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Brachytherapy for Buccal Cancer: From Conventional Low Dose Rate (LDR) or Mold Technique to High Dose Rate Interstitial Brachytherapy (HDR-ISBT)

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Abstract. *Background/Aim: To examine the effectiveness of newly-installed high-dose-rate interstitial brachytherapy (HDR-ISBT) for buccal cancer. Patients and Methods: We retrospectively reviewed 36 patients (25 men and 11 women) with buccal cancer treated with curative brachytherapy with or without external radiotherapy with a median follow-up of 99 months. A total of 15 HDR-ISBT (median 48 Gy/ 8 fractions, range=24-60 Gy) patients were compared to conventional 15 cases LDR-ISBT (70 Gy, range=42.8-110 Gy) and 7 molds techniques (15 Gy, range=9-74 Gy). A total of 31 patients also underwent external radiotherapy (30 Gy, range=24-48 Gy). They comprised of 3T1, 23 T2, 8 T3, 3 T4 including 11 node positive cases. Results: HDR-ISBT provided 82% of local control rate at 5 years, whereas conventional brachytherapy showed 72% [p=0.44; LDR-ISBT (65%), mold therapy (85.7%)]. Patients with early lesions (T1-2 or stage I-II) showed better local control rates than those with advanced lesions (T3-4 or stage III-IV). Severe late grade 3 complications developed in two patients treated with LDR-ISBT and EBRT. There is no significant difference in toxicity grade ≤2 between conventional brachytherapy (5/15=33%) and HDR-ISBT (7/32=32%, p=0.92). Conclusion: HDR-ISBT achieved good and comparable local control rates to conventional brachytherapy without elevating the toxicity.*

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Key Words: Brachytherapy, buccal cancer, high dose rate, low dose rate, image-guided brachytherapy.

Buccal cancer is a relatively rare tumor in North America and Western Europe, accounting for only 2% of all carcinomas of the oral cavity (1), but is somewhat more common in Japan at 4.8% (2). Surgical treatment may be used for minor lesions (1 cm or smaller) with primary closure, unless they involve the lip commissure, in which case they are sometimes treated with radiation therapy. Larger lesions, 2 to 3 cm in size, can be treated with surgery and/or radiation therapy, and usually the former. A combination of surgery and postoperative radiotherapy is currently recognized as the optimal treatment modality for most advanced buccal cancers.

For this reason, treatment results for buccal cancer are mainly available for surgical series, or for surgery combined with either radiotherapy or chemotherapy (3-8). Although radiotherapy is a good alternative to surgery when surgery is refused or the patient is medically fragile, few reports mention results of conventional brachytehapy [mold therapy or low-dose-rate (LDR) interstitial brachytherapy (ISBT)] (9-11) and only two reports on high dose rate brachytherapy (12, 13) could be found. We have experienced brachytherapy for buccal cancer nearly fifty years started from 1960s (1). Initially, it has been performed with mold therapy or low-dose-rate interstitial brachytherapy (11, 14-17). In 1990s, we installed high dose rate (HDR) brachytherapy using the Remote After Loading System (RALS) to provide optimum protection for operating personnel against risk of radiation, and enabled patients to stay in a normal ward, so that quality of life during treatment is

Table I. *Patient characteristics*.

		HDR-ISBT(n=15)		Conventional brachytherapy				*p*-Value
				LDR-ISBT(n=15)		Molds (n=7)		
		Median (range) or No. pts (%)		Median (range) or No. pts (%)				
Age	(y)	64 (42-90)		64 (19-78)		62 (50-73)		0.64
Follow-up periods	(months)	42 (2-193)		100 (6-224)		115 (39-242)		0.18
	for alive patients	136 (45-193)		141(100-224)		203(165-242)		
Gender	Male	11	(73)	10	(67)	4	(57)	0.75
	Female	4	(27)	5	(33)	3	(43)	
Histology	SCC	15	(100)	12	(80)	7	(100)	0.3
	Adeno	0	(0)	2	(13)	0	(0)	
	ACC	0	(0)	1	(7)	0	(0)	
Modality	BT+EBRT	11	(73)	14	(93)	6	(86)	0.31
	BT alone	4	(27)	1	(7)	1	(14)	
Chemotherapy	None	12	(80)	8	(53)	2	(29)	0.059
	Performed	3	(20)	7	(47)	5	(71)	
T-classification	T1	2	(13)	1	(7)	0	(0)	0.12
	T2	8	(54)	9	(60)	6	(86)	
	T3	5	(33)	2	(13)	1	(14)	
	T4	0	(0)	3	(20)	0	(0)	
N-classification	N0	11	(73)	9	(60)	5	(72)	0.674
	N1	3	(20)	3	(20)	1	(14)	
	N2b	1	(7)	2	(13)	1	(14)	
	N2c	0	(0)	1	(7)	0	(0)	
Clinical Stage	I	2	(13)	1	(7)	0	(0)	0.44
	II	6	(40)	6	(40)	4	(57)	
	III	6	(40)	4	(27)	2	(29)	
	IV	1	(7)	4	(27)	1	(14)	
Subsite	Cheek	13	(93)	11	(73)	7	(100)	0.28
	Sulcus	0	(0)	2	(13)	0	(0)	
	Retromolar	1	(7)	2	(13)	0	(0)	
Localized in cheek	Yes	9	(60)	6	(40)	6	(86)	0.12
	No	5	(40)	9	(60)	1	(14)	

LDR: Low-dose-rate; HDR: high-dose-rate; ISBT: interstitial brachytherapy; SCC: squamous cell carcinoma; Adeno: adenocarcinoma; ACC: adenoid cystic carcinoma; BT: brachytherapy; EBRT: external beam radiotherapy.

likely to be better (14-17). In addition, recently, we were able to install three-dimensional treatment planning (CT simulation and MRI image fusion) in HDR-ISBT, so called image guided brachytherapy (14, 15).

The aim of this study was to examine the compatibility of HDR-ISBT to conventional LDR-ISBT or mold therapy. We examined outcomes for local control, survival, and radiation-induced toxicity for buccal caner patients treated with brachytherapy with or without external beam radiotherapy (EBRT).

Patients and Methods

Patients. All patients underwent brachytherapy for buccal carcinoma as the initial curative therapy between March 1968 and October 2010. Patients with multiple synchronous or metastatic tumors were excluded. The patients' characteristics are shown in Table I. There were three cases with T1, 23 with T2, 8 with T3, and 3 with T4 cases, comprising 25 men and 12 women with a median age of 64 years (range=19-90 years). The median follow-up time was 99 months (range=2-242 months). Histologic disease confirmation was obtained for all patients (34 squamous cell carcinoma, 2 adenocarcinomas, and 1 adenoid cystic carcinoma). The subsite of the tumor origin was determined from the epicenter of the tumor and the tumor was categorized according to the criteria established by the International Union Against Cancer (UICC 7th edition, 2009). All patients provided written informed consent.

Treatments. Of the 31 patients who were treated with a combination of EBRT, 19 without evidence of regional lymph node involvement received prophylactic lymph node irradiation and boost irradiation for primary lesion (median: 30Gy, range=24.5-70 Gy). The other 12 patients with clinically enlarged lymph nodes in the neck received regional EBRT after ISBT, with or without boost EBRT to the nodes and primary lesion (median: 38.75 Gy, range=26-68 Gy). Fifteen patients received

Table II. *Treatment of each Modalities of brachytherapy.*

	No.pts	Median dose (Gy)	Range (Gy)
LDR ISBT			
Radium needle	10	70	50-70.36
Iridium hairpin	2	51,4	42.8-60
Au-198 grain	2	65,75	61.5-70
I-125 seed	1	110	110
Molds			
Iridium (Ralstron)	5	10	9-21.2
Cesium tube mold	2	71	68-74
HDR ISBT			
Iridium (microselectron)	15	48	24-60

LDR: Low-dose-rate; HDR: high-dose-rate; ISBT: interstitial brachytherapy.

chemotherapy (13 cases concurrent, 2 sequential) using bleomycin or peplomycin. Brachytherapy only was used for 6 patients none of whom initially showed any nodal metastasis. All implantations were done under local or general anesthesia. We performed LDR-brachytherapy with the interstitial or mold technique and with the HDR-mold brachytherapy using Ralstron, the remotely controlled afterloading system, from 1968 to 1980. HDR-ISBT has been used at our institutions since 1992. Those brachytherapy included LDR–ISBT for 15 patients (10 with radium needles, 2 with Iridium hairpins, 3 with permanent source implants (2 with Au grains and 1 with I-125 seeds) and HDR-ISBT with microselectron HDR (Elekta AB, Stockholm Sweden) for 15 patients. Seven superficial lesions were treated with the mold technique, 5 with Ralstron (Shimadzu Corporation, Kyoto, Japan) and 2 with Cesium tube mold brachytherapy.

Patient distributions for the three groups are shown in Table I. No significant differences were noted among the backgrounds of the three groups (Table I). Details of prescribed dose in each treatment were depicted in Table II. The prescribed median dose was 48 Gy (24-60 Gy) for the HDR-ISBT group. The doses for the HDR-ISBT combined with external irradiation group (11 patients) ranged from 24 to 48 Gy. Four patients were treated with HDR-ISBT only with a dose of 54-60 Gy. HDR-ISBT treatment consisted of twice-a-day irradiation of 6 Gy each with at least a 6-h interval to provide the total prescribed dose (Figure 1). The LDR-ISBT dose was 42.8-110 Gy (median: 70 Gy). The total brachytherapy dose for patients treated with EBRT was 42.8-110 Gy and 69.69 Gy for one patient without EBRT, while the median dose for the mold technique was 15 Gy (9-74 Gy). For one patient treated with mold brachytherapy alone the dose was 68 Gy. Thirty-one patients received EBRT. Telecobalt gamma beams were used for 22 patients, 8 were treated with a 4-MV photon linear accelerator and 1 patient with a 10-MeV electron beam. A unilateral field was used for 22 patients; bilateral field irradiation was for 7 patients, a wedged-pair field for 2 patients. Unilateral field irradiation was mainly used for the LDR-ISBT and mold groups. Half of the HDR-ISBT group was treated with bilateral irradiation, and the other half with unilateral and wedged-pair fields. Toxicities were assessed according to the Common Terminology Criteria for Adverse Events versions 3.0 (CTCAE-ver. 3).

Table III. *Univariate analysis according to local control rate.*

Variable	No.pts	5-year local control rates	*p*-Value
Gender			
Male	25	74%	0.12
Female	12	82%	
Age			
<=65	23	73%	0.17
>65	14	84%	
T-classification			
T1-2	26	87%	0.01
T3-4	11	53%	
N-classification			
N–	25	83%	0.15
N+	12	64%	
Clinical Stage			
I-II	19	88%	0.04
III-IV	18	64%	
Localized within cheek			
Yes	21	84%	0.07
No	16	64%	
Ulceration			
Yes	16	77%	0.37
No	21	75%	
Chemotherapy			
Yes	15	66%	0.80
No	22	84%	

Statistical analysis. All statistical tests were performed with the aid of the *JMP 9.02* statistical software (SAS Institute, Cary, NC, USA). Percentages were analyzed using the chi-square test, and Student's *t*-test was used for normally distributed data. The Mann–Whitney *U*-test for skewed data was used to compare means or medians. We calculated local control, overall survival rates by using the Kaplan-Meier method and the differences were assessed with the log-rank test. The follow-up times for local control and survival calculated from start of radiotherapy (EBRT or BT). $p<0.05$ was considered to indicate a significant difference.

Results

Local and nodal control. In terms of primary tumor status, 5-year local control rates were 76.4% (95% confidential interval; 95%CI=62.0-90.8%) for all patients (100% for T1, 85.6% for T2, 60.0% for T3, and 33.3% for T4). HDR-ISBT provided 82% of 5-year local control rate (95%CI=59.1-105%), whereas conventional brachytherapy showed 72% (95%CI=52.6-90.9%, $p=0.44$) (Figure 2a). In detail, LDR-ISBT showed 65% (95%CI=40.2-89.8%) of 5-year local control rate and mold therapy 85.7% (95%CI=59.8-116%) ($p=0.17$, Figure 2b).

Of the 16 patients showing progression of the disease, 15 presented locoregional failure (local only 10, nodal only 4, local and nodal 1), while 1 developed distant metastasis

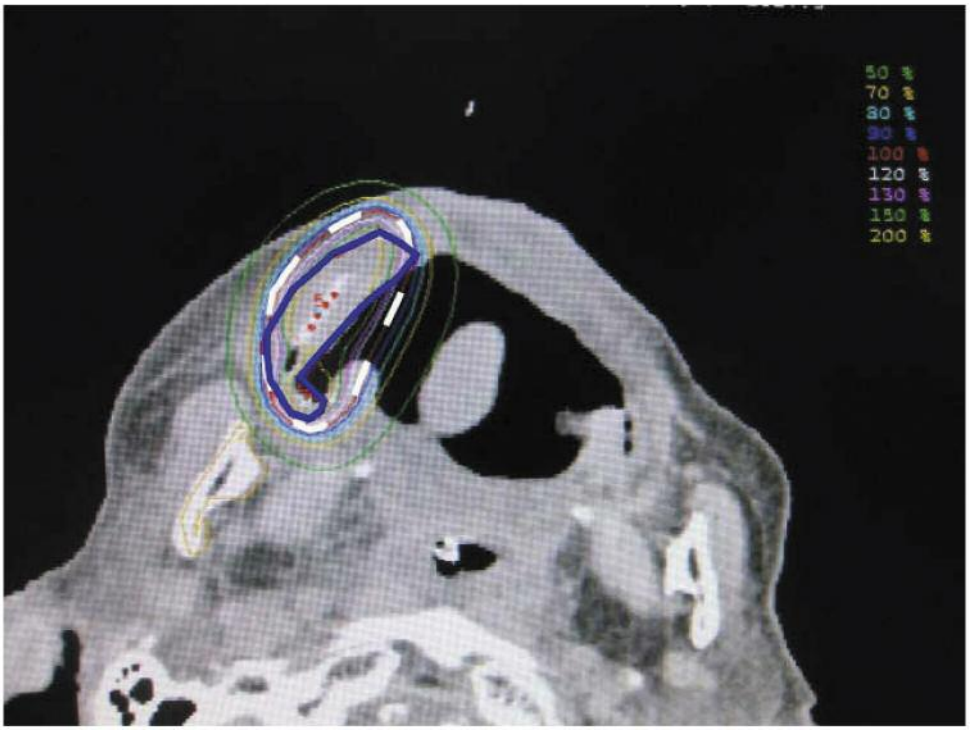

Figure 1. *A representative image of three-dimensional treatment planning by image guided HDR-ISBT using CT simulation. Detail of image-guided HDR-ISBT was prescribed elsewhere (17). Thick line: Clinical target volume; Dotted line: prescription dose.*

Table IV. *Complications according to brachytherapy techniques.*

	HDR-ISBT(n=15)		LDR-ISBT(n=15)		Molds (n=7)		*p*-Value
	No. Pt	(%)	No. Pt	(%)	No. Pt	(%)	
Grade 0-1	10	(67)	8	(53)	7	(100)	0.15
Grade 2	5	(33)	5	(33)	0	(0)	
Grade 3	0	(0)	2	(13)	0	(0)	

(lung). Nodal progression was found in five cases and the overall 5-year nodal control rate was 88.4%. All nodal recurrences appeared on the ipsilateral side. Only two of the 25 node-negative patients developed nodal metastasis, and were treated without prophylactic regional irradiation. Nodal recurrence was observed in 3 of the 12 patients with nodal-positive cases at first presentation.

Univariate analysis indicated that low T-classification and earlier clinical stage were associated with good local control (Table III). Early lesions (T1-T2) showed a significantly better outcome than advanced lesions (T3-4) (Table III, 87.2% and 53.0%; p=0.009), and earlier clinical stage (stage I-II 88%) revealed a better outcome (stage III-IV 64%, p=0.04). Extension to adjacent sites (gingivobuccal sulcus, retromolar area) outside the buccal mucosa seemed to provide the poorest outcome. Limited disease showed 5-year local control of 84%, and extensive tumors 64% (boarder line significance p=0.07).

Survival and second malignancy. Seven patients (19%) deceased from buccal cancer, 6 of local progression and 1 of nodal relapse. 5-year overall survival was 55.2%. HDR-ISBT provided 46.7% of the 5-year overall survival rate (95%CI=21.4-71.9%), whereas conventional brachytherapy

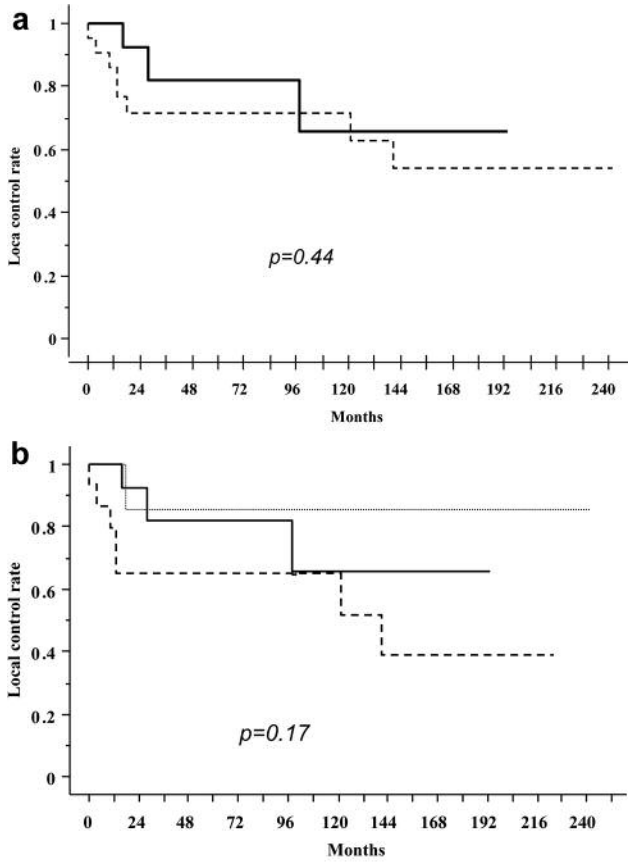

Figure 2. *Local control of buccal cancer with brachythrerapy. (a) Local control rates between HDR-ISBT and conventional brachytehapy. Thick line: HDR-ISBT; Dotted line: conventional brachytherapy. (b) Local control rates according to the modality groups of brachytherapy. Thick line: HDR-ISBT; Dashed line: LDR-ISBT; Dotted line: mold brachytherapy.*

provided 63.6% (95%CI=43.5-83.7%, p=0.48). Lower T-classification (T1-2; 65% 5-year survival rate) was significantly associated with longer overall survival compared to higher T-classification (T3-4; 27%, p=0.02). Second malignancy developed in one patient (esophageal cancer).

Complications. Two patients treated with LDR-brachytherapy and EBRT showed grade-3 adverse events (Table IV). One patient whose bucco-alveolar sulcus T2 tumor was irradiated with combination of 70.36 Gy radium needles and w30Gy of telecobalt therapy developed bony exposure. The other patient with a retromolar T2 tumor received concurrent chemoradiotherapy (EBRT 30Gy and bleomycin) followed by 61.5 Gy Au-198 grain implantation, developed grade 3 mucositis, deep ulcer, and bony exposure. As for Grade-2 complications, oral mucositis was found in 2 cases, dry mouth in 2 patients, and trismus in 2 patients. There is no significant difference in grade 2≤ toxicity between conventional brachytherapy (5/15=33%) and HDR-ISBT (7/32=32%, p=0.92).

Discussion

As buccal cancer has been mainly treated with surgery, a substantial body of surgical studies reported the outcomes; with a local control rate ranging from 30% to 89%, which largely depend on tumor stage (3-8). Advanced cases (T3-4) showed a poorer loco-regional control rate (22.8%) than that for T1- T2N0 patients (52.7%) (8). One reason for the high local recurrence rate of buccal carcinoma is reportedly due to the lack of anatomical barriers other than the buccinator muscle and its overlying fascia (6). The tumor can therefore invade through many tracts, especially in advanced cases (6).

For definitive radiation therapy, LDR brachytherapy has been used (10, 15-18). Nair *et al*. reported a 3-year local control rate of 58% for 234 patients (100% for T1N0, 73% for T2N0, 69% for T3N0, 50% for T4N0 cases) (9). Shibuya *et al*. (10) also experienced a good 3-year local control rate of 87% for 45 patients (T1:T2:T3=8:30:7) treated with 81.4 Gy LDR-brachytherapy using mainly Au-198 with or without external irradiation.

For our study, the 5-year local control rates were 76.4% for all patients, 100% for T1, 85.6% for T2, 60% for T3, and 33.3% for T4 patients, which were compatible with those preceding outcomes. In line with previous reports that relapse at the primary site increased with T classification (5, 9). For the same reason, we postulated that limited 'localized in cheek' lesions could have a better outcome.

HDR brachytherapy using a remote afterloading technique has been introduced in several brachytherapy centers, including ours. HDR-ISBT interstitial brachytherapy has the following advantages (14-17): (i) accurate calculation facilitated by complete fixation of the guide tubes; (ii) parallel source arrangement with the linked double-button technique; (iii) homogeneous dose distribution as a result of stepping-source optimization; and (iv) better patient care by elimination of radiation exposure of medical staff. We had performed LDR-brachytherapy since 1968 and changed to HDR-brachytherapy in the 1990s (11, 16). To the best of our knowledge, this is the first retrospective review concerning comparison between HDR-brachytherapy and conventional brachytherapy for buccal carcinoma. We proved the efficacy of HDR-brachytherapy with a local control (5-year local control rate 82%) as good as that for conventional brachytherapy (72%). In addition, the mold technique showed excellent outcome (85.7%) for superficial tumors and therefore we hope that it should be maintained in academic institutions for buccal cancer treatment.

Nodal control is another important issue in the treatment of buccal cancer. To prevent following nodal metastasis,

several institutions employed prophylactic external irradiation. However, fortunately, only two of the nodal negative patients showed nodal recurrence regardless of no prophylactic external irradiation. At present, therefore, a watch-and-wait policy without prophylactic treatment for the lymph node region could be adequate for node-negative buccal cancer cases.

Limitations of this study should also be considered. This is a retrospective review dealing with a small number of patients with heterogeneous brachytherapy techniques in a wide range of time; therefore, there may be several treatment biases of physicians and institutional references. Thus, results should be confirmed in a prospective clinical trial, if possible.

In conclusion, HDR-ISBT achieved good and comparable local control rates to conventional brachytherapy without elevating toxicity.

Conflicts of Interest

The Authors state no conflicts of interest.

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