

## Dose reduction trial from 60 Gy in 10 fractions to 54 Gy in 9 fractions schedule in high-dose-rate interstitial brachytherapy for early oral tongue cancer

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To compare the effects of 60 Gy/10 fractions (twice a day) with those of 54 Gy/9 fractions in high-dose-rate interstitial brachytherapy (HDR-ISBT) for early tongue cancer, we performed a matched-pair analysis of patients with early tongue cancer (T1-2N0M0), who were treated with 60 or 54 Gy of radiation between 1996 and 2004. Seventeen patients treated with 54 Gy and 34 matched-pair patients treated with 60 Gy were extracted and analyzed. Local recurrence occurred in two patients in the 54-Gy arm and five patients in the 60-Gy arm. The 2-year local control rates were 88% for both the 54-Gy arm and 60-Gy arm (not significant). The 2-year overall survival rates were 88% in the 60-Gy arm and 82% in the 54-Gy arm. Two-year actuarial complication-free rates were 91% in the 60-Gy arm and 83% in the 54-Gy arm (not significant), respectively. There was no significant association between the total dose and local control rate and late complications. The outcome of 54 Gy/9 fractions was similar to that of 60 Gy/10 fractions in patients with early tongue cancer.

**Keywords:** tongue cancer; brachytherapy; interstitial radiotherapy; high dose rate

### INTRODUCTION

Because radiation therapy is considered to be a minimally invasive treatment procedure, it has the advantage of preserving the shape and functions of the tongue, which vitally affect not only speech but also coordination of chewing and swallowing [1]. Oral tongue carcinoma is highly curable with radiotherapy; therefore, patients are usually treated with low-dose-rate (LDR) interstitial brachytherapy (LDR-ISBT) using <sup>137</sup>Cs needles or <sup>192</sup>Ir hair pins and a single pin at our hospital [2]. However, because

radiation exposure of medical staff cannot be avoided during LDR-ISBT, we introduced a high-dose-rate (HDR) brachytherapy unit comprising a 370-GBq microiridium source that allowed us to use HDR remote afterloading interstitial radiotherapy [3]. On the basis of the results of a Phase I/II study of HDR interstitial radiotherapy [3], 60 Gy in 10 fractions administered over 1 week was selected as the standard schedule for definitive HDR interstitial radiotherapy because early mucosal reactions treated with a total dose of 60 Gy/10 fractions of HDR-ISBT were almost the same as those treated with a total dose of 70 Gy of

LDR-ISBT [4]. Thereafter, we performed a Phase III study, which showed an equivalent outcome for HDR-ISBT and LDR-ISBT. The 5-year local control rates in the LDR and HDR groups were 84% and 87%, respectively, and the 7-year local control rates were 77% and 87%, respectively. There were no differences in the treatment outcomes between the two groups. We concluded that HDR fractionated interstitial brachytherapy can be an alternative to traditional LDR brachytherapy for early tongue cancer.

A few studies have reported the use of HDR-ISBT for the radical treatment of head and neck cancer [5–9]. From a biological standpoint, HDR has the disadvantage of a low therapeutic ratio [10]. However, from the perspective of radiation physics, HDR has the advantage of homogeneous dose distribution. Careful consideration of the advantages and disadvantages of HDR brachytherapy is necessary because some authors have reported lower control rates and higher adverse reaction rates with this form of treatment [5]. Mazon *et al.* stated that the results of HDR brachytherapy remain to be validated in prospective studies. If it is the only technique available but not included in a prospective study, treatment should be delivered in fractions of <3–4 Gy according to the Groupe Européen de Curiethérapie–European Society for Therapeutic Radiology and Oncology recommendations [1]. Some of the American Brachytherapy Society panel members had concerns about the potential morbidity with fraction sizes as large as 6 Gy delivered to the oral cavity [11], and several reports have shown good outcomes using lower total doses with smaller single fraction doses [5–9]. Our schedule of 60 Gy/10 fractions appeared to be one of the most intensive treatments described in the literature. According to the linear quadratic (LQ) model, an HDR-ISBT dose equivalent to 70 Gy of LDR-ISBT was calculated as 48 Gy in late reaction ( $\alpha/\beta = 3.8$ ) and 54 Gy in acute reaction ( $\alpha/\beta = 10$ ) [12]. A dose of 60 Gy of HDR-ISBT in our schedule is higher than the doses calculated on the basis of the LQ model for 70 Gy of LDR-ISBT. Therefore, we initiated a prospective randomized trial wherein the dose was reduced from 60 Gy to 54 Gy to adjust for 70 Gy of LDR-ISBT ( $\alpha/\beta = 10$ ). However, the number of patients treated in our institution has decreased since 2002, which resulted in difficulty in recruiting enough patients for this phase III study. Because 17 patients have been treated in the 54-Gy arm so far, we performed a case-control matched-pair analysis for the comparison of outcomes between the 54-Gy and 60-Gy schedules.

## PATIENTS AND METHODS

Between 1996 and 2005, 51 patients with previously untreated early mobile tongue cancer (T1–2N0) were treated with HDR-ISBT at Osaka University Hospital. Patients treated with combined chemotherapy or external radiotherapy was excluded from the study. The criteria for patient

selection for the study were: (i) presence of a T1T2N0 tumor, which could be treated with single-plane implantation; (ii) performance status (World Health Organization) between 0 and 3; and (iii) absence of any severe concurrent disease. All tumors were histologically identified as squamous cell carcinoma. Because we had treated 17 patients with the 54-Gy schedule, we extracted 34 patients treated with the 60-Gy schedule (from 54 patients); these patients were matched by T1/T2 ratio and type of tumor. Table 1 illustrates the characteristics of the patients in the 54-Gy and 60-Gy arms. There were 7 T1 and 10 T2 tumors in the 54-Gy arm and 16 T1 and 18 T2 tumors in the 60-Gy arm (International Union Against Cancer TNM Classification of Malignant Tumors; 1987). The median age was 57 years, with an age range of 28–81 years [54-Gy arm:  $56 \pm 12$  years, 60-Gy arm:  $54 \pm 13$  years, not significant (NS)]. The 54-Gy arm comprised 12 males and 5 females, whereas the 60-Gy arm comprised 26 males and 8 females (NS). All implantations were performed under local anesthesia using 3–16 (median 4) catheters. The treatment method used has been described previously [4]. The patients received a total dose of 54 Gy or 60 Gy in 9 or 10 fractions (6 Gy/fraction), respectively, over 1 week at a 5 mm distance from the radioactive source. Two fractions were administered per day. The time interval between fractions was >6 h. Dose rates at the reference point were 1.0–3.4 Gy/min. Patients were followed up over at least 12 months or until death. The median follow-up duration was 45 months (range: 10–116 months; 52 months for surviving patients). Tumor appearance was classified according to a previous report [4]; there were 7 exophytic, 23 indurative/infiltrative, 14 superficial and 7 ulcerative types. There was no difference in distribution of types between the 54-Gy and 60-Gy arms. All patients were enrolled in the study after their informed consent had been obtained prior to radiotherapy in accordance with the guidelines of the intramural ethics committee.

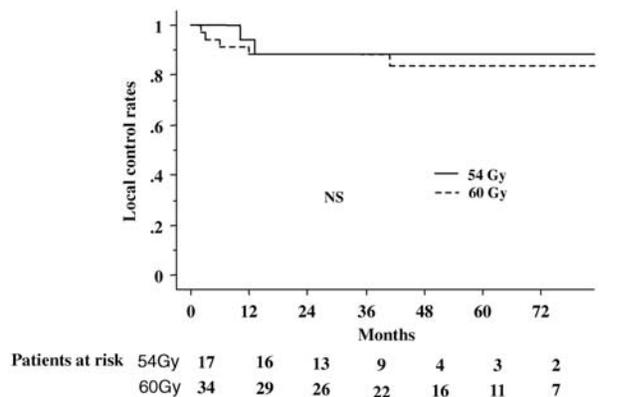
For statistical analysis, Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for skewed data were used. Percentages were analyzed using the chi-squared test. Local control rates, lymph node control and survival data were estimated according to the Kaplan–Meier method and examined for significance with a logrank test. Results with *P* values <0.05 were considered to be statistically significant.

## RESULTS

Seventeen patients treated with 54 Gy and 34 matched-pair control arm patients treated with 60 Gy were analyzed. Seven cases showed local recurrence (two cases in the 54-Gy arm and five cases in the 60-Gy arm). Local control rates for both arms are shown in Fig. 1. The 2- and 3-year local control rates were 88% in both the 54-Gy arm and in the 60-Gy arm, respectively. Local recurrences occurred within 2 years after treatment in six out of the seven cases

**Table 1** Patient characteristics

Strata	Variables	60 Gy (n = 34)	54 Gy (n = 17)	P
Gender	Female	8 (24%)	5 (29%)	NS
	Male	26 (76%)	12 (71%)	
Stage	T1	16 (47%)	7 (41%)	NS
	T2	18 (53%)	10 (59%)	
Age		54 ± 13	56 ± 12	NS
Largest diameter	(mm)	23 ± 8	25 ± 8	NS
Thickness	(mm)	7 ± 3	8 ± 6	NS
Technique	Single plane	28 (82%)	13 (76%)	NS
	Double plane	5 (15%)	3 (18%)	
	Volume implant	1 (3%)	1 (6%)	
Type of tumor	Superficial	10 (29%)	4 (24%)	NS
	Exophytic	4 (12%)	3 (18%)	
	Indurative	16 (47%)	7 (41%)	
	Ulcerative	4 (12%)	3 (18%)	
Follow-up periods	(month)	52 (12–116)	44 (13–112)	NS

**Fig. 1.** Local control rates of early tongue carcinoma treated with 60-Gy and 54-Gy interstitial radiotherapy.

with recurrence. In the 60-Gy arm, one patient developed local recurrence 41 months later. There was no recurrence more than 5 years after treatment. All seven local recurrence cases were treated with salvage surgery; however, only one patient was cured. Six of the seven patients with recurrence showed lymph node metastasis during follow-up and three patients died with recurrent tumors. The 2-year nodal control rates were 65% in the 60-Gy arm and 47% in the 54-Gy arm (NS). Nodal metastases occurred in 12 patients in the 60-Gy arm and 9 patients in the 54-Gy arm (Table 2). All but one nodal recurrence occurred within 2 years after brachytherapy. One patient showed lymph node

**Table 2** Treatment results of interstitial brachytherapy for early oral tongue cancer using 60 Gy and 54 Gy radiation doses

	60 Gy	54 Gy
Local failure	5	2
Nodal metastasis	13	9
Death	5 <sup>a</sup>	4
<b>Late complications</b>		
Soft tissue ulcer	1 (3%)	1 (6%)
Bone exposure	1 (3%)	0 (0%)
Both	2 (6%)	2 (12%)

<sup>a</sup>One death from unknown causes.

metastasis 61 months after treatment; she showed local recurrence before lymph node metastasis. Of the 22 patients with nodal metastasis, 21 were treated with radical neck dissection (RND) and 1 was treated with radiotherapy for subsequent Rouviere's lymph node metastasis. Eight of the 21 patients treated with RND died with nodal metastasis and/or subsequent distant metastasis, while the other 13 patients were controlled. The patient who was treated with radiotherapy died with nodal metastasis. Ultimately, nodal metastases were controlled in 13 of 22 patients. The 2- and 3-year overall survival rates were both 88% in the 60-Gy arm and 88% and 82% in the 54-Gy arm (n.s.). Four

patients died with nodal metastases in both groups (two with local failure in the 60-Gy arm and one with local recurrence in the 54-Gy arm). One patient died of another cause without any evidence of tongue cancer. As for late complications, tongue ulcers were observed in three patients in each arm. Bone exposure occurred in three patients in the 60-Gy arm and two patients in the 54-Gy arm (Table 2). In detail, 18% and 12% patients in the 54-Gy arm had soft tissue ulcers (4, 8 and 14 months after treatment) and bone exposure, respectively, and 9% and 9% patients in the 60-Gy arm had soft tissue ulcers and bone exposure, respectively. The 1- and 2-year actuarial complication-free rates were 97% and 91%, respectively, in the 60-Gy arm and 83% each in the 54-Gy arm (NS;  $P=0.52$ ), respectively.

## DISCUSSION

Interstitial irradiation is conventionally performed at LDR (2 Gy/h or lower). Many institutes have reported successful results of LDR brachytherapy for tongue cancer [1]. In the 1980s, however, HDR irradiation, performed at a dose rate of 12 Gy/h or higher by remote control, was clinically applied for uterine cancer. Since then, HDR brachytherapy using a remote afterloading technique has been installed in several brachytherapy centers, including ours [3, 4]. HDR hyperfractionated interstitial brachytherapy has the following advantages: (i) accurate calculation enabled by complete fixation of the guide tubes; (ii) parallel source arrangement by the linked double-button technique; (iii) homogeneous dose distribution by stepping source optimization; and (iv) better patient care aided by the elimination of radiation exposure of the medical staff. For those reasons, we have installed HDR brachytherapy through Phase I/II and Phase III studies on head and neck cancer [3, 4].

In some reports, pulsed-dose-rate (PDR) irradiation or daytime PDR was applied for head and neck cancer. Strnad *et al.* reported that PDR interstitial brachytherapy for head and neck cancer gave results comparable with those of LDR brachytherapy [13]. Brenner *et al.* reported the superiority of daytime PDR over continuous LDR [14]. However, if PDR or daytime PDR are used to treat patients with curative intent, a treatment unit must be occupied by the patient for 1 week; moreover, no other patient can be treated with that unit. We have only one HDR remote-controlled afterloading unit with which we treat more than 80 patients per year (mainly uterine, prostate and breast cancer patients). Because of the heavy use of the machine, we cannot use PDR or daytime PDR for patients with head and neck cancer.

Based on a retrospective analysis, Yamazaki *et al.* reported that the 5-year local control rates were compatible

between the HDR and LDR groups; the control rates for patients treated solely by brachytherapy were 80% in the LDR group ( $n=341$ ; T1:T2=171:170) and 84% in the HDR group ( $n=58$ ; T1:T2=22:36) [15]. Kakimoto *et al.* reported that the 2- and 3-year local control rates were 67% and 71% for patients with T3 tumors treated with LDR-ISBT and HDR-ISBT, respectively [16]. Therefore the local control rate of patients treated with HDR-ISBT was similar to that of patients treated with LDR-ISBT for T1 to T3 tumors.

In addition, we undertook several efforts to improve HDR-ISBT. To employ a clinical target volume (CTV)-based dose prescription for HDR brachytherapy after CT-based treatment planning installment, Yoshida *et al.* used metal markers in 47 patients (32 with head and neck cancer, 11 with pelvic cancer, 3 with soft tissue cancer and 3 with breast cancer) [17]. At treatment planning, they prescribed and applied a tumoricidal dose to an isodose surface that covered the marked CTV; in addition, they reduced the dose to lower than the constraints for organs at risk. The maximum doses were selected as 80%, 150%, 100%, 50% and 200% of the prescribed doses for the rectum, urethra, mandible, skin and large vessels, respectively. The doses were compared with those calculated by the Paris system theory. If the Paris system (a reference dose of 85% of the basal dose is prescribed to an isodose surface) had been used, 16 patients would have been underdosed and 4 patients (2 with rectal and urethral cancer, 1 with urethral cancer and 1 with large vessel cancer) would have been overdosed. Of the 42 patients treated with doses higher than the tumoricidal dose, 2 had local recurrence, which was also seen in 4 of 7 underdosed patients ( $P<0.0001$ ). They concluded that metal markers were useful for prescribing tumoricidal doses to CTVs and safety doses to organs at risk. We experienced higher incidence of soft tissue ulcers in the 54-Gy arm (18%) than the 60-Gy arm (9%, NS). We can not explain the reason at present because the same technique had been carried out and no significant differences were found in the long diameter ( $22 \pm 11$  mm vs.  $23 \pm 8$  mm), short diameter ( $17 \pm 6$  mm vs.  $16 \pm 4$  mm) and thickness ( $9 \pm 10$  mm vs.  $8 \pm 3$  mm) between the ulcer positive and negative groups. Dose volume analysis in 3D treatment planning is underway and may shed a light in analyzing this side effect [17]. Following the trends in image innovation, we have tried to fuse magnetic resonance images into computer tomographic images. Further investigation of image guided brachytherapy is warranted.

Some studies have reported that 60 Gy/10 fractions results in a 14% increase compared with 70 Gy LDR in  $\alpha/\beta=10$  and a 54% increase in late responding tissue, which is considered very dangerous [6]. An equivalent dose of HDR-ISBT to 70 Gy of LDR-ISBT was calculated as 48 Gy in late reaction ( $\alpha/\beta=3.8$ ) and 54 Gy in acute

reaction ( $\alpha/\beta=10$ ) cases. Therefore we initiated this dose reduction trial to examine whether this strategy is plausible and tactically advantageous if total doses can be reduced without worsening local control rates. As in the present studies no significant differences in outcome were observed between the total doses of 54 Gy and 60 Gy, a total dose of 54 Gy appears to be feasible and was applied thereafter. However, the number of patients in this pilot study was small, and it is difficult to draw firm conclusions. Further studies with a larger number of patients are required.

In conclusion, the outcome of an HDR-ISBT dose of 54 Gy in 9 fractions was similar to that of an HDR-ISBT dose of 60 Gy in 10 fractions in patients with early tongue cancer.

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