considered to compose another prognostic factor independent of Masaoka stage,[5-7] thymomas are divided into 5 types; A, AB, B1, B2, and B3.

Although to our knowledge no randomized controlled trial has been conducted to date to establish a standard treatment for a thymoma, empiric evidence has led surgical resection to become the mainstay therapy. However, thymomas are also sensitive to radiation therapy (RT), which is often used in nonresectable patients and after surgery as an adjuvant therapy. The impact of postoperative RT on survival after complete resection of a thymoma has been reported in several reports, although the results vary.[8-15] All of those reports used Masaoka stage to stratify their patients; however, to our knowledge, no known correlations between the effects of postoperative RT and WHO cell type have been presented to date. We conducted the current retrospective study to determine whether certain patients with a thymoma could achieve prolonged survival by receiving postoperative RT after a complete resection, by stratifying the patients according to Masaoka stage and WHO cell type. The relation between RT status and pattern of disease recurrence was also examined to investigate the effects of RT on the clinical course of thymoma patients.

MATERIALS AND METHODS

We reviewed the records of 324 patients who underwent complete resection of a thymoma at Osaka University Hospital and its affiliated hospitals during the 36-year period between 1970 and 2005. Those with a final diagnosis of thymic carcinoma and those who underwent a biopsy alone were not included. The patients included 160 males and 164 females, who ranged in age from 17 to 83 years (mean, 51 years). Postoperative RT was initially recommended for all patients who underwent a complete resection; however, it was not performed in cases of patient refusal. In addition, the criteria for postoperative RT at Osaka University Hospital changed during the study period, that is, Masaoka stage I patients were first eliminated from this recommendation in 1985, followed by stage II patients in 1998. Conversely, postoperative RT was not always recommended to patients at other hospitals that participated in this study. As a result, 134 patients received postoperative RT, of whom 119 were treated at Osaka University Hospital.

Postoperative RT was administered using megavoltage technology. Cobalt-60 and 6-megavolt (MV) x-ray devices were used from 1970 through 1981; cobalt-60 and 10-MV x-ray devices were used from 1982 through 1993; and 4-MV, 6-MV, and 10-MV x-ray devices were used from 1993. In 1997, evaluation of dose distribution using computed tomographic images and 3-dimensional planning became available ($n = 20$). The typical volume treated included the entire tumor bed and part of the involved adjacent lung when there was parenchymal involvement or as delineated by surgical clips, with at least a 1.5-cm margin. For some patients, the entire mediastinum was included in the treatment field, whereas noninvolved supraclavicular fossa was never included. Treatment portals included opposing anterior-posterior fields with differential weighting (1:1, 3:2, 2:1, 3:1) or a single anterior field. For all patients, a total dose of 40 to 50 grays (Gy) with 2 Gy per fraction was intended, although the RT course could not be completed in 12 patients. We adopted in principle 40 Gy, which adhered fundamentally to the recommendation stated in a study performed at our former institute.[9] Thus, 84% of the patients in the postoperative RT group received a dose of 40 Gy (median, 40 Gy; average, 39.3 Gy [range, 10-50 Gy]).

Patient characteristics in regard to Masaoka stages and other perioperative therapy with reference to the status of postoperative RT are summarized in Table 1. Actuarial disease-specific and overall survival rates for all patients and those in each stage were calculated after dividing them by the status of postoperative RT. As we previously reported, the survival rates of patients with a stage III thymoma were found to be correlated with the involved organs.[3] Therefore, stage III patients were divided into 3 groups according to the involved organs: those with invasion to the great vessels (V[+]L[+ or −]P[+ or −]), invasion to the lung but not the great vessels (V[−]L[+]P[+ or −]), and invasion to the pericardium but not the great vessels or lungs (V[−]L[−]P[+]).

Pathologic examinations were performed using hematoxylin and eosin-stained sections derived from paraffin-embedded blocks. Histologic diagnosis with reference to the WHO classification system was performed to classify the patients according to cell type A, AB, B1, B2, or B3, which was identified in 290 patients. Actuarial survival rates were calculated, and patterns of disease recurrence were reviewed based on each cell type.

Table 1. Patient Characteristics According to Postoperative RT Status

Postoperative RT	Yes	No
Masaoka stage		
I	31	119
II	43	33
III	53	30
IVA	4	5
IVB	3	3
Total	134	190
Preoperative therapy	6	25
RT	2	9
Chemotherapy	4	10
Steroids	2	11
Postoperative therapy other than RT	17	18
Chemotherapy	8	5
Steroids	12	13

RT indicates radiation therapy.

When considering the clinical course of a patient with a thymoma, which lasts for more than a decade in many, disease-specific survival rates may accurately reflect the clinical course of thymomas as compared with overall survival rates. Therefore, both disease-specific and overall survival rates were calculated in the current study. Patients who died from a disease other than the thymoma were regarded as censored at the time of death in treating disease-specific survival rates. Actuarial disease-specific and overall survival rates were calculated using the Kaplan-Meier method, and statistical differences between survival curves were examined with a log-rank test. The frequencies of distribution between groups were tested with a chi-square test. A P value of <.05 was considered significant. Statistical analyses were performed using the personal computer software package StatView 5 (SAS Institute, Cary, NC). The institutional review board of Osaka University Hospital approved the design of the study and consented to waive the need to obtain informed consent from the patients.

RESULTS

The actuarial 10-year and 20-year disease-specific survival rates for patients who received postoperative RT were 92.8% and 83.5%, respectively, whereas they were 94.4% and 94.4%, respectively, for those treated without RT (P = .2208). Conversely, the actuarial 10-year and 20-year overall survival rates for those who received postoperative RT were 80.7% and 56.5%, respectively, whereas they were 86.2% and 40.4%, respectively, for those treated without RT (P = .0640). The distribution of patients in regard to Masaoka stage was skewed in the present population, thus disease-specific and overall survival rates for the patients were calculated by stage (Table 2). The disease-specific survival rate for patients with stage I and II was >90% regardless of the status of postoperative RT. Furthermore, in all patients with stage III disease, there were no significant differences noted in disease-specific survival rate between those treated with and without postoperative RT (Table 2). Next, we compared stage III patients after dividing them according to the involved organs. The actuarial 10-year and 20-year disease-specific survival rates for patients in the V(+)L(+ or −)P(+ or −) group who underwent postoperative RT (n = 12) were 62.3% and 41.6%, respectively, whereas they were 77.1% and 77.1%, respectively, for those treated without RT (n = 13; P = .48). Similarly, those rates for the V(−)L(+)P(+ or −) group treated with postoperative RT (n = 27) were 93.8% and 54.8%, respectively. Although the follow-up period for those treated without postoperative RT in this group (n = 12) was not adequate to calculate the 10-year disease-specific survival rate, the disease-specific survival rate after 9 years was 80.0% (P = .2565). No patients in the V(−)L(−)P(+) group died during the follow-up period of between 1.8 to 20.6 years (median, 9.9 years), which included 14 patients treated with postoperative RT and 5 treated without it. In patients with stage IVA disease, all 5 patients without postoperative RT and 3 of 4 patients with postoperative RT survived >5 years, whereas the remaining 1 patient with postoperative RT died 1.4 years after surgery. With regard to those with stage IVB disease, all 6 died within 5 years.

The overall survival rate for patients with stage I and II disease without postoperative RT was >90%, whereas it was smaller in those treated with postoperative RT compared with those treated without. Furthermore, in all patients with stage III disease, there were no significant differences in the overall survival rate noted between those treated with and without postoperative RT. With regard to patients with stage IV disease, all deaths that occurred were because of the tumor, thus, the overall survival rates were identical to the disease-specific survival rates, which were analyzed above (Table 2).

Table 2. Patient Survival Rate Based on Masaoka Stage

Stage	Postop RT	No.	10DSR, %	20DSR, %	P	10OSR, %	20OSR, %	P
I	+	31	96.3	90.3		77.3	58.7	
	–	119	100	100	NA	92.3		.0126
II	+	43	100	100		85.0	73.6	
	–	33	100		NA	96.7		.2486
III	+	53	87.7	62.3		79.9	35.5	
	–	30	85.1	85.1	.8010	69.1	46.1	.4852
IV	+	7	62.5 (5DSR)			62.5 (5OSR)		
	–	8	66.7 (5DSR)		.6628	66.7 (5OSR)		.6628

Postop RT indicates postoperative radiation therapy; 10DSR, 10-year disease-specific survival rate; 20DSR, 20-year disease-specific survival rate; 10OSR, 10-year overall survival rate; 20OSR, 20-year overall survival rate; +, received; –, not received; NA, not applicable; 5DSR, 5-year disease-specific survival rate; 5OSR, 5-year overall survival rate.

Table 3. Survival Rates and Patterns of Disease Recurrence According to WHO Cell Type

WHO Cell Type	Postop RT	Masaoka Stage					Total	10DSR, %	20DSR, %	10OSR, %	20OSR, %	Patten of Disease Recurrence
		I	II	III	IVA	IVB						
A	+	2		1			3	100	100	66.7	66.7	None
	–	12	1	1			14	100	–	100	–	None
AB	+	9	12	5		2	28	92.4	84.0	88.9	66.6	PD (2), local, unknown
	–	47	15	1		1	64	100	–	85.1	–	None
B1	+	6	10	3			19	100	100	88.8	66.0	PD
	–	25	5	5			35	100	–	90.5	–	None
B2	+	10	12	25	3	1	51	94.9	73.9	76.5	48.3	PD (8), lung, local, brain, and pericard
	–	21	6	12	5	1	45	92.9	92.9	82.5	41.3	Lung and PD (2)
B3	+		7	4	1		12	88.9	–	67.9	–	PD + local + liver, local + lung, and PD + lung
	–	4	3	3		1	11	65.6	–	65.6	–	Lung
Others*	+						0					
	–	6	1	1			8					
Total		142	72	61	9	6	290					

WHO indicates World Health Organization; Postop RT, postoperative radiation therapy; 10DSR, 10-year disease-specific survival rate; 20DSR, 20-year disease-specific survival rate; 10OSR, 10-year overall survival rate; 20OSR, 20-year overall survival rate; +, received; –, not received; PD, pleural dissemination, pericard, pericardial dissemination.

* "Others" in WHO cell type includes cases that could not be assigned to type A, AB, B1, B2, or B3.

The distribution by WHO cell type according to Masaoka stage and status of postoperative RT for each category is summarized in Table 3. None of the patients with WHO cell types A (n = 17) or B1 (n = 54) died during the median follow-up period of 5.4 years and 8.3 years, respectively, regardless of the status of postoperative RT. Furthermore, no patient of disease recurrence occurred in cases with cell type A, whereas 1 patient with cell type B1 developed disease recurrence with pleural dissemination, which had been classified as stage III disease at the time of resection and the patient received postoperative RT. Among those with cell type AB (n = 92), 3 patients treated with postoperative RT died at 1.5 years, 3.8 years, and 16.7 years, respectively, after surgery, whereas no patient treated without postoperative RT died. Patterns of disease recurrence were found in 1 patient with pleural and pericardial dissemination, 1 with pleural dissemination and lymph node metastasis, and 1 with disease recurrence at the site of a needle biopsy. The actuarial 10-year and 20-year disease-specific survival rates for all patients with these 3 cell types who underwent postoperative RT (n = 50) were 95.8% and 91.5%, respectively, whereas the 15-year disease-specific survival rate for those treated without postoperative RT was 100% (n = 113).

Of 96 patients with WHO cell type B2, 8 died, which included 6 with stage III disease and 2 with stage IVA disease. All but 1 of the patients who died received postoperative RT. There was no significant difference noted with regard to actuarial disease-specific survival rate between patients treated with and those treated without postoperative RT ($P = .4368$) (Table 3). Disease recurrence occurred in 16 patients, which included 1 patient with stage II disease, 11 patients with stage III disease, and 4 patients with stage IVA disease, with postoperative RT performed in 13 of those. The pattern of disease recurrence in most included pleural or pericardial dissemination and distant metastases. Local disease recurrence without the existence of other recurrent disease occurred in 1 patient with stage III disease who underwent postoperative RT.

Among patients with WHO cell type B3, 3 died from the thymoma, 2 of whom received postoperative RT. No significant difference in actuarial disease-specific survival rates were found between those treated with and without postoperative RT ($P = .3501$). Disease recurrence occurred in 4 patients, which included 2 with stage III, and 1 each with stage IVA and stage IVB disease, with postoperative RT performed in 3 of those. The patterns of disease recurrence included pleural dissemination, distant metastases in the liver and lung, and local disease recurrence. Local disease recurrence accompanied by distant metastasis occurred in 2 patients.

No group of patients divided by WHO cell type demonstrated a significant difference in overall survival rate according to status of postoperative RT ($P = .7496$, .9634, .1837, and .7229 for WHO cell types AB, B1, B2, and B3, respectively) (Table 3). Statistical analysis of overall survival rates for patients with WHO cell type A was not attempted because no events occurred in those patients treated without postoperative RT, and the number of patients treated with postoperative RT was too small.

DISCUSSION

In the current study, no significant improvement in survival was noted for patients who were treated with postoperative RT compared with those without, regardless of Masaoka stage, which is consistent with previously reported results.[10-16] With regard to those with Masaoka stage I and II disease, the results of the current study can be explained in part by the finding that the long-term outcomes of our thymoma patients who did not undergo postoperative RT were satisfactory, which made it difficult to demonstrate that postoperative RT had a further benefit on survival, thus suggesting that complete resection alone was sufficient to achieve a good prognosis in this population. Although the survival rates of stage III and IV disease patients were reduced compared with those with stage I and II, the differences in survival according to status of postoperative RT among each stage were not found to be significant, which may indicate that postoperative RT after complete resection in patients with stage III and IV disease does not alter long-term survival.

The indication of postoperative RT for thymoma after complete resection has long been considered controversial, mainly because, to the best of our knowledge, no randomized controlled study has been conducted to date. For patients with stage II and III disease, Curran et al.[8] and Nakahara et al.[9] advocated postoperative RT. Curran et al.reviewed 19 patients with stage II disease and 7 with stage III disease, and their findings supported postoperative RT for stage II disease based on their finding that mediastinal recurrence occurred in 6 of 18 patients treated without RT within 5 years, whereas no recurrence was noted in 1 stage II case and 4 stage III patients treated with postoperative RT. The mediastinum was the most common site of disease recurrence in their report. In addition, reports on the outcome of patients with a thymoma have been accumulating,[7,11,12,14,16,17] which led us to speculate regarding the effects of postoperative RT on stage II thymomas. Those reports studied from 25 to 61 patients with stage II disease, and noted a low rate of disease recurrence (range, 2.0-9.8%), with a frequent pattern of disease recurrence being pleural dissemination, which is consistent with the findings in the current study. Although this issue would ideally be settled by a prospective randomized controlled study, we consider that the accumulated data are sufficient to judge that postoperative RT for stage II thymoma is not effective.

Conversely, Nakahara et al insisted that a patient with a stage III thymoma should undergo postoperative RT for the entire mediastinum after a complete resection.[9] That report, produced by our former institute, was based on a 1-arm observation study that did not include patients who did not undergo postoperative RT. Later, after accumulating clinical data for an additional 20 years, we reported that the prognosis and pattern of disease recurrence in patients with a stage III thymoma depended on the involved organs, and that recurrence was most often noted as pleural dissemination.[3,18] Thus, we currently consider that establishment of a strategy against pleural dissemination, rather than mediastinal recurrence, is more important than postoperative RT for this group of patients, as described earlier. To the best of our knowledge, no beneficial effect of postoperative RT on the survival of individuals with stage III thymoma has been demonstrated to date in reports published from other institutions,[11,15] which is consistent with the results of the current study.

Long-term survival rates for patients with WHO cell types A, AB, and B1 were considered adequate without postoperative RT, making it difficult to demonstrate further improvement because of postoperative RT and suggesting that its role was not apparent in this population, which indicates that surgery alone is a sufficient treatment strategy for thymoma patients with WHO cell types A, AB, and B1, as well as those classified as having Masaoka stage I and II disease who undergo a complete resection. Thus, such patients may be eliminated as candidates for postoperative RT. Furthermore, of the 56 patients in the current study classified as having stage III, IVA, or IVB disease, and WHO cell types B2 or B3, 37 were Masaoka stage III and WHO cell type B2, and there was no significant difference in survival noted with regard to the status of postoperative RT among them (data not shown). The other combinations included no more than 8 patients, which was not considered to be a sufficient number with which to demonstrate the effect of RT on long-term survival.

Patterns of disease recurrence are another issue regarding postoperative therapy for patients with completely resected thymomas. The irradiation area in the patients in the current study was the mediastinum, which may function as a prophylactic against local recurrence of the tumor. The most frequent pattern of disease recurrence was pleural dissemination, followed by distant metastasis, mainly in the lungs. However, that phenomenon was common in patients who were treated both with and without postoperative RT and thus it does not appear that postoperative RT to the mediastinum prevents local recurrence. Other reports have also noted that the pleura is the most frequent site of recurrence,[11,15,19] and that performance of postoperative RT does not affect the rate of pleural recurrence.[11] Therefore, it would be reasonable to form a strategy against pleural dissemination and distant metastasis, rather than local control in the mediastinum, for thymomas that may require treatment in addition to complete resection. Some investigators have reported reductions in disease recurrence rates after entire hemithorax RT of approximately 15 Gy as adjuvant therapy after complete resection of a thymoma.[20,21] However, they also noted that radiation pneumonitis of grade 2 or greater occurred in 15% to 25% of those patients who underwent entire hemithorax RT, which led us to consider that this treatment should not be routine. In this context, systemic chemotherapy may be a good candidate modality. Although we could not find any reports in literature indicating that adjuvant chemotherapy after complete resection would ameliorate the outcome, there are studies describing favorable effects of systemic chemotherapy for patients with advanced thymomas. Various therapeutic regimens were used in those, including the quadruplet of doxorubicin, cisplatin, vincristine, and cyclophosphamide[22] and triplets of cisplatin, doxorubicin, and cyclophosphamide[23]; cisplatin, doxorubicin, and cyclophosphamide[24]; cisplatin, epirubicin, and etoposide[24,25]; and cisplatin, doxorubicin, and methylprednisolone,[26] as well as others. Because to our knowledge there is no standard chemotherapeutic protocol for a thymoma, it is important to determine the most suitable regimen as well as establish a multimodality treatment strategy for patients with stage III/IV thymoma and WHO cell types B2/B3.

A limitation of the current study is its retrospective design. We clearly understand that it would be ideal for a sufficient number of patients to be recruited within a short period to form a prospective study; however, the relative rareness of the disease makes it quite difficult to do so. In addition, confirmation of the effects of treatments require a long period, because the clinical course of a thymoma is slow, making it difficult to perform prospective randomized clinical studies of affected individuals. Therefore, the distribution of patients in the current study in regard to RT status was not randomized. However, we are certain that the bias used for selecting patients who received postoperative RT was minimal, because we determined the criteria for postoperative RT based on Masaoka stage, not on a "case-by-case" basis. Conversely, the majority of the patients who received postoperative RT underwent surgery at Osaka University Hospital, which might cause a bias from the differences among the hospitals in this study. Nevertheless, all thoracic surgeons who participated in the current study were trained under a system established by Osaka University Hospital and its affiliated hospitals, and we therefore are confident that quality of the surgical procedures as well as perioperative care was maintained at a high level. Another important issue in the current study may be the long duration required to accumulate an adequate number of patient records because of the rareness of the disease, as such a long period may skew the outcome of a retrospective study. Over the study period of several decades, many aspects of thymoma treatment have changed, such as application of thoracoscopic surgery, new apparatuses for RT, new chemotherapeutic agents, and improvements in radiographic imaging technologies. Any of those variations in the patients in the current study might have skewed our results.

In conclusion, the effects of postoperative RT on survival and disease recurrence after complete resection in patients with thymoma were examined based on Masaoka stage and WHO cell type. A good candidate group of thymoma patients could not be identified after dividing by Masaoka stage and WHO cell type. However, patients with stage I and II thymoma, as well as those with WHO cell types A, AB, and B1, can be eliminated from the list of candidates for postoperative RT. Conversely, establishment of an optimal treatment strategy for patients with Masaoka stage III and IV disease, and WHO cell types B2 and B3, is needed to further improve their long-term outcome.

Conflict of Interest Disclosures

The authors made no disclosures.

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BRACHYTHERAPY

High-dose-rate interstitial brachytherapy for previously untreated cervical carcinoma

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ABSTRACT

PURPOSE: The aim of the study was to evaluate the results of high-dose-rate interstitial brachytherapy (HDR-ISBT) for patients with advanced cervical carcinoma in which intracavitary radiation therapy may result in a suboptimal dose distribution.

METHODS AND MATERIALS: Between 1995 and 2005, 25 patients of median age 64 years were treated with external beam radiation therapy and HDR-ISBT. The International Federation of Gynecology and Obstetrics stages of the patients were I (4%), II (16%), III (68%), and IVA (12%). Whole pelvic irradiation of 30 Gy/15 fractions was followed by HDR-ISBT of 30 Gy/5 fractions/3 days. Subsequently, additional pelvic external beam radiation therapy of 20 Gy/10 fractions was delivered with a midline block. The median followup period was 55 months.

RESULTS: The actuarial 5-year progression-free survival and overall survival rates for all cases were 42% and 54%, respectively. For the 17 patients with a Stage III tumor, the 5-year local control and overall survival rates were 73% and 51%, respectively. Two patients (8%) developed late toxicities of Grade 3.

CONCLUSIONS: A high rate of pelvic control and survival with acceptable level of late toxicities were obtained for patients with advanced cervical carcinoma treated with HDR-ISBT.

Keywords: Cervical carcinoma; Previously untreated; Interstitial; Brachytherapy; High dose rate

Introduction

Radiotherapy has long been considered as the most effective treatment for advanced cervical carcinoma, using a combination of external beam radiation therapy (EBRT) and intracavitary radiation therapy (ICRT) (1). However, in some clinical situations, such as a tumor extending to the lower vaginal wall and/or the parametrium, ICRT may result in a suboptimal dose distribution. Moreover, the structure of the uterus makes it impossible to insert a tandem applicator in some patients. To solve these problems, since 1995 we have performed interstitial brachytherapy (ISBT) to treat tumors for which the dose distribution in ICRT is probably insufficient. The American Brachytherapy Society recommends ISBT in these cases, because a better dose distribution can be achieved (2). In 1999, Demanes *et al.* reported an excellent 5-year local control (LC) rate of 94% for 62 patients with a median followup period of 40 months (3). High-dose-rate (HDR) ISBT has been described in a few other reports, but all of these have had a limited number of cases with various schedules and total doses (4–7).

Here, we present a retrospective analysis of our use of HDR-ISBT for previously untreated cervical carcinoma.

Methods and materials

Patient characteristics

Among 244 patients with previously untreated cervical carcinoma who received definitive radiotherapy in our

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department between February 1995 and January 2005, 25 patients underwent EBRT and HDR-ISBT. These patients had a median age of 64 years (range, 35–77 years). International Federation of Gynecology and Obstetrics staging was made by consensus of the radiation oncologist and gynecologic oncologist, without general anesthesia. Chest X-rays, abdominal and pelvic computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, complete blood counts, and liver and renal function tests were performed as additional examinations. None of the patients had undergone any surgical procedures for the purpose of staging, including pelvic or para-aortic lymphadenectomy. ISBT was chosen over ICRT for the following reasons: a bulky mass in 20 cases, lower vaginal extension of the tumor in 5 cases, and the impossibility of tandem insertion due to a previous supracervical hysterectomy in 6 cases (multiple reasons were present in some patients).

Tumor characteristics

The median maximum tumor diameter measured using CT or MRI was 6.0 cm (range, 4.0–10.0). Regarding the tumor pathology, 21 patients (84%) had squamous cell carcinoma and 4 (16%) had adenocarcinoma. All patients were staged according to the International Federation of Gynecology and Obstetrics system: 1 (4%) as Stage IB2, 1 (4%) as Stage IIA, 3 (12%) as Stage IIB, 1 (4%) as Stage IIIA, 16 (64%) as Stage IIIB, and 3 (12%) as Stage IVA. Nineteen patients (76%) had a tumor that reached the pelvic wall, including 9 with bilateral extension to the pelvic wall. Eight patients (32%) had hydronephrosis diagnosed by CT or intravenous pyelogram, including 6 of 16 patients (38%) with Stage IIIB and 2 of 3 patients (67%) with Stage IVA. Seventeen patients (68%) had histologically proven vaginal wall invasion, including 5 with a tumor extending to the lower third of the vagina. Four patients (16%) showed evidence of lymphadenopathy (short axis > 1 cm) on CT or MRI at the time of diagnosis, including 1 patient with adenopathy of multiple lymph nodes. The characteristics of the patients and tumors are shown in Table 1.

Radiotherapy

Patients were treated with a combination of EBRT and HDR-ISBT without concurrent chemotherapy. EBRT was delivered to the whole pelvis through anterior and posterior parallel-opposed portals using 10-megavolt X-rays. The common field borders were at the interspace of the L4–L5 vertebrae superiorly, at the inferior border of the obturator foramen inferiorly in cases without vaginal wall invasion, and 1–2 cm lateral to the bony pelvis. Whole pelvic irradiation was delivered at 30 Gy/15 fractions, and HDR-ISBT was started in the week after completion of this procedure. The implant technique and treatment planning were similar to those used for prostate cancer (8–10). Implantation was performed under epidural anesthesia, with interstitial stainless needles inserted using the Martinez Universal Perineal Interstitial Template. A tandem applicator was not used. The template was sutured to the perineal skin and transrectal ultrasound (TRUS) imaging was used to guide the insertions. Under real-time TRUS monitoring of the largest cross-section of the tumor, the applicators were placed on a line encompassing the tumor and within the tumor at 1 cm intervals. On the rectal side, the applicators were positioned at 0–3 mm inside the tumor. The top 2 cm of the applicators was placed in the corpus uteri. After this procedure, an orthogonal radiograph with tungsten markers was inserted into the needles and a CT scan was performed to determine the position of the needles. Computerized optimization and isodose distribution plots were obtained with the Nucletron treatment-planning systems, PLATO (Nucletron International B.V., Veenendaal, The Netherlands), based on the postinsertion radiograph.

The clinical target volume (CTV) comprised the whole tumor plus 5 mm in all directions except for the posterior (rectal) margin. The posterior margin varied from 2 to 5 mm depending on the distance to the rectal wall. The planning target volume (PTV) was the same as the CTV except in the cranial direction. The top 2 cm of the applicators was placed into the corpus uteri, so that the PTV included a 1-cm margin in the cranial direction from the CTV. Treatment planning was performed using geometric optimization (volume method) and one prescription dose point, which was positioned 5 mm distant from one source in the central plane. In principle, this source was the closest to the rectum with the prescription dose point into the direction of the rectum. The source dwell positions were located on the tumor surface and inside the tumor (except

Table 1
Patient characteristics

Age (yr)	64 (35–77)
Maximum tumor diameter (cm)	6 (4–10)
	$n = 25$
Histology	
Squamous cell carcinoma	21 (84%)
Adenocarcinoma	4 (16%)
FIGO Stage	
IB2	1 (4%)
IIA	1 (4%)
IIB	3 (12%)
IIIA	1 (4%)
IIIB	16 (64%)
IVA	3 (12%)
Pelvic wall extension[a]	19 (76%)
Hydronephrosis[b]	8 (32%)
Vaginal wall extension[c]	17 (68%)
Pelvic LN adenopathy	4 (16%)
Supracervical hysterectomy	5 (20%)

FIGO = International Federation of Gynecology and Obstetrics.
[a] 9/19 (47%); Bilateral extension.
[b] 6/8 (75%); Stage IIIB patients, 2/8 (25%); Stage IVA.
[c] 5/17 (29%); Lower third of vagina.

in the cranial direction, where the position was located 1 cm outside the tumor). The first fraction of irradiation was administered on the afternoon on the day of the implant procedure, with a prescribed dose of 6 Gy. For the following 2 days, twice-a-day irradiation of 6 Gy each with at least a 6-h interval was performed to give a total dose of 30 Gy. After HDR-ISBT, EBRT was given to the pelvic sidewall through anterior and posterior fields with a midline block constructed to match the 100% HDR-ISBT isodose line in the simulated radiography. Midline-shielding radiotherapy was delivered at 20 Gy/10 fractions.

Dosimetric analysis

The volumes receiving 100%, 150%, and 200% of the prescribed dose (V_{100}, V_{150}, and V_{200}, respectively) and the dose nonuniformity ratio (DNR) (DNR = V_{100}/V_{150}) were calculated in 22 cases for which data were available. Note that these V_{100}, V_{150}, and V_{200} are not the percentages of the PTV, but absolute volumes regardless of the PTV. The maximal irradiated doses for the rectum and bladder were calculated by overlaying the dose distribution on any of the CT, MRI, or TRUS images in each case. The dose to the whole rectal or bladder wall should be <100% of the prescribed dose in the absence of direct tumor invasion of the bladder or rectal wall.

Outcome assessment

Overall survival (OS), progression-free survival (PFS), and LC were estimated using the Kaplan–Meier method from the first day of treatment to the date of the event or, if no event occurred, to the date of last followup. Local failure was defined as disease progression within the pelvis by clinical or radiographic examination. Para-aortic lymphoadenopathy was considered as distant metastasis.

Toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 3.

Results

Radiotherapy parameters

The median overall treatment time was 48 days with a range from 30 to 59 days. The median doses of EBRT (including whole pelvic irradiation and midline shielding) and HDR-ISBT were 50 Gy (range, 30–50 Gy) and 30 Gy (range, 24–36 Gy), respectively. The total tumor doses of EBRT and ISBT were transformed and expressed in units of biologically effective dose (BED), using the following formula:

$$BED_{10} = n_{ext}d_{ext}(1 + d_{ext}/10) + n_{HDR}d_{HDR}(1 + d_{HDR}/10)$$

where n_{ext} is the number of EBRT fractions, d_{ext} is the EBRT fractionation dose, n_{HDR} is the number of ISBT fractions, and d_{HDR} is the ISBT fractionation dose. The α/β ratio was taken to be 10 Gy. The median BED_{10} was 84 Gy with a range from 80 to 106 Gy, and the median V_{100} was 127 cc (range, 57–217 cc), the median V_{150} was 32 cc (range, 8–75 cc), and the median V_{200} was 7.5 cc (range, 3–11 cc) in 22 patients. The median DNR was 0.24 (range, 0.13–0.59).

The dose to the anterior surface of the rectal mucosa was <100% of the prescribed dose in all cases except one in which the tumor was shown to have invaded the outer membrane of the rectum in MRI at diagnosis (subsequently, the patient developed recto-vaginal fistula).

Treatment outcomes

The median duration of followup was 55 months with a range from 8 to 124 months. The 5-year OS and PFS rates were 54% and 42%, respectively (Fig. 1). The status at the time of last followup for all patients is listed in Table 2: 13 patients (52%) died, including 10 (40%) deaths due to cervical carcinoma and 3 (12%) due to unrelated or other causes (one to colon cancer and two the senility); and 12 patients (48%) were alive, with no evidence of disease in

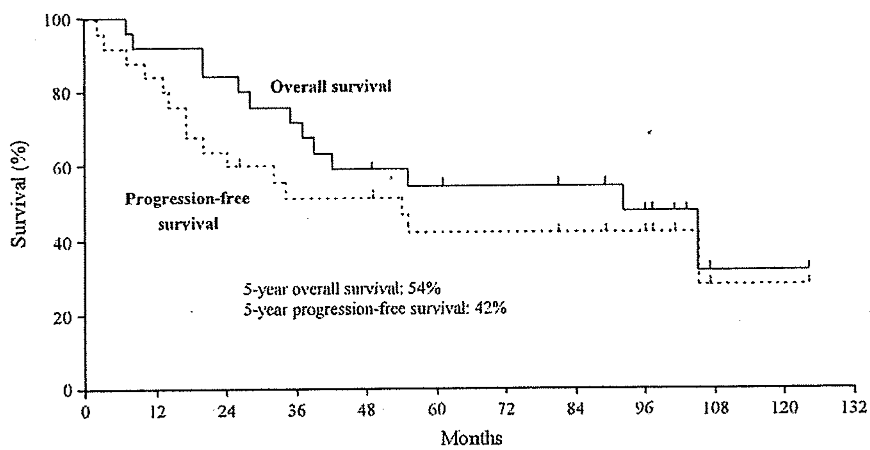

Fig. 1. Overall and progression-free survival rates after high-dose-rate interstitial brachytherapy.

Table 2
Patient status and cause of death

Status and cause of death	No. of patients	%
Dead	13	52
Cervical carcinoma	10	40
Unrelated or other diseases	3	12
Alive	12	48
NED	11	44
Alive with disease	1	4

NED = no evidence of disease.

all but one of these patients. In the 17 patients with a Stage III tumor, the 5-year actuarial LC and OS rates were 73% and 51%, respectively (Fig. 2).

Patterns of initial recurrence are shown in Table 3. The overall incidence of local recurrence was 32% (8 patients) and the incidence of pelvic lymph node recurrence was 8% (2 patients). The overall incidence of distant metastasis was 32% (8 patients), including three cases in the lung, four in the para-aortic lymph node, two in the bone, two in the mediastinal lymph node, one in the supraclavicular lymph node, and one in the peritoneum. Some patients had multiple metastases.

Toxicities

One patient developed Grade 2 vaginal narrowing that interfered with function. The crude risk rate for development of Grade 3 toxicity was 8% (2/25): one of these patients developed recto-vaginal fistula and the other had complete vaginal obliteration (Table 4).

Discussion

In this study, the 5-year PFS and OS were 42% and 54%, respectively. Of the 25 patients, 17 (68%) were in Stage III. Moreover, 7 patients had a tumor involving the bilateral pelvic wall, 5 had a tumor that extended to the lower third of the vagina, and 3 had both extensions in Stage III. Despite inclusion of many advanced cases, the 5-year OS and LC rates of Stage III patients were 51% and 73%, respectively. Previous studies have reported a survival rate from 30% to 50% and LC rates from 50% to 70% for patients with Stage III disease treated with radiotherapy alone (11). Kavadi and Eifel (12) reported a 5-year survival rate of 25% for patients with tumors in the lower third of the vagina and with parametrial involvement in a radium ICRT series, and Logsdon and Eifel found 5-year disease-specific survival rates of 48% and 35% for patients with tumors fixed to both pelvic walls and those with a tumor involving the lower third of the vagina, respectively, in a low-dose-rate (LDR)-ICRT series (13). Compared with these studies, the outcome using HDR-ISBT in the present study appears to be at least the same or even better, especially for more locally advanced cases.

Several randomized trials have set the current standard of care for locally advanced cervical carcinoma as radiotherapy with concurrent chemotherapy. All these trials except for the NCI Canada study have shown a survival benefit (14–19) and meta-analysis has also shown a benefit (20). However, in the Radiation Therapy Oncology Group 90-01 trial (15, 21), a subset analysis of Stage IB–IIB and III–IVA patients indicated no survival benefit for concurrent chemotherapy for Stage III–IVA cases. In a meta-analysis in the Cochrane Collaboration (20), a greater beneficial effect was also seen in trials that included a higher proportion of Stage I–II patients.

The above data suggest that improvement of treatment outcome in cases of clinical Stage III or IVA disease remains a significant challenge. The key factor for successful radiation treatment is that the entire tumor is covered with an optimal radiation dose. However, in some cases of locally advanced tumors, intracavitary applicators such as the tandem ovoid or tandem ring often give only inadequate target coverage with significant heterogeneity. Therefore, HDR-ISBT seems to have the possibility to improve the outcome in Stage III or IVA cases of cervical carcinoma

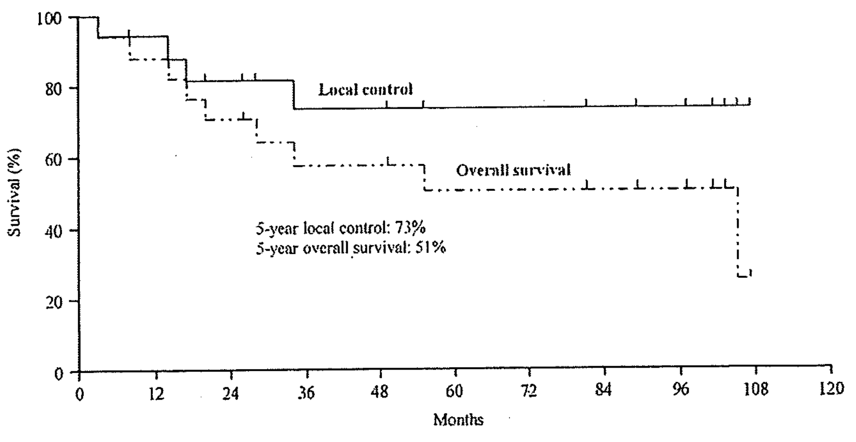

Fig. 2. Local control and overall survival rates for Stage III patients.

Table 3
Initial recurrence sites

Site of initial recurrence	No. of patients
Local	7
Pelvic LN	0
Para-aortic LN	4
Lung	1
Bone	1
Total	13

Table 4
Late toxicities

	Grade			
	1	2	3	4
Gastrointestinal				
Colitis	1	0	0	0
Rectal bleeding	8	0	1[a]	0
Genitourinary				
Urinary incontinence	3	0	0	0
Vaginal stenosis	7	1	1[b]	0
Lymphatics				
Lymphedema	3	0	0	0

Some patients showed multiple events.
[a] Developed recto-vaginal fistula.
[b] Developed complete vaginal obliteration.

that cannot be fully irradiated using intracavitary irradiation.

Concurrent chemotherapy was not used in the present study and the American Brachytherapy Society recommends that chemotherapy should not be administered concurrently with HDR-ISBT until further studies have been performed (2). However, EBRT and concurrent chemotherapy are the current standard of care for locally advanced cervical carcinoma. Therefore, we have started a new protocol for cervical carcinoma that is not suitable for ICBT. In this new protocol, patients received chemotherapy concurrent with EBRT followed by ISBT (with no chemotherapy during ISBT).

Three patients (12%) experienced Grade 2 or higher complication, and the frequency of complications appeared to be identical compared with previous data for HDR-ICRT brachytherapy at Osaka University Hospital, in which 14% of patients developed Grade 2 or higher late complications (22). In the present study, 1 patient developed a recto-vaginal fistula. Her tumor had invaded the outer membrane of the rectum on MRI at diagnosis; therefore, the required rectal dose was very high to achieve LC.

No cases of lymphoadenopathy with a diameter of more than 2 cm were observed at diagnosis. Pelvic lymph node metastases were examined using a CT scan, and without surgical lymphadenectomy, suggesting that our data may underestimate the rate of metastases to lymph nodes. Such underestimation might be the reason why the overall incidence of distant metastasis in our study was relatively high (32%) compared with recent trials using surgical evaluation of nodal metastasis (23). Consequently, PFS may have improved further if we had conducted a surgical lymph node evaluation. Since the 1970s, there have been many studies of LDR-ISBT in the United States (24), with reported LC rates of 50–80%. In these reports, the LC rate was excellent in comparison with ICRT; however, the incidence of adverse effects was also comparatively high. Therefore, LDR-ISBT has generally not been concluded to be superior to ICRT. HDR has a biologic disadvantage compared with LDR, but an optimization program for HDR can be used to establish, ideal dosimetry that delivers a higher dose to the tumor while decreasing the dose to critical organs such as the rectum or bladder (25). However, the effects of using a high or low dose rate remain uncertain (26).

In our procedure, we used a TRUS at implantation to improve the application, and performed a postimplantation CT scan to check the dose distribution before irradiation. However, evaluation of an accurate tumor dose or critical organ dose is difficult, and an artifact of the metal needles on the CT scan is a major problem. These difficulties may be addressed by the recent announcement of image-guided brachytherapy by groups in the United States and Europe (27–29). A new combination tandem and ring with an interstitial applicator with simultaneous use of fractionated HDR (30, 31) has also shown very good results in short-term followup, and HDR-ISBT may be further improved using MRI-based pretherapeutic planning.

Conclusions

Despite the limited number of patients, this retrospective study demonstrated a high rate of pelvic control and survival with an acceptable level of late toxicities for patients with advanced cervical carcinoma treated with HDR-ISBT.

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Assessment of influence of smoking, drinking, leukoplakia and dental irritation on local control of early oral tongue carcinoma treated with brachytherapy: age and dental factors are potential prognostic factors

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ABSTRACT

Background. To examine the background characteristics of elderly patients (65 years or older) with node-negative mobile tongue cancer (T1-2N0M0) who showed worse local control than a younger group.

Materials and methods. We retrospectively analyzed background data for 265 patients treated with brachytherapy with or without external radiotherapy between 1967 and 1999. We examined dental factors (such as irritation by prosthesis), leukoplakia, tobacco smoking and alcohol consumption for comparisons between the elderly (age ≥65 years; n = 83) and a control group (64 years or younger; n = 182).

Results. The elderly patients showed a worse outcome than the control group (respectively 86% and 70% at 5 years; P <0.05). Incidence of dental factors tended to be higher for elderly patients (53%) than the control group (40%, P = 0.07). Dental factors proved to have prognostic importance for local control. Five-year local control rate was 85% for patients with and 76% for patients without dental factors (P = 0.04). The elderly group positive for dental factors showed a lower 5-year local control rate (61%) than the other three groups [(elderly without the dental factor (-) group (80%), control with the dental factor (+) group (84%), and control without the dental factor (-) group (87%)] (P <0.05). Leukoplakia was found more frequently in the control (23%) than in the elderly group (5%) (P = 0.006) but had no effect on treatment outcome.

Conclusions. Age and dental factors (including prosthesis irritation) are potentially important prognostic factors for local control of oral tongue cancer treated with brachytherapy, especially for elderly patients.

Key words: aged patients, brachytherapy, dental factors, high dose rate, low dose rate, tongue cancer.

Introduction

Oral tongue carcinoma is a highly curable cancer when treated with surgery or radiation therapy, especially interstitial brachytherpay[1-4]. Iridium-192 (^{192}Ir) hairpin or cesium-137 (^{137}Cs) needles are usually used for low-dose–rate (LDR) interstitial radiotherapy in Japan. Our institution is equipped with a high-dose–rate (HDR) remote-controlled after-loading system, which uses an ^{192}Ir microsource known as microSelectron-HDR, MS-HDR (Nucletron; Veenendaal, The Netherlands)[5,6]. As there is no risk of radiation exposure except to the patient, HDR makes it possible to treat patients in a normal ward, and the quality of life may be better during treatment because of the advantages for medically fragile patients like the elderly. However, we

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found that elderly patients with early oral tongue cancer showed poor local control, which prompted us to explore the reason for this poor outcome[6].

We therefore conducted a detailed retrospective review of background characteristics of T1-2N0 tongue cancer patients, including smoking, alcohol consumption, dental factors and presence of leukoplakia.

Materials and methods

Between 1967 and 1999, 572 patients with previously untreated mobile T1-2N0M0 tongue cancer were treated with brachytherapy at the Osaka University Hospital. For detailed background analysis, we were able to retrieve data for 265 of these patients. All tumors were histologically identified as squamous cell carcinoma.

The items we examined were smoking, alcohol consumption, dental factors and presence of leukoplakia. Smoking habits were classified as smoking (+) or smoking (-), including ex-smokers. Alcohol consumption was also categorized as alcohol drinking (+) or drinking (-), including ex-drinkers. The dental factor was defined as patients complaining of an unpleasant sensation or pain and/or tumors being considered adjacent to teeth or prostheses if the head and neck specialist team considered the epicenter of the lesion to be in contact with a tooth and/or prosthesis. Presence of leukoplakia was defined as leukoplakia nearly surrounding or contiguous to the tumor. The elderly group (aged 65 years or older) included 51 male and 32 female patients, and 126 male and 56 female patients made up the control group (aged 64 years or younger). The elderly group featured 38 T1 and 45 T2 tumors and the control group 75 T1 and 107 T2 tumors (UICC TNM classification of 1987). Table 1 gives the patient and treatment characteristics.

Details of treatment have been described elsewhere[5-7]. In brief, all implants were performed under local anesthesia, even for elderly patients. The treatment sources consisted of an ^{192}Ir pin for 146 (52 elderly and 94 control) patients, a ^{226}Ra needle for 80 (23 elderly and 57 control) patients, and MS-HDR for 39 (8 elderly and 31 control) patients. LDR implants were performed via the oral and HDR via the submental/submandibular approach. MS-HDR (^{192}Ir source) was used for 39 patients (1991-present). The dose rates at the reference point for the LDR group were 0.30 to 0.8 Gy/h, and for the HDR group 1.0 to 3.4 Gy/min. Each needle or pin was implanted with the Paterson-Parker system using a reference point 5 mm distant from the implant plane. The median dose for treatment with LDR brachytherapy only was 70 Gy (range, 61-84). Patients in the HDR group received a total dose of 60 Gy (range, 48-60; median 60) in 10 fractions during one week at a distance of 5 mm from the radioactive source. Two fractions were administered per day, and the interval between fractions was more than 6 h.

Table 1 - Patient, tumor and treatment characteristics according to age

		Control (≤64 yr) n = 182	Aged (≥65 yr) n = 83	*P*
Sex	Male	126 (69)	51 (61)	
	Female	56 (31)	32 (39)	NS
T classification	T1	75 (41)	38 (46)	
	T2	107 (59)	45 (54)	NS
Tumor size				
Longest diameter (mm)		23 ± 8	23 ± 7	NS
Shortest diameter (mm)		16 ± 5	16 ± 4	NS
Thickness (mm)		7 ± 4	8 ± 5	=0.07
Type of tumor				
Superficial		68 (40)	22 (25)	
Exophytic		33 (19)	17 (22)	
Indurative		38 (22)	22 (29)	
Ulcerative		32 (19)	18 (24)	
Tobacco smoking				
Negative		79 (45)	44 (58)	
Positive		97 (55)	32 (42)	=0.07
Alcohol drinking				
Negative		83 (47)	43 (57)	
Positive		94 (53)	33 (43)	=0.09
Dental factor				
Negative		106 (60)	35 (47)	
Positive		71 (40)	40 (53)	=0.07
Leukoplakia				
Negative		87 (77)	55 (95)	
Positive		26 (23)	3 (5)	=0.006
Source				
Radium-226		57 (32)	23 (29)	
Iridiuim-192		94 (14)	52 (58)	
MS-HDR		31 (55)	8 (14)	NS
External radiotherapy				
Brachytherapy only		144 (79)	66 (80)	
Combined w/external radiotherapy		38 (21)	17 (20)	
Prescribed dose				
Brachytherapy (Gy)		69 ± 7	69 ± 7	NS
External radiotherapy (Gy)		30 ± 6	30 ± 5	NS

In parenthesis, percentage.
MS-HDR, Microselectron high dose rate.

A total of 55 patients (12 T1 and 43 T2, 5 MS-HDR and 50 LDR) underwent external radiotherapy with a ^{60}Co teletherapy unit or a linear accelerator. The patients received 2-3 Gy per fraction for a median dose of 30 Gy (range, 15-50). Patients were treated with a single lateral field that involved the primary site and the upper jugular lymph nodes. External beam therapy for all 55 patients was followed by interstitial implants. Patients were followed for at least 2 years or until their death, with a median follow-up of 13 years (range, 2-25). We compared the outcomes of local control and lymph node control and of cause-specific survival.

For statistical analysis, Student's *t*-test for normally distributed data and the Mann Whitney U-test for skewed data were used. Percentage was analyzed using the chi-squared test. Local control and survival data were estimated according to the Kaplan-Meier method and were examined for significance with the logrank test. All analyses used the conventional $P < 0.05$ level of significance.

Results

Patient characteristics. Leukoplakia was found more frequently in the control group (23%) than in the elderly group (5%, $P = 0.006$) (Table 1). The respective incidences of superficial, exophytic, indurative and ulcerative tumors were respectively 25%, 22%, 29% and 24% for the elderly and 40%, 19%, 22% and 19% for the control group ($P = 0.003$), with elderly patients showing a markedly lower frequency of the superficial tumor type. The dental factor (+) groups showed a frequency of 18% (19/107) for ulcerative (+) tumor and the control groups a frequency of 22% (not significant). The incidence of the dental factor tended to be higher for elderly patients (53%) than for the control group (40%, $P = 0.07$). There was no significant correlation among the dental factor and the other three items, i.e., leukoplakia, alcohol consumption, and smoking. Smoking and drinking habits showed a strong correlation ($P = 0.0001$). In the tobacco-smoking group, 76% (98/129) also consumed alcohol, compared to only 23% (28/123) of non-smokers ($P < 0.0001$). The control group tended to show higher incidences of smoking and alcohol consumption than the elderly group.

Local control. Elderly patients showed a worse local control rate than the control group (5-year survival, 86% and 70%, respectively; $P < 0.05$). In addition, the 5-year local control rates for patients with the dental factor (+) and without were 85% and 76%, respectively ($P < 0.05$; Figure 1). Detailed analysis showed that the elderly dental factor (+) group showed the lowest 5-year local control rate (61%) compared to the other three groups (elderly dental factor (-) group, 80%; control and dental factor (+) group, 84%; control and dental factor (-) group, 87%; $P < 0.05$) (Figure 2A). Leukoplakia, alcohol consumption and smoking were not significantly related to outcome. Leukoplakia did not affect local control since the leukoplakia (+) group showed a 5-year local control rate of 76% and the leukoplakia (-) group of 82% ($P = 0.66$). The elderly group with leukoplakia showed a 5-year local control rate of 50%, whereas it was 66% for the elderly leukoplakia (-), 83% for the control leukoplakia (-), and 85% for the control and leukoplakia (+) group (Figure 2B) (NS; $P = 0.12$). Although the elderly patients with leukoplakia seemed to show a lower control rate, it should be noted that only 3 patients were included in this category. The alcohol drinkers had a local control rate of 81% and the non-drinkers of 83% (NS; $P = 0.22$). The non-drinker group had a 5-year local control rate of 90%, the drinker control group 84%, the elderly non-drinker group 71%, and the elderly non-drinker group 66% ($P = 0.01$) (Figure 2C). The smoking group had a 5-year local control rate of 82% and the non-smoking group 80% (NS; $P = 0.54$). The elderly non-smoking group had a 5-year local control of 62%, the elderly smoking group 75%, the control non-smoking group 89%, and the control smoking group 86% ($P = 0.01$) (Figure 2D).

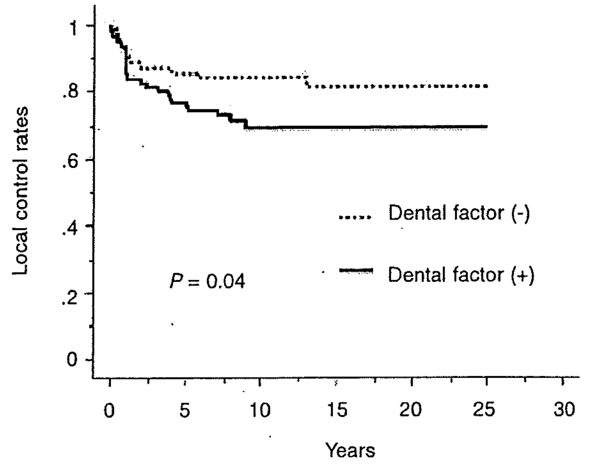

Figure 1 - Local control rates for oral tongue cancer treated with interstitial radiotherapy according to the dental factor. The dental factor is a prognostic factor in local control: the 5-year local control rate was 85% for patients with and 76% for patients without the dental factor ($P = 0.04$).

Regional control. Five-year regional control rates were 67% for the elderly group and 70% for the control group (NS). There was no significant difference in the incidence of lymph node metastasis between dental factor (+) patients (72% at 5 years) and dental factor (-) groups (78% at 5 years) (ns). Detailed analysis showed that the elderly dental factor (+) group had a similar 5-year local control rate (74%) compared to the other three groups (elderly dental factor (-) group, 74%; control dental factor (+) group, 85%; and control dental factor (-) group, 83%)(NS). The 5-year regional control rate for smokers was 72% and 76% for non-smokers (NS), for alcohol-consuming patients it was 78% and 70% for non-drinkers (NS), and for leukoplakia (+) patients it was 65% and 66% for the leukoplakia (-) group (NS).

Cause-specific survival. The 5-year cause-specific survival rate for both the dental factor (+) and (-) groups was 81% (NS). The elderly group showed a 5-year cause-specific survival (75%) that was lower with borderline significance than that of the control group (84%) ($P = 0.08$). The 5-year cause-specific survival for smokers was 80% and for the non-smokers 81% ($P = 0.58$). For the alcohol drinkers it was 81% and for the non-drinkers 81% ($P = 0.98$). Finally, the leukoplakia (+) group showed a 5-year cause-specific survival of 89% and the leukoplakia (-) group, 73% ($P = 0.08$).

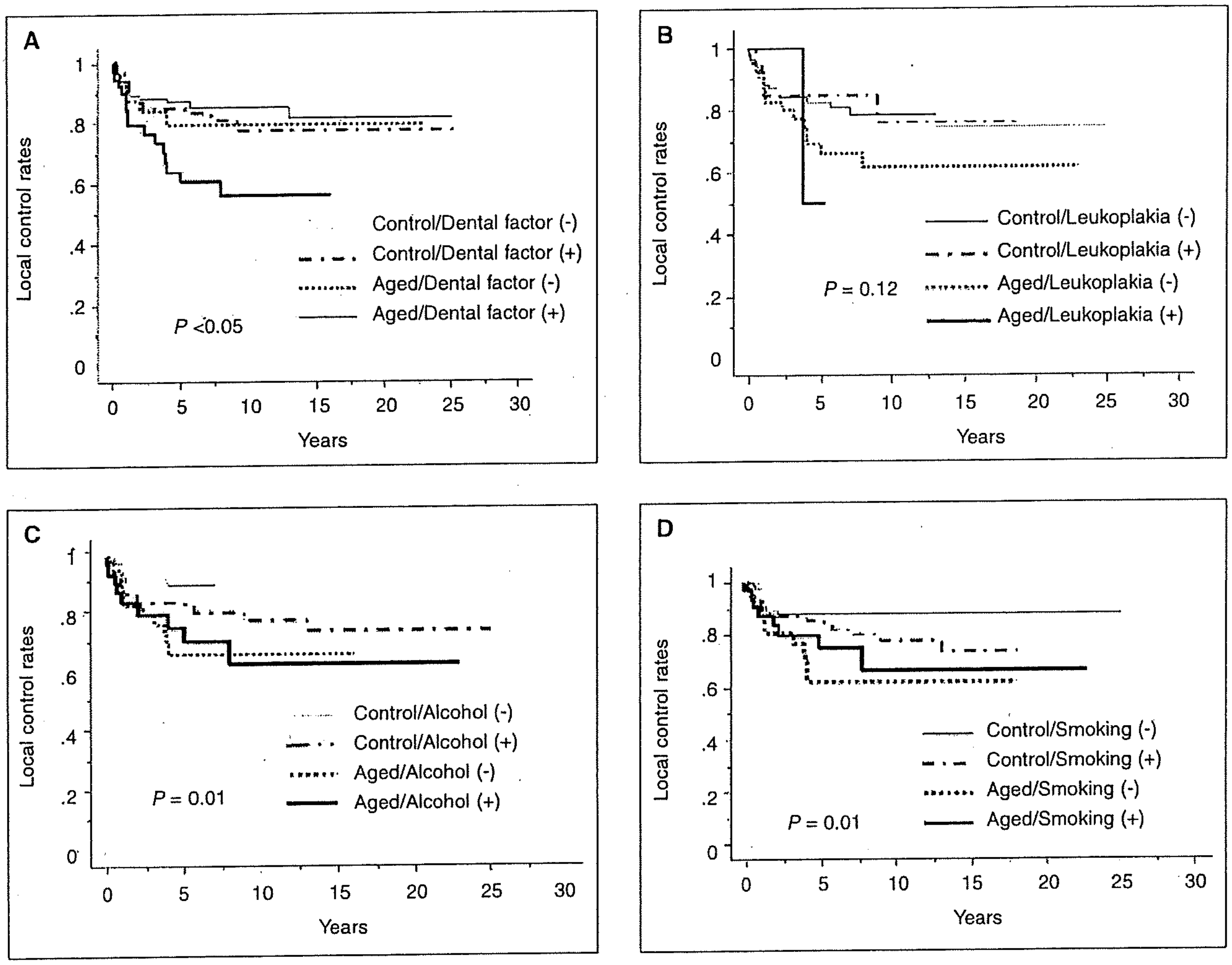

Figure 2 - A) Local control rates for oral tongue cancer treated with interstitial radiotherapy according to age and the dental factor. The elderly group dental factor (+) showed a lower 5-year local control rate (61%) than the other three groups (elderly without dental factor (-) group (80%), control with dental factor (+) group (84%), and control without dental factor (-) group (87%) ($P<0.05$). B) Local control rates for oral tongue cancer treated with interstitial radiotherapy according to age and leukoplakia. C) Local control rates for oral tongue cancer treated with interstitial radiotherapy according to age and alcohol consumption. The alcohol (-) control group had a 5-year local control rate of 90%, the alcohol (+) control group 84%, the elderly alcohol (+) group 71%, and the elderly alcohol (-) group 66% ($P = 0.01$). The elderly patients showed a worse outcome. There was a borderline significance between drinkers and non-drinkers ($P = 0.08$; 78% and 88% 10-year local control rates) in the younger population. D) Local control rates for oral tongue cancer treated with interstitial radiotherapy according to age and tobacco smoking. The elderly non-smokers had a 5-year local control of 62%, the elderly smoker 75%, the control non-smoker group 89%, and the control smoker group 86% ($P = 0.01$). The elderly patients showed a worse outcome. Young smokers tended to have a worse local control rate than non-smokers ($P = 0.13$; 79% and 89% 10-year local control rates).

Complications. There were no significant differences between the dental factor (+) and (-) groups (Table 2), and alcohol consumption, smoking and leukoplakia did not have a significant effect on complication rates.

Discussion

Oral tongue cancer, located anterior to the circumvallate papillae, vitally affects not only speech, but also coordination of chewing and swallowing. Since radiation therapy is considered to be a minimally invasive treatment procedure, it has the advantage of preserving the shape and functions of the tongue. Brachytherapy used to be performed with ^{226}Ra, which involved exposure of the surrounding tissue. To minimize undesirable radiation to normal tissues, an after-loading technique using ^{192}Ir was introduced. This LDR procedure has come into widespread use and become the gold standard for brachytherapy. Many institutes have reported successful results for treatment of tongue cancer with LDR brachytherpay[1-4]. Since then, several brachytherapy centers, including ours, have been equipped with an HDR brachytherapy apparatus using a remote after-loading technique[5,6].

Table 2 - Complications according to the presence of leukoplakia, dental factor, alcohol drinking and tobacco smoking

Complication, absent (–) or present (+)	Soft tissue/ulcer		Osteonecrosis/ bone exposure	
	–	+	–	+
Leukoplakia –	136 (96)	5 (4)	134 (94)	8 (6)
Leukoplakia +	28 (97)	1 (3)	28 (97)	1 (3)
Dental factor –	133 (94)	8 (6)	134 (95)	7 (5)
Dental factor +	107 (97)	3 (3)	102 (92)	9 (8)
Alcohol drinking –	120 (96)	5 (4)	120 (95)	6 (5)
Alcohol drinking +	121 (95)	6 (5)	117 (92)	10 (8)
Tobacco smoking –	117 (96)	5 (4)	117 (95)	6 (5)
Tobacco smoking +	123 (95)	6 (5)	119 (92)	10 (8)

No. of cases; in parenthesis, percentage.

HDR hyperfractionated interstitial brachytherapy has the following advantages: (*i*) accurate calculation made possible by complete fixation of the guide tubes, (*ii*) parallel source arrangement with the linked double-button technique, (*iii*) homogeneous dose distribution by stepping source optimization, and (*iv*) better patient care in addition to the elimination of radiation exposure of the medical staff.

Whether being young or elderly constitutes a prognostic factor for therapeutic outcome for tongue cancer patients remains controversial. We demonstrated that elderly patients had a poor local control and younger patients did not[6,7]. Since HDR-brachytherapy can provide comfortable treatment for fragile patients, especially the elderly, further analysis is needed to identify the underlying factors of aging. In addition, the number of elderly patients has recently been increasing dramatically in Japan because of advances in both health and medical care. The importance of treatment for elderly patients is therefore also rapidly increasing.

Several papers have reviewed risk factors for head and neck cancer[8-19] and found that tobacco smoking may account for over 70% of these malignancies and associated deaths[8]. Our data also revealed that smoking and drinking habits seemed to have borderline significance especially in a younger control population. Although it is difficult to implicate alcohol as such as a risk factor, one group has reported that alcohol consumption in the absence of smoking is a risk factor[9].

In addition to tobacco and alcohol, long-standing irritation from chronic periodontal disease, poor oral hygiene, ill-fitting dentures, sharp teeth, mouthwashes, electrogalvanism and edentulism have all been implicated as cofactors in the genesis of oral cancer[8-12]. However, whether these entities are cofactors or simply examples of poor compliance with overall healthcare is difficult to assess. Lockhart *et al.*[11] reported that dental factors are instrumental in the genesis of squamous cell carcinomas of the oral cavity[11]. For example, all 10 oral tongue lesions in their study arose on the lateral borders and all 6 floor of the mouth primary tumors developed at the flange extension of a lower denture.

Leukoplakia is considered to be a pre-cancerous lesion and becomes a cancer in about 5-20% of cases[17-20]. Older patients, particularly females (who may have lesions of longer duration) are more at risk than younger patients, whereas those who never used tobacco are paradoxically at greater risk than smokers. Estimates of the prevalence of leukoplakia vary depending on the populations studied, selection criteria, and methods of data collection, but the best estimates suggest a global prevalence of 2-3%. Age distribution analysis revealed a prevalence of leukoplakia in the 51-60 year age group and of carcinoma in the 61-70 year age-group. Sex distribution showed a male-female ratio of 3.2:1 for the leukoplakia group and 1.9:1 for the carcinoma group. Leukoplakia on the tongue, floor of the mouth and retromolar-soft palate complex appears to be twice as likely to develop into a carcinoma as does leukoplakia on the buccal mucosa, palate or gingivae[19].

Our findings support these data in that leukoplakia in tongue cancer patients increased with age and peaked (28%) in the 50's and then decreased in the 70's (3%) and 80's (0%; $P = 0.02$). We included adjacent leukoplakia in the clinical target volume to treat and found it did not influence local outcome.

The present study is the first to explore whether the dental factor can be an influential prognostic factor for local control. This would imply that dental hygiene could be important for local control in tongue cancer, because it could be modified by oral care after brachytherapy. Before brachytherapy, dentition in poor condition, including the presence of prosthesis, is identified and generally considered to be a candidate for extraction to minimize the subsequent risk of osteoradionecrosis. Specifically, those teeth located within the area of high-dose radiation volume and that demonstrate significant periodontal disease, advanced caries, abscess formation, or are otherwise in a state of disrepair should be extracted. In addition, impacted teeth, unopposed teeth, and teeth that could oppose a segment of a resected jawbone should be considered for extraction if they are anticipated to be located within the area of a high-dose radiation treatment volume. In our study, we could not estimate the influence of modifications of dental factors such as grinding of sharp teeth or tooth extraction, but since elderly patients tend to show a high incidence of prosthesis use, this may critically influence our findings. We speculate that extraction and continuing follow-up with dental care may improve symptoms and simultaneously improve outcome, especially for elderly patients, although we cannot present concrete data because of the retrospective fashion of our study.

Lockhart *et al.*[11] reported that patients with partial or full dentures had significantly fewer lymph node metastasis than patients without a prosthesis. Analysis of dentulous patients revealed a trend for the presence of larger tumors (T4) in patients with primaries adjacent to teeth and/or appliances ($P = 0.081$) and for dentulous patients to have a higher tumor stage ($P = 0.021$). However, our data do not indicate that the dental factor affects regional control rate, and that accordingly cause-specific survival is not affected by dental factors partly due to the fact that we analyzed only early stage cancer. Further larger-scale prospective studies including surgical population are needed to examine the importance of the dental factor and oral hygiene.

In conclusion, we have presented findings indicating that age and dental factors including irritation by prosthesis are potentially important prognostic factors for local control by brachytherapy of early oral tongue cancer, especially for elderly patients.

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ORIGINAL ARTICLE

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Verification of air-kerma strength of ^{125}I seed for permanent prostate implants in Japan

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Abstract
Background. To assure the physical quality of brachytherapy, we investigated the difference between measured and manufacturer's stated source strengths in a single model SourceTech Medical (STM)1251 ^{125}I seed.
Methods. A well-type ionization chamber with a single-seed holder was used to measure the source strength of 2412 ^{125}I seeds before implant in 34 patients. The air-kerma strength was 0.450 U for all cases. The mean source strength for each patient was measured and compared with the manufacturer's stated value. The deviation from the measured value was compared with the tolerance range of the American Association of Physicists in Medicine (AAPM) TG-56 report's recommendation.
Results. The measured source strength was higher than the manufacturer's stated value, with a median difference of 1% (range, –2% to 5%). Sixteen of the total of 2412 seeds (0.7%) were more than 5% different from the manufacturer's stated value. The median SD from the mean value was 2.2% (range, 1.1% to 2.5%) for all patients.
Conclusion. This is the first report of a single-seed assay performed for the model STM1251 ^{125}I seed. In this study the manufacturer's stated strength agreed well with the measured value. Nevertheless, the advisability of performing a single-seed assay at every institution should be considered, by referring to the appropriate regulations; for example, those used in the United States.

Key words Brachytherapy · Single-seed assay · Permanent implant · Source calibration

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Introduction

Reimbursement by the Japan national health insurance scheme for permanent prostate implant using ^{125}I seeds has been in effect since September 2003. Currently two manufacturers supply sources, the Amersham Health model 6711 source (Amersham Healthcare, Arlington Heights, IL, USA) and the SourceTech Medical (STM) model STM1251 (C.R. Bard, Murray Hill, NJ, USA).[1] Quality assurance of air-kerma source strength assays is essential, because, historically, medical physicists in the United States have come across dead seeds without any radioactivity or miscalibration by several vendors based on a single-seed assay, which is the most commonly used method for measuring source strength individually.[2–5] For ^{125}I seeds, the Radiological Physics Center (RPC) reported that mean differences between the RPC-measured strength of 51 ^{125}I seeds and manufacturers' nominal source strength was –0.6%.[5] Data prior to 1995, as presented in the American Association of Physicists in Medicine (AAPM) summer school publications[6,7] and in a categorical course at the Radiological Society of North America (RSNA),[8] indicated that the air-kerma strength of some sources was found to be 10% greater than the labeled output strength. The AAPM Task Group (TG)-40,[9] and the TG-56[10] and TG-64[11] therefore recommended that the manufacturer's stated source output strength should be independently verified before clinical use by the medical physicist. These recommendations have been adopted by some United States federal and state regulatory bodies.[12,13]

To our knowledge, however, few investigations have been conducted into manufacturer's stated versus actual source strength for a large number of single model ^{125}I seeds,[14] especially in Japan. The policy at our institution is to check the air-kerma strength of every ^{125}I seed with an ionization chamber before clinical use. In this report, we present the results of a single-seed assay for the model STM1251. We also discuss the impact of our findings on routine quality assurance (QA) procedures for permanent prostate implant, with reference to the circumstances and regulations in the United States.