Brachytherapy in the Treatment of Head and Neck Cancer

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Brachytherapy is a therapeutic modality that may provide a significant improvement in the therapeutic ratio when appropriately applied, and hence, is an appealing treatment strategy for the head and neck. For several

Brachytherapy has a significant role in the management of head and neck squamous cell carcinoma (SCC),[1] largely due to the importance of locoregional control and the desire to minimize treatment-related functional deficits and preserve quality of life. In addition, the ongoing risk of second malignancies and locoregional recurrences in the head and neck requiring reirradiation make brachytherapy implants particularly appealing.

The use of a brachytherapy implant affords a unique approach to local dose intensification, improving the likelihood of functional organ preservation and minimizing treatment morbidity as a result of reduced irradiation to the surrounding normal tissues. In early-stage lesions, where the risk of nodal metastases is low, brachytherapy may be employed definitively or in an adjuvant fashion following surgery. In more advanced lesions, it is often combined with external-beam radiation therapy (EBRT) of the head and neck. The ability to provide specific, intensive local irradiation also permits the selective use of brachytherapy in the setting of recurrent or second head and neck SCC occurring within a previously irradiated region.

The optimal delivery of a brachytherapy implant necessitates a collaborative multidisciplinary team approach. This should involve a radiation oncologist trained in brachytherapy techniques, a head and neck surgeon and an oncologic nurse familiar with issues specific to brachytherapy implants, a physicist trained in brachytherapy treatment planning, and a dental surgeon experienced in radiation complications and the fabrication of spacers and lead-embedded prostheses. Such a team permits a smooth and efficient integration of treatment modalities, which may influence local control rates.

This review will elaborate on the current indications for brachytherapy in the head and neck, highlighting multidisciplinary issues pertinent to achieving these therapeutic goals. Technical aspects of brachytherapy are beyond the scope of this review, and the reader is referred elsewhere.[2-7]

Basic Principles

Patient Selection
Appropriate application of a brachytherapy implant begins with patient selection. This requires assessment of the patient’s understanding and ability to comply with the inherent radiation precautions associated with brachytherapy implants, especially for continuous low-dose-rate implants. Patients should be selected for their ability to provide baseline self-care needs in addition to treatment-related needs, such as the care of a tracheostomy, nasogastric feeds, and a patient-controlled analgesic pump, as indicated.

Patients subject to periods of confusion and disorientation may not be suitable for this mode of therapy. The potential for alcohol or narcotic withdrawal should be addressed to avoid complications with the delivery of the implant. Age alone is not a contraindication, but associated comorbidities may preclude the older patient from complying with the additional responsibilities noted.

Risk-Benefit Assessment
Considerations of the indications and the relative risk-benefit ratio of an implant require an assessment of not only the location, size, and extent of the tumor volume, but also of organ function, and hence, the appropriateness of an organ-preserving strategy. For the head and neck, attention to the status of oral/dental hygiene is important, with particular regard to the risk of mandibular osteoradionecrosis. Evaluation by a dentist familiar with these risks is mandatory. Other factors associated with an increased risk of severe soft-tissue complications include severe diabetes, liver failure, and compromised arterial status.[8]
Permanent vs Temporary Implants
The provisional technique should then be selected to enable appropriate planning and preparation. Several considerations influence the decision as to a permanent or a temporary implant.

Permanent Implants—Permanent implants, emitting radiation over the lifetime of their radioactivity, use sources that provide low-dose-rate irradiation. Suboptimal placement of a permanent implant and the potential adverse dosimetric effects of organ swelling and movement pose potential risks for an unfavorable therapeutic ratio. However, a permanent implant affords the delivery of a very high total dose of radiation and may be advantageous when implanting complex, irregular surfaces that are not amenable to the placement of temporary catheter-based implants, ie, where chinking of the catheters is a significant risk. The judicious use of permanent radiation sources with low-energy photons, such as iodine-125, may be advantageous when critical normal structures, such as the spinal cord, are adjacent to the implant.

Temporary Implants—Temporary implants are more commonly applied in the head and neck, as they permit a more deliberate and accurate placement of the applicator system without the radiation exposure concerns associated with a permanent implant. Typically, nylon catheters are used to mimic the desired position of the radioactive sources, which are subsequently afterloaded with low-dose-rate radioactive seeds embedded at defined positions within a nylon strand. This technique affords optimization of the implant dosimetry following placement of the implant applicator system. Commonly, this involves obtaining orthogonal plain x-rays of the implant, with dummy seeds placed within the selected applicator system and digitization of the relative seed positions into treatment-planning software. Variations in the activity, number of radioactive sources, loading duration—and for high-dose-rate computer-guided remote afterloading systems, variations in the dwell time and position—allow for dosimetric optimization. However, optimization cannot obviate the adverse dosimetry associated with poor implant geometry.

Temporary low-dose-rate implants also offer several radiobiologic advantages, including a reduced treatment time, the ability to irradiate a potentially less hypoxic tumor bed early in the postoperative period, a reduced adverse influence of hypoxia itself, and exploitation of cell-cycle-specific radiosensitization. This technique further exploits the differential repair capacities between tumor and normal tissues, reducing the risk of normal late complications. However, the risk of exposure to staff necessitates good source handling skills and strict radiation precautions.

High-Dose-Rate Implants—Alternatively, high-dose-rate sources with computer-guided remote afterloading significantly reduce the radiation exposure risks and required precautions. Fractionated radiotherapy is delivered with a single iridium-192 source fixed to the end of a guidewire that may be variably stepped along the length of each catheter. High-dose-rate implants have greater flexibility in conforming the implant dosimetry to the target volume and yield a relatively more homogeneous dose distribution, compared to that of low-dose-rate implants. Moreover, as the delivery of the radiation occurs over a shorter time, it is less subject to the effects of organ movement. This precise geometric sparing may yield a lower complication rate. However, concerns remain regarding the risk of increased late complications from the higher dose rate of radiation.[9] This has prompted studies to define optimal fractionation schedules to reduce this risk.

Pulsed-Dose-Rate Implants—The use of pulsed-dose-rate radiation has been studied as a technique to exploit the logistical advantages and reduced radiation exposure of remote afterloading and the low-dose-rate biologic advantages that may be mimicked by this technique.[10,11] The physical delivery system is analogous to high-dose-rate systems but with reduced source activity. Typically, a medium-dose-rate source is afterloaded to deliver radiation every hour for 10 to 30 minutes over several days. The optimal pulse size and pulse interval remains to be determined. Between pulses, radiation precautions do not need to be in effect, thereby facilitating improved treatment compliance. This technique remains promising but investigational to date.[1,12]

Intraoperative Radiation Therapy—An appealing alternative to the use of temporary implants is the use of high-dose-rate intraoperative radiation therapy. This technique has the advantage of accurately delivering radiation to the surgical bed and areas at risk of tumor recurrence, as defined at the time of the resection. In addition, intraoperative irradiation may optimize the cytotoxicity of the irradiation, as the tumor burden is at its lowest and the adverse effects of hypoxia are likely to be less influential than during the postoperative period. Optimized implant geometry results from the use of prefabricated commercially available applicator systems that maintain a uniform plane of catheters, which may then be molded to conform to curved and irregular surfaces. This modality remains investigational and limited to centers with expertise in the technique.[13]

Surgical Support
Surgical support is integral to the care of the implanted patient. Assessment and management of the upper aerodigestive airway is fundamental, particularly if the implant involves the pharyngeal airway or the base of the tongue, due to the potential for edema and bleeding. Coordination of the surgery and the planned brachytherapy implant is crucial for a successful implant. For permanent implants, surgical exposure of the area for implantation may be required. Coordination of surgical approach and implant technique is required not only to optimize the implant geometry but also to reduce the risk of wound complications. For temporary implants, surgical drains and wound dressings must be placed so as not to preclude the loading and unloading of any catheters. The placement of catheters and the wound-closure technique must also be coordinated to ensure minimal tension and potential distortion of the implant geometry.

In the setting of a neck dissection or when other surgical wounds lie near implant catheters, we prefer to delay the implant loading for a minimum of 5 days postoperatively. This is due to concerns of increased wound complications resulting from irradiation of the wound before sufficient fibroblast proliferation has occurred, as has been observed in the treatment of extremity sarcomas.[14] Although these concerns remain to be validated in the head and neck, this time is often required for treatment planning and for the patient to acclimatize to the increased self-care needs related to the surgical procedure(s), to maximize their adherence to radiation precautions.

Brachytherapy Indications and Optimal Management

Most of the scientific literature reporting on the role of brachytherapy in the head and neck is limited to institutional observational studies, many of which are retrospective. In part, this is the result of the requisite skills and experience limiting the generalized application of brachytherapy. Furthermore, a paucity of rigorous study designs exists due to the inherent limitations resulting from the study of skilled interventions. Despite this, studies providing clear delineation of patient selection criteria, consistency in independently reported series, and large patient cohorts with mature follow-up provide confidence in defining specific indications for brachytherapy in the head and neck.

Nasopharynx

The primary indication for a brachytherapy implant is in the management of recurrent disease, for which several institutional series have reported sustained local control rates of 20% to 60%, with the variability due to the extent of disease (both initially and at recurrence) and the dose of reirradiation.[15-19] Most experience has been with low-dose-rate implants. In selected series treating disease confined to the nasopharynx mucosa amenable to either an intracavitary or interstitial implant, sustained local control rates of 50% to 60% have been realized. The use of interstitial iodine-125 implants may be particularly useful for discrete lesions located in the posterior or superior nasopharynx.[20] However, these series have also demonstrated a significant risk of developing late radiation-related complications, including soft-tissue and bone necrosis, trismus, fistula formation, and neurologic complications such as radiation myelitis and temporal lobe necrosis.

In a study of over 600 patients who were reirradiated, the selection of small EBRT fraction size and the use of a brachytherapy implant was associated with a reduced risk of late complications.[15,16] Hence, a brachytherapy implant is an integral part of treating early disease recurrences, either alone or in combination with EBRT, to provide a sufficient dose (at least 60 Gy) while minimizing the risk of late complications.

Persistent Disease—A limited number of studies have reported on the role of an implant in patients with persistent disease following standard therapy.[16-19,21,22] These studies have suggested that further irradiation in early-stage disease, amenable to intracavitary (Figure 1) and interstitial techniques, results in local control rates comparable to those achieved in patients demonstrating a prompt complete response.[21]

The use of intracavitary techniques is appropriate for superficial lesions and should not be used for more extensive lesions.[22] Hence, dose escalation may be adequate in compensating for tumors demonstrating a low radioresponsiveness. The optimal dose schedule remains to be determined, with both 60 Gy low-dose-rate and 22.5 to 25 Gy high-dose-rate schedules reported.

A confounding factor in these reports is the timing of the diagnosis of persistent disease, as diagnosis soon after EBRT may select for more favorable but slow-to-regress lesions. Late toxicities do not appear to be increased in this setting. In light of the poorer local control and survival rates in patients managed for local recurrences, a brachytherapy implant should be considered in the management of patients demonstrating persistent disease.

Dose Escalation—Several investigators have also examined the value of dose escalation with
adjuvant brachytherapy in unselected patients as part of the initial management.[17,22-25] Again, implants were limited to T1 and T2 lesions amenable to mainly intracavitary techniques with high-dose-rate schedules. Notwithstanding the inherent limitations of retrospective comparative studies, consistent observations of an improvement in local control and survival with a modest increased risk of chronic mucosal complications have been noted. The impact of the tumor histologic grade on these results remains unclear. The clinical benefits of an implant may be modest and limited to patients with node-negative early-stage lesions. Recent comparative reports of cohorts initially treated with EBRT alone suggest an improved local control rate for T1 and T2 lesions with adjuvant brachytherapy, although the EBRT dose delivered may have been suboptimal.[24,25] The utility of brachytherapy in patients treated with concurrent chemoradiotherapy for advanced lesions is likely to be limited, but in a preliminary study, a radiosurgical boost has been demonstrated to be safe, effective, and able to encompass larger tumor volumes.[26]

**Soft Palate and Tonsil**

Several institutions have reported their experience with brachytherapy implants at these sites, typically administered as a boost (20 to 30 Gy) following EBRT (45 to 50 Gy) due to the risk of lymph node metastases.[27-35] This is particularly relevant for posterior tonsillar pillar lesions requiring treatment of the retropharyngeal lymph nodes. Most experience has been with temporary interstitial low-dose-rate implants using iridium-192. When combined with EBRT, brachytherapy produces local control rates of 85% or greater for T1 and T2 lesions and 65% to 70% for selected T3 lesions. Protracted overall treatment time beyond 7 weeks and a time interval between EBRT and the brachytherapy implant of greater than 20 days may adversely affect treatment outcomes, possibly due to the risk of tumor repopulation.[32] Hence, appropriate planning and coordination of the implant with the external-beam radiotherapy is an important consideration. In addition, meticulous attention to treatment details may minimize treatment interruptions and excessive acute toxicities. Pernot and colleagues at the Centre Alexis Vautrin recently updated their series of 361 patients treated from 1977 to 1991, with 343 patients receiving EBRT (50 Gy) followed by an implant (20 to 30 Gy) using the Paris system.[31] The 5- and 10-year local control rates were 80% and 74%, respectively. When considering only lesions treated with combined therapy (no recurrences were noted in the 18 T1 lesions treated with implant alone), the 5-year local control rates for T1, T2, and T3 lesions were 89%, 85%, and 67%, respectively. No significant difference was observed between T1 and T2 lesions.

Multivariate analysis demonstrated that T1 and T2 lesions, treatment duration less than 55 days, and lesions confined to the tonsil, soft palate, and posterior pillars were associated with improved rates of local control. On univariate analysis, an EBRT-implant interval greater than 20 days was associated with an adverse local control rate. Adjusting total dose to the extent of the lesion was not a significant factor for local control. In a further update, Hoffstetter et al demonstrated that a prolonged treatment duration also independently reduced the 5-year overall survival rate.[32]

**Tongue Involvement**—Extension of the carcinoma to the tongue has been demonstrated to be associated with an adverse prognosis. Conflicting results have been reported in retrospective reviews regarding the value of a brachytherapy implant for this indication.[33,34]

Leborgne et al reported the results of radiation therapy in 144 patients with tonsillar carcinomas.[33] Of this group, 15 patients with T1-4 lesions presented with tongue involvement and were treated with 58 to 62 Gy of EBRT followed 2 to 3 weeks later by an interstitial implant to the original tumor volume, delivering 18 to 26 Gy. The crude local recurrence for T1/2, Nx lesions was 20% (1/5) and for T3/4, Nx lesions, 40% (4/10), compared to 71% (5/7) and 62% (20/32), respectively, for a cohort with tongue extension but treated with external-beam radiotherapy alone (60 to 75 Gy). Complications were not increased by the implants.

There are clear limitations with such small patient numbers, and selection and treatment factors may account for the results. Nevertheless, these results are provocative in light of the high risk of local relapse and poor prognosis with tongue involvement. Given the conflicting results reported by Garrett et al, who studied a cohort of 68 patients treated with an adjuvant brachytherapy implant for similar indications, further evaluation is warranted.[34]

**Complications**—Mild to moderate self-healing soft-tissue complications are the most common side effects of brachytherapy for SCC of the soft palate and tonsil. Such effects may be seen in 10% to 20% of patients, but the risk of serious soft-tissue complications or osteoradionecrosis is minimal in experienced hands.[28,31] The prescribed dose rate significantly influences the risk of soft-tissue complications.[31] The risk of mandibular osteoradionecrosis may be minimized by ensuring a margin of 5 mm between the medial surface of the ascending ramus and the catheters.[2] Despite
the proximity to the carotid vessels, serious bleeding complications are rarely seen in this setting. **Remote Afterloading**—Levendag et al recently reported on their experience with the use of both high-dose-rate and pulsed-dose-rate brachytherapy schedules in a small but mature series of 38 patients with tonsillar fossa and soft palate SCC of various stages.[11] Thirty-six of these patients were prospectively evaluated, including all 26 patients treated with pulsed-dose-rate brachytherapy. The majority received EBRT with a brachytherapy boost. A promising 3-year locoregional control rate of approximately 90% was reported, given that 11 of 38 patients presented with T3 and T4 tumors. Conclusions regarding the efficacy of these brachytherapy schedules are limited, because the study involved historical controls who were suboptimally treated with external-beam irradiation only. However, the risk of late complications appears to be comparable to that seen after low-dose-rate brachytherapy, with a suggestion that the pulsed-dose-rate strategy may offer a lower risk of late complications. Continued prospective evaluations in well-defined, uniformly selected patient populations are required to confirm these results and to better evaluate the therapeutic ratio for these remote afterloading techniques.

The vast majority of patients with base of tongue squamous cell carcinomas present with advanced disease because of the insidious natural history of the tumor and the rich surrounding lymphatics. Unfortunately, surgical resection is associated with significant functional deficits at this site. Hence, organ-preserving strategies are highly desired in this setting.

Several independent investigators have consistently demonstrated that a brachytherapy implant boost (20 to 30 Gy) following EBRT (45 to 55 Gy) is associated with effective local control rates (Table 1). No significant functional deficits with this organ-preserving strategy have been reported when several quality-of-life domains were studied, even for advanced lesions.[36,37] The greatest experience has been with temporary interstitial low-dose-rate iridium-192 implants. Mature local control rates of 85% or greater may be expected for T1 and T2 lesions and 80% to 85% for T3 lesions.[38] Similar results have been reported in numerous studies.[7,39-46]

In general, the more advanced lesions treated have been selected based upon favorable exophytic growth patterns. The experience of a brachytherapy implant in T4 lesions remains limited.[38,40,42,43,45] For these lesions, Puthawala et al reported a mature crude local control rate of 67%, with an increased number of relapses observed in patients with more advanced neck disease.[43] A higher brachytherapy boost dose of 30 to 40 Gy compared to 20 to 25 Gy for T1/2 lesions was prescribed. The value of an implant for T4 lesions appears promising but requires further evaluation, particularly when combined with combination chemoradiotherapy,[43] as late swallowing complications may compromise the benefits of an organ-preserving treatment strategy. Typically, the implant has been placed 2 to 4 weeks following completion of the EBRT. A paucity of data are available with which to determine the potential adverse effects of protracted treatment duration. Nevertheless, judicious attention to these issues is recommended.

**Early vs Advanced Disease**—Housset et al reported a retrospective comparative study demonstrating comparable local control rates for early-stage T1/2 lesions treated with an EBRT and an implant and those treated with surgery followed by postoperative EBRT.[44] In contrast, local control rates with conventional fractionated EBRT alone were inferior.

Similar results have been reported by Regueiro et al in their analysis of factors influencing local control rates for 65 patients with T1-3 lesions treated with EBRT alone or with a brachytherapy boost.[42] Although there was an imbalance of N stages in favor of the implanted group, N stage was not significant when modeled in the regression analysis. Advanced N stage has been associated with reduced local control rates.

The Stanford group reported a trend toward improved relapse-free survival for a small cohort treated with EBRT and an implant, compared to a cohort treated with surgery and postoperative radiotherapy, despite more advanced disease in the nonsurgery cohort.[7] Hence, compelling data support the use of interstitial implants in the management of base of tongue SCC when effective organ-preserving therapy is required (Figure 2).

**Toxicity**—Toxicities have in general been limited to mild-to-moderate soft-tissue necrosis occurring in 15% to 30% of cases, with severe ulceration seen in approximately 5%.[38,41,42] Biopsy of suspicious areas early in the posttreatment period should be avoided unless there are clear clinical indications of progression or recurrence. This may precipitate the development of soft-tissue ulcerations.[43] Bone complications may be seen in 10% to 15% of patients.

More serious complications may rarely include mandibular osteoradionecrosis (5%), aspiration pneumonitis (and the risk of airway complications), and arterial bleeding. Airway complications may be avoided by the routine use of a temporary tracheostomy, which further minimizes the risk of aspiration in the event of bleeding complications at implant placement and/or removal.
High-Dose-Rate Brachytherapy—Recently, Hungarian investigators studied high-dose-rate brachytherapy as a boost (mean dose: 20 Gy, range: 12 to 24 Gy) following EBRT (60 to 66 Gy, n = 17 patients) or as the sole adjuvant treatment modality following surgery for early-stage T1/2, N0 lesions of the base of tongue (mean dose: 27 Gy, range: 24 to 30 Gy).[47] The boost brachytherapy was delivered 2 to 3 weeks after EBRT, at 3 to 4 Gy per fraction twice daily in six to seven fractions. Four patients received a single 12-Gy boost. The indications for postoperative brachytherapy included positive or close margins delivered 2 to 3 weeks after surgery in six fractions twice daily with 4 to 5 Gy per fraction. At a mean follow-up of 32 months, an overall crude local control rate of 62% was reported. All four patients receiving postoperative brachytherapy remained free of disease. A crude local control rate of 53% (9/17) was reported in the cohort treated with EBRT and brachytherapy boost. These promising results require further evaluation in a larger patient cohort and with longer follow-up before they can be applied more generally.

Oral Tongue

Treatment options for early-stage oral tongue SCC include surgery, external-beam radiotherapy, and brachytherapy, all of which appear to offer comparable rates of local control. Hence, the associated toxicity and functional impairments often guide treatment selection. In general, surgery is preferred when the risk of functional deficits is minimal, as external-beam radiotherapy may be associated with greater xerostomia, and brachytherapy carries the risk of osteoradionecrosis. When surgery is not feasible, brachytherapy may be a particularly attractive treatment option. Indeed, a significant body of literature supports a role for brachytherapy in the management of oral tongue SCC. Brachytherapy has been used alone or in combination with EBRT, demonstrating local control efficacy. In the largest such experience—over 600 patients from the Curie Institute—researchers reported local control rates of 86%, 78%, and 71% for T1, T2, and T3 lesions, respectively.[48] Early T1 and T2 lesions were treated with temporary interstitial low-dose-rate iridium-192 implants alone, delivering 70 Gy in 6 to 9 days. Larger T2 and T3 lesions were treated with EBRT (50 to 55 Gy) followed by an implant (20 to 30 Gy). Other investigators have demonstrated comparable results, showing a high rate of local control.[9,49-58]

Brachytherapy Alone—Several groups have reported local control rates of 90% or greater for selected lesions (< 1 cm in thickness) often amenable to a single-plane implant alone.[49,58] Mazeron et al reported their series of 121 patients with T1/2, N0 tumors treated with 60 to 70 Gy by the Paris system.[59] The crude local control rates for T1, T2a (2.1 to 3 cm), and T2b (3.1 to 4 cm) tumors were 86%, 89%, and 74%, respectively. The prescribed dose was significantly associated with the probability of local control, with doses less than 65 Gy associated with a fivefold risk of relapse. Selection by the growth pattern has been shown to influence 5-year local control rates, with 85%, 79%, and 45% reported for superficial, exophytic, and infiltrative lesions, respectively.[54]

Combination Radiotherapy—The risk of occult nodal disease in patients with early-stage, node-negative oral tongue SCC usually necessitates elective neck treatment, especially for T2 lesions. Often, a combination of EBRT and an iridium-192 implant is used. Several retrospective reports suggest that the greater the proportion of dose delivered with the implant, the greater the probability of local control.[51,52,55,56,60,61] A retrospective comparative study of 147 patients with T2, N0 oral tongue SCC treated with either an iridium-192 implant alone or with EBRT and an implant reported 5-year local control rates of 89.8% and 50.6%, respectively.[52] Favorable locoregional control rates and cause-specific survival were reported for the group receiving an implant alone. The retrospective nature of these reports may be subject to treatment and selection biases, including the preference for external-beam irradiation for more advanced primary lesions. However, the consistency of these independent reports suggests that this may reflect the inherent biologic and physical advantages unique to brachytherapy implants. This observation may be exploited when the majority (if not all) of the dose is delivered with the implant.

Not surprisingly, a time interval between the EBRT and the implant of greater than 20 days has been demonstrated to adversely affect local control rates, again possibly reflecting the adverse influence of tumor repopulation during treatment interruption.[51] In cases for which elective neck irradiation has been preferred, a dose of 40 to 45 Gy has been used. Alternatively, neck dissection may be performed with subsequent neck irradiation when indicated.

Toxicity—Implant of the oral tongue has been associated with a 10% to 20% risk of mild-to-moderate self-limiting soft-tissue ulceration and a low risk (< 10%) of mandibular osteoradionecrosis in experienced hands. Custom lead-embedded mandibular prostheses and spacers are recommended and have been demonstrated to reduce the risk of bone osteoradionecrosis.
complications.[49] A predicted 5-year probability of osteoradionecrosis of 38% was reduced to 4% with the use of a spacer.

**High vs Low Dose Rates**—Several studies of high-dose-rate brachytherapy alone for selected early-stage T1/2 node-negative lesions have been reported.[9,58,62] Lau et al reported on the results of a phase I/Ill trial of high-dose-rate brachytherapy in node-negative, early-stage oral tongue SCC in 27 patients.[9] The schedule consisted of 45.5 Gy in seven fractions of 6.5 Gy per fraction delivered twice daily over 3.5 days. An interfraction period of at least 6 hours was calculated to be isoeffective with the low-dose-rate schedule of 60 Gy over 6 days. Disappointing local tumor control was observed, with a suggestion of an increased incidence of late complications, compared to a historical cohort of patients treated with low-dose-rate brachytherapy. The authors concluded that low-dose-rate brachytherapy should remain the standard brachytherapy modality.

In contrast, Inoue et al reported a small randomized trial of 29 patients comparing low-dose-rate brachytherapy (70 Gy over 4 to 9 days) to a high-dose-rate schedule (60 Gy in 10 fractions of 6 Gy per fraction delivered twice daily over 6 days) for a selected group of patients with T1/2, N0 SCC of the lateral oral tongue.[58] The lesions had a thickness of 10 mm or less, such that they were treated with a single-plane high-dose-rate implant with the dose prescribed at 0.5 cm from the reference plane.

The 1-year local control rate was 86% and 100% (P = .157) in the low-dose-rate (n = 15) and high-dose-rate (n = 14) groups, respectively.[58] The 2-year local control rate was identical, but the median follow-up of 24 months (range: 10 to 32 months) limits this observation. One soft-tissue ulceration and one bone exposure complication arose in the high-dose-rate arm, although a prosthetic spacer was not used in the later case.

Leung et al have reported preliminary results treating eight patients with the same high-dose-rate schedule showing 100% local control rate at a median follow-up of 26 months.[62] Although the data are promising, the short follow-up and significant risk of a false-negative error limit any definitive conclusions regarding the generalized application of high-dose-rate brachytherapy in place of standard low-dose-rate implants for the oral tongue.

A subset of patients with a close or positive surgical excision margin and no indication for neck irradiation has been treated with a brachytherapy implant alone (iridium-192 low-dose-rate to 60 Gy). This obviates the risk of further major surgery or EBRT-related toxicities including xerostomia. A promising mature local control rate of 89% has been observed in a small retrospective series.[63] Similar results have been reported elsewhere.[64-66]

As with oral tongue carcinomas, several treatment options exist for floor of mouth carcinomas, although surgical resection is often preferred due to the minimal functional deficits and high rates of local control achieved. Brachytherapy implants may have a role in the management of floor of mouth carcinomas but must be judiciously applied due to the proximity of the mandible, which increases the risk of osteoradionecrotic complications.[67]

Several institutions have demonstrated that an iridium-192 implant alone (60 to 70 Gy) may yield local control rates of over 90%, 70% to 75% and 50% to 55% for T1, T2, and T3 lesions, respectively.[68,69] Mazeron et al demonstrated that local control rates significantly decrease for tumors with gingival extension or when the lesion is greater than 3 cm.[68] Pernot et al reported similarly adverse results with increasing lesion size in a series of 207 patients with primarily T1/2, N0 lesions.[69] Grade 1 and 2 self-resolving soft-tissue and bone complications were observed in 17% and 12%, respectively. Complications requiring surgical intervention were observed in 6%.

Brachytherapy alone was found to be advantageous, compared with combined EBRT and an implant for T1/2, N0 lesions.[69]

A small retrospective comparative study has demonstrated comparable local control rates in early-stage lesions with either a high- or low-dose-rate implant.[70] Iridium-192 implants (60 Gy) have also been demonstrated to offer excellent mature local control rates—ie, 85% to 90% in lesions with close or positive margins following surgical excision.[63-65,71]

**Lip**

Cancer of the lip is the most common malignancy of the oral cavity, typically occurring as an early-stage lesion on the lower lip. Treatment options include surgery, EBRT, and a brachytherapy implant. As with oral tongue lesions, an implant affords minimal functional and cosmetic disabilities, especially for lesions near the commissure, with the advantage of a shorter overall treatment time.

Several large series, including one treating over 700 patients, confirm comparably high rates of local control, as would be expected with surgical resection.[72-76] The vast majority of the reported series have used temporary low-dose-rate iridium-192 or iodine-125 implants, delivering a typical dose of 60 Gy over 6 days for T1/2 lesions of the lower lip, with local control rates in excess of 90% and 85%,
respectively. A higher dose may be used for more infiltrating thicker lesions.[75] A brachytherapy implant boost (20 to 30 Gy) may be integrated with the appropriate neck management strategy for selected, more advanced T2/3 lesions, with an expected control rate of approximately 75%. [72] Customized lead-embedded dental prostheses are recommended especially for large implants lying in close proximity to bony structures, to reduce the risk of complications.[75]

**Recurrent and Second Primary Head and Neck SCC**
The optimal management for recurrent non-nasopharyngeal head and neck SCC and second primary head and neck SCC remains to be defined and is complicated by retrospective series reporting on heterogeneous groups of patients. However, reirradiation of the head and neck is possible with increased but potentially acceptable toxicities. A brachytherapy implant for reirradiation can play an important role in improving the therapeutic ratio, as full-dose irradiation is required if cure is to be achieved. Other treatment options exist and have recently been reviewed.[77] Surgery is preferred for resectable lesions in the absence of unacceptable functional and cosmetic sequelae. In this setting, there is often a need for management of microscopic residual disease with radiotherapy. A planned introduction of nonirradiated tissue flaps with coordination of the implant placement and wound reconstruction can reduce the risk of wound complications. Both pedicled myocutaneous flaps[78] and microvascular free flaps have been described.[79] Nevertheless, complication rates of 20% to 50%—including a risk of carotid rupture when the implant is placed in the neck—have been reported (Figure 3). Factors other than the radiation may be contributing to the increased risk of complications. This is tempered by local control rates of 44% to 80%, suggesting a limited therapeutic ratio.[80-83] Hence, patient selection is particularly important for this indication.

**Brachytherapy Alone**—A brachytherapy implant alone may be used for selected second primary head and neck SCC. Peiffert et al reported the results of an iridium-192 implant alone for 73 patients with tonsil carcinoma treated at the Centre Alexis Vautrin (Figure 4).[84] The majority presented with early node-negative disease, and a median dose of 60 Gy was prescribed according to the Paris dosimetry system. The 5-year actuarial local control rate for T1, N0 and T2, N0 lesions was 80% and 67%, respectively. Acceptable grade 2 self-resolving complications—mostly soft-tissue necrosis caused by doses > 60 Gy—were observed in 10 cases (13%). This incidence was increased, compared to the same institution’s series of tonsillar implants in unirradiated tissues.[85] The 5-year actuarial disease-specific survival and overall survival were 64% and 30%, respectively. No long-term survivors were observed, reflecting the increased risk of other malignancies and other alcohol- and smoking-related comorbidities in this patient population.

Other retrospective series have reported the results of reirradiation with an implant but include both patients with a second primary SCC and those with recurrent SCC, confounding the overall analyses. Treatment of recurrent head and neck SCC may be expected to have lower local control rates due to the treatment of more radioresistant clonogens—an observation that is consistent with clinical[86-88] and in vitro data.[89] Langlois et al reported the results of reirradiation in a larger, heterogeneous group treated at the Centre Alexis Vautrin. These 123 patients with T1-3 disease were treated with an iridium-192 implant at a mean dose of 62 Gy.[87] A 5-year actuarial local control rate of 59% was observed. Local control correlated with size < 3 cm, second primary (vs recurrent lesions), dose > 60 Gy, and tumor site (oral cavity more favorable than oropharynx). A 5-year actuarial survival rate of only 24% was realized, with the achievement of local control and an interval of more than 2 years between radiation sessions associated with a better prognosis. Mucosal necrosis was observed in 28 cases (23%).

**Other Prognostic Factors**—Stevens et al also noted favorable local control rates with a reirradiation dose ≥ 60 Gy for second primary head and neck SCC, a treatment interval > 1 year for recurrent lesions, and the use of an implant in addition to EBRT.[86] Mazeron et al reported a 5-year actuarial local control rate of 69% for 70 patients with oropharyngeal carcinomas reirradiated with an iridium-192 implant alone, delivering a mean dose of 60 Gy with the Paris system.[90] Similarly, tumor site (glosso-tonsillar sulcus and base of tongue) and tumor size (> 2 cm) adversely influenced the local control rate, with larger lesions occurring more frequently in the base of tongue. Only 7 of 69 patients (10%) developed nodal relapses. Soft-tissue necrosis was the main complication (27%) and was self-resolving in 13 of 14 patients. The incidence of this complication appeared to increase among cases in which a large lesion was treated with an implant.

**EBRT vs Implant**—Levandag reported results in 73 patients with either a second primary or recurrent head and neck SCC, comparing EBRT reirradiation (n = 55) to brachytherapy implant with
or without EBRT reirradiation (n = 18). Significant heterogeneity existed in the treatment applied in each of the patient cohorts, precluding definitive conclusions.[91] That said, selection bias was minimized, as the two cohorts represented sequential treatment periods resulting from an institutional policy change. Crude local control rates of 29% and 50% were reported, suggesting improved control rates with an implant, although this was confounded by the higher mean dose delivered in the implant cohort. The high rate of temporary mucosa ulcerations (13/18 vs 9/55) was likely related to the implant technique used.

Split-Course Implants—To reduce the increased risk of mucosal ulceration associated with an implant, Housset et al employed a planned treatment interruption, delivering the intended dose in two separate implants with a source shift.[88] A total of 55 patients with recurrent and second primary base of tongue SCC underwent implantation, with 31 patients receiving a single-course implant of 60 Gy and 24 patients receiving a split-course implant delivering 35 Gy and 30 Gy with a 1-month interruption. A significant reduction in the risk of mucosal necrosis was observed with the introduction of a treatment interruption (16% vs 43%), but a trend toward a lower crude local control rate (37.5% vs 52%) suggests that such a strategy warrants further investigation.

Summary—In summary, a brachytherapy implant may be selectively applied for reirradiation in view of the poor prognosis associated with this patient population. Favorable local control rates may be expected in patients with a second primary head and neck SCC, small tumor sizes, tumor sites other than the base of the tongue, and the delivery of 60 Gy or more. For recurrent head and neck SCC, a treatment interval greater than 1 year appears to select for lesions that are less radioresistant. Soft-tissue complications appear to be increased in this setting, with an incidence ranging from 20% to 30%, and with the majority being self-resolving.

Postoperative Brachytherapy
Several institutional retrospective reports have suggested that the addition of a brachytherapy implant where surgical margins are positive or close may improve upon local control rates for a mixture of tumor sites.[92-94] As such, site-specific indications are difficult to discern. Pernot et al reported a 5-year local control rate of 89% for 97 patients treated with either postoperative EBRT followed by an implant or an implant alone for oral cavity tumors.[92] Self-resolving grade 1 and 2 complications occurred in 19% and 12% of patients, respectively, with only 6% of complications requiring surgical intervention (grade 3). These results are particularly promising in light of the fact that one-third of the patients treated had T3/4 lesions. The moderate incidence of self-resolving complications appears to be comparable to that seen when brachytherapy implants are used for definitive indications.

Two other institutional series have also reported high local control rates in a smaller cohort of patients treated with postoperative EBRT and a permanent iodine-125 implant. Beitler et al reported a 2-year actuarial local control rate of 92% (median follow-up: 26 months, range: 5 to 86 months) in 29 patients receiving 120 to 160 Gy from the implant.[93] The majority of the lesions arose from the tonsil and were implanted for either a positive or close surgical margin. Vikram and Mishra reported only one local recurrence (4%) in 25 patients consecutively treated with EBRT (60 Gy) and a permanent iodine-125 implant for a positive surgical margin following a median follow-up period of 1.5 years (range: 1 to 5 years).[94]

Despite the potential for selection factors influencing these results, the high local control rates suggest an intriguing treatment strategy that addresses the higher burden of residual microscopic disease at the surgical margin. To date, no comparative studies have been reported, although higher local failure rates would be expected in this cohort of patients. Further reports to define the therapeutic ratio for specific sites are required. Coordinated preoperative and intraoperative assessments to guide an accurate determination of the region at risk (ie, requiring a brachytherapy implant) are recommended.

Conclusions

A brachytherapy implant may be used in the management of head and neck SCC for several tumor sites including the tonsil and soft palate, base of tongue, and lip. The use of an implant in the lip, oral tongue, and base of tongue has the advantage of being a functional organ-preserving treatment strategy. In specific circumstances, it may be used as an alternative to surgery for selected cancers of the floor of the mouth.

A brachytherapy implant or high-dose-rate intraoperative radiation therapy (which remains investigational) is a particularly attractive treatment option for reirradiation, permitting a higher total dose to be delivered with an increased but acceptable risk of soft-tissue necrosis. A brachytherapy
implant may also be used for postoperative irradiation in the setting of a close or positive surgical margin.

References:


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