High-dose-rate Interstitial Brachytherapy for Mobile Tongue Cancer: Influence of the Non-irradiated Period

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Abstract. *Background: It has been demonstrated that the outcome of primary radiotherapy in squamous cell carcinomas of the head and neck is strongly influenced by overall treatment time. The purpose of this study was to evaluate the results of high-dose-rate (HDR) interstitial brachytherapy (ISBT) for early mobile tongue cancer and to examine whether the non-irradiated period affected treatment results. Materials and Methods: Seventy-one patients with early mobile tongue cancer (T1-T2N0M0) were treated with HDR ISBT alone. The total dose was 54-60 Gy/9-10 fractions/5-9 days. All patients were classified into 4 groups: R0, maximum non-irradiated period (NIP) was less than 24 h (n=16); R1, maximum NIP was from 24 to 48 h (n=24); R2, maximum NIP was from 48 to 72 h (n=26); R3, maximum NIP was from 72 to 96 h (n=5). Results: The 3-year local control rate was 94% in R0, 83% in R1, 85% in R2 and 100% in R3. The 3-year overall survival rate was 84% in R0, 92% in R1, 71% in R2 and 80% in R3. There was no significant difference in the local control rate, overall survival rate, or complications among the 4 groups. Conclusion: In HDR ISBT for early mobile tongue cancer, the non-irradiated period did not affect the treatment results or complications.*

Interstitial brachytherapy (ISBT) is one of the most effective treatment methods for early stage mobile tongue cancer because of its precise local control rate and preservation of oral function (1-6). Even in advanced tongue cancers of T3 and stage III, ISBT showed good treatment results (7, 8). Low-dose-rate (LDR) ISBT had been used for the treatment of tongue cancers. In 1991, treatment with the microSelectron HDR (Nucletron, Veenendaal, The Netherlands) was initiated and high-dose-rate (HDR) ISBT was applied for tongue cancers (9). According to a randomized trial for early tongue cancer, the local control rate and late complications of HDR ISBT were similar to those of LDR ISBT (10, 11).

In hyperfractionated HDR ISBT, a total dose of 54-60 Gy/9-10 fractions/5-9 days was implemented. The typical treatment schedules of 60 Gy/10 fractions/5 or 8 days are provided in Figure 1. One treatment schedule does not include the non-irradiated day (Figure 1A), whereas the other include the non-irradiated days (Figure 1B). These two treatment schedules were, thus, different in terms of overall treatment time. Recently, it was demonstrated that the outcome of primary radiotherapy in squamous cell carcinomas of the head and neck was strongly influenced by overall treatment time (12-15). However, the influence of overall treatment time for HDR ISBT has not been examined clinically.

In this study, the treatment results of HDR ISBT for early mobile tongue cancer was evaluated and the influence of the non-irradiated period on the treatment results was examined.

Materials and Methods

Between July 1991 and December 2000, 71 patients (58 male and 13 female) with previously untreated early mobile tongue cancer (T1-T2N0M0) were treated with HDR ISBT alone. All tumors were histopathologically confirmed as squamous cell carcinoma. The median age was 59 years, ranging from 28 to 81 years. Patients were staged using the UICC TNM classification of 2002 (16). T1 is defined as a primary tumor of 2 cm or less and T2 as more than

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Key Words: Interstitial radiotherapy, tongue carcinoma, high-dose-rate, non-irradiated period.

A

	Mon	Tue	Wed	Thu	Fri
AM	Implant ISBT-1	ISBT-3	ISBT-5	ISBT-7	ISBT-9
PM	ISBT-2	ISBT-4	ISBT-6	ISBT-8	ISBY-10 remove

B

	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed
AM		ISBT-2	ISBT-4	rest	rest	ISBT-6	ISBT-8	ISBT-10 remove
PM	Implant ISBT-1	ISBT-3	ISBT-5	rest	rest	ISBT-7	ISBT-9	

Figure 1. *Typical treatment schedules of high-dose-rate (HDR) interstitial brachytherapy (ISBT) for tongue cancer. The treatment schedule of 60 Gy/10 fractions/5 days did not include the non-irradiated day (A). The treatment schedule of 60 Gy/10 fractions/8 days included two non-irradiated days (B).*

Table I. *R-classification, incidence of lymph node metastasis and complications.*

Group	Non-irradiated period (NIP) (h)	No. of patients	N0→N+	Complications	
				Soft tissue	Bone
R0	maximum NIP <24	16	5	2	1
R1	24≤ maximum NIP <48	24	8	3	3
R2	48≤ maximum NIP <72	26	11	3	5
R3	72≤ maximum NIP <96	5	2	1	1
Total		71	26	9	10

2 cm but not exceeding 4 cm in the greatest dimension. The tumor size was measured by vernier calipers. Neck node metastases were evaluated primarily with palpation and confirmed with computed tomography and/or magnetic resonance imaging. A chest radiograph was used for the evaluation of lung metastases. Twenty-eight patients were classified as T1N0M0 and 43 as T2N0M0.

Four groups, R0-3, were defined using the maximum non-irradiated period (NIP). A maximum NIP less than 24 h was defined as R0 (n=16); a maximum NIP from 24 to 48 h was defined as R1 (n=24); a maximum NIP from 48 to 72 h was defined as R2 (n=26); and a maximum NIP from 72 to 96 h was defined as R3 (n=5) (Table I).

In HDR ISBT, the implant was achieved with flexible applicators followed by irradiation with a remotely controlled after-loading system and a dose optimization program. The total dose was 54-60 Gy/9-10 fractions/5-9 days. Two fractions were administered per day. The time interval between fractions was greater than 6 h. The treatment planning was done with the aid of PLATO (Nucletron, Veenendaal, The Netherlands) using geometric optimization and one reference point which was 5 mm from one source. A single plane implant was adopted when the tumor thickness was 10 mm or less. A two-plane implant was adopted when the tumor thickness was more than 10 mm and did not exceed 20 mm. A volume implant was adopted when the tumor thickness was more than 20 mm.

Fifty-five patients were treated with a single plane implant, 14 patients were treated with a two-plane implant and 2 patients were treated with a volume implant. We routinely used a spacer made of silicone rubber between the lateral border of the tongue and the mandibular bone to reduce the radiation dose of the mandible. The patients were followed for at least 6 months or until their death (median 39 months).

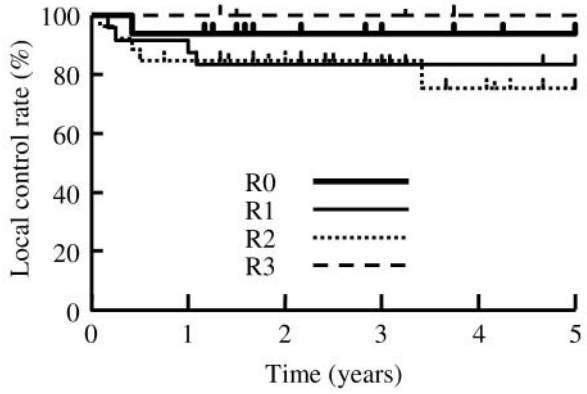

Figure 2. *Local control rates of tongue cancer treated with high-dose-rate (HDR) interstitial brachytherapy.*

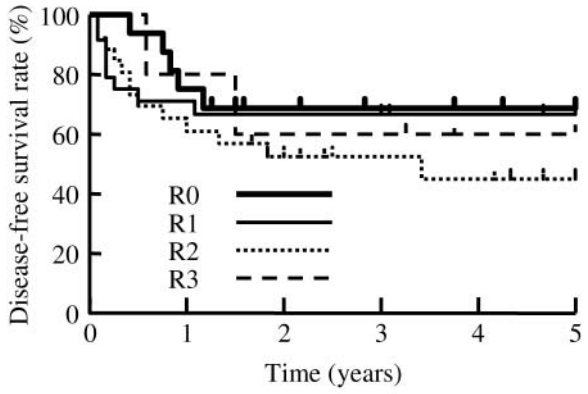

Figure 3. *Disease-free survival rates of tongue cancer treated with high-dose-rate (HDR) interstitial brachytherapy.*

Local control and survival rates were calculated with the Kaplan-Meier method. Statistical differences were evaluated using the log-rank test. A Chi-square test was used for the comparison of the incidence of lymph node metastasis and complications. All analyses used the conventional $p<0.05$ levels of significance.

Results

The 3-year local control rate of all patients was 87%. The 3-year local control rates were 94% for R0, 83% for R1, 85% for R2 and 100% for R3 (Figure 2). There was no significant difference among the 4 groups ($p=0.54$).

Regional lymph node metastasis occurred in 26 out of 71 patients (37%). Seventeen out of the 26 patients (65%) who exhibited regional lymph node metastasis were salvaged by surgery with or without post-operative radiotherapy. Regional lymph node metastasis for R0, R1, R2 and R3 appeared in 5/16 (31%), 8/24 (33%), 11/26 (42%) and 2/5 (40%) patients, respectively (Table I). There was no significant correlation between R-classification and the occurrence of regional lymph node metastasis ($p=0.87$).

The 3-year disease-free survival (DFS) rate of all patients was 61%. The 3-year DFS rates were 69% for R0, 67% for R1, 53% for R2 and 60% for R3 (Figure 3). There was no significant difference among the 4 groups ($p=0.57$).

The 3-year cause-specific survival (CSS) rate of all patients was 84%. The 3-year CSS rates were 91% for R0, 92% for R1, 71% for R2 and 80% for R3 (Figure 4). There was no significant difference among the 4 groups ($p=0.23$).

The 3-year overall survival (OS) rate of all patients was 81%. The 3-year OS rates were 84% for R0, 92% for R1, 71% for R2 and 80% for R3, respectively (Figure 5). There was no significant difference among the 4 groups ($p=0.36$).

Nine out of the 71 (13%) patients exhibited soft tissue ulcers and 10 out of 71 (14%) exhibited bone exposure and/or radiation osteomyelitis. Soft tissue ulcers in R0, R1, R2 and R3 appeared in 2/16 (13%), 3/24 (13%), 3/26 (12%) and 1/5 (20%) patients, respectively (Table I). Bone exposure and/or radiation osteomyelitis in R0, R1, R2 and R3 appeared in 1/16 (6%), 3/24 (13%), 5/26 (19%) and 1/5 (20%) patients,

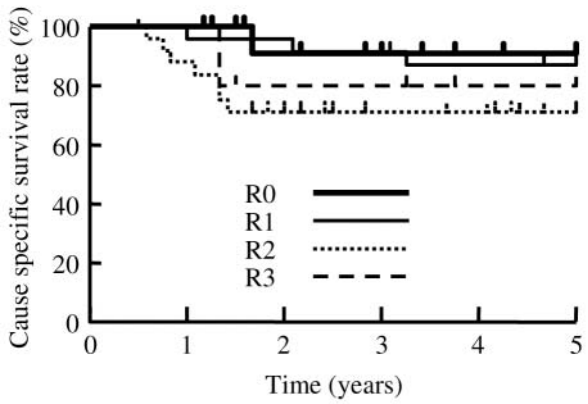

Figure 4. *Cause-specific survival rates of tongue cancer treated with high-dose-rate (HDR) interstitial brachytherapy.*

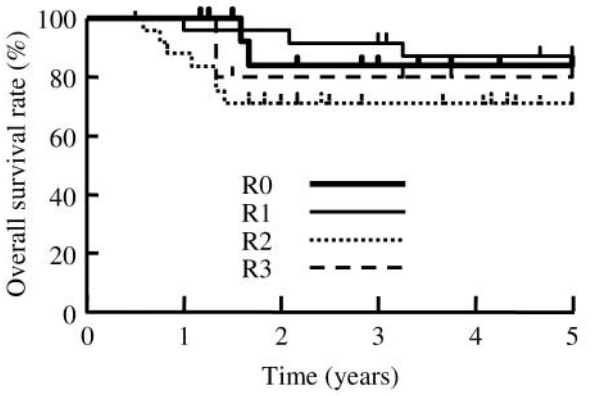

Figure 5. *Overall survival rates of tongue cancer treated with high-dose-rate (HDR) interstitial brachytherapy.*

respectively (Table I). There were no significant correlations between R-classification and the incidence of soft tissue ulcers ($p=0.96$) or bone exposure and/or radiation osteomyelitis ($p=0.67$). The implant methods in the 9 cases with soft tissue ulcers were 6 cases of a single plane implant, 2 cases of a two-plane implant and one case of a volume implant. The implant methods in the 10 cases with bone exposure and/or radiation osteomyelitis were 4 cases of a single plane implant, 5 cases of a two-plane implant and one case of a volume implant. Almost all patients with complications were treated conservatively. None of the patients who exhibited soft tissue ulcers required surgery. One patient underwent surgery for radiation osteomyelitis.

Discussion

ISBT is an effective treatment method for early mobile tongue cancer because it shows an excellent local control rate and has the advantage of preserving oral function (1-6). In Japan, LDR sources, for example Iridium-192 hairpin or Cesium-137 needle, are usually used for ISBT in tongue cancers. Since LDR ISBT is continuous, there is no non-irradiated period.

In 1991, we started the treatment with the microSelectron-HDR (Nucletron, Veenendaal, The Netherlands) and applied HDR ISBT for the tongue cancer (9). HDR ISBT has many advantages, such as complete fixation of guide tubes, paralleled guide tube implantation, homogeneous dose distribution using a dose optimization program, no radiation exposure for the medical staff and no need to isolate patients in a shielded room.

Teshima *et al.* reported that HDR ISBT of 60 Gy/10 fractions/week was equivalent to a LDR ISBT of 70 Gy in terms of mucosal reaction and early tumor response (9). Inoue *et al.* reported that the local control rate, cause-specific survival rate and late complications of HDR ISBT of 60 Gy/10 fractions/6 days were similar to those of LDR ISBT of 70 Gy/4 to 9 days for early tongue cancer (10, 11).

HDR ISBT is hyperfractionated irradiation for the tumor. The total dose was 54-60 Gy/9-10 fractions when patients with tongue cancer were treated with HDR ISBT alone. Two fractions were administered per day. The time interval between fractions was greater than 6 h. However, we treated tongue cancers with several irradiation schedules. Between July 1991 and May 1995, we irradiated 6 days a week (Monday through Saturday). After July 1995, we irradiated 5 days a week (Monday through Friday) due to the government policy on national university hospitals. Occasionally, national holidays were included in the overall treatment time of HDR ISBT. Therefore, the overall treatment time of 54-60 Gy/9-10 fractions ranged from 5 to 9 days. The non-irradiated day was not included in the 5- or 6-day treatment schedule, but it was included after the 6th day.

Since the late '80s there has been a strong focus on the importance of overall treatment time for the outcome of curative radiotherapy in head and neck carcinomas (15). Results of split-course irradiation therapy have repeatedly indicated that such treatment yielded inferior results (17) and the overview by Withers *et al.* found that accelerated repopulation was a prominent clinical feature (18). These authors reported that accelerated repopulation by malignant clonogenic cells may begin, on average, 3-5 weeks after the initiation of radiotherapy (19). HDR ISBT is similar to conventional external radiotherapy in terms of the dose rate, so the equivalent biological effects of radiation by HDR ISBT and conventional external radiotherapy are expected. We predicted that treatment results might have been similar among the 4 groups of R0-3, excluding late complications. Clinical HDR ISBT data have not been reported to date.

In the present study, there were no significant differences among R0-3 regarding local control rate, regional control, survival rates or late complications in HDR ISBT for early mobile tongue cancer. These results show that the overall treatment time of HDR ISBT of 54-60 Gy/9-10 fractions/5-9 days did not affect the treatment results. Since the number of cases was small with only 5 cases in R3, we focused on the remaining 3 groups (R0, R1 and R2). There were no significant differences among the 3 groups for local control rate ($p=0.53$), regional control ($p=0.56$), disease-free survival rate ($p=0.38$), cause-specific survival rate ($p=0.11$), overall survival rate ($p=0.20$) or late complications (soft tissue ulcer: $p=0.99$; bone complication: $p=0.48$). Therefore, it was suggested that the non-irradiated period of 0 to 3 days in the HDR ISBT of 54-60 Gy/9-10 fractions did not affect treatment results or complications for early mobile tongue cancer.

The ultimate application of the measurement of the potential doubling time (Tpot) is the ability of the technique to provide useful prognostic or predictive information in clinical studies (20-22). Wilson reported that the median Tpot of head and neck cancer was between 4 and 5 days (21). In the present treatment schedule of HDR ISBT, the non-irradiated period was less than 4 days. Since the non-irradiated period was less than the median Tpot, it is suggested the non-irradiated period of 0 to 3 days did not influence the treatment results.

In terms of accelerated repopulation and Tpot, we expected the same tumor control among the 4 groups and were able to confirm this with our present data. However, the occurrence rate of late complications was also similar among the 4 groups. Therefore, a total dose 54-60 Gy may be the maximum tolerable dose of HDR ISBT for mobile tongue cancer.

There were no serious problems in patient care, even when the overall treatment period changed from 5 to 9 days.

In HDR ISBT treatment, there is no radiation exposure for the medical staff and no need to isolate patients in a shield room, therefore insuring adequate physical and mental care from the medical staff.

We treated early mobile tongue cancers using several treatment schedules of HDR ISBT considering the non-irradiated period. According to the results of this study, local control rate, regional control, survival rates and late complications were the same among the groups classified by the non-irradiated periods. In conclusion, a non-irradiated period less than 96 h did not affect the treatment results or complications in HDR ISBT for early mobile tongue cancer.

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