Clinical outcomes with high-dose-rate surface mould brachytherapy for intra-oral and skin malignancies involving head and neck region

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Abstract

Purpose: The literature and experience of high-dose-rate (HDR) surface mould brachytherapy (SMB) in head and neck cancer is sparse. We report our institutional experience of SMB for such tumours.

Material and methods: Thirty-five patients with malignant localized early T1/T2, N0 (21 intra-oral and 14 skin) tumours treated with SMB during 2008-2014 were analyzed. Treatment was delivered using HDR 192Ir source to a median dose of 49 Gy (range, 38.5-52.5 Gy) as radical brachytherapy and 18 Gy (range, 15.5-30 Gy) as boost with 3-4 Gy/fraction twice daily using customized surface mould.

Results: Median follow-up was 52 months (range, 6 to 98 months). Local control (LC) for skin tumours and intra-oral malignancies at 5 years were 92% and 76%, respectively. Five-year cause specific survival was 92%. For T1 and T2 tumours, 5 year LC was 94.2% and 68.2%, respectively. T stage (p < 0.04) and dose/fractions (p < 0.003) were the only significant prognostic factors for LC on univariate analysis.

Conclusions: Surface mould brachytherapy results in excellent LC rates for skin tumours and T1 intraoral tumours when considered as radical treatment, and preferable to consider it as a boost for T2 intraoral tumours. Surface mould brachytherapy results in excellent organ and function preservation.

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Purpose

Surface mould brachytherapy (SMB) is a well-established treatment for early stage head and neck cancers involving accessible sites. It has evolved from the radium era to low-dose-rate (LDR) and now to high-dose-rate (HDR) intensity modulated interventional brachytherapy [1]. The use of brachytherapy (BT), both in radical setting and as salvage procedure, have resulted in satisfactory outcomes for head and neck malignancies [2,3]. Surface mould brachytherapy has shown excellent outcomes using LDR brachytherapy [4]. High-dose-rate brachytherapy is now widely used in many parts of the world and has shown to have equivalent outcomes compared to other dose rates for some head and neck malignancies [5]. There have been few reports regarding the use of SMB in the HDR era for skin malignancies involving skin of face (including nose, pinna) resulting in outcomes comparable with other treatment strategies [6,7,8,9]. However, very limited literature is available for SMB for intra-oral malignancies and involved less number of patients [10,11,12]. This analysis was undertaken to find out the clinical outcomes of superficial tumours of head and neck region treated with SMB, in terms of survival and toxicity.

Material and methods

Between January 2008 and December 2014, 35 patients were treated with HDR brachytherapy using surface mould. Data was retrieved from prospectively maintained database and patient charts.

Patient selection

Superficial tumours of head and neck region (T1-T2N0 M0) over accessible sites like hard palate, hard-soft palate junction or over the skin like cheek, nose, and ear were considered for treatment with SMB. The decision of treating with SMB was undertaken after reviewing the disease site, and discussing with the medical physicist and mould room technician regarding feasibility of the procedure and possibility of adequate target volume coverage. For patients...
with primary over hard palate or soft palate, additional consultation with the dental department was done regarding preparation of the dental carrier material.

**Procedure**

The workflow of procedure for SMB is shown in Figure 1. Customized mould was made for each patient. Gross tumour with 1 cm margin was considered as the clinical target volume and was marked on the patient. First component of SMB included preparation of the carrier material. The area, over which the cast was to be prepared, was marked over the skin. For tumours located over skin, a negative impression was made using dental alginate material (Alginate Dental Impression Material, The Bombay Burmah Trading Corporation Ltd.) (Figure 2A). Stone cast or plaster of Paris cast was used to remove the alginate. The negative impression was obtained by removing the assembly after 15 to 20 minutes. The positive cast using stone cast (kalstone) powder was made by filling the hollow of the alginate cast, which was then kept for 10-15 hours. The carrier material (2 mm thick) was made by use of self-curing dental acrylic material to cover the target area and a part of the body contour surrounding it. As per necessities, velcro straps were attached to the carrier for comfortable fitting during treatment (Figure 2B). For intra-oral tumours, the carrier prosthesis was made using similar procedure of negative and positive cast making in the dental department (Figure 2C). A dental obturator was made over the positive cast, which was used as a carrier material.

Wax sheets were applied over the carrier material for reinforcement of the catheters to obtain a distance of 5 mm from the surface. Nylon catheters were placed over the wax at a spacing of 10 mm to ensure coverage of the target volume. After the catheters were fixed to the carrier, the entire assembly was tested over the patient for proper fitting (Figure 2B, 2D).

**Brachytherapy planning and treatment**

Three dimensional computed tomography (CT) based planning was done using thin CT slices of 1 to 1.25 mm slice thickness on Somatom Emotion (Siemens Medical Systems, Germany). To ensure proper visualization, metallic markers or thin copper wires were placed at the edges of the tumour and in the tubes. On the planning scan, the proper fitting of

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**Fig. 1.** Workflow of the procedure of surface mould brachytherapy
the mould material was verified, and in case of improper fitting with intervening air gaps, repeat images were undertaken or the entire procedure was repeated on some occasions. Planning was done using Oncentra brachytherapy version 3.3 and 4.1 (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). Catheter reconstruction was done using multiplanar reconstruction, and loading was decided based on the target volume marked on patient. Dose points were defined at 5-7 mm from the source and dose distribution was obtained. Dose point optimization was done for all the patients. Evaluation of the plan was done with slice-by-slice visualization of the target coverage. Dose was prescribed at 100% isodose line in 33 patients and at 85% in 2 patients. Parameters such as $V_{100}$, $V_{150}$, $V_{200}$, and dose homogeneity index ($DHI$) were evaluated for each patient. In SMB, majority of $V_{150}$ and $V_{200}$ were observed inside the carrier prosthesis, and hence had little impact on the plan evaluation process. Dose per fraction of 3-4 Gy, twice daily, 6 hours apart was considered. Total dose ranged from 38.5 Gy to 52.5 Gy in 11-15 fractions in radical setting, and 15-30 Gy in 5-10 fractions as boost.

Radical brachytherapy was considered for tumours of skin and T1 tumours of intraoral region. The aim was to deliver doses of 54-60 Gy equivalent dose of 2 Gy ($EQD_2$) (Table 1). Combined external beam radiotherapy (EBRT) and SMB boost was considered in intraoral tumours with T2 lesions. The external beam radiotherapy was considered prior to SMB to a dose ranging from 44 to 60 Gy (median, 50 Gy) at 2 Gy per fraction. In these patients, the aim was to achieve total combined dose of 66-72 Gy $EQD_2$ (Table 1). The appropriate fitting of the mould was verified and presence of airgap checked clinically before each fraction by the treating radiation oncologist.

On completion of the treatment, in case of skin reactions, patients were prescribed topical steroid creams. The radiation related toxicities were classified according to the Radiation Therapy Oncology Group (RTOG) grading system. The first review was done at 2 weeks from completion, then at 6 weeks, and subsequently every 3 months, till 2 years and then 6 monthly. On follow-up, detailed clinical examination was undertaken and further investigations were done only if warranted clinically. Pre-radiotherapy

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![Fig. 2. Preparation of carrier material and assembly during treatment in patients treated with surface mould brachytherapy for head and neck cancers. A) Application of alginate material over pinna and surrounding region for preparation of the carrier for a patient with basal cell carcinoma of pinna. B) The mould with catheters in situ connected to the treatment machine. C) Dental impression prepared for a patient with squamous carcinoma of hard palate. D) The mould assembly in position for the same patient just prior to treatment delivery.](image-url)
and post-radiotherapy visual evaluation of cosmetic outcome was done in all patients. The outcomes were subjectively scored as excellent, good, fair, or poor by the treating radiation oncologist. For assessment of function preservation for skin or hard palate tumours, integrity of the organ without any complication was taken as desired end point.

**Statistics**

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS V21) software. Kaplan Meier methods were used for analysis of survival outcomes and curves were plotted accordingly. The date of starting radiotherapy was taken for calculation of the survival, and date of recurrence was the date of clinically or radiologically relapsed disease. The prognostic factors for survival were compared using log-rank test (Mantel-Cox) for univariate analysis, and Cox regression for multivariate analysis. A p-value of less than 0.05 was considered to be of statistical significance. X² test was performed for assessment of toxicity and relation with various factors.

**Results**

**Patient and treatment characteristics**

The patient characteristics and treatment details are summarized in Table 1. The median time from onset of symptoms to diagnosis was 5 months (range, 1-36 months). In 31 patients, SMB was used as the primary...
treatment modality, and in four patients, for disease recurrence as the second primary. The growth was ulcerative in 13 patients, ulceroproliferative in 12, proliferative in 6, infiltrative and superficial creeping in 2 patients each.

In 8 patients, SMB was used as boost after EBRT. Of these, 7 patients had lesions in palate (3 soft palate, 2 hard palate, and 2 over the soft palate/hard palate junction), and 1 over tonsil. Seven patients were treated using parallel opposed portals, while in 1 patient IMRT (soft palate primary) was considered. Median gap between EBRT and BT was 14 days (range, 8 to 28 days). Concurrent weekly chemotherapy with cisplatinum (30 mg/m²) was used during EBRT in 2 patients with carcinoma soft palate due to bulky disease. For patients treated with brachytherapy alone, the treatment duration ranged from 5 to 11 days (median, 7 days). Dosimetric data was available for 30 patients and has been summarized in Table 1.

### Outcomes

#### Local control

The median follow-up for surviving patients was 52 months (range, 6 to 98 months). Two and 5-year local control (LC) was 82% for the entire cohort. There were 6 local failures (1 nose, 3 hard palate, 1 hard-soft palate junction, 1 tonsil). The median time to recurrence was 6 months (range, 5 to 15 months). For skin and intra-oral malignancies, 5-year LC rates were 92% and 76%, respectively (Figure 3). The 5-year LC rate for basal cell carcinoma was 100%, while for squamous carcinoma it was 79%. Patients treated in upfront setting had 5-year LC of 86% while it was 50% for recurrent disease. Patients with hard palate lesions had 5-year LC of 79%.

#### Patterns of failure

In addition to the 5 local recurrences, 1 patient had combined primary and nodal failure. Two patients (both hard palate) had isolated nodal failures (involv-

### Table 2. Patterns of failure in 35 patients treated with surface mould brachytherapy for head and neck cancers

| Site                        | Recurrence (months) | Treatment of recurrence | Response | Last follow-up (months) | Status during last follow-up |
|-----------------------------|---------------------|-------------------------|----------|-------------------------|------------------------------|
| Isolated primary failure    |                     |                         |          |                         |                              |
| Hard palate                 | 5                   | MCT                     | Progression | 16                      | Death due to disease         |
| HP-SP junction              | 6                   | MCT                     | Progression | 20                      | Death due to disease         |
| Tonsil (rec)                | 6                   | Surgery with B/L MND    | CR       | 8                       | Alive NED                    |
| Nose                        | 8                   | Surgery                 | CR       | 47                      | Died of cardiac cause        |
| Hard palate                 | 15                  | Wide local excision     | CR       | 59                      | Alive NED                    |
| Primary and nodal failure   |                     |                         |          |                         |                              |
| Hard palate (rec)           | 5                   | Planned for surgery     | Treatment pending | 6                      | Alive with disease           |
| Isolated nodal failure      |                     |                         |          |                         |                              |
| Hard palate                 | 7                   | B/L MND                 | CR       | 49                      | Alive NED                    |
| Hard palate                 | 18                  | I/L MND f/b adj EBRT    | CR       | 67                      | Alive NED                    |
| Third primary (both were treated for second primary) | | | | | |
| Hard palate (rec)           | 4 (3rd primary in tonsil with suprasternal nodes) | MCT | Progression | 17 | Died of progression from 3rd primary |
| Hard palate (rec)           | 20 (small primary in lateral tongue) | WLE | CR | 91 | Alive NED |

MCT – metronomic chemotherapy, B/L – bilateral, MND – modified neck dissection, CR – complete response, NED – no evidence of disease, I/L – ipsilateral, EBRT – external beam radiation therapy, WLE – wide local excision, last follow-up measured from baseline date
ing ipsilateral level IB and II). Two patients who were treated for second primary, developed third primary cancer subsequently (1 soft palate and hard palate each) (Table 2).

Survival

For the entire cohort, 2 and 5-year disease free survival (DFS) was 69%. Of the 5 local recurrences, 3 patients underwent successful salvage surgery and 2 were considered for palliative metronomic chemotherapy (in view of extensive local disease). One patient with primary and nodal disease was being considered for surgical salvage at the last follow-up. Two patients with nodal recurrence underwent salvage neck dissection. Of the 2 patients with 3rd primary tumour, 1 underwent successful salvage surgery, while another patient was considered for metronomic chemotherapy. The 2-year and 5-year cause specific survival (CSS) was 92%.

Of all the patients with recurrent disease, 3 patients on palliative metronomic chemotherapy died due to disease. Two other unrelated deaths were seen (1 each from cardiac cause and pyrexia of likely infective etiology), both controlled of disease. The 2 and 5-year, overall survival (OS) was 86% and 81%, respectively.

Prognostic factors

Various prognostic factors for LC are summarized in Table 3. T stage (T1 vs. T2) and dose per fraction (3 Gy or more) were the only significant factors. Local control for T1 and T2 tumours were 94.2% and 68.2%, respectively ($p = 0.04$). Patients treated with $> 3$ Gy had 5-year LC of 92% when compared to 50% for those treated with $3$ Gy/fraction ($p = 0.003$). Although statistically insignificant, better control rates were seen for tumours treated in upfront setting, basal cell histology and tumours located over skin. On multivariate analysis, none of the prognostic factors were found to be significant. Also, none of the factors were seen to impact DFS, CSS, or OS significantly.

Toxicity

Grade 1 late subcutaneous fibrosis was seen in 17%. Three patients developed hypopigmentation (all for nose primary). Telangiectasia was seen in 9 patients. Grade 1 xerostomia was seen in 6 patients, all of them had received EBRT. One patient developed palatal perforation of the soft palate, and in 1 patient bone was exposed. None of the factors (patient, tumour, or treatment related) were significantly associated with toxicity on univariate or multivariate analysis. Surface mould brachytherapy resulted in organ and function preservation in all patients (Figure 4A, 4B). The late cosmesis was excellent in patients with skin tumours (Figure 4C, 4D).

Discussion

Surface mould brachytherapy is a well-established treatment for the surface tumours of head and neck region, and used since many decades. However, there are only few reports of outcome with SMB using HDR brachytherapy, and have been summarized in Table 4. Amongst the published data, majority of the studies have focused on SMB for skin cancers [6,7,8,9]. In our study, there were 21 patients with intraoral tumours and 14 patients with skin malignancies. This appears to be one of the largest series of SMB for intraoral malignancies.

We have observed 5-year LC rate of 92% in patients with skin malignancies. Local recurrence was observed in a single patient with tumour located over the nose. Recurrence was observed 8 months after SMB and was successfully salvaged with surgery. The LC rate in our series is comparable to that of the reported literature. In the series reported by Maronas et al., all the 5 patients who had recurred (of total 48), the tumour was located

| Parameter | Number of events (total patients) | 5-year local control (%) | p value |
|-----------|-------------------------------|------------------------|---------|
| **Age**   |                               |                        |         |
| 50 years or less | 2 (15)                   | 86.7                   | 0.66    |
| More than 50 years | 4 (20)                   | 79.1                   |         |
| **Presentation** |                      |                        |         |
| Upfront | 4 (31)                     | 86.4                   | 0.05    |
| Recurrent | 2 (4)                       | 50                     |         |
| **Site**  |                               |                        |         |
| Oral cavity | 5 (21)                    | 75.9                   | 0.22    |
| Skin      | 1 (14)                      | 92.3                   |         |
| **Histology** |                             |                        |         |
| Squamous carcinoma | 6 (29)                   | 78.7                   | 0.24    |
| Basal cell carcinoma | 0 (6)                   | 100                    |         |
| **T stage** |                               |                        |         |
| T1  | 1 (19)                     | 94.2                   | 0.04    |
| T2  | 5 (16)                     | 68.2                   |         |
| **Treatment** |                             |                        |         |
| Boost (after EBRT) | 3 (8)                     | 62.5                   | 0.05    |
| Radical | 3 (27)                     | 88.2                   |         |
| **Dose (radical setting only)** |                     |                        |         |
| Less than 49 Gy | 2 (13)                    | 84.6                   | 0.46    |
| 49 Gy or more | 1 (14)                    | 92.3                   |         |
| **Dose per fraction** |                     |                        |         |
| 3 Gy  | 4 (8)                       | 50.0                   | 0.003   |
| More than 3 Gy | 2 (27)                    | 91.9                   |         |

EBRT – external beam radiotherapy

Table 3. Prognostic factors affecting local control in 35 patients treated with surface mould brachytherapy for head neck cancers
over the nose [9]. Extra caution is therefore required for treating tumours over nose. In such cases, proper fitting of the carrier material needs to be ensured since chances of missing the target volume exist owing to curved surface.

With a median follow-up of 52 months, we have observed LC rate of 76% for the intraoral tumours. In 15 patients with hard palate primary, the 5-year control rate was 79% (including 2 treated in recurrent setting). Radical radiotherapy has been reported to result in a 5-year local control of 75% and 79% for T1/T2 lesions of hard palate [13,14]. In the present study, of the 7 patients who had T2 lesion of the hard palate, 3 developed nodal failure, which were seen in ipsilateral level IB and II. These patients were treated with SMB alone. In the series reported by Yorozu et al., 5 of 19 SCC patients had developed nodal recurrence subsequently. Similarly, in a series of 17 patients, Mourouzis et al. reported 4 nodal failures in hard palate squamous carcinoma for advanced cases [15]. We suggest elective nodal irradiation for T2 squamous carcinomas of hard palate, and volumes should encompass ipsilateral level IB and II.

T stage ($p = 0.04$) and dose per fraction ($p = 0.003$) were the only 2 factors, which were statistically significant on univariate analysis of LC. T2 tumours had higher failure rates when compared to T1. Local control rates have been reported to be poor with increasing tumour size for nasal skin cancers [16]. The LC rate for $> 3$ Gy/fraction was 92%, while it was 50% for 3 Gy per fraction. This could however be due to the fact that $> 3$ Gy was considered for skin, while 3 Gy was commonly used for intraoral malignancies. Local control was inferior for recurrent tumours but did not reach significance (Table 3). Similar observation was made by Guix et al. where recurrent tumours had performed inferiorly. In the present study, although significant values were not achieved, all the recurrences were seen in squamous carcinoma. In the series by Guix et al., the only patient to fail for primary treatment setting was of squamous histology.

For preparation of the mould, we had used individualized carrier material. The major benefit of such customized mould is proper fitting of the mould, avoiding underdosage due to improper fitting. Similar technique for treatment of skin tumours were adopted by other authors while fixed applicators were used in some studies [6,7,8,9]. For tumours over palate and tonsil, the prepa-
ration of the mould was done in coordination with department of dentistry. Appropriate fitting was confirmed on planning CT scans. Several authors had reported use of similar technique for intra-oral tumours [10,12,17]. In all patients, we have used CT based planning to ensure proper coverage of tumour. Also in few patients, due to improper fitting, the procedure of making the mould was repeated. We suggest careful and meticulous evaluation of the imaging to ensure absence of any air gap between the surface and carrier. The HDR allows the advantage of optimization while planning, and faster treatment delivery. Presently, techniques are under development regarding preparation of computerized 3D mould based on cross sectional imaging. This can be convenient as automated generation and exact reproduction of body contour can possibly lead to better fitting. Clinical outcomes using such techniques are expected to be available in near future.

The compliance was excellent and all patients completed planned treatment. Of significant late toxicities, asymptomatic palatal perforation (approx. 1 x 1 cm size) was seen in one patient treated for recurrent setting. Patient was asymptomatic and did not require any intervention for the perforation. The other toxicity seen was exposed bone for primary over hard palate. However, there was disease recurrence at the site of initial disease, so more likely it being due to disease process rather than toxicity. Restricting the depth of prescription to 5-7 mm can be postulated as plausible reason for reducing late toxicities in our series. The cosmesis was seen to be excellent for all the patients with few developing minimal hypopigmentation.

Conclusions

Surface mould brachytherapy results in excellent LC rates for skin tumours and should be considered as a standard for management of superficial localized head and neck tumours. This technique results in good LC rate in T1 intraoral tumours when considered as radical treatment, while it may be preferable to consider it as a boost for T2 intraoral tumours. Surface mould brachytherapy results in minimal toxicity with excellent cosmesis and function preservation.

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Disclosure

Authors report no conflict of interest.

Table 4. Different studies for high-dose-rate surface mould brachytherapy in head and neck region

| Author (year) | Number of patients | Site | Dose and fraction | Follow-up | Local control | Toxicity | Cosmesis |
|---------------|--------------------|------|-------------------|-----------|---------------|----------|----------|
| Svoboda et al. (1995) [3] | 76 | All site skin (9 pinna, 28 head neck) | Radical 18-22 Gy/1 fr. to 50 Gy/15 fr. | 9.6 months (avg) | 100% | Moist desquamation in 22.5% | Excellent |
| Allan et al. (1998) [4] | 13 | Pinna | Radical 44 Gy @ 5.5 Gy/fr. | 18 months (minimum) | 100% | Acute skin toxicity | Excellent |
| Guix et al. (2000) [5] | 136 | Face | Radical 60-80 Gy @ 1.80 Gy/fr. | 12 months (minimum) | 5 year – 98% | 100% skin erythema 10% skin ulceration (acute) | 92% good or excellent cosmesis |
| Maronas et al. (2011) [6] | 48 | Face | Radical 48-57 Gy @ 3-4 Gy/fr. | 45 months (median) | 2 year – 91% 5 year – 89% | Acute skin toxicity 78% | Good or very good late cosmesis |
| Ariji et al. (1999) [14] | 4 | FOM, BM, gingival | Boost 25-30 Gy @ 2.5-3.5 Gy/fr. | 14-26 months | 100% | No late toxicity | Not reported |
| Kudoh et al. (2010) [7] | 2 | Maxillary gingiva | Boost (residual) 50 Gy @ 5 Gy/fr. | 2 and 8 months | 100% | Grade 3 mucositis in 1 | NA |
| Matsuzaki et al. (2012) [8] | 6 | BM, lip | Boost 24 Gy @ Gy/fr. | 27 months (median) | 1 of 6 had local recurrence | Grade 2 acute mucositis in all | NA |
| Unetsubo et al. (2015) [9] | 17 | BM, gingival, lip, HP, FOM | Boost 24 Gy @ 6 Gy/fr. | 53 months (median) | 3 year and 5 year – 54.1% | Acute mucositis in 100% | Not reported |
| Present study (2017) | 35 | Face, HP, SP, tonsil | Radical 38.5-52.5 Gy Boost 15.5-30 Gy @ 3-4 Gy/fr. | 52 months | 5 year for skin – 92.3% and intra-oral – 75.9% | Grade II or more acute skin toxicity in 17% and mucosal in 31% | Excellent |

LC – local control, FOM – floor of mouth, BM – buccal mucosa, HP – hard palate, SP – soft palate, NA – not applicable, fr. – fraction
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