High dose rate brachytherapy for oral cancer

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Brachytherapy results in better dose distribution compared with other treatments because of steep dose reduction in the surrounding normal tissues. Excellent local control rates and acceptable side effects have been demonstrated with brachytherapy as a sole treatment modality, a postoperative method, and a method of reirradiation. Low-dose-rate (LDR) brachytherapy has been employed worldwide for its superior outcome. With the advent of technology, high-dose-rate (HDR) brachytherapy has enabled health care providers to avoid radiation exposure. This therapy has been used for treating many types of cancer such as gynecological cancer, breast cancer, and prostate cancer. However, LDR and pulsed-dose-rate interstitial brachytherapies have been mainstays for head and neck cancer. HDR brachytherapy has not become widely used in the radiotherapy community for treating head and neck cancer because of lack of experience and biological concerns. On the other hand, because HDR brachytherapy is less time-consuming, treatment can occasionally be administered on an outpatient basis. For the convenience and safety of patients and medical staff, HDR brachytherapy should be explored. To enhance the role of this therapy in treatment of head and neck lesions, we have reviewed its outcomes with oral cancer, including Phase I/II to Phase III studies, evaluating this technique in terms of safety and efficacy. In particular, our studies have shown that superficial tumors can be treated using a non-invasive mold technique on an outpatient basis without adverse reactions. The next generation of image-guided brachytherapy using HDR has been discussed. In conclusion, although concrete evidence is yet to be produced with a sophisticated study in a reproducible manner, HDR brachytherapy remains an important option for treatment of oral cancer.

Keywords: brachytherapy; oral cancer; high dose rate

INTRODUCTION

Because adjacent normal tissues, such as the salivary glands, mandible, and mastication muscles, are at risk of damage during treatment with external beam radiation therapy (EBRT), brachytherapy is an important alternative to conventional radiotherapy. Brachytherapy provides a high localized dose of radiation, with rapid fall-off and short overall treatment time [1]. It can be applied as a sole treatment, as a treatment complementary to surgery, and as a local boost in combination with EBRT.

Low-dose-rate (LDR) brachytherapy has been employed in the treatment of carcinoma of the lip, tongue, floor of the mouth, oral mucosa, base of the tongue, tonsillar region, soft palate, and nasopharynx, and has been the gold standard for brachytherapy. With the advent of new
technologies, high-dose-rate (HDR) and pulsed-dose-rate (PDR) brachytherapy have been adapted in many institutes to avoid exposure of health care providers to radiation. HDR and PDR stepping source technology offer the advantage of optimizing dose distribution by varying dwell times [1]. The application of HDR brachytherapy has expanded to many sites, having been used in treatment of gynecological cancer, breast cancer, and prostate cancer [2, 3]. Guede et al. reported that gynecological brachytherapy remains the most common application, although the use of brachytherapy in prostate cancer and breast cancer has increased in Europe [4].

CT-based dosimetry has become increasingly common since 2002. Use of HDR and PDR techniques has increased markedly, while use of both LDR and medium-dose-rate brachytherapy has declined. However, for head and neck cancer, HDR usage decreased in Group I institutes (those in countries with the highest GDP) from 5% (2002) to 2% (2007) [4]. LDR and PDR interstitial brachytherapies (ISBT) were utilized instead. Accordingly, HDR brachytherapy has not become widely used in the radiotherapy community for treating head and neck cancer because of lack of experience and biological concerns [5, 6].

Mazeron et al. noted that the efficacy and safety of HDR brachytherapy must be validated in prospective studies. If it is the only technique available, treatment should be delivered in fractions of <3–4 Gy, according to GEC-ESTRO recommendations [1]. Several members of the American Brachytherapy Society expressed concern about potential morbidity with fraction sizes as large as 6 Gy to the oral cavity [6]. On the other hand, very little clinical evidence has been found suggesting a higher risk of high-dose fractionation (≥6 Gy). Acceptable results have been obtained from a few institutes.

To enhance the role of HDR brachytherapy, we reviewed the results of HDR brachytherapy, including our experiences in Phase I/II and III trials, to investigate the next generation of image-guided brachytherapy using HDR.

**HDR brachytherapy for tongue cancer**

Tongue cancer located anterior to the circumvallate papillae vitaly affects not only speech, but also coordination of chewing and swallowing. 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. Brachytherapy alone is recommended for T1N0 and T2N0 tumors <4 cm. For tumors >3–4 cm or N1 lesions, although surgery is often preferred, brachytherapy can be delivered as a boost after 40–45 Gy of EBRT to the neck and oral cavity. In general, the local control rate is higher than 90% for T1 and T2N0 tumors treated with LDR brachytherapy alone [1]. The local control rate is lower in patients with larger tumors treated with EBRT and a brachytherapy boost. Approximately 10–30% of patients may develop soft tissue necrosis within the implant volume. Osteoradionecrosis may occur in 5–10% of cases. The vast majority of necroses heal spontaneously after medical treatment. Surgical intervention is necessary in only 1–2% of patients [1].

Lau et al. initiated a Phase I/II protocol using HDR-ISBT [7] (Table 1). In that study, 27 patients were treated (T1, n = 10; T2, n = 15; and T3, n = 2). Seven fractions × 6.5 Gy of HDR-ISBT were administered twice-daily, with a minimum interval time of 6 h over a period of 3.5 days. The actual tumor control probability after HDR brachytherapy was 53% at 5 years. Local control rates for T1 and T2 tumors were lower than those for comparable historical controls treated at our institution using LDR radium (Ra-226) or cesium (Cs-137) needle implants and iodiridium (Ir-192) wire implants. In addition, a trend was observed toward a higher incidence of severe complications for HDR patients compared with the historical controls treated with LDR brachytherapy.

On the other hand, Leung et al. reported good outcomes for eight patients treated solely with HDR-ISBT. Five patients had T1N0 disease, and the remaining three had T2N0 disease [8]. The median follow-up period for these patients was 26 months. The median dose administered was 60 Gy/10 fractions over 6 days. Mandibular and maxillary shields were inserted prior to treatment. Mucositis for 6–20 weeks (median, 10 weeks) was observed in all patients. No local failure was evident after the median follow-up period. One patient treated with a double planar implant developed Grade 3 necrosis of the soft tissue and bone. Leung et al. [8] concluded that the HDR remote after-loading technique is useful because it provides a local control rate of 100% with acceptable morbidity. On further investigation in 2002, they found that a protocol of 5.5 Gy/10 fractions was feasible, resulting in a local control rate of 94% at 4 years in ten T1 and nine T2 patients without severe morbidity [9].

Ohga et al. treated 28 patients with N0 oral tongue cancer using HDR-ISBT combined with local injection of bleomycin [10]. A median dose of 5 mg bleomycin was injected locally, and 16–20 Gy was delivered to the area surrounding the applicators within the first two days for control of the tumor implant. The 2-year local recurrence-free survival rate in that study was 96% [T1/2: 100% (8/8, 15/15); T3: 80% (4/5)]. The minimum tumor dose was decreased step-by-step. Local recurrence rates of 12.5% (1/8), 0% (0/14), and 0% (0/6) were observed in patients with median minimum tumor doses of 60, 50 and 40 Gy, respectively. Local recurrence rates did not increase when the minimum tumor dose decreased. Late adverse effects included the following: tongue ulcer (11%, 3/28), oral floor ulcer (4%, 1/28), and osteonecrosis (4%, 1/28). These results suggest that decrease in the minimum tumor dose to <60 Gy may be possible in combination treatment with local injection of bleomycin.
Table 1. Results of HDR brachytherapy for oral tongue cancer

| Author (year) Institute | n | T category | Schedule | Local control | Toxicity | Remark |
|-------------------------|---|------------|----------|---------------|----------|--------|
| Lau (1996) [7] British Columbia Cancer Agency, Canada | 27 | 10T1, 15T2, 2T3 | Bx only: 6.5 Gy × 7 fr | 53% 5/10 T1, 7/15 T2, 2/2 T3 | 37% toxicity | HDR; lower local control rate higher severe complication rate |
| Leung (1997) [8] Tuen Mun HP, Hong Kong | 8 | 5T1, 3T2 | Bx only: 6 Gy × 10 fr | 100% | 1G3 both S + B | HDR feasible |
| Leung (2002) [9] Tuen Mun HP, Hong Kong | 19 | 10T1, 9T2 | Bx only: 5.5 Gy × 10 fr | 94% (4 y) | 1G2 both S + B | HDR feasible |
| Ohga (2003) [10] Fukuoka, Japan | 28 | 8T1, 15T2, 5T3 | Bleomycin + EBRT: 40–65 Gy + Bx: 4–5 Gy × 2–4 | 96% (2 y) | late 18% S15%, B4% | chemoradiotherapy Bleomycin reduce Bx dose |
| Umeda (2005) [11] Kobe, Japan | 26 HDR | 8T1, 18T2 | Bx only: 6 Gy × 9–10 | 65% | NA | surgery optimal Tx |
| | 78 LDR | 42T1, 36T2 | Bx only: 61 Gy (Ra–226, Cs–137) | 83% | | |
| | 71 surgery | 42T1, 29T2 | | | 94% | |
| Nishioka (2006) [12] Sapporo, Japan | 4 | 1T3, 3T4 | Ia CDDP: 100–120 mg + EBRT: 30 Gy + Bx: 6 Gy × 7 (S–8) | LRC 100% | 100% G3 mucositis | intraarterial chemoradiotherapy ia can reduce Bx dose |
| Patra (2009) [13] Kolkata, India | 33 | advanced 18, early 15 | EBRT: 50 Gy (46–66 Gy) + Bx: 3–3.5 Gy × 4–7 (14–21 Gy) | 79% CR + 21% PR 100% early, 78% advanced disease** | 12% G3 mucositis and other*** | |
| Guinot (2010) [14] Valencia, Spain | 50 | 42T1–2, 8T3 | 33PT EBRT: 50 Gy + Bx: 3 Gy × 6 (12–24.5 Gy) | 94% T1, 84% T2, 0% T3 | 16% S, 4% B | 3–4 Gy/fr feasible |
| | 16N+ | 17PT Bx only: 4 Gy × 11 (42–49 Gy) | Bx 100% vs EBRT + Bx 69% (P = 0.04) | | | |
| Osaka University | | | | | | |
| Teshima (1992) [18] Phase II/II dose escalation trial | 7 various (4 tongue) | T1–3N0 | EBRT: (32–52 Gy) + Bx: 3.5 Gy × 10 ⇒ 6 Gy × 10 | 100% CR | no early complication | HDR 6 Gy × 10 feasible |
| Inoue Ta (2001) [21] Phase III randomized trial | 25 HDR | 14T1, 11T2 | Bx only: 6 Gy × 10 | 87% | 15% toxicity | HDR ≃ LDR prospective study |
| | 26 LDR | 14T1, 12T2 | Bx only: 70 Gy/4 9 days | 84% | HDR B2, Both arms S1 | T1–2N0 HDR vs LDR |

Continued
| Author (year) | Institute | Vn | T category | Schedule | Local control | Toxicity | Remark |
|--------------|-----------|----|------------|----------|---------------|---------|--------|
| Yamazaki (2003) [22] | T1–2N0 Bx only | 58 HDR | 22T1, 36T2 | Bx only: 6 Gy × 8–10 | 84% | S2%, B2%, both 1% | HDR ≃ LDR in T1–2 |
| | | 341 LDR* | 171T1, 170T2 | Bx only: 70 Gy (6–84 Gy) | 80% | S3%, B3%, both 1% |
| Yamazaki (2007) [23] | T1–2N0 | 80 HDR | 24T1, 47T2, 9T3 | EBRT: 37 Gy ± Bx: 6 Gy × 6–10 | 87%T1, 79%T2, 89%T3 | Bx 19%, Bx + EBRT 29% | HDR ≃ LDR in T1–3 |
| | | 217 Ra–226 | 77T1, 103T2, 37T3 | EBRT: 29 Gy ± Bx: 72 Gy (59–94 Gy) | 85%, 75%, 62% | Bx 9% Bx + EBRT 24% | EBRT elevated toxicity |
| | | 351 Ir–192 | 111T1, 202T2, 38T3 | EBRT: 30 Gy ± Bx: 72 Gy (59–94 Gy) | 79%, 73%, 64% | Bx 10%, Bx + EBRT 28% |
| Kakimoto (2001) [24] | T3N0–2 | 14 HDR | All T3 | EBRT: 30 Gy (12.5–60 Gy) ± Bx: 6 Gy × 10 | 71% (2 y) | S21% B0% | HDR ≃ LDR in T3 |
| | | 61 LDR Ir–192 | EBRT: 30 Gy (12.5–60 Gy) ± Bx: 72 Gy (5–94 Gy) | 67% (2 y) | S5% B20% |
| Akiyama (2012) [25] | T1–2N0 60 Gy vs 54 Gy | 17 54 Gy arm | 7T1, 10T2 | Bx only: 6 Gy × 10 | 88% (2 y) | S0%, B6%, both 12% | 6 Gy × 9 ≃ 6 Gy × 10 |
| | | 60 Gy arm | 16T1, 18T2 | Bx only: 6 Gy × 9 | 88% (2 y) | S3%, B3%, both 6% |

* n = number of patients, EBRT = external beam radiotherapy, Bx = brachytherapy, B = bone exposure and/or necrosis (late complication), S = ulcer soft tissue (late complication), ia = intraarterial infusion, CR = complete response, PR = partial response, LRC = locoregional control, NA = not available, CRT = chemoradiotherapy, G = grade, *227Ir:192:113 Ra:226:1 both, **including surgical salvage, ***9% transient hemorrhage (3% local infection, 3% severe dysphasia, 15% xerostomia Grade 3–4), † HDR unless otherwise stated, ‡ twice a day unless otherwise stated, § 5 y unless otherwise stated.
Umeda et al. reported the results of a retrospective study comparing the efficacy of LDR-ISBT, HDR-ISBT, and surgery for early tongue cancer [11]. In total, 180 patients with Stage I/II tongue cancer were divided into three treatment groups: LDR \((n = 78)\), HDR \((n = 26)\) and surgery \((n = 71)\). Local recurrence was seen in 13 patients (17%) in the LDR group, 9 (35%) in the HDR group, and 4 (6%) in the surgery group. After salvage therapy, a final local cure was achieved in 71 patients (91%) in the LDR group, 22 (85%) in the HDR group, and 71 (100%) in the surgery group. The respective 5-year overall survival rates for the LDR, HDR and surgery groups were 84.0%, 72.9% and 95.4% for patients with Stage I tumors and 72.2%, 51.5% and 93.8% for patients with Stage II tumors, respectively. Umeda et al. [11] concluded that surgery is the optimal treatment method for patients with Stage I/II tongue cancer. However, a substantial treatment bias was present in that study because of its retrospective nature.

Nishioka evaluated the efficacy and safety of intraarterial cisplatin infusion plus EBRT and HDR brachytherapy [12]. Superselective intraarterial infusion of cisplatin (100–120 mg) was performed concomitantly with EBRT in four patients with locally advanced carcinoma of the tongue. All patients received an HDR-ISBT boost after combination therapy. Brachytherapy was performed twice daily after EBRT with a fraction of 6 Gy up to a total of 30–48 Gy. All patients completed the therapy as scheduled. No vascular or neurological complications were observed. Grade 3 acute radiation mucositis developed in all patients, but this did not necessitate a treatment break. After a mean follow-up period of 35 months, locoregional control had been achieved for all patients.

Patra et al. treated 33 patients with oropharynx and oral cavity carcinomas with HDR-ISBT after EBRT at Medical College Hospital, Kolkata [13]. Early stage disease (Stage I/II) was noted in 15 patients, and advanced stage disease (Stage III/IV) was diagnosed in 18. All received EBRT at a median dose of 50 Gy (range, 46–66 Gy) to the primary tumor and regional lymph nodes before brachytherapy. Node-negative patients with residual neck disease also underwent neck dissection. The brachytherapy dose in combination with EBRT ranged from 14–21 Gy (3–3.5 Gy per fraction, two fractions daily). The follow-up period was between 18 and 40 months. At the end of radiation treatment, complete response was achieved in 79% of patients, and partial response was achieved in 21%. The ultimate control rates (including surgical salvage) were 100% and 78% for early and advanced disease, respectively. Local failure occurred in three patients (9%) after complete response. No distant metastasis was observed during follow-up. Grade 3 mucositis was observed in 12% of cases. Transient hemorrhage occurred in three (9%) patients and local infection in one (3%) patient. Severe dysphagia developed in one (3%) patient. Severe xerostomia (Grade 3/4) occurred in five of 33 (15%) patients; most patients experienced less severe xerostomia (Grade 1/2).

Guinot et al. reported on 50 patients treated for oral cavity carcinoma with HDR-ISBT [14], 42 of whom were diagnosed as having Stage T1/2 tumors and 8 of whom had Stage T3 tumors. In addition, minimal lymph node involvement (Stage N1) was confirmed in 16 patients, but no lymph node involvement was observed in the other 34 patients (N0 stage). ISBT alone was administered to 17 (T1/2N0) patients (34%), and 33 patients (66%) received ISBT complementary to EBRT. A perioperative technique was performed for 14 patients. The median total radiation dose was 44 Gy when HDR brachytherapy was used alone (4 Gy/fraction), and 18 Gy was used when HDR brachytherapy was complementary to 50 Gy EBRT (3 Gy/fraction). Actual disease-free survival rates at three and five years were 81% and 74%, respectively (median follow-up, 44 months). Local failure developed in 7 patients. Local control rates at three and five years, respectively, were as follows: 87% and 79% (T1/2); 94.5% and 91% (T3); and 43% and 43% (with salvage surgery). Local control was maintained in all the cases in which HDR brachytherapy was the sole treatment. Local control rates in the combined treatment group (EBRT + HDR-ISBT) were 80% and 69% at three and five years, respectively \((P = 0.044)\). Soft tissue necrosis developed in 16%, and bone necrosis developed in 4% of the cases. Guinot et al. [14] concluded that HDR brachytherapy is an effective method for the treatment of tongue carcinoma in low-risk cases. Doses per fraction of 3–4 Gy yielded local control, and complication rates were similar to those observed in LDR brachytherapy. Results using the perioperative technique are also encouraging.

**Osaka experiences**

**Phase I/II study: early mucosal reaction and late tongue atrophy**

At Osaka University Hospital, more than 1450 patients with mobile tongue cancer were registered over the course of 30 years (Table 1) [15]. In the early years of treatment, Cobalt-60 needles were used for ISBT; however, in 1968, these were replaced by Ra-226 needles, which were used until 1987. In 1973, the first Ir-192 wire was installed in the delivery system, and manual after-loading with a guide gutter technique began. Ir-192 hairpins or Cs-137 needles are now usually used for LDR interstitial radiotherapy in Japan.

In 1991, Inoue et al. installed an HDR remote-controlled after-loading system using an Ir-192 microsource, the MicroSelectron-HDR (Nucletron, Veenendaal, The Netherlands) [16]. They initiated a Phase I/II study for head and neck cancer to determine the optimal schedule for multifractionated HDR brachytherapy because of the lack of a standard treatment schedule [2, 16]. Initially, a dose rate conversion factor of approximately 0.54–0.6 from LDR to HDR was...
adopted, based on the results of the previous studies [6] of cervical cancer [17]. An overall treatment time of one week was established, which is the same as that of LDR brachytherapy. The dose was increased at 20% intervals starting at 35 Gy up to 60 Gy (Table 2), using the standard of 2 fractions per day with a minimum gap of 6 h because of its suitability for routine practice [18].

In Case No. 1, a dose schedule of 35 Gy/10 fractions per week was selected. A dose equivalent to 50–60 Gy of LDR interstitial radiotherapy was used for HDR brachytherapy, in this case after the administration of 52 Gy of EBRT. However, the acute mucosal reaction was milder than expected. In Case No. 2, a dose equivalent to 70 Gy of LDR interstitial radiotherapy was necessary after 30 Gy of EBRT; therefore, a dose schedule of 42 Gy/10 fractions per week was selected. However, the acute mucosal reaction was again milder than expected. In Case No. 3, the dose of HDR was increased to 50 Gy/10 fractions per week after EBRT (50 Gy) because of tumor size. Case No. 4 received no previous treatment. Therefore, a dose schedule of 60 Gy/10 fractions per week was selected [16].

No early adverse reaction related to HDR brachytherapy was observed in any of these cases. A dose schedule ranging from 35 Gy with EBRT to 60 Gy without EBRT was therefore deemed safe in terms of early mucosal reaction. Three of the four patients were alive, with no evidence of disease more than seven years after treatment. No spacer could be inserted because of the posterior location of the tumor in one patient, in whom bone exposure healed spontaneously. Of the two patients who developed soft tissue ulcers, one had previously received mantle field irradiation of 40 Gy for Hodgkin’s disease. Inoue et al. [16] concluded that HDR brachytherapy at a dose of 60 Gy in 10 fractions over one week had the same effects as LDR of 70 Gy over one week for mobile tongue cancer.

### Fading of mucosal reaction and late tongue atrophy

The EORTC/RTOG score for mucosal reaction after HDR-ISBT was almost identical to that produced by LDR brachytherapy. The development and course of mucositis were slightly faster for HDR than for LDR, although the time to peak reaction was similar (10 days after treatment). To compare LDR and HDR brachytherapy objectively, a new scoring system for mucositis was introduced. Assessment of the degree of mucosal reaction in the fading phase can be difficult using the EORTC/RTOG scoring system for intraoral mucosal reactions. Therefore, the EORTC/RTOG scoring system was modified, and the LENT-SOMA tables were developed. In a study comparing mucosal reactions between brachytherapy treatments, Sasaki et al. reported that the slopes of developing and fading mucosal reactions were almost the same in the LDR and HDR groups [19]. Spotted mucositis appeared 3 days after HDR hyperfractionated ISBT. Confluent mucositis developed and peaked about 10 days after treatment, but resolved after 4–8 weeks (Fig. 1) [18, 19].

In addition, to evaluate tongue hemiatrophy as a late effect of brachytherapy, Yoshioka et al. established a new grading system for patients who had received LDR or HDR brachytherapy for early tongue cancer [20]. In that study, 49 patients who had received brachytherapy for early tongue cancer (T1/T2, 22:27) were investigated. All patients had undergone either LDR or HDR brachytherapy with Ir-192 (LDR/HDR, 30:19) between 1980 and 1998. Atrophic changes in the tongue were classified into four categories (G0–G3) as follows: unable to protrude the tongue beyond

| Case No. | Age | Sex | Site | T | EBRT Gy | Frx | Bx Gy | Frx | BED10 | BED3 | Results | Status | Follow-up (months) | Adverse effect |
|----------|-----|-----|------|---|---------|-----|-------|-----|-------|------|---------|--------|-------------------|----------------|
| 1        | 65  | M   | floor | 4 | 52      | 23  | 35    | 10  | 91    | 98   | DT      | NED    | 17                | (--)            |
| 2        | 84  | M   | lip   | 2 | 30      | 15  | 42    | 10  | 80    | 90   | DID     | NED    | 29                | (--)            |
| 3        | 72  | M   | tongue | 2 | 50      | 25  | 50    | 10  | 113   | 130  | DN      | DT     | 44                | erosion         |
| 4        | 82  | M   | buccal | 3 | 51      | 21  | 50    | 10  | 116   | 163  | DT      | NED    | 10                | (--)            |
| 5        | 40  | M   | tongue | 1 | 60      | 10  | 60    | 10  | 80    | 108  | NED     | NED    | 65                | (--)            |
| 6        | 65  | M   | tongue | 2 | 60      | 10  | 60    | 10  | 80    | 108  | NED     | NED    | 91                | bone exposure# |
| 7        | 68  | M   | tongue | 2 | 60      | 10  | 60    | 10  | 80    | 108  | NED     | NED    | 91                | ulcer*           |
| 8        | 73  | M   | tongue | 3 | 48      | 24  | 60    | 10  | 128   | 156  | DN      | NED    | 7                 | ulcer           |
| 9        | 58  | F   | tongue | 2 | 60      | 10  | 60    | 10  | 80    | 108  | NED     | NED    | 91                | (--)            |

From [16] and [18]. EBRT = external beam radiotherapy, Bx = brachytherapy, DT = death from primary tumor, DN = death from lymph node, DID = death from intercurrent disease, NED = no evidence of disease, #without spacer, *prior radiotherapy for Hodgkin’s Disease.
the incisors (G3, n = 1); hemiatrophy of the tongue on the irradiated side in the resting position (G2, n = 5); deviation of the tip of the tongue to the irradiated side when protruded (G1, n = 29); and none of these signs (G0, n = 14). The relationships between tongue hemiatrophy and tumor factors, treatment factors, and functional impairment were then investigated. The median time from treatment to assessment was 75 months (range, 8–219 months). No speech or swallowing dysfunction, pain or contracted feeling, or general dissatisfaction with post-treatment tongue status was observed in G0 patients. There was a tendency for such problems to increase with higher grades of tongue hemiatrophy. The frequency of T2 and non-superficial type tumors also tended to increase with increased tongue hemiatrophy grade. The volume index of the G2 and G3 groups was significantly larger than that of the G0 and G1 groups ($P = 0.041$). No significant difference in atrophic change was observed between LDR-ISBT and HDR-ISBT treatments.

**Phase III study comparing outcomes of HDR and LDR brachytherapy**

Inoue et al. conducted a prospective Phase III study comparing outcomes of HDR and LDR brachytherapy for early oral tongue cancer [21]. The criteria for patient selection were as follows: (i) presence of a T1/T2N0 tumor treatable via single plane implantation; (ii) tumor localization at the lateral border of the tongue; (iii) tumor thickness ≤10 mm; (iv) performance status 0–3; and (v) absence of severe concurrent disease. In that study, which was undertaken from April 1992–October 1996, 26 patients were treated with LDR interstitial radiotherapy (ISBT: 70 Gy/4–9 days) and 25 patients with HDR-ISBT (60 Gy/10 fractions/1 week). The 5-year local control rates in the LDR and HDR groups were 84% and 87%, respectively (Fig. 2). Nodal metastasis occurred in 6 patients in each group. The 5-year nodal control rates in the LDR and HDR groups were 77% and 76%, respectively. Inoue et al. [21] concluded that local control rates in hyperfractionated HDR-ISBT for early mobile tongue cancer are similar to those in continuous LDR-ISBT, and that hyperfractionated HDR-ISBT is an effective alternative treatment to continuous LDR-ISBT. Concerning adverse effects, a tongue ulcer occurred in one patient in both groups. Bone exposure occurred in two patients in the HDR group. For one of these two patients, the spacer, which reduced the dose of radiation to the mandible, could not be used because the lesion extended to the posterior part of the tongue.

**Retrospective reviews**

Yamazaki et al. [22] conducted a general retrospective analysis of 648 T1–3N0 tongue cancer patients treated with brachytherapy with or without EBRT [23]. The 5-year local control rates for patients treated with Ra-226 and Ir-192
were 85% and 79% for T1, 75% and 73% for T2, and 62% and 64% for T3 tumors, respectively. For patients in the HDR group, 5-year local control rates were 87% for T1, 79% for T2, and 89% for T3. Furthermore, 5-year local control rates for patients treated solely with brachytherapy were 80% and 84% in the LDR (n = 341; T1:T2 = 171:170) and HDR groups (n = 58; T1:T2 = 22:36), respectively [22]. In a study of the role of HDR brachytherapy in T3 tumors, Kakimoto et al. reported 2- and 3-year local control rates of 67% in patients treated with LDR-ISBT. Local control rates after 2 and 3 years in patients treated with HDR-ISBT were 71% [24]. Thus, the local control rates for patients treated with HDR-ISBT were similar to those of patients treated with LDR-ISBT.

**Dose reduction trials**

Akiyama et al. analyzed the effect of a dose reduction in HDR brachytherapy from 60 Gy/10 fractions to 54 Gy in 9 fractions for early oral tongue cancer [25]. Some studies reported that 60 Gy/10 fractions results in a 14% increase in BED compared with 70 Gy LDR in α/β = 10, and a 54% increase in late responding tissue, which is considered formidable [8, 9]. Mochizuki et al. found that a dose of 6.5 Gy × 7 fractions is equivalent to 60 Gy of LDR and may actually represent an underdose [26]. An equivalent dose of HDR-ISBT to 70 Gy of LDR-ISBT was calculated as 48 Gy in late reaction (α/β = 3.8) and 54 Gy in acute reaction (α/β = 10) cases [26].

Akiyama et al. conducted a matched-pair analysis of early oral tongue cancer patients (T1/2N0M0) treated at doses of 60 Gy (n = 34) and 54 Gy (n = 17) between 1996 and 2004 [25]. Local recurrence was observed in 2 patients in the 54 Gy arm and in 5 patients in the 60 Gy arm. The 2-year local control rate was 88% in both groups. The 2-year overall survival rates were 88% and 82% in the 60 Gy and 54 Gy arms, respectively. The 2-year actuarial complication-free rates were 91% and 83% in the 60 Gy and 54 Gy arms, respectively (n.s.). No significant association was found between total dose, local control rate, and late complications. Akiyama et al. [25] concluded that a dose of 54 Gy in 9 fractions was comparable to a dose of 60 Gy/10 fractions for early oral tongue cancer. A dose of 54 Gy/9 fractions for oral tongue cancer was used thereafter.

**CTV-based dosimetry**

To determine a clinical target volume (CTV)-based dose prescription for HDR brachytherapy, Yoshida et al. used metal markers in 47 patients (32 head and neck, and others) [27]. During treatment planning, they administered a tumoricidal dose to an isodose surface covering the marked CTV and reduced the dose to the organs at risk to a level lower than the constraints. Maximum doses were 80%, 150%, 100%, 50%, and 200% of the prescribed doses for the rectum, urethra, mandible, skin, and large vessels, respectively. These doses were compared with the doses theoretically calculated using the Paris system. If the Paris system (reference dose applied to an isodose surface of 85% of the basal dose) had been used, 16 patients would have been underdosed, and 4 patients (2 rectum + urethra, 1 urethra, and 1 large vessel) would have been overdosed.

In the study by Yoshida et al. [27] using the CTV-based dose prescription, the dose non-uniformity ratio was 0.31 ± 0.05, and the maximum diameter of the hyperdose sleeve was 4–49 mm (median, 7 mm). A statistically significant difference was observed between CTV-based dose prescription and the dosage using the Paris system (0.28 ± 0.08, 3–99 mm, median: 6 mm; P < 0.002, 0.0002). Of the 42 patients treated with doses higher than the tumoricidal dose, 2 experienced local recurrence, while 4 of 7 underdosed patients experienced local recurrence (P < 0.0001). The authors concluded that metal markers were useful in determining the optimal tumoricidal dose in relation to CTV, thus minimizing the dose to organs at risk.

**Image-guided brachytherapy**

Advances in HDR brachytherapy in the next decade will include integration of imaging (CT, magnetic resonance imaging (MRI), intraoperative ultrasonography, positron-emission tomography, and functional imaging) and optimization of dose distribution. Better tumor localization and improved normal tissue definition will help to optimize dose distribution to the tumor and reduce normal tissue exposure [28]. Dose distribution is calculated using the Treatment Planning System based on images of the implant (using dummy sources). Although imaging for the purposes of dose distribution was successfully achieved in the past using two orthogonal fields, the use of 3D imaging such as CT and/or MRI in head and neck brachytherapy to delineate the gross tumor volume (GTV) and CTV (despite some uncertainties) and the organs at risk (including the mandible) makes it possible to obtain objective data on dose volume histograms.

Yoshida et al. initiated MRI-aided image-based ISBT for evaluating gynecological tumors. They obtained MRI images after implantation and combined them with CT images in the process of planning brachytherapy [29]. CT images were obtained daily to adjust needle displacement as needed in another study [30]. Similar efforts are underway for lesions in the head and neck area.

**HDR brachytherapy for other lesions**

Donath et al. utilized HDR as the sole treatment in 13 patients with T1/2N0 malignancies of the lip (n = 3), tongue (n = 1), buccal mucosa (n = 1), floor of the mouth (n = 1), and other sites (n = 6) (Table 3) [31]. In total, 10 treatments at doses of 4.5–5 Gy each were delivered twice daily with a minimum of 5–6 h between treatments. At a
| Author (year), Institute | Subsite | T category | Schedule | Local control | Toxicity | Remark |
|--------------------------|---------|------------|----------|---------------|----------|--------|
| **Interstitial brachytherapy** | | | | | | |
| Donath (1995) [31], McGill Univ, Canada | 13 various | T1–3N0 | Bx only: 4.5–5 Gy × 10 | 92% (MFT:9M) | acute SE resolved in 6 weeks | HDR feasible |
| Inoue Ta (1996) [33], Osaka Univ, Japan | 16 HDR FM | T1, T2, T3 | EBRT: 30–40 Gy ± Bx: 6 Gy × 6–8 | 94% (T1: 100%, T2:100%) | 38% S + B | HDR ≃ LDR |
| Rudoltz (1999) [32], St Vincent’s Medical Center, USA | 55 various | T1, T2, T3, T4 | EBRT: 55.2 Gy (45–70.2 Gy) | 79% (2Y) | 16% toxicity (all OPC) | feasible for T1–2 tumor |
| Guinot (2003) [34], Valencia, Spain | 39 LP | T1, T2, T3 | EBRT: 6.5–10 Gy × 8 fr | 87% T1–2 vs 47% T3–4, P < 0.01 | more aggressive Tx required for T3–4 tumor | HDR ≃ LDR |
| Kotsuma (2012) [35], Osaka Univ, Japan | 36 BM | 3T1, 2T2, 7T3, 3T4 | EBRT*: 40.5 Gy ± Bx: 4.5–5.5 Gy × 8–10 fr | 100% T1, 85.6% T2, 53.6% T3, 33.3% T4 | Grade 3 LDR HDR ≃ LDR |
| **Mold** | | | | | | |
| Nishimura (1998) [36], Kinki Univ, Japan | 8 | 2T1, 6T2 | EBRT: 40–60 Gy + Bx: 3–4 Gy × 4–7 | 88% CR | no serious SE | thick/RMT tumor |
| Ariji (1999) [37], Nagasaki, Japan | 4 | 2T1, 3T2 | EBRT: 22–40 Gy + Bx: 2.5–3 Gy × 10 | 100% | no SE | unfavorable for mold |
| Obinata (2007) [38], Sapporo, Japan | 2 | 1 OPC, 1 MSC | EBRT: 60 Gy/24 fr residual ⇒ Bx: 6 Gy × 2 QD | 50% | no SE | importance of dental technique |
| | | | 1 RMT rec | | | |

Continued
median follow-up time of 9 months, local failure was observed in only 1 patient.

Rudoltz *et al.* reported the results of HDR-ISBT for 55 patients with primary untreated squamous cell carcinomas of the oral cavity and/or pharynx ([32](#)) of Stage T1 (n = 16), T2 (n = 26), T3 (n = 8), and T4 (n = 5). All patients received EBRT followed by HDR-ISBT. A total of 38 patients received hyperfractionated (twice daily) EBRT followed by HDR-ISBT two or three times daily. Hyperthermia was induced and an electron boost was administered to the site(s) of positive nodes in patients with cervical adenopathy. Median follow-up time in this study was 2.7 years. HDR-ISBT was extremely well tolerated. Complications developed in only 9 patients (16%): osteoradionecrosis (n = 4) and soft tissue necrosis (n = 5). These conditions resolved with conservative medical management. No complications required surgical intervention or hospitalization. Local control rates were 87% for patients with T1 (l/16) and T2 (2/26) tumors versus 47% for T3 (5/8) and T4 tumors (P < 0.011). Rudoltz *et al.* ([32](#)) concluded that HDR-ISBT is feasible as a boost for patients with primary squamous cell carcinomas of the oral cavity and oropharynx. Patients with Stage T1/T2 tumors fared exceptionally well; those with more advanced tumors may require more aggressive treatment, such as higher radiation doses, surgical resection, or systemic chemotherapy.

### Cancer of the floor of the mouth

Patients with cancer of the floor of mouth are treated with radiation for functional and cosmetic reasons. Inoue *et al.* evaluated treatment results of HDR- and LDR-ISBT alone, and in combination with other therapeutic modalities, for cancer of the floor of mouth ([33](#)). From January 1980 through March 1996, 41 patients with cancer of the floor of mouth were treated with LDR-ISBT using irradiated gold (Au-198) grains, and from April 1992 through March 1996 16 patients were treated with HDR-ISBT. This study included 26 T1 tumors, 30 T2 tumors, and 1 T3 tumor. For 21 patients treated with ISBT alone, a total radiation dose of 60 Gy/10 fractions/6–7 days was used in HDR brachytherapy. In LDR brachytherapy, the dose was 85 Gy/10 fractions in 1 week. For 36 patients treated with combination therapy, a total dose of 30–40 Gy of EBRT followed by a total dose of 48 Gy/8 fractions/5–6 days of HDR-ISBT or 65 Gy in 1 week of LDR-ISBT were delivered. The 2- and 5-year local control rates of patients treated with HDR-ISBT were 94% and 94%, respectively, and the rates for patients treated with LDR-ISBT were 75% and 69%, respectively. Local control rates for patients treated with HDR brachytherapy were slightly higher than those for patients treated with Au-198 grains (P = 0.113). As for late complications, bone exposure or an ulcer occurred in 6 of 16 (38%) patients treated with HDR-ISBT and 13 of 41 (32%) patients treated with LDR-ISBT. Inoue

| T category | Subsite | Schedule | Toxicity | Remark |
|------------|---------|----------|----------|--------|
| T1-2N0     | T1N0, 1 T1N1 | EBRT: 60 Gy + Brx: 5 Gy × 10 QD | no serious SE, bone exposure | not only palliation but also curative TX |
| T3T2N0     | T2N0, 2T2N0 | EBRT: 60 Gy + Brx: 5 Gy × 10 QD | no serious SE, bone exposure | not only palliation but also curative TX |
| T1-2N0     | T1N0, 1 T1N1 | EBRT: 60 Gy + Brx: 5 Gy × 10 QD | no serious SE, bone exposure | not only palliation but also curative TX |
| T3T2N0     | T2N0, 2T2N0 | EBRT: 60 Gy + Brx: 5 Gy × 10 QD | no serious SE, bone exposure | not only palliation but also curative TX |

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### Table 3. Continued

| Author (year), Institute | T category | Schedule | Toxicity | Remark |
|-------------------------|------------|----------|----------|--------|
| Kudoh (2010) [40], Tokushima, Japan | T2N0, 1 T2N0 | EBRT: 60 Gy + Brx: 5 Gy × 10 QD | no serious SE, bone exposure | not only palliation but also curative TX |
| Chatani (2011) [41], Osaka Rosai HP, Japan | T2N0, 2T2N0 | EBRT: 60 Gy + Brx: 5 Gy × 10 QD | no serious SE, bone exposure | not only palliation but also curative TX |
| Matsuzaki (2012) [42], Okayama, Japan | T2N0, 2T2N0 | EBRT: 60 Gy + Brx: 5 Gy × 10 QD | no serious SE, bone exposure | not only palliation but also curative TX |
| Inoue (2012) [43], Osaka | T2N0, 1 T2N0 | EBRT: 60 Gy + Brx: 5 Gy × 10 QD | no serious SE, bone exposure | not only palliation but also curative TX |
et al. [33] concluded that fractionated HDR-ISBT is a safe alternative to LDR-ISBT for cancer of the floor of the mouth.

**Lip cancer**

Guinot et al. discussed the cases of 39 patients with lip carcinoma treated with HDR-ISBT [34] at doses of 5–5.5 Gy/8–10 fractions twice daily (total dose: 40.5–45 Gy). The 3-year cause-specific survival and local control rates were 91% and 88%, respectively (95% T1–2, 74% T4, \( P = 0.05 \)). Acute and chronic reactions were similar to those in cases treated with LDR-ISBT. The authors therefore concluded that results using HDR-ISBT are equivalent to those using LDR-ISBT.

**Cancer of the buccal mucosa**

Kotsuma et al. retrospectively reviewed data for 36 patients (25 men, 11 women) with cancer of the buccal mucosa treated with curative brachytherapy with or without EBRT [35] (Stage T1, \( n = 3 \); T2, \( n = 23 \); T3, \( n = 7 \); and T4, \( n = 3 \); Clinical Stage I, \( n = 3 \); II, \( n = 16 \); III, \( n = 11 \); IV, \( n = 6 \)). Nodal metastasis was evident in 12 patients at the start of treatment. LDR-ISBT (median dose: 70 Gy, range: 42.8–110 Gy) was used in 15 cases, and HDR-ISBT (median dose: 48 Gy/8 fractions, range: 24–60 Gy) was used in 11 cases. The mold technique (median dose: 15 Gy, range: 9–74 Gy) was used in 7 cases, while 13 patients also underwent EBRT (median dose: 30 Gy, range: 24–48 Gy). The period of observation ranged from 19–242 months (median: 75.5 months). The 5-year local control and progression-free survival rates were 75.7% (100% for T1, 85.6% for T2, 53.6% for T3, and 33.3% for T4) and 67.7%, respectively. HDR-ISBT achieved good local control (80%) comparable with or superior to that of LDR-ISBT (65%) or mold therapy (85.7%, \( P = 0.13 \)). Local control rates were higher in patients with early-stage lesions (T1/2 and/or localized). Severe late complications of Grade 3 or higher developed in 2 patients treated with LDR-ISBT.

**HDR brachytherapy using molds**

Nishimura et al. initiated a Phase III protocol to assess the toxicity and efficacy of HDR intracavitary brachytherapy [36] using molds in the treatment of squamous cell carcinoma of the oral cavity. A total of 8 patients with squamous cell carcinoma of the oral cavity were treated using this technique. The primary sites of the tumors included the buccal mucosa, oral floor, and gingiva. Two of the buccal mucosal cancers were located in the retromolar trigone. For each patient, a customized mold was fabricated, in which 2–4 after-loading catheters were placed for the Ir-192 HDR source, and 4–7 fractions of 3–4 Gy were administered 5 mm below the mold surface following EBRT of 40–60 Gy/2 Gy. The total dose of HDR brachytherapy ranged from 16–28 Gy. Although a good initial complete response rate of 7/8 (88%) was achieved, local recurrence was seen in 4 of these 7 patients. Marginal recurrence occurred in both of the retromolar trigone tumors. No serious late radiation damage (e.g. ulcer or bone exposure) has been observed thus far in the follow-up period of 15–57 months. The authors concluded that HDR brachytherapy using the mold technique is a safe and useful treatment method for early and superficial oral cavity cancer in selected patients. However, this treatment is not indicated for thick tumors and/or tumors located in the retromolar trigone.

Ariji et al. reported the usefulness of intraarterial chemotherapy in 4 patients with oral squamous cell carcinoma [37]. The molds were made from transparent acrylic resin, borrowing from a dental technique. The combined approach was applied as a boost therapy after EBRT. No tumor recurrence or radiation injury was observed in these 4 patients by the end of the follow-up period.

Obinata et al. presented a report of their clinical experience with HDR brachytherapy for head and neck cancer using a customized intraoral mold technique [38]. Two patients were treated with dental prostheses as the radiation carriers for HDR brachytherapy of head and neck cancer. HDR brachytherapy using a customized intraoral technique can be a viable treatment option for patients who are not candidates for surgery or EBRT. It was strongly suggested that specialized dentists are needed who are familiar with not only the anatomy and function of the head and neck region but also radiotherapy.

Kudor et al. introduced a novel customized intraoral mold treatment for maxillary gingival carcinoma [39]. Two patients with maxillary gingival carcinoma were treated using this technique as salvage therapy. The mold was designed using lead to shield normal soft tissues adjacent to the tumor from the radioactive source as much as possible. The radiation dose to the buccal mucosa and tongue was measured on the inner and outer surfaces of the intraoral mold before initiation of HDR brachytherapy by the remote after-loading system. The dose was reduced close to 10% of that applied to the tumor. No recurrence and no severe adverse effects to the normal soft tissue adjacent to the tumor were observed until the end of the follow-up period (2–8 months). HDR brachytherapy using the novel customized intraoral mold designed by Kudor et al. [39] might be a treatment option, not only in salvage therapy, but also in definitive therapy for maxillary gingival carcinoma.

Based on their experiences with 9 controlled cases, Chatani et al. [40] reported that mold therapy after chemoradiotherapy is a non-invasive procedure yielding a reproducible distribution of the radiation dose that closely fits the tumor volume. This technique seems to be a safe and effective treatment method for selected early and superficial squamous cell carcinomas of the oral cavity, although the indications for this treatment method are limited. Mold therapy after chemoradiotherapy may be indicated in
previously untreated superficial squamous cell carcinomas of the oral floor, soft palate, or gingiva, T1/2 tumors, and tumors showing complete response at the end of chemoradiotherapy.

Matsuzaki et al. showed that HDR brachytherapy using a customized mold is a minimally invasive treatment for oral cancer [41]; however, use of this technique for buccal mucosa and lip cancers involving the commissura labiorum is difficult for anatomical reasons. These authors introduced an improved customized mold with two added pieces to allow use of the mold at these sites. Five patients with buccal mucosa carcinoma and 1 patient with lip carcinoma were treated using this technique after EBRT. One patient with neck metastasis underwent both neck dissection and partial tumor resection before HDR brachytherapy. At the end of the follow-up period (2–40 months), no tumor recurrence had occurred in 5 patients, but 1 patient had suffered local recurrence. Thus, the study concluded that HDR brachytherapy using a customized mold is a viable therapeutic option for patients with buccal and lip carcinomas in whom the use of other therapeutic modalities is limited by age, performance status, and other factors.

**HDR brachytherapy for postoperative, reirradiation, and palliative purposes**

Postoperative brachytherapy is an elegant way to deliver adjuvant irradiation in cases with narrow or positive margins, including those with T4 tumors not involving the bone (Table 4) [1, 3]. The recommended postoperative dose in HDR brachytherapy is currently under investigation.

Glatzel et al. reported the results of a study using ISBT and endocavitary brachytherapy in recurrent head and neck cancer [42]. Between 1991 and 2000, 90 consecutive patients (68 men, 22 women) were treated with interstitial (n = 68) or intracavitary (n = 22) HDR brachytherapy in the head and neck area. Primary tumor locations were as follows: oropharynx (n = 26), tongue/floor of mouth (n = 22), nasopharynx (n = 10), nose/paranasal sinuses (n = 9), salivary glands (n = 5), hypopharynx (n = 5), and others (n = 8). Carcinoma with unknown primary tumor location was also treated (n = 5). HDR brachytherapy was administered to 51 patients with recurrent disease and 32 patients with residual tumor after primary chemoradiotherapy. HDR brachytherapy was also administered to 7 patients in primary palliative care. Each single dose per fraction ranged from 1.5–7.5 Gy (median, 5 Gy), and the total HDR brachytherapy dose ranged from 4–42 Gy (median, 17.5 Gy). The overall remission rate was 81%; complete remission was achieved in 46% of patients. No tumor change or progression was observed in 17 cases (19%).

Complete remission rates and median overall survival time differed in the three therapy groups. In cases of recurrent disease, complete remission was achieved in 28% of patients and the median overall survival time was 6 months. In cases of residual tumor, complete remission was achieved in 84% of patients and the median overall survival time was 25 months. For patients in primary palliative care, no complete remission was achieved, and the median overall survival time was 1 month. Late toxicity Grade 3 and 4 (RTOG score) occurred in 6 of the 90 (6.7%) patients. Glatzel et al. [42] concluded that HDR brachytherapy was an effective treatment modality in locoregional recurrent head and neck cancer. In cases with persistent or residual tumor after primary chemoradiotherapy, a local boost with brachytherapy improved the chance of complete remission from tumor disease.

Martínez-Monge et al. examined the feasibility of combined perioperative HDR brachytherapy and intermediate-dose EBRT as an alternative to full-dose adjuvant EBRT in patients with unirradiated squamous cell cancer of the oral cavity and oropharynx [43]. A total of 40 patients were treated with surgical resection and perioperative HDR brachytherapy at a dose of 4 Gy twice daily ×4 (16 Gy total) for R0 resections, and 4 Gy twice daily ×6 (24 Gy total) for R1 resections. EBRT (45 Gy/25 fractions) was performed postoperatively. Patients with Stage III and IVa tumors and some recurrent cases received concomitant cisplatin-paclitaxel chemotherapy during EBRT. The rate of protocol compliance was 97.5%; 11 patients (27.5%) developed toxicity of RTOG Grade 3 or higher; 4 patients (10%) presented complications requiring a major surgical procedure (RTOG 4); 1 patient died due to excessive blood loss (RTOG 5). Three complications (7.5%) occurred in the perioperative period, and 8 (20.0%) occurred more than 3 months after completion of the treatment program. Severe complications were more frequent in posteriorly located implants than in anterior implants (P = 0.035). After a median follow-up time of 50 months for living patients (range, 2.5–86.1 +), the 7-year actuarial rates of local and locoregional control were 86% and 82%, respectively, and the 7-year disease-free survival and overall survival rates were 50.4% and 52.3%, respectively.

The study of Martínez-Monge et al. [43] demonstrated that perioperative HDR brachytherapy can be integrated into the management of patients with resected cancer of the oral cavity who are candidates to receive postoperative radiation or chemoradiation. Local control and toxicity rates were similar to those expected after standard chemoradiation. Perioperative HDR brachytherapy was associated with high toxicity in posterior locations; thus, the scheduled perioperative HDR brachytherapy dose was adjusted to the closest lower level.

Do et al. reviewed their experience with patients with T4N0–3M0 locally advanced oral cavity and oropharyngeal squamous cell carcinoma who underwent definitive chemoradiotherapy or radiotherapy followed by HDR brachytherapy [44]. Radiotherapy doses ranged from 45–50.4 Gy. Patients were reassessed after receiving the first dose, and if
### Table 4. Results of HDR brachytherapy for boost, recurrence or reirradiation

| Author (year), Institute | PTNO | Group | Treatment | Schedule | Local control | Toxicity |
|--------------------------|------|-------|-----------|----------|---------------|----------|
| Glatzel (2002) [42], Sulh, Germany | 90 | 51 Recurrence | 11END + 40 | EBRT 37 Gy (30–60) + Bx 19.7 Gy (5–42 Gy) | CR 28% (MST6mo) | 6.7% RTOG G3-
| | | | ISBT† | | | |
| | 22 Oral | | | | | |
| | 32 Boost/residual | 10 END + 21 ISBT | EBRT 59.3 Gy (42–70 Gy) + Bx 12.9 Gy (4–37.5 Gy) | 84% (25m) | | |
| | | 7 Palliation | 7 ISBT | Bx 23.9 Gy (4–37.5 Gy) | 0% (1m) | |
| Martinez-Monge (2008) [43], Navarre, Spain | 40 | Primary 34 | Surgery + EBRT 45 Gy + Bx 16–24 Gy | 82% LRC (7y) | 15% RTOG G3, 10% G4, 2.5% G5 |
| | 28 Oral | Recurrence 6 | | | | |
| Do (2009) [44], Long beach, USA | 20 T4N0–3 | Boost for T4 tumor | 14CRT⇒BT | 45–50.4 Gy EBRT + platinum + Bx 3–4 Gy×8–10 | 61% | 30% S, 5% B, other** |
| | 10 Oral | | 6RT⇒BT | | | |
| Reirradiation | Previous treatment | | | | | |
| Donath (1995) [31], McGill Univ., Canada | 16 | Postop adjuvant | EBRT 50 Gy – | 3 Gy × 8 | 4 local rec | 1 fistula, 8 surgery |
| | 6 Oral | | | | | |
| | | 12 positive margin | | | | |
| Krüll (1999) [45], Hamburg, Germany | 19 (11 rec 8 PD) | 2T1, 5T2, 6T3, 6T4 | EBRT 50–76.5 Gy | 10 Gy once a week | 5 CR | 1S |
| | 13 Oral, 6 OPC | | | | | |
| | | 13N + | | | | |
| Hepel (2005) [46], Long Beach, USA | 30 (36 sites) | EBRT 59 Gy (23–75 Gy) | Bx 3–4 Gy × 3–12 (18–48 Gy) | 69% | G 3/4 late 16% |
| | 7 Oral | | | | | |
| Narayana (2007) [47], MSK, USA | 30 | 18 OP + Bx | 23 EBRT 20–40 Gy | 3.4 Gy × 10 | 71% (2 y) | 6G2 4G3 in OP + BT |
| | 6 Oral | | | | | |
| | | 3 EBRT + Bx | 9 sole Bx | EBRT 39.6 Gy + Bx 4 Gy × 10 | 88% OP + Bx >40% | |
| | | | | Bx 4 Gy × 10 | EBRT ± Bx, P = 0.05 | |
| Schiefke (2008) [48], Leipzig, Germany | 13 rec | 11 PT EBRT 60–69.9 Gy | EBRT 60–69.9 Gy + Bx 3 Gy × 10 (21–36 Gy) | 80% (2 y) | Early 61% | S 1, B 2, other*** |
| | Oral 9 | | | | | |
| | | 2 Sole BT 2 | | | | |
| Bartochowska (2011) [49], Poznań, Poland | 106 PDR + 50 HDR | 8 CRT, 16 HT | 142 PT (91%) EBRT | HDR 3–6 Gy × 3–10 (12–30 Gy) | 37.7% CR + PR (MFT 6 Mo) | 35% |
| | Oral (23 PDR + 17 HDR) | | | | | |
| | 142 reirradiation | | | | | |
| | | | | | | |
| PTNO = number of patients, EBRT = external body irradiation, OPC = oropharyngeal cancer, CR = complete response, PR = partial response, S = ulcer soft tissue (including early complication), B = bone exposure and/or necrosis, MST = median survival time, MFT = median follow-up period, END = endocavitary brachytherapy (nasopharyngeal and nasal carcinoma), ISBT = interstitial brachytherapy, MSK = Memorial Sloan-Kettering Cancer Center, HT = interstitial hyperthermia, G = grade, LRC = locoregional control, OP = surgery, CRT = chemoradiotherapy, 1*5.0 Gy (range, 3.0–7.5 Gy) twice a week, (3.0 Gy) or weekly (5.0–7.5 Gy, 19 patients) | | | | | |
| *Metal needles 11PT single dose 5.0–Gy (1 PT 7 Gy, 1 Pt 7.5 Gy) once a week. Plastic tubes single dose 3.0 Gy (1.5–7.5 Gy) daily or twice a day | | | | | |
| **4 dysphasia, 2 xerostomia, 1 tube feeding, 2 hoarseness, *** 2 nerve palsy, 4 wound healing disorder, †HDR unless otherwise stated, ‡twice a day treatment unless otherwise stated, ¶5 y unless otherwise stated | | | | | |
the response was inadequate, brachytherapy was performed at doses ranging from 24–30 Gy at 3–4 Gy/fraction twice daily with 6 h between fractions. Concurrent chemotherapy was platinum-based. In their study, 20 patients were treated with chemoradiotherapy or radiotherapy alone followed by brachytherapy. Soft tissue invasion was observed in 13 patients, bone and cartilage invasion was observed in 7, 14 patients were treated with chemoradiotherapy followed by brachytherapy, and 6 patients were treated with radiotherapy alone followed by brachytherapy. The 5-year locoregional control was 61%. The 5-year overall survival was 29%. When patients treated with EBRT alone were excluded, the 5-year overall survival was 36%. Nodal status was the only prognostic factor. The study of Do et al. [44] suggests that chemoradiotherapy followed by HDR brachytherapy is a feasible treatment option for patients with T4 locally advanced cancer of the oral cavity and oropharynx. In patients with poor response to chemoradiotherapy, HDR brachytherapy may be used for dose escalation to increase locoregional control.

Donath et al. utilized HDR in a postoperative adjuvant setting following wide local excision of tumors in patients who presented with recurrent disease (n = 12) or a second primary tumor site in the head and neck (n = 4) [31]. All patients had previously received EBRT to the head and neck. Due to this previous course of irradiation, only 8 treatments of 3 Gy each were delivered, for a total of 24 Gy over a period of 4 days. However, during the follow-up period of 2–16 months, only 3 patients remain disease-free.

Krüll et al. reported on 19 patients with progressive or recurrent head and neck cancer, who had been treated with HDR-ISBT [45]. All patients had previously undergone EBRT. Initial therapy also included surgery in 9 cases and chemotherapy in 3 patients. Staging according to the TNM system revealed advanced stage tumors in the majority of patients. Interstitial brachytherapy was carried out with the isotope Ir-192. The applied total dose at the reference isodose varied from 10–30 Gy. Application was fractionated once a week. Complete remission was achieved in 5 patients and partial remission was achieved in 10 patients. In 4 patients, the tumor continued to grow despite administration of HDR brachytherapy. The mean follow-up time in this study was 21 months. The local control rate was 34% at 24 months. The survival rate was 49% at 12 months and 35% at 24 months. Krüll et al. [45] recommended HDR-ISBT as a palliative treatment in preirradiated squamous cell carcinoma with local recurrence or progression.

Hepel et al. reported their experiences with reirradiation using HDR brachytherapy in 30 patients [46]. All patients had inoperable cancer, refused surgery, or had gross residual disease after salvage surgery for recurrent disease. In the 30 patients, 36 sites were implanted by application of HDR-ISBT at a mean tumor dose of 34 Gy (18–48 Gy) in twice daily fractions of 3–4 Gy/fraction. Local tumor control was achieved in 69% of implanted sites. Overall survival at 1 and 2 years was 56% and 37%, respectively. Grade 3/4 late complications occurred in 16% of the patients. No fatal complications were observed. Hepel et al. [46] concluded that although HDR-ISBT has a potential to cure a part of oral cancer recurrences, only superficial small tumors can be treated at this time, partly because of the inexperience of health care providers.

Narayana et al. reported the preliminary results of a study including 30 patients with recurrent head and neck cancer treated with HDR-ISBT [47] between September 2003 and October 2005. Local or regional recurrence in the area of previous EBRT was evident in 77% (23/30) of patients. Treatment sites included the oral cavity/oropharynx (11/30), neck (10/30), face/nasal cavity (6/30), and parotid bed (3/30). Whereas 18 patients underwent surgical resection followed by HDR-ISBT, 3 patients were treated with combined EBRT and HDR-ISBT, and the remaining 9 were treated with HDR-ISBT alone. The dose and fractionation schedules were as follows: 3.4–34 Gy twice daily for postoperative cases, 4–20 Gy twice daily when combined with 40–50 Gy EBRT, and 4–40 Gy twice daily for definitive treatment. HDR-ISBT was initiated 5 days after catheter placement to allow for tissue healing.

During the median follow-up period of 12 months, 6 local recurrences were observed 1–10 months after completion of the procedure. The 2-year local control and overall survival rates for the entire group were 71% and 63%, respectively. Patients treated with surgical resection and HDR-ISBT had better 2-year local control rates compared with the patients treated with HDR-ISBT ± EBRT alone (88% vs 40%, P = 0.05). Six Grade 2 and four Grade 3 complications were noted in 5 patients, all in the postoperative HDR-ISBT group. The preliminary results of the study of Narayana et al. [47] on HDR brachytherapy indicated acceptable local control and morbidity in recurrent head and neck cancers using this treatment method. Planned surgical resection followed by HDR brachytherapy was associated with improved tumor control in the high-risk patients in this study.

Schiefke et al. examined the potential of HDR-ISBT to improve safety and survival after surgical resection [48]. From 2000–2006, 13 patients with pretreated, recurrent head and neck cancer (oral, maxillary sinus, lips) were treated with a curative approach by resection of the recurrent tumor and subsequent HDR-ISBT. Treatment included coverage of the surgical defect and sealing of the brachytherapy applicators with free microvascular or myocutaneous flaps. Conventional radiotherapy and chemotheraphy were added as required. The patient group was evaluated with respect to survival and outcome. Additionally 5 patients who received combination therapy for primary carcinomas were included in this report in order to evaluate the rate of complications and adverse effects. Kaplan–Meier
curves revealed a 2-year overall survival rate of 65.3%. The mean survival time for recurrent carcinomas was 22.8 months. Patients treated for primary carcinoma had a mean survival time of 34.5 months. Of the 5 patients with primary head and neck cancer, 4 (80%) were alive and without evidence of disease 2 years after treatment. The acute and chronic adverse side effects were manageable. No relevant complications concerning tissue transfer were observed. Schiefke et al. [48] concluded that surgical resection combined with HDR-ISBT can lead to long-term remission, and that simultaneous microvascular defect reconstruction provides tissue cover for brachytherapy.

Bartochowska et al. reported the results of HDR- and PDR-ISBT in the palliative treatment of patients with locally or regionally recurrent head and neck cancers [49]. PDR- and HDR-ISBT were used in 106 and 50 patients, respectively, from January 2002 to November 2008. In 8 patients, brachytherapy procedures were performed in combination with simultaneous chemotherapy (details were not shown). Sixteen patients were additionally treated with interstitial hyperthermia. All patients were regularly followed up within 6 months of final treatment. Local control, complication, and survival rates were assessed. Complete remission and partial remission 6 months after final treatment were achieved in 37.7% of patients, whereas survival rates 12 and 24 months after brachytherapy were 40% and 17%, respectively. The overall complication rate was 35%. The results of the study by Bartochowska et al. [49] suggest that HDR- and PDR-ISBT are safe alternatives in the palliative treatment of patients with locally or regionally recurrent head and neck cancers with relapse in a previously irradiated area who were not qualified for, or rejected surgery. These treatments offer a good palliative effect with acceptable complication rates.

**DISCUSSION**

The oral cavity is essential in coordinating the complex functions of deglutition, phonation and airway protection. Preserving its function is a difficult challenge when treating carcinoma in this anatomical region. The treatment modalities available include surgery, EBRT, brachytherapy and various combinations of the three. The wide range of results in the literature leaves considerable uncertainty as to the treatment of choice, but years of experience in the treatment of head and neck tumors with radiotherapy has demonstrated that a high tumor dose is required to achieve local control.

Sresty et al. reported that the ISBT treatment modality produces equal or superior planning results when compared with intensity-modulated radiation therapy (IMRT) [50]. Fifteen patients with tongue cancer treated with HDR-ISBT were replanned. Tongue cancer was evaluated using the IMRT planning system. Contouring of target volume, including all critical structures, was done using the IMRT treatment planning system to closely match the implant brachytherapy planning system. Prescription goals were specified and treatment plans generated. The conformity index and doses to critical organs were then calculated and compared between IMRT and ISBT. Planning time was also recorded for both the techniques in all the cases. Very good dose conformity was observed in ISBT, similar to that observed in IMRT. Dose to critical structures was lower in ISBT in all cases. Planning time was also less in ISBT for many cases. These results encouraged the authors to continue ISBT [50]. They concluded that ISBT is an ideal solution for high-dose delivery exclusively to the primary tumor volume, while limiting the risks of severe xerostomia or trismus [1, 3, 6].

HDR hyperfractionated ISBT has the following advantages: (i) accurate calculations made possible by complete fixation of the guide tubes, (ii) parallel source arrangement with the sophisticated technique, (iii) homogeneous dose distribution due to stepping source optimization, (iv) better patient care in normal wards with elimination of radiation exposure to medical staff, administration on an outpatient basis in several cases, and (v) shorter treatment times than with EBRT. Future uses of HDR-ISBT include the introduction of a 3D image-based approach for GTV and CTV assessment. Development is in progress of a common language to describe the concepts and define the terms to be used in this promising field [1].

HDR-ISBT treatment should be executed carefully, because the short treatment times allow no time for correction of errors that could result in harm to patients. Hence all personnel involved in HDR brachytherapy must be well trained and constantly alert during treatment delivery [28]. The development of well-controlled randomized trials addressing issues of efficacy, toxicity, quality of life, and costs-versus-benefits will ultimately define the role of HDR brachytherapy [28].

One of the limitations of HDR-ISBT is a lack of experience. For example, studies examining prognostic factors in LDR-ISBT allowed improvement of the technique. Treatment now involves leaded protection of the mandible, optimal intersource spacing (1.2–1.4 cm), calculations of volume treated (30 cm³, i.e. three loops), accurate safety margins (5 mm), and effective dose rates (0.5 Gy/h). The total dose [65 Gy in brachytherapy alone, 25 Gy in combination with EBRT (50 Gy) in primary carcinomas of the oral cavity, 60 Gy in recurrent cancer in previously irradiated tissues] and an optimal interval between EBRT and brachytherapy (<20 days) have also been determined for LDR-ISBT [1, 3, 6]. Those factors remain to be established for HDR-ISBT.

PDR-ISBT appeared to be functionally equivalent to continuous ISBT. The results of PDR-ISBT should improve with better dose rate control and optimization of the dose.
distribution [51, 52]. Brenner et al. reported the superiority of daytime PDR-ISBT over continuous LDR-ISBT [51]. However, if PDR-ISBT is applied with curative intent, the treatment unit is unavailable for treatment of other patients. As HDR-ISBT remote-controlled after-loading units are not available at all institutions, and many patients require treatment with the units that are available, continuous LDR-ISBT and daytime PDR-ISBT are difficult to perform for patients with head and neck cancer.

Due to the paucity of evidence in the literature, and the fact that few institutions are equipped to test the potential of HDR-ISBT for the convenience of patients and medical staff, the future of HDR-ISBT is uncertain. However, many studies conclude that this therapeutic mode should be explored further. In summary, although more concrete evidence is warranted, HDR-ISBT may be an important option for treatment of oral cancer.

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REFERENCES

1. Mazeron JJ, Ardiot JM, Haie-Meder C et al. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiother Oncol 2009;91:150–6.
2. Paine CH, Ash DV. Interstitial brachytherapy: past-present-future. Int J Radiat Oncol Biol Phys 1991;21:1479–83.
3. Erickson BA, Demanes DJ, Ibott GS et al. American Society for Radiation Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2011;79:641–9.
4. Guedea F, Venselaar J, Hoskin P et al. Patterns of care for brachytherapy in Europe: updated results. Radiother Oncol 2010;97:514–20.
5. Petera J, Matula P, Paluska P et al. High dose rate versus LDR brachytherapy in the treatment of tongue carcinoma - a radiobiological study. Neoplasma 2009;56:163–8.
6. Nag S, Cano ER, Demanes et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for head-and-neck carcinoma. Int J Radiat Oncol Biol Phys 2001;50:1190–8.
7. Lau H, Hay J, Flores A et al. Seven fractions of twice daily high dose-rate brachytherapy for node-negative carcinoma of the mobile tongue results in loss of therapeutic ratio. Radiother Oncol 1996;39:15–8.
8. Leung TW, Wong VY, Wong CM et al. High dose rate brachytherapy for carcinoma of the oral tongue. Int J Radiat Oncol Biol Phys 1997;39:1113–20.
9. Leung TW, Wong VY, Kwan KH et al. High dose rate brachytherapy for early stage oral tongue cancer. Head Neck 2002;24:274–81.
10. Ohga S, Uehara S, Miyoshi M et al. High-dose-rate brachytherapy with local injection of bleomycin for N0 oral tongue cancer – possibilities of the control of tumor implant by inserting applicators and the decrease in tumor dose. Nihon Igaku Hoshasen Gakkai Zasshi 2003;63:47–50 (in Japanese).
11. Umeda M, Komatsubara H, Ojima Y et al. A comparison of brachytherapy and surgery for the treatment of stage I-II squamous cell carcinoma of the tongue. Int J Oral Maxillofac Surg 2005;34:739–44.
12. Nishioka T, Homma A, Furuta Y et al. A novel approach to advanced carcinoma of the tongue: cases successfully treated with combination of superselective intra-arterial chemotherapy and external/high-dose-rate interstitial radiotherapy. Jpn J Clin Oncol 2006;36:822–6.
13. Patra NB, Goswami J, Basu S et al. Outcomes of high dose rate interstitial boost brachytherapy after external beam radiation therapy in head and neck cancer – an Indian (single institutional) learning experience. Brachytherapy 2009;8:248–54.
14. Guinot JL, Santos M, Tortajada MI et al. Efficacy of high-dose-rate interstitial brachytherapy in patients with oral tongue carcinoma. Brachytherapy 2010;9:227–34.
15. Shigematsu Y, Masaki N, Ikeda H et al. Current status and future of brachytherapy. Gan No Rinsho 1983;29:695–701 (in Japanese).
16. Inoue To, Inoue Ta, Teshima T. High dose rate interstitial brachytherapy for mobile tongue cancer: part I. Phase II/II study of HDR hyperfractionated interstitial brachytherapy for oral cancer. Jpn J Cancer Chemother 2000;27 Suppl II:287–90.
17. Orton CG, Seyedsadr M, Somnay A. Comparison of high and LDR remote afterloading for cervix cancer and the importance of fractionation. Int J Radiat Oncol Biol Phys 1991;21:1425–34.
18. Teshima T, Inoue T, Ikeda H et al. Phase I/II study of high dose rate interstitial radiotherapy for head and neck cancer. Strahlenther Onkol 1992;168:617–21.
19. Sasaki S, Teshima T, Murayama S et al. Comparison of radiation mucositis after interstitial brachytherapy between LDR and HDR. Head and Neck Cancer 1993;19:197–200.
20. Yoshioka Y, Yoshida K, Shimizu K et al. Proposal of a new grading system for evaluation of tongue hemiatrophy as a late effect of brachytherapy for oral tongue cancer. Radiat Oncol 2001;61:87–92.
21. Inoue T, Inoue T, Yoshida K et al. Phase III trial of high vs. LDR interstitial radiotherapy for mobile tongue cancer. Int J Radiat Oncol Biol Phys 2001;51:171–5.
22. Yamazaki H, Inoue T, Yoshida K et al. Brachytherapy for early oral tongue cancer: LDR to high dose rate. J Radiat Res 2003;44:37–40.
23. Yamazaki H, Inoue T, Yoshida K et al. Comparison of three major radioactive sources for brachytherapy used in the treatment of node negative T1-T3 oral tongue cancer: influence of age on outcome. Anticancer Res 2007;27:491–497.
24. Kakimoto N, Inoue T, Inoue T et al. Results of low- and high-dose-rate interstitial brachytherapy for T3 mobile tongue cancer. Radiother Oncol 2003;68:123–8.
25. Akiyama H, Yoshida K, Shimizutani K et al. 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. J Radiat Res 2012;53:722–6.

26. Mochizuki S, Kamehira C, Sekine H et al. A study on optimum time-dose relationship in high dose rate interstitial radiotherapy. Jpn J Clin Radiol 1994;39:1151–4.

27. Yoshida K, Nose T, Koizumi M et al. The usefulness of metal markers for CTV-based dose prescription in high-rate-rate interstitial brachytherapy. J Jpn Soc Ther Radiol Oncol 2002;13:253–60.

28. Nag S. High dose rate brachytherapy: its clinical applications and treatment guidelines. Technol Cancer Res Treat 2004;3:269–87.

29. Yoshida K, Yamazaki H, Takenaka T et al. A dose-volume analysis of magnetic resonance imaging-aided high-dose-rate image-based interstitial brachytherapy for uterine cervical cancer. Int J Radiat Oncol Biol Phys 2010;77:765–72.

30. Mikami M, Yoshida K, Takenaka T et al. Daily computed tomography measurement of needle applicator displacement during high-dose-rate interstitial brachytherapy for previously untreated uterine cervical cancer. Brachytherapy 2011;10:318–24.

31. Donath D, Vuong T, Shenouda G et al. The potential uses of high-dose-rate brachytherapy in patients with head and neck cancer. Eur Arch Otorhinolaryngol 1995;252:321–4.

32. Rudoltz MS, Perkins RS, Luthmann RW et al. High-dose-rate brachytherapy for primary carcinomas of the oral cavity and oropharynx. Laryngoscope 1999;109:1967–73.

33. Inoue Ta, Inoue To, Yamazaki H et al. High dose rate versus LDR interstitial radiotherapy for carcinoma of the floor of mouth. Int J Radiat Oncol Biol Phys 1998;41:53–8.

34. Güniot JL, Arribas L, Chust ML et al. Lip cancer treatment with high dose rate brachytherapy. Radiother Oncol 2003;69:113–5.

35. Kotsuna T, Yoshida K, Yoshida M et al. Brachytherapy for buccal cancer: evaluation of HDR-IBST. 2008;20:s141.

36. Nishimura Y, Yoshihiko Yokoe Y et al. High-dose-rate brachytherapy using molds for oral cavity cancer: The technique and its limitations. Int J Clin Oncol 1998;3:351–6.

37. Ariji E, Hayashi N, Kimura Y et al. Customized mold brachytherapy for oral carcinomas through use of high-dose-rate remote afterloading apparatus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87:508–12.

38. Ohnata K, Ohmori K, Shirato H et al. Experience of high-dose-rate brachytherapy for head and neck cancer treated by a customized intraoral mold technique. Radiat Med 2007;25:181–6.

39. Kudoh T, Ikushima H, Kudoh KT et al. High-dose-rate brachytherapy for patients with maxillary gingival carcinoma using a novel customized intraoral mold technique. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:e102–8.

40. Chatani M, Tsuboi K, Yagi M et al. High dose rate brachytherapy using molds after chemoradiotherapy for oral cavity cancer. Jpn J Radiol 2012;30:40–4.

41. Matsuoka H, Takemoto M, Hara M et al. Two-piece customized mold technique for high-dose-rate brachytherapy on cancers of the buccal mucosa and lip. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2012;113:118–25.

42. Glatzel M, Büntzel J, Schröder D et al. High-dose-rate brachytherapy in the treatment of recurrent and residual head and neck cancer. Laryngoscope 2002;112:1366–71.

43. Martínez-Monge R, Gómez-Iturriaga A, Cambeiro M et al. Phase I-II trial of perioperative high-dose-rate brachytherapy in oral cavity and oropharyngeal cancer. Brachytherapy 2009;8:26–33.

44. Do L, Puthawala A, Syed N: Interstitial brachytherapy as boost for locally advanced T4 head and neck cancer. Brachytherapy 2009;8:385–91.

45. Krüll A, Friedrich RE, Schwarz R et al. Interstitial high dose rate brachytherapy in locally progressive or recurrent head and neck cancer. Anticancer Res 1999;19:2695–7.

46. Heipel JT, Syed AM, Puthawala A et al. Salvage high-dose-rate (HDR) brachytherapy for recurrent head-and-neck cancer. Int J Radiat Oncol Biol Phys 2005;62:1444–50.

47. Narayana A, Cohen GN, Zaider M et al. High-dose-rate interstitial brachytherapy in recurrent and previously irradiated head and neck cancers – preliminary results. Brachytherapy 2007;6:157–63.

48. Schiefke F, Hildebrandt G, Pohlmann S et al. Combination of surgical resection and HDR-brachytherapy in patients with recurrent or advanced head and neck carcinomas. J Cranio-maxillofac Surg 2008;36:285–92.

49. Bartochowska A, Wierzbicka M, Skowronek J et al. High-dose-rate and pulsed-dose-rate brachytherapy in palliative treatment of head and neck cancers. Brachytherapy 2012;11:37–43.

50. Sresty NV, Ramanjappa T, Raju AK et al. Acquisition of equal or better planning results with interstitial brachytherapy when compared with intensity-modulated radiotherapy in tongue cancers. Brachytherapy 2010;9:235–8.

51. Brenner DJ, Schiff PB, Huang Y et al. Pulsed-dose-rate brachytherapy: design of convenient (daytime-only) schedules. Int J Radiat Oncol Biol Phys 1997;39:809–15.

52. Strnad V, Melzer W, Geiger M et al. Role of interstitial PDR brachytherapy in the treatment of oral and oropharyngeal cancer. A single-institute experience of 236 patients. Strahlenther Onkol 2005;181:762–7.