POSTOPERATIVE BRACHYTHERAPY ALONE AND COMBINED
POSTOPERATIVE RADIOTHERAPY AND BRACHYTHERAPY
BOOST FOR SQUAMOUS CELL CARCINOMA OF THE ORAL
CAVITY, WITH POSITIVE OR CLOSE MARGINS

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Abstract: Background. Postoperative radiotherapy is necessary for squamous cell carcinoma (SCC) of the oral cavity with positive or close margins. The aim of the study is to define the indications of postoperative brachytherapy (BRT).

Methods. From 1979 to 1993, 82 patients with positive or close margins had postoperative BRT (58 T1–2, 24 T3–4, and 45 mobile tongue, 37 floor of mouth). Forty-six patients had combined radiotherapy (RT) with a mean dose of 48 Gy, and BRT boost with a mean dose of 24 Gy. Thirty-six patients had BRT alone with a mean dose of 60 Gy. BRT was performed with interstitial low dose rate Iridium 192.

Results. Overall survival (OS), cause-specific survival (CSS), and local control (LC) at 5 years were, respectively, for T1–2/N0N+C0 with BRT, 75%, 85%, and 88%; and with RT-BRT, 72%, 93%, and 96%; for T3–4/N0N+C0 with RT-BRT, 72%, 93%, and 96%; for T3–4/N+ with RT-BRT, 42%, 90%, and 80%; and for T3–4/N+ with RT-BRT, 22%, 43%, and 57%. Prognostic factors for OS, CSS, and LC were N+ (p ≤ .009), extracapsular spread (ECS+; p ≤ .000001), and T stage for LC only (p = .02). Prognostic factors for complications were a high number of wires with a cutoff at five wires (p = .008), a high dose rate with a cutoff at 0.57 Gy/hr (p = .01), and a high total dose (BRT + RT) with a cutoff at 71 Gy (p = .07).

Conclusions: BRT alone for SCC T1–2/N0N+ is better than RT-BRT because, with equivalent results, it avoids the adverse events of postoperative RT (xerostomia) and permits the treatment of a second head and neck primary in nonirradiated tissue. The results for the T3–4/N+ are acceptable with this approach (ie, RT-BRT) but may be improved for N+. © 2004 Wiley Periodicals, Inc. Head Neck 26: 216–223, 2004

Keywords: postoperative; brachytherapy; head and neck; squamous cell carcinoma; radiotherapy

The surgical treatment of squamous cell carcinoma (SCC) of mobile tongue or floor of mouth is usually carried out alone for small tumors T1–2...
without nodal invasion. It is associated with postoperative radiotherapy (RT) in the case of bulky tumors (T3–4) or if there is a risk of cervical relapse (N+, lymphatic invasion, perineural spread). Despite the evaluation of the margins during surgery, final inadequate margins are found in 10% to 16%.1 Positive or close (< 5 mm) margins in surgically resected squamous cell carcinoma are associated with an increase of local relapse.2 Patients with margins at risk undergo postoperative RT, which shows its effectiveness by reducing the risk of locoregional relapse.3–8 The dose delivered by RT on the primary site ranges from 60 to 66 Gy, with 1.8- to 2-Gy daily fractions.4,8,9 Moreover, for small tumors without risk of cervical recurrence and with a local risk only (positive or close margins), postoperative RT limits the therapeutic possibilities in the case of a second head and neck primary tumor.

To treat the primary site, the alternative to RT is brachytherapy (BRT). Indeed, its characteristics make it possible to deliver a significant dose in a short time while sparing normal tissues, thus increasing the therapeutic ratio. From a radiobiologic point of view, these various criteria are known to improve local control after surgery.4,10–12 Moreover, when BRT is carried out alone for small tumors T1–2 N0 N–, it is possible to treat a second primary in nonirradiated tissue.

The aim of this study was to evaluate the effectiveness and the toxicity of postoperative BRT for patients with SCC of mobile tongue or floor of mouth with positive or close margins and to define its indications.

MATERIALS AND METHODS

From 1978 to 1993, 82 patients had postoperative BRT for SCC of floor of mouth or mobile tongue with positive or close margins. There were 45 floor-of-mouth and 37 mobile-tongue cancers. Tumor stage was T1–2 (n = 58) and T3–4 (n = 24). Disease in 63 patients was N0 (Table 1). The mean age was 56.5 years (range, 26–81 years). The sex ratio was 72 men to 10 women.

All patients had curative-intent surgery (partial surgery in 62, extensive surgical resection with flap reconstruction in 20). Twenty-four patients had no neck surgery, 32 had a unilateral, 26 a bilateral neck dissection, 31 had a functional neck dissection, and 27 had a radical neck dissection (Table 2). The pathologic margins were positive (25 patients), in situ carcinoma (2 patients), severe dysplasia (1 patient), and margins <5 mm or unknown but close according to the surgeon (54 patients). Thirty-five patients had N– disease, nine patients had one N+, four patients two N+, and 10 patients more than two N+. Eight patients had N+ with extracapsular spread (ECS).

Forty-six patients had postoperative RT because of cervical risk or tumor size (two lateral opposed fields treating the surgical bed and the upper neck and one anterior field for the lower neck). Energy used was cobalt or x-ray 6 MV with electron posterior fields. The mean dose delivered to the surgical bed was 48 Gy (range, 40–51.5 Gy) in 35 days (range, 24–55 days) and 24 fractions (range, 19–28). The mean interval between surgery and RT was 7 weeks (range, 2–12 weeks). A boost on the N+ECS+ was carried out delivering 12 to 21 Gy by electrons. A BRT boost on the primary site delivered 24 Gy on the reference isodose (range, 12–35 Gy) 3 weeks after radiotherapy (range, 1–7 weeks). Thirty-six patients had BRT alone (T1–2 N0 N–) 36 days after surgery (range, 16–68 days). The mean dose to the primary site was 60 Gy on the reference isodose (range, 50–67 Gy) (Table 3).

Before initiation of BRT or RT, all patients had prior precautionary dental management to prepare the lead protection of the mandible when it was possible. All implants were done under either local or general anesthesia. The technique used consisted of plastic tubes afterloaded with low-dose-rate iridium-192. The tubes were placed

| Table 1. Classification of the 82 patients treated by postoperative brachytherapy. |
|------------------|---|---|---|---|---|
| N0 | N1 | N2 | N3 | Total |
| T1 | 28 | 1 | 0 | 0 | 29 |
| T2 | 23 | 5 | 1 | 0 | 29 |
| T3 | 5 | 3 | 2 | 0 | 10 |
| T4 | 7 | 4 | 2 | 1 | 14 |
| Total | 63 | 13 | 5 | 1 | 82 |
within the primary site and surrounding tissues (junction flap, remaining tongue or flap, positive margin, or in the suture region in the cases of transoral resection). One or two plane implants were performed according to the loop or modified bridge technique for floor-of-mouth tumors.\textsuperscript{13} The implantation followed the rules of the Paris system and was optimized using preoperative imaging (CT scan) as well as postoperative pathology reports. The number of wires ranged from 2 to 12 (mean, 7), the spacing between the wires ranged from 1.2 to 1.5 cm, and the size of the hyperdose sleeves ranged from 3 to 19 mm. The mean dose rate was 0.61 Gy/hr (range, 0.29–1.66 Gy/hr), and the mean activity was 1.44 mCi/cm (range, 0.89–1.96 mCi/cm). Dosimetry was based on the Paris system.\textsuperscript{14} Forty patients had lead protection of the mandible during BRT (28 oral tongue, 12 floor of mouth). In the remaining patients, no lead protection was used because of the proximity of the tumor to the gingiva. The complications were graded according to the Centre Alexis Vautrin classification (ie, grade 1, limited mucosal necrosis or bone exposure; grade 2, necrosis > 1 cm or requiring hyperbaric oxygen therapy; grade 3, complication requiring surgery or necrosis with sequelae; grade 4, lethal complication).

All statistical analyses were performed with PIGAS software. The actuarial curves were calculated according to the Kaplan-Meier method. Comparisons were made using either the log-rank or the chi-square test as appropriate. The mean follow-up of the entire group was 69 months (range, 6–74 months), with a minimum follow-up of 3 years.

**RESULTS**

**Survivals and Local Control.** The 5-year actuarial overall and cause-specific survival rates of the entire group were 68% and 80%, respectively. Local control was achieved in 81% of patients at 2 years, with a plateau apparent after 23 months (Figure 1).

The 5-year actuarial overall survival rate for T1–2/N0N– 75% was (BRT alone); for T1–

<table>
<thead>
<tr>
<th>T1/T2</th>
<th>T3/T4</th>
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<tr>
<td>N0/N</td>
<td>N+</td>
</tr>
<tr>
<td>Radiotherapy + brachytherapy</td>
<td>13</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
</tr>
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**FIGURE 1.** Overall survival, cause-specific survival, and local control in a series of 82 patients with positive or close margins.

**FIGURE 2.** Overall survival by tumor stage and treatment (BRT, brachytherapy; RT, radiotherapy).

**FIGURE 3.** Overall survival by nodal status.
2/N0N−, was 70% (RT + BRT); for T1–2/N+, 44%; for T3–4/N−, 42%; and for T3–4/N+, 22% (Figure 2). The prognostic factors for overall survival were N+ (30% vs 72% at 5 years; \( p = .000001 \); Figure 3) and ECS (12% vs 63% at 5 years; \( p = .000001 \)).

The 5-year actuarial specific survival for T1–2/N0N− was 85% (BRT alone); for T1–2/N0N−, 92% (RT + BRT); for T1–2/N+, 67%; for T3–4/N−, 90%; and for T3–4/N+, 43% (Figure 4). The prognostic factors for specific survival were N+ (53% vs 87% at 5 years; \( p = .0004 \); Figure 5) and ECS (17% vs 84% at 5 years; \( p = .000001 \)).

The 5-year actuarial local control for T1–2/N0N− was 88% (BRT alone); for T1–2/N0N−, 92% (RT + BRT); for T1–2/N+, 78%; for T3–4/N−, 80%; and for T3–4/N+, 57% (Figure 6). The prognostic factors for local control were N+ (65% vs 88% at 5 years; \( p = .009 \); Figure 7), ECS (37% vs 86% at 5 years; \( p = .000001 \)), and tumor stage (T1–2 vs T3–4; 88% vs 67% at 5 years; \( p = .02 \)).

No other tumor or treatment factors were significantly correlated with the development of a local recurrence: surgery-to-BRT or RT interval \( F \) 6 weeks (\( p = .36 \)), dose rate (\( p = .84 \)), total dose (\( p = .31 \)), and pathologic margins (\( p = .37 \)).

**Neck Control.** A cervical relapse occurred in 12 patients, without local recurrence in three patients. The mean time before relapse was 8.5 months (range, 3–23 months). There were three isolated node relapses, all occurring after mobile tongue SCC (two from the posterior third and one from the tip of the mobile tongue; one T1, and two T2). One patient had undergone an elective neck dissection (N0, treated by postoperative BRT alone), one had no previous neck dissection (N0, treated by postoperative BRT alone), and one had undergone previous neck surgery (1N + ECS + treated by postoperative RT + RT). Two patients could be salvaged by neck surgery with, for one only, postoperative RT.

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**FIGURE 4.** Cause-specific survival by tumor stage and treatment (BRT, brachytherapy; RT, radiotherapy).

**FIGURE 5.** Cause-specific survival by nodal status.

**FIGURE 6.** Local control by tumor stage and treatment (BRT, brachytherapy; RT, radiotherapy).

**FIGURE 7.** Local control by nodal status.
Metastases. Four patients (5%) had distant metastases develop. The mean time before metastases was 14.5 months (range, 5–25 months). They occurred after SCC of the floor of mouth in one patient and mobile tongue in three patients. The primary tumors were two T4 (N1 and N2) and two T2 (N0 and N2). One patient had a concurrent locoregional relapse (one mobile tongue).

Second Primary Tumors. Twenty-one patients (25%) had a second primary tumor develop within a mean time lapse of 60 months (range, 1–460 months) (two esophagus, nine lung, three colorectum, four head and neck, two skin, and one cerebral metastasis with unknown primary tumor). The four patients with head and neck cancers could undergo definitive treatment (RT and BRT, or surgery ± RT). Two patients were alive without evidence of disease at 31 and 33 months. The two others died of locoregional relapse. Fourteen (67%) of the 21 patients died of their second localizations.

Complications. Complications were observed in 36 patients (43%) in a mean interval of 14 months (range, 0–99 months). There were 12 grade 1, 17 grade 2, and 8 grade 3. The prognostic factors for complications were a high dose rate with a cutoff at 0.57 Gy/hr (25% vs 55%; \( p = .01 \)), a high number of wires that correlates to a large target volume (± 5 wires; 16% vs 50.7%; \( p = .008 \) and ± 4 wires; 7.7% vs 51%; \( p = .004 \)). For the 46 patients with RT + BRT, a high total dose was a prognostic factor with a cutoff at 71 Gy (32% vs 66%; \( p = .07 \)). Postoperative treatment was not a prognostic factor for the occurrence of a complication (42% [15 of 36] for BRT vs 46% [21 of 46] for RT + BRT; \( p = .72 \)), but grade 3 complications occurred in seven (15%) of the 46 treated with RT + BRT and only one (3%) of the 36 treated with BRT alone (\( p = .059 \)).

No other tumor or treatment factors were significantly correlated with the development of complications, including localization (51% for floor of mouth vs 35% for mobile tongue; \( p = .15 \)), tumor stage (46% for T1–2 vs 37% for T3–4; \( p = .45 \)), lead protection (\( p = .80 \)), and hyperdose sleeves (\( p = .98 \)).

DISCUSSION

Our results suggest that postoperative BRT alone for SCC T1–2/N0N− is better than post-operative RT-BRT because it is associated with equivalent actuarial overall and cause-specific survivals and local control and it reduces xerostomia and major complications (3% grade 3). For T3–4/N−, postoperative RT-BRT is acceptable (90% CSS at 5 years) as long as the number of wires can be kept to ≤5 to avoid complications. For N+, it may be improved, and concurrent postoperative chemoradiotherapy seems to be a new approach.\(^{15}\)

Because this is a retrospective study including selected patients, all treated at Centre Alexis Vautrin, there is a problem of bias. Although this series includes only a small number of patients in each subgroup, these results are noteworthy, given the homogeneity of the patients and the rarity of this situation (most T1–2 squamous cell carcinomas of the oral cavity have negative margins after surgery, and most T3–4 are not technically suitable for brachytherapy boost after radiotherapy to 50 Gy). Moreover, this bias is increased by the fact that the patients with objective margins less than 5 mm are grouped with patients with unknown margins but considered at risk by the surgeon. This bias was deemed acceptable because even though the margin status was unknown, in the first years of our experience, it was most likely less than 5 mm. In addition, the margin status does not affect the complications.

Survival and Local Control. Postoperative irradiation for patients with margins at risk is necessary. Huang et al\(^{3,16}\) observed in 125 patients with ECS and/or positive margins a benefit from systematic postoperative irradiation as opposed to postoperative irradiation for salvage, in terms of locoregional control (59% vs 31% \( p = .0001 \) at 5 years), cause-specific survival (72% vs 41% \( p = .0003 \) at 3 years), and overall survival (50% vs 30% \( p = .01 \) at 5 years). Moreover, oral-cavity localization is of poor prognosis. Data from the United States suggest that locoregional control rates after postoperative irradiation are lower for oral-cavity primary tumors than for other head and neck sites.\(^{4,7,17–19}\) Parsons et al\(^{19}\) showed in 134 patients with oral cancers treated by surgery and postoperative irradiation that prognostic factors for locoregional control were T stage (\( p = .04 \)), pathologic margin (\( p = .0007 \)), and ECS+ (\( p = .07 \)).

These series and ours demonstrate the advantage of postoperative RT, but there is still room for improvement in the case of positive nodes with ECS+. 
**Dose and Surgery Interval.** The surgery-irradiation interval should be 3 to 4 weeks and not longer than 6 weeks,\(^6,21\) even if complete healing is not obtained, because patients heal during or after irradiation.\(^{22}\)

Data from the literature show a dose-response relationship.\(^4,23\) When there is a positive or close margin at the primary site, a dose of 60 to 68 Gy is recommended.\(^4,8,10,24\) For definitive BRT, Mazeron et al\(^{25}\) and Simon et al\(^{26}\) showed that for stage 1–2 floor of mouth and mobile tongue, doses of 65 Gy or greater with intersource spaces of 1.2 to 1.4 cm result in a superior local control rate with low risk of complications.

Because the dose delivered by BRT is a minimum dose based on a peripheral isodose, it should range from 50 to 65 Gy for BRT alone.\(^27\) After 50 Gy delivered by RT to the primary site, this dose ranges from 10 to 20 Gy. In our experience dose level should be adapted to the pathologic margin (Table 4), and because of the 66% complication rate when the cumulative dose of RT and BRT exceeded 71 Gy, total dose should be 70 Gy or lower.

**Postoperative Brachytherapy.** Of note, apart from data from the Centre Alexis Vautrin,\(^{13,27–29}\) there are a few series that reported results of postoperative BRT in these patients. Beitler et al\(^{30}\) reported a series of 29 patients with positive or close margins treated by BRT (iodine-125) as a local boost after postoperative RT. The local control was 93%. The authors believed that good collaboration among the radiation oncologist, surgeon, and pathologist was necessary to optimize this approach. Chao et al\(^{31}\) reported a series of 55 T1–2 squamous cell carcinomas of mobile tongue and floor of mouth treated with postoperative BRT (iridium-192). Local control was achieved in 70% of patients who received BRT (77% of the patients with positive margins) versus 84% treated with RT alone (21% of positive margins). The authors concluded that BRT resulted in a high local control in patients with positive margins comparable to negative margins treated with RT. Two series\(^{32,33}\) demonstrated that it is possible to avoid major surgery after excisional biopsy in patients with squamous cell carcinoma of the oral cavity with good local control.

These series and ours demonstrate the benefit of postoperative BRT in patients with oral cavity tumors with close or positive margins and illustrate the feasibility of this approach. Postoperative BRT alone for SCC T1–2/N0N\(^{-}\) is better than postoperative RT-BRT because, with equivalent control, adverse effects of postoperative RT (xerostomia) are avoided, grade 3 complications are reduced, and it permits the treatment of a second head and neck primary tumor in nonirradiated tissue. The results for T3–4/N\(^{-}\) are acceptable, but to optimize the number of wires (< 6 to reduce the risk of complications), we confirm that a good relationship between surgeon, pathologist, and radiation oncologist is mandatory.

**Complications.** Beitler et al\(^{30}\) reported a rate of 17% complications in a series of 29 patients with positive or close margins treated by BRT (iodine-125) as a local boost after postoperative RT. Ange et al\(^{33}\) reported a series of 23 T1–2 N0 squamous cell tumors of mobile tongue and floor of mouth treated with BRT after excisional biopsy. Severe chronic sequelae were seen in four patients, and moderate chronic sequelae developed in eight of 23 patients. Mendenhall et al\(^{32}\) treated 15 patients with tumors of the floor of mouth and mobile tongue with BRT after excisional biopsy. Seven patients (46.7%) had late complications develop (bone exposure). Smith et al\(^{34}\) reported 55% early wound complications after postoperative 192 Ir BRT in nine patients (one of five had a grade 3 complication). No prognostic factors were found. This treatment was deemed acceptable because even though complications occurred in many patients (55%), they were only minor. However, the incidences of complications in patients treated with postoperative RT is not negligible. In a series of 134 patients with oral cavity tumors treated with postoperative RT, Parsons et al\(^{20}\) reported

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**Table 4. Dose levels based on the pathologic margin used at the Centre Alexis Vautrin.**

<table>
<thead>
<tr>
<th>Margins</th>
<th>Dose on the reference isodose (Paris system) (Gy)</th>
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<tbody>
<tr>
<td></td>
<td>Brachytherapy alone</td>
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<tr>
<td>Margin unknown but close</td>
<td>50–55</td>
</tr>
<tr>
<td>according to the surgeon</td>
<td></td>
</tr>
<tr>
<td>Close margin*</td>
<td>55–60</td>
</tr>
<tr>
<td>Positive margin</td>
<td>60–65</td>
</tr>
<tr>
<td>Macroscopic residual tumor</td>
<td>65–70</td>
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*MARGIN <5 MM OR CARCINOMA IN SITU.
that the incidence of minor and severe complications were 10% and 5%, respectively.

To minimize necrosis, Mazeron et al., in a series of 279 patients treated by BRT alone, recommended for stage 1–2 carcinomas of the oral cavity, a dose rate of 0.3 to 0.5 Gy/hr. Pernot et al reported, in a series of 1134 patients, prognostic factors for complications after definitive irradiation for cancers of the oral cavity and oropharynx. In multivariate analyses, these factors were dose rate greater than 0.7 Gy/hr (p = .01), total dose greater than 80 Gy (BRT + RT), absence of lead protection (p < .006), and number of wires greater than 6 (p = .001).

In our study, the total dose greater than 71 Gy, dose rate 0.57 Gy/hr, and the number of wires greater than 5 were prognostic factors. These results suggest that postoperative tissues are more radiosensitive after surgery because of damaged vascularization. For these reasons, the total dose, the dose rate, and the number of wires must be inferior to those applied to macroscopic tumors.

**Technical Developments.** When tumor location precludes the use of lead protection, recent innovations such as “the modified bridge technique” and “resin space” should be used.

To optimize the dose rate, Peiffert et al demonstrated that pulse dose rate (PDR) BRT is feasible in a series of 30 head and neck carcinomas but probably necessitates the modification of the implantation techniques. Strand et al reported early results of postoperative BRT for 40 head neck carcinomas, with a dose rate of 0.5 and 0.7 Gy/hr. After a median follow-up of 12 months (5–18 months), complications were one grade 1–2 tissue necrosis and one grade 3 bone necrosis.

More recently, progress in imaging and computers may further decrease the risk of sequelae by a better evaluation of the dose distributions in three dimensions.

Our long experience with low-dose-rate BRT, in combination with new developments (PDR, progress in imaging and computers), should lead to an improved therapeutic ratio.

The results of this study indicate that postoperative BRT alone for SCC T1–2/N0/N1 is better than postoperative RT-BRT because, with equivalent actuarial overall survival, cause-specific survival, and local control, the adverse effects of postoperative RT (xerostomia, dysgeusia, fibrosis) are avoided, grade 3 complications are reduced, and it permits the treatment of a second head and neck primary tumor in nonirradiated tissue. The results for T3–4/N+ are acceptable with this approach (ie, RT-BRT), as long as the number of wires is low but may be improved for N+.

We recommend a dose level based on the pathologic margin (Table 4). To improve the optimal number of wires, a multidisciplinary approach is required (surgeon, pathologist, and radiation oncologist) to estimate the volume at risk. The surgery-BRT or RT-BRT interval should be as short as possible (< 6 weeks). Technical progress in implantation (modified bridge, resin spacer), in imaging, in the use of three-dimensional treatment planning, and PDR (optimized dose rate = 0.5 Gy/hr) should further improve this approach in terms of local control and complications.

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