Stage IIB–IVA, the most common EBRT doses are 45 Gy (n = 26, 36%), 50.4 Gy (n = 27, 38%), and 54 Gy (n = 5, 7%).

All respondents prescribe concurrent chemotherapy with EBRT. In addition, 4% (three respondents) consider giving neoadjuvant chemotherapy before concurrent chemoradiation. The chemotherapy agents marked on the survey included cisplatin (97%), 5-flourouracil (4%), carboplatin (5%), paclitaxel (5%), and nedaplatin (2%).

Brachytherapy

With regard to dose rate, 61 respondents (85%) have HDR available, 13 (18%) had LDR, and 8 (11%) have pulse-dose-rate. Chemotherapy is given on the same day as an HDR fraction by four respondents (6%). An HDR fraction is given on the same day as an EBRT fraction by three respondents (4%). A total of 38% of respondents might hospitalize patients overnight for HDR treatment. For those using LDR, an equal number of respondents use on average one or two fractions, with a per-fraction dose ranging from 10 to 40 Gy. Three respondents administer chemotherapy during an inpatient LDR hospitalization.

The tandem and ovoid is the most frequently used applicator for HDR, pulse-dose-rate, and LDR, with 54% using this applicator for more than 75% of their cases annually. The tandem and ring applicator is used in 24% of cases, tandem and cylinder in 4%, tandem and interstitial in 3%, and interstitial only in 1%. For applicator insertion, 97% of respondents' patients receive anesthesia, consisting of general (46%), spinal (27%), intravenous conscious sedation (28%), and/or oral pain medication (14%). Ultrasound is used for assistance with applicator insertion by 62% of respondents; 24% use ultrasound less than 10% of the time, 12% use it for 10–25% of cases, 7% use it for 26–50% of cases, 1% use it for 51–75% of cases, and 18% use it for more than 75% of their cases.

With regard to imaging the brachytherapy applicator after insertion, 17 centers (24%) reported that they use plain x-ray films, either alone or in combination with MRI and/or CT. By contrast, CT is the most commonly used imaging modality (n = 41, 57%); 27 respondents use CT for every fraction, and 14 use CT for the first fraction only. MRI is used by 18 centers (25%), of which eight use MRI for every fraction and 10 for the first fraction only; of these 10, eight acquire a CT scan for every fraction. In terms of prescribing to the cervix, 56 (78%) prescribe to point A, 8 (11%) follow the GEC-ESTRO guidelines (14, 15) alone, 15 (21%) follow the GEC-ESTRO and report dose to point A, 4 (6%) follow the ABS guidelines alone, and 8 (11%) use both the ABS and point A.

The major HDR fractionation patterns are depicted in Fig. 1 and listed in the table. For Stage IB–IIA patients, the most common HDR fractionation pattern is 6 Gy for five fractions (n = 11, 15%), as it is for Stage IIB–IVA patients (n = 14, 19%). A total of 28 fractionation regimens are reported, of which 18 are used by only one institution. The most common fractionation regimen, 6 Gy for five fractions, is prescribed by centers in the United States, Canada, Australia, New Zealand, the United Kingdom, Spain, Italy, and Germany. The second most common regimen, 7 Gy for four fractions, is prescribed by centers in the United States, Australia, Austria, and the Netherlands. For HDR dose reporting, of the 68 respondents to this question, 32 (47%) calculate equivalent dose using the 2-Gy (EQD2) formula, whereas 31 (46%) use only the biologic equivalent dose formula, and five (7%) multiply the raw cumulative dose by 1.33.

The recommended mean combined EBRT plus brachytherapy EQD2 was 78.9 Gy (standard deviation [SD] 10.7) for Stage IB–IIA patients and 83.3 Gy (SD 11.2) for Stage IIB–IVA patients for all countries (p = 0.02 Stage IB–IIA vs. IIB–IVA). For all stages and all countries, the mean EBRT plus brachytherapy dose was 80.9 (SD 10.14). By region, the mean combined EQD2 for Australia/New Zealand was 81.18 (SD 4.96); for Europe, 83.35 (SD 10.75); for North America, 81.66 (SD 6.05); and for Asia, 71.2 Gy (SD 12.65; p = 0.02 for Asia vs. other regions). The mean EBRT plus brachytherapy dose for Japan was 62.73 (SD 6.7), and for Korea it was 83.9 (SD 6.86). Therefore, the only significant difference was between Japan and the other countries in the survey. Overall, 17 centers (7 Europe, 3 North America, 6 Japan, and 1 New Zealand) had EQD2 cumulative values ranging from 56.8 to 75 Gy; 6 centers (all in Europe) reported EQD2 values over 95 Gy, ranging from 97.6 to 115.4 Gy. The highest reported dose was from a center that uses a fractionation regimen of 7 Gy for seven fractions after full-dose radiation to the pelvis. Figure 2 depicts the EQD2 by region.

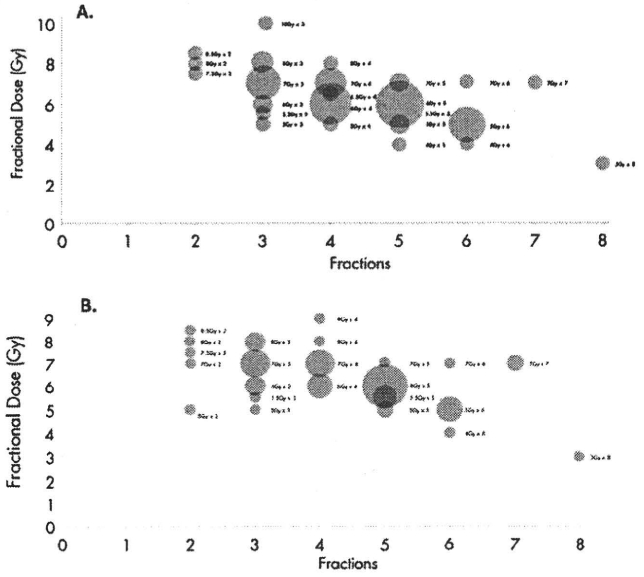

Fig. 1. Cervical cancer high-dose-rate brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. (A) Respondents' answers regarding the fractionation pattern prescribed for Stages IB–IIA cervical cancer. (B) Fractionation pattern recommended for Stages IIB–IVA cervical cancer. The size of the circle is proportional to the number of respondents, with the largest number reporting 6 Gy for five fractions.

The average ratio of brachytherapy dose to total sum (EBRT plus brachytherapy) dose was 0.45 (SD 0.08) for Stage IB–IIA and 0.44 (SD 0.08) for Stage IIB–IVA (p = NS). However, for Japanese respondents, the all-stages ratio was 0.51 (SD 0.03), which was significantly different from the average ratio for all other countries (p = 0.0002). When stratified by stage, this difference in brachytherapy ratio was seen only for the Stage IB–IIA subgroup. For Japanese respondents, the ratio of brachytherapy to EB plus brachytherapy was 0.58 (SD 0.05) for Stage IB–IIA and 0.45 (SD 0.06) for Stage IIB–IVA (p = 0.002). In other words, to accommodate their reduced EBRT dose, the Japanese use a higher brachytherapy dose for patients with Stage I–IIA tumors than that typically used elsewhere.

Complications

When queried about the number of patients treated for cervical cancer who were hospitalized annually for a complication, most respondents indicated 0 (n = 12, 17%), 1 (n = 37, 60%), or 2 (n = 9, 13%).

DISCUSSION

The primary goal of this survey was to gauge variation in HDR fractionation for cervical cancer and to determine brachytherapy practice patterns internationally, in order to assist with the development of the brachytherapy portion of international randomized clinical trials. Inasmuch as cervical cancer remains a leading cause of mortality in developing countries, international collaborative randomized trials that can advance treatment approaches on a global level are needed. In particular, before undertaking this study, we questioned whether the heterogeneity of brachytherapy practice might hinder standardization. As part of this survey, other items of interest were queried, including the utilization of three-dimensional (3D) imaging during brachytherapy. Other questions were designed to provide a 3-year update to selected general management information queried on the 2007 survey (16).

With regard to the general management of cervical cancer, this survey showed that the use of concurrent chemoradiation is similar to that reported in the 2007 survey, as are EBRT doses. In terms of brachytherapy, a greater proportion of respondents in this survey reported the use of HDR than in a United States–based survey from 1999 (4). However, the use of HDR in the United States also seem to be increasing, with 85% of ABS members having HDR brachytherapy available in their practices in 2007, indicating a growing acceptance of HDR brachytherapy in the United States that matches international implementation (3). The transition from LDR to HDR has been based on an increased acceptance of the feasibility, safety, and efficacy of HDR when carefully administered, with a concomitant increase in the use of 3D imaging. Three-dimensional imaging allows dose optimization away from the normal tissues in an attempt to spare them the large fractional dose used in HDR brachytherapy.

Overall, a significant proportion of GCIG members have access to 3D imaging for gynecologic brachytherapy. The most frequently used method for brachytherapy imaging is CT. In a recent ABS survey, 70% of respondents used CT after brachytherapy applicator insertion, and 57% used CT imaging in this survey (3). Before the 1990s, plain x-ray film simulation was the standard of care. After the integration of CT into radiation oncology departments, 3D imaging use increased and now represents the standard for external beam. The integration of 3D imaging into brachytherapy has also expanded, albeit later than for EBRT. This study found a significant proportion using the best available 3D imaging modality available at their institution, either CT or MRI, for cervical cancer brachytherapy planning.

In this survey, HDR brachytherapy dose fractionation recommendations varied considerably. The most common fractionation internationally was 6 Gy for five fractions, although this regimen is used by fewer than 20% of reporting institutions. Despite the high degree of individuality in brachytherapy prescribing, the biologic equivalence was remarkably similar for all countries and regions except Japan. All six Japanese respondents follow a regimen of treating to 20 to 30 Gy for early stage disease, then place a midline block, which significantly reduce the cumulative EQD2 cervical dose compared to that used in other countries. Nevertheless, the EQD2 dose to the cervix was equivalent, on average 80 Gy for all regions of the world surveyed. The Japanese cervix dose reduction to approximately 70 Gy, instead of the international standard of 80 Gy, must be further analyzed, including comparison of recurrence rates and toxicities; an upcoming abstract shows reasonable rates of local control (17). The Japanese regimen, in use for several decades, was implemented

Table 1. Routine high-dose-rate brachytherapy fractionation regimens for cervical cancer as used by Gynecologic Cancer Intergroup surveyed physicians

Standard fractionation for Stages IB–IIA cervical cancer				Standard fractionation for Stages IIB–IVA cervical cancer			
% Respondents (*n*)	Dose/fraction	Fractions (*n*)	EQD2	% Respondents (*n*)	Dose/fraction	Fractions (*n*)	EQD2
18% (11)	6	5	40	23% (14)	6	5	40
15% (9)	6	4	32	10% (6)	7	4	40
12% (7)	7	3	29.75	10% (6)	7	3	30
8% (5)	5	6	37.5	8% (5)	6	4	32
8% (5)	7	4	39.7	7% (4)	5.5	5	35.5
5% (3)	5	5	31.25	5% (3)	5	6	37.5
5% (3)	5.5	5	35.52	5% (3)	7	6	59.5
3% (2)	8	3	36	5% (3)	6	3	24
1.6% (1)	3	8	26	5% (3)	8	3	36
1.6% (1)	4	5	23.3	3% (2)	7	7	69.4
1.6% (1)	4	6	28	3% (2)	5	5	31.3
1.6% (1)	5	3	18.75	1.6% (1)	3	8	26
1.6% (1)	5	4	25	1.6% (1)	4	6	28
1.6% (1)	5.5	3	21.3	1.6% (1)	7	5	49.6
1.6% (1)	6	3	24	1.6% (1)	8	4	48
1.6% (1)	6.5	4	35.75	1.6% (1)	9	4	57
1.6% (1)	7	5	49.6	1.6% (1)	5	3	18.8
1.6% (1)	7	6	59.5	1.6% (1)	5.5	3	21.3
1.6% (1)	7	7	69.4	1.6% (1)	5	2	12.5
1.6% (1)	7.5	2	21.9	1.6% (1)	7.5	2	21.9
1.6% (1)	8	2	24	1.6% (1)	8	2	24
1.6% (1)	8	4	48	1.6% (1)	8.5	2	26.2
1.6% (1)	8.5	2	26.2				
1.6% (1)	10	3	50				

Abbreviation: EQD2 = Equivalent dose in 2 Gy fractions.
Results indicate the diversity of responses.
The EQD2 formula was used to convert the high-dose-rate dose and number of fractionations.

upon the observation that Japanese women, potentially because of their small body size, had very high bowel and bladder toxicity rates when treated with higher pelvic EBRT doses (18). The current Japanese regimen begins HDR intracavitary brachytherapy once per week after 20 Gy. Whether a genetic difference in sensitivity to radiation exists is unknown, but one implication of the successful outcomes in Japanese women is that brachytherapy may be the more critical component for treatment to the cervix, particularly for early stage disease with a lower risk of nodal spread.

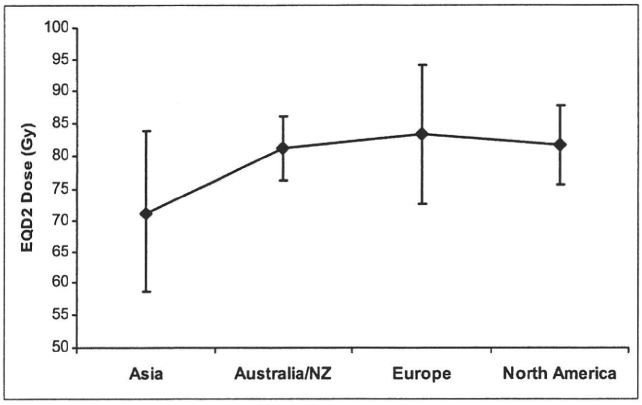

Fig. 2. The sum external beam plus brachytherapy dose with the error bars indicating the standard deviation (SD), converted using the equivalent dose in 2-Gy fractions (EQD2) assuming an $\alpha/\beta = 10$, by region of the world. The mean EQD2 dose was 80.9 Gy (SD 10.14).

A previously unassessed difference in brachytherapy administration was identified with regard to the proportional relationship of brachytherapy to the sum total dose. For early-stage patients, the Japanese respondents administer a significantly higher proportion of the dose using brachytherapy than practitioners from other countries. The reliance on HDR brachytherapy fractionation may indicate that a large dose given with HDR can compensate for a lower external beam dose in patients with small tumors. This assumption of proportionality must be corroborated with recurrence information.

For all respondents (including those from Japan), the mean EBRT plus brachytherapy cumulative EQD2 dose was 80.4 Gy, with a standard deviation of 10 Gy. Patients with higher-stage disease (Stage IIB–IVA) received a significantly higher dose than did those with earlier-stage cervical cancer. Therefore, a dose of 80 Gy may be considered the universally accepted international baseline dose overall, with on average 79 Gy for Stage IB–IIA and 84 Gy for Stage IIB–IVA cases. A dose of 80 Gy is approximately equivalent to 45 Gy delivered with EBRT and 5.5 Gy for five fractions delivered with HDR brachytherapy. A dose of 84 Gy is approximately equivalent to 45 Gy with EBRT and 6 Gy for five fractions or 7 Gy for four fractions of HDR.

Standardization of HDR brachytherapy on an international level will assist institutions in terms of comparing toxicities and outcomes in patients with cervical cancer, and will also allow for the exchange of information and uniformity in a multi-institutional international randomized clinical trial that permits HDR brachytherapy. A cumulative dose of 80 Gy should be considered an achievable goal for patients with locally advanced cervical cancer. Analysis of the outcomes in Japanese patients treated with a lower total dose is necessary. Future randomized trials in the era of chemoradiation may attempt radiation dose variation based on response and on improved sparing of normal tissues with 3D imaging, to determine the acceptable safe threshold level that results in equivalent eradication of disease while minimizing toxicities.

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High-dose-rate Intracavitary Brachytherapy Combined with External Beam Radiotherapy for Stage IIIb Adenocarcinoma of the Uterine Cervix in Japan: A Multi-Institutional Study of Japanese Society of Therapeutic Radiology and Oncology 2006–2007 (Study of JASTRO 2006–2007)

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Objective: The current study was a retrospective questionnaire survey of stage IIIb adenocarcinoma of the uterine cervix treated with high-dose-rate intracavitary brachytherapy combined with external beam radiation therapy in Japan aimed to investigate the optimal dose on the basis of the biological effective dose and prognostic factors.

Methods: Between 1990 and 2000, 61 patients with stage IIIb adenocarcinoma of the uterine cervix underwent high-dose-rate intracavitary brachytherapy combined with external beam radiation therapy in 19 major hospitals in Japan. This retrospective questionnaire survey was performed by mail including survey charts to be fulfilled by radiation oncologists in these 19 major hospital. Fifty had only adenocarcinoma components and 11 had adenosquamous cell carcinoma components. All patients were treated with high-dose-rate intracavitary brachytherapy combined with external beam radiation therapy. Total biological effective dose ($T\text{-}BED_{10}$) was calculated from the sum of the biological effective doses of the external beam radiation therapy and the intracavitary brachytherapy. Thirty-two patients underwent chemotherapy.

Results: The 5-year overall survival rate of all patients was 20.2%. Stratified by total biological effective dose, the 5-year overall survival rate was 0% for $T\text{-}BED_{10}$ <75 Gy, 24.7% for $T\text{-}BED_{10}$ between 75 and 100 Gy and 0% for $T\text{-}BED_{10}$ >110 Gy ($P = 0.15$). Stratified by histopathology, the 5-year overall survival rate was 22.1% for adenocarcinoma and 13.6% for adenosquamous cell carcinoma ($P = 0.43$). Stratified by chemotherapy, the 5-year overall survival rate was 20.3% in patients who received chemotherapy and 20.4% in patients who did not receive chemotherapy ($P = 0.96$).

Conclusions: The 5-year overall survival rate of stage IIIb adenocarcinoma of the uterine cervix in this retrospective questionnaire survey was 20.2%. The optimal T-BED_{10} and evident prognostic factors were not clear from this questionnaire survey.

Key words: high-dose-rate intracavitary brachytherapy – adenocarcinoma of the uterine cervix – multi-institutional study

INTRODUCTION

Prognosis of stage IIIb adenocarcinoma of the uterine cervix has been reported to be much worse than that of squamous cell carcinoma of the same stage. The 5-year overall survival (OS) rates of stage IIIb adenocarcinoma of the uterine cervix treated with high-dose-rate intracavitary brachytherapy (HDR-ICBT) combined with external beam radiotherapy (EBRT) have been reported to be 0–51.0% (1–3), whereas the survival rates for stage IIIb squamous cell carcinoma of the uterine cervix have been reported to be 47.1– 55.2% (4–6). HDR-ICBT combined with EBRT for stage IIIb adenocarcinoma of the uterine cervix is the community standard treatment in Japan. In the US and some European countries, low-dose rate intracavitary brachytherapy (LDR-ICBT) combined with EBRT is often performed. Eifel et al. (7) and Grigsby et al. (8) have reported that the treatment outcomes of adenocarcinoma of the uterine cervix were almost the same as those of the squamous cell carcinoma using LDR-ICBT. However, these results were from Ib to IIb stage uterine cervical carcinomas. Grigsby et al. (8) pointed out that the 5-year disease-free survival rate after treatment with LDR-ICBT of stage III adenocarcinoma of the uterine cervix (25%) was worse than that of the squamous cell carcinoma (59.1%) ($P = 0.007$).

The optimal radiation dose in this situation has not been established, but in practice the same dose as is given for squamous cell carcinoma, 67–86 Gy_{10},with Gy_{10} the biological effective dose if α/β is 10 (6). Although a recent preliminary study has suggested that a higher biological effective dose (BED) might improve prognosis (3), no large studies have been performed to evaluate this issue. The prognostic factors other than the total dose also have not been defined. Therefore, the purpose of the current retrospective questionnaire survey was to investigate the optimal dose on the basis of the BED and to investigate prognostic factors for stage IIIb adenocarcinoma of the uterine cervix treated with HDR-ICBT combined with EBRT.

PATIENTS AND METHODS

Between 1990 and 2000, 61 patients with stage IIIb adenocarcinoma of the uterine cervix were treated with HDR-ICBT combined with EBRT in 19 Japanese university hospitals and cancer centers. Surveys of the charts were completed by radiation oncologists who fulfilled the JASTRO institutional criteria and who responded 'yes' to the pre-questionnaire survey of willingness to engage in this retrospective questionnaire study. The questionnaires were mailed to 19 Japanese university hospitals and cancer centers in 2007. Patient characteristics are listed in Table 1. The median age was 61.5 years with a range of 30–86 years. Fifty patients had only adenocarcinoma components and 11 had adenosquamous cell carcinoma components. The median tumor diameter was 6.0 cm with a range of 2–15 cm. Thirteen of the 61 patients had vaginal invasion. All patients were staged by physical and pelvic examinations, and according to the Japanese standards of pretreatment investigation were examined by computed tomography in order to rule out patients with distant metastases. All patients were then treated with HDR-ICBT combined with EBRT.

Treatment characteristics are listed in Table 2. HDR-ICBT was performed once a week in 55 patients and twice a week in 6 patients. The median dose per fraction was 6 Gy to point A (range: 5–8 Gy). The median total fraction delivery times was five times (range: one to six times). As for the applicator, 58 patients were treated with tandem plus ovoid applicators and 2 patients were inserted by tandem plus cylinder applicators; only 1 patient was inserted by only the tandem applicator. The total dose of HDR-ICBT to point A was 6.0–30 Gy and the total dose of EBRT midway between the isocenter and the lateral field was 40–59.4 Gy. In the current study, the total BED was calculated as follows: total BED (T-BED_{10}) = BED of EBRT (E-BED_{10}) + BED of HDR-ICBT (A-BED_{10}). The median E-BED_{10} was 60 Gy (range: 48–70.1 Gy), the median A-BED_{10} was 31 Gy (range: 9.6–52.5 Gy) and the median T-BED_{10} was 106.3 Gy (range: 66.9–115.2 Gy). The median overall treatment time (OTT) was 53 days (range: 37–153 days).

Table 1. Patient and tumor characteristics

Age, median (range)	61.5 years (30–86 years)
Maximum tumor diameter (cm), median (range)	6.0 (2.0–15.0)
Histopathology (*n*)	
Adenocarcinoma	50
Adenosquamous cell carcinoma	11
Vaginal invasion (*n*)	13

Table 2. Treatment characteristics

Treatment types (*n*)	
EBRT	61
HDR-ICBT	61
Chemotherapy	
None	29
Any	32
Biological effective dose (BED_{10}) (Gy), median dose (range)	
E-BED_{10}	60.0 (48.0–70.1)
A-BED_{10}	31.0 (9.6–52.5)
T-BED^{a}_{10}	106.3 (66.9–115.2)

EBRT, external radiotherapy; HDR-ICBT, high-dose-rate intracavitary brachytherapy; E-BED, external beam radiation therapy; T-BED, total biological effective dose; A-BED_{10}, BED of HDR-ICBT.
[a]T-BED_{10} = (E-BED_{10}) + (A-BED_{10}).

As is shown in Table 2, 32 patients underwent chemotherapy. Chemotherapy regimens were as follows: 23 underwent treatment with platinum drugs, 3 received CPT-11 and 6 received other chemotherapy. In total, 20 of the 32 patients underwent concurrent chemotherapy, and all of those patients received platinum chemotherapy. After the treatment, all patients were followed by physical and pelvic examinations and computed tomography or magnetic resonance imaging.

For statistical analysis, survival curves were constructed by the Kaplan–Meier method and log-rank test was performed to compare between total dose and clinicopathologic valuables using Dr. SPSS II for Windows (SPSS Inc., USA). Statistical significance was assumed for a two-tailed P value <0.05.

RESULTS

Of the 61 patients, 41 patients relapsed. As for the first site of failure, 20 relapsed in the field, 14 relapsed out of field and 7 relapsed both in field and out of field.

The 5-year OS rate of all patients was 20.2% (Fig. 1), the 5-year relapse-free survival (RFS) rate was 13.4% (Fig. 1) and the 5-year local control rate (LC) was 36.0% (Fig. 2). As shown in Fig. 3, stratified by T-BED_{10}, the 5-year OS was 0% for T-BED_{10} <75 Gy ($n = 2$), 24.7% for 110 Gy ≥ T-BED10 ≥ 75 Gy ($n = 50$) and 0% for T-BED_{10} >110 Gy ($n = 9$) ($P = 0.15$). Stratified by histopathology, the 5-year OS was 22.1% for adenocarcinoma and 13.6% for adenosquamous cell carcinoma ($P = 0.43$). The 5-year OS and 5-year LC were not significantly correlated with the E-BED_{10} or A-BED_{10}. Stratified by age, the 5-year OS was 12.0% when the patient's age was <60 years and 31.0% when the patient's age was ≥60 years ($P = 0.175$). Stratified by PS, the 5-year OS was 17.2% when PS was 0 or 1 and was 33.3% when PS was 2 or 3 ($P = 0.366$).

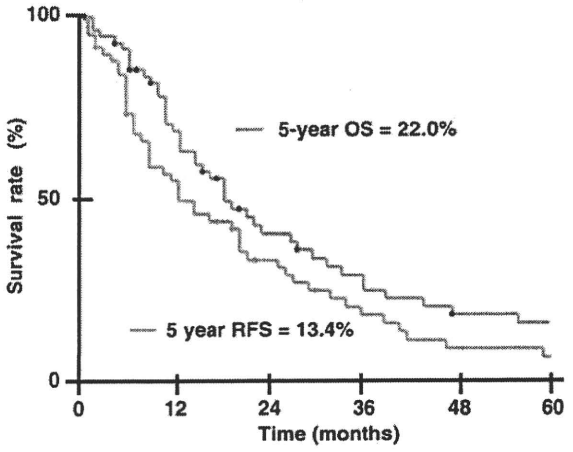

Figure 1. Overall survival (OS) and relapse-free survival curves (RFS) of all patients. The 5-year OS rate was 20.2%. The 5-year RFS rate was 13.4%.

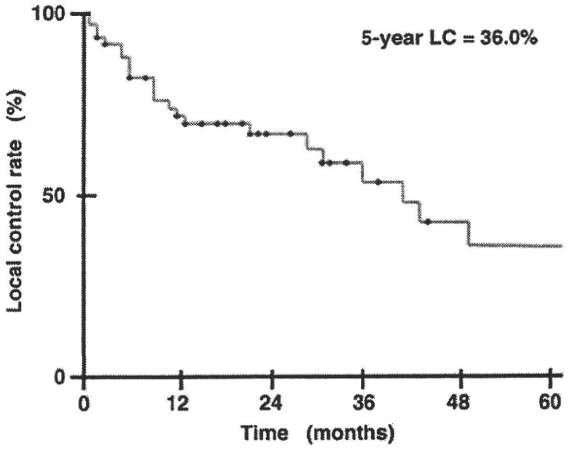

Figure 2. Local control (LC) curve of all patients. The 5-year LC rate was 36.0%.

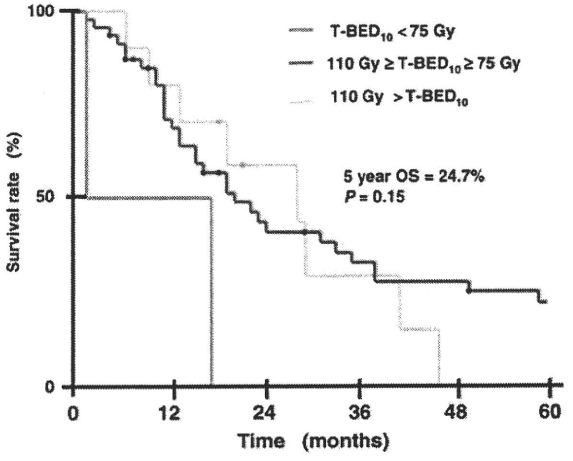

Figure 3. OSl curves stratified by total biological effective dose (T-$BED)_{10}$.

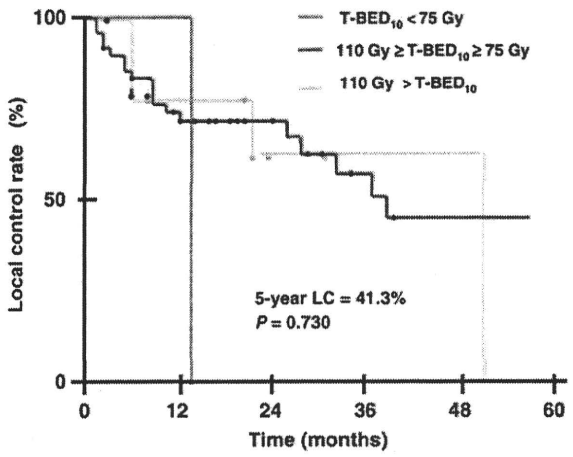

Figure 4. LC curves stratified by Tl-BED_{10}.

Stratified by tumor size, the 5-year OS was 22.2% when the maximum tumor size was <7 cm and 20.0% when the maximum tumor size was ≥7 cm ($P = 0.763$). Stratified by vaginal invasion, the 5-year OS was 50.0% when the lower one-third of the vagina had been invaded: 15.6% when the upper two-thirds of the vagina had been invaded and 19.8% when the vagina was not involved ($P = 0.745$). Stratified by OTT, the 5-year OS was 22.9% when OTT was ≤56 days and 17.8% when it was >56 days ($P = 0.43$). Stratified by chemotherapy, the 5-year OS was 20.3% among those who had undergone chemotherapy and 20.4% among those who had not ($P = 0.96$). Furthermore, the 5-year OS was 15.8% among those who had undergone concurrent chemotherapy and 23.4% among those who had not ($P = 0.566$). As for LC rate stratified by T-BED_{10}, the 5-year LC was 0% for T-BED_{10} <75 Gy, 41.3% for 110 Gy ≥ T-BED_{10} ≥ 75 Gy, and 0% for T-BED_{10} >110 Gy ($P = 0.730$) (Fig. 4).

Eight patients (13.1%) had late morbidity of Grade 2 or greater. Grade 2 late morbidity involved chronic proctitis (rectal bleeding), Grade 3 was characterized by uteric stenosis and recto-vaginal fistula, and Grade 4 involved severe ureter stenosis requiring surgery.

DISCUSSION

The 5-year OS of stage IIIb squamous cell carcinoma of the uterine cervix treated with HDR-ICBT combined with EBRT has been reported to be 47.2–55.2% in Japan (4–6). In the current study, the 5-year OS of stage IIIb adenocarcinoma of the uterine cervix was 20.2% and the 5-year RFS of stage IIIb adenocarcinoma of the uterine cervix was 13.4%, indicating that the prognosis of stage IIIb adenocarcinoma of the uterine cervix is much worse than that of the squamous cell carcinoma of the same stage.

The optimal dose of HDR-ICBT combined with EBRT for stage IIIb adenocarcinoma of the uterine cervix has not been established in a prospective manner. In Japan, 30 years' experience with the use of HDR-ICBT with EBRT for locally advanced uterine cervical carcinoma suggests that 67–86 Gy_{10} is acceptable dose, and this is recognized as the community standard dose (6). Radiation oncologists in the USA have many years of experience using LDR-ICBT with external beam radiotherapy for locally advanced uterine cervical carcinoma, and have calculated the optimal dose of HDR-ICBT from that of LDR-ICBT without performing clinical trials. The American Brachytherapy Society recommends HDR-ICBT dose of 100–108 Gy_{10} for locally advanced uterine cervical carcinoma (9), much higher dose than that generally used in Japan. In both the USA and Japan, the above-mentioned recommendations for the HDR-ICBT dose have been based on locally advanced squamous cell carcinoma rather than adenocarcinoma. Accordingly, the optimal dose of HDR-ICBT combined with EBRT for stage IIIb adenocarcinoma has not been established from any clinical studies.

Recently, a preliminary study of stage IIIb adenocarcinoma of the uterine cervix treated with HDR-ICBT combined with EBRT in Japan suggested that higher T-BED was associated with better prognosis (3). In contrast, in the current study, 5-year OS was 0% for T-BED_{10} >110 Gy (high dose), 24.7% for 110 ≥ T-BED_{10} ≥ 75 (intermediate dose) and 0% for T-BED_{10} <75 (low dose) ($P = 0.15$) (Fig. 3). Furthermore, the 5-year LC was 0% for T-BED_{10} <75 Gy, 41.3% for 110 Gy ≥ T-BED_{10} ≥ 75 Gy and 0% for T-BED_{10} >110 Gy ($P = 0.730$) (Fig. 4). These results suggest that higher total dose does not improve LC or OS of stage IIIb adenocarcinoma of the uterine cervix, although considering that this study is retrospective questionnaire survey.

Modern standard treatment of locally advanced uterine cervical carcinoma comprises concurrent chemoradiotherapy. However, the current study revealed no survival benefit of chemotherapy. Similarly, the RTOG phase III study suggested that the treatment results of stages III and IV uterine cervical carcinoma treated with radiation therapy alone and concurrent chemoradiotherapy were the same by a sub-set analysis (10). This analysis suggests that stage III or IV tumors may require new chemotherapeutic regimens. Vrdoljak et al. (11) reported that concurrent chemoradiotherapy for locally advanced uterine cervical carcinomas including adenocarcinomas using cisplatin and ifosfamide followed by consolidation chemotherapy might be promising. Zarba et al. (12) also reported that concurrent chemoradiotherapy using cisplatin and gemcitabine was efficacious and well tolerated.

In the current study, the extent of vaginal invasion also did not impact the prognosis of stage IIIb adenocarcinoma of the uterine cervix. This suggests that biological behavior has much more influence on the prognosis than the insertion technique of applicators in stage IIIb adenocarcinoma of the uterine cervix. Recently, Niibe et al. (13) reported that concomitant positive expression of HER2 and HIF-1α in locally advanced uterine cervical carcinoma including adenocarcinoma achieved 20-month OS rate of 37.5%, whereas concomitant negative