CLOSE OR POSITIVE MARGINS AFTER SURGICAL RESECTION FOR THE HEAD AND NECK CANCER PATIENT: THE ADDITION OF BRACHYTHERAPY IMPROVES LOCAL CONTROL

JONATHAN J. BEITLER, M.D., MBA,* RICHARD V. SMITH, M.D.,† CARL E. SILVER, M.D.,‡ ASTRID QUISH, M.D.,§ SHIVAJI M. DEORE, PH.D.,* EDUARD MULLOKANDOV, PH.D.,* DORACY P. FONTEMLA, PH.D.,* SCOTT WADLER, M.D.,# MARY KATHERINE HAYES, M.D.,† AND BHADRA SAIN VIKRAM, M.D.*

*Department of Radiation Oncology, †Department of Otolaryngology, ‡Department of Surgery, §Department of Pathology, Department of Medical Oncology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, #Department of Radiation Oncology, New York Hospital, NY, NY, †Department of Medical Oncology, Montefiore Medical Center, Bronx, NY, and ™Beth Israel Medical Center, NY, NY

Purpose: Microscopically positive or close margins after surgical resection results in an approximately 21-26% local failure rate despite excellent postoperative external radiation therapy. We sought to demonstrate improved local control in head and neck cancer patients who had a resection with curative intent, and had unexpected, microscopically positive or close surgical margins.

Methods and Materials: Twenty-nine patients with microscopically close or positive margins after curative surgery were given definitive, adjuvant external radiation therapy and ¹²⁵I brachytherapy. All 29 patients had squamous cell cancer and tonsil was the most common subsite within the head and neck region. After external radiation therapy and thorough discussions with the attending surgeon and pathologist, the slides, gross specimens, and appropriate radiographs were reviewed and a target volume was determined. The target volume was the region of the margin in question and varied in size based on the surgery and pathologic results. Once the target volume was identified the patient was taken back to the operating room for insertion of ¹²⁵I seeds. Activity implanted (range 2.9-21.5 millicuries) was designed to administer a cumulative lifetime dose of 120-160 Gy.

Results: Twenty-nine patients were followed for a median of 26 months (range 5-86 months). Two-year actuarial local control was 92%.

Conclusion: ¹²⁵I, after external radiation therapy, is an excellent method to improve local control in the subset of patients with unexpectedly unsatisfactory margins. © 1998 Elsevier Science Inc.

Brachytherapy, ¹²⁵I, Positive margins, Close margins, Head and neck, Squamous cell carcinoma.

INTRODUCTION

The treatment of locally advanced squamous cell head and neck cancer has evolved from surgery alone to surgery with either pre- or postoperative radiation to surgery plus postoperative radiation therapy (12). Although advanced cancer of the larynx (21) and hypopharynx (15) may best be treated with induction chemotherapy external radiation and salvage surgery, most advanced oropharyngeal and oral cavity cancer are still treated with surgical resection and postoperative external radiation. Despite the use of intraoperative frozen sections, final pathology reveals an inadequate margin of resection in 10-16% of patients (5, 11).

Without adjuvant radiation therapy, the local failure rate for those patients who undergo resection with positive margins is 71-80% (5, 16). With postoperative external radiation, local recurrence in the presence of microscopically positive or close margins ranges from 21-26% (10, 11, 24).

We hypothesized that interstitial brachytherapy applied to boost the immediate region of the close or positive margin would further improve local control when compared to postoperative external radiation alone (23).

METHODS AND MATERIALS

Twenty-nine consecutive patients who underwent curative resection had invasive cancer at or less than one high powered field (HPF) from the margin and went on to ex-


Reprint requests to: Jonathan J Beiter, M.D., MBA, Associate Professor and Deputy Chairman for Clinical Affairs, Dept. of Radiation Oncology, Montefiore Medical Center, 3335 Steuben Ave., Bronx, NY 10467.
ternal radiation and $^{125}\text{I}$ implantation form the basis of this report. Surgical margins were usually inked at the time of processing, and in most cases the attending surgeon oriented the specimen for the processing pathologist. Each patient was reviewed at a multidisciplinary tumor board attended by surgeons, pathologists, and radiation oncologists to determine the need for implantation. First the tumor and the operation were described, then the intraoperative photographs, the gross specimen photographs, and finally the microscopic pathological margins were reviewed. In no case was known gross tumor left behind after curative surgery.

The histologic features and primary site are described in Table 1.

Postoperative external radiation was administered to a median dose of 60 Gy (range 50–65 Gy) using 1.8–2.0 Gy daily fractions, 5 days a week. To allow for some resolution of the acute reactions to external radiation, we waited 3–6 weeks after the completion of external radiation to perform the implantation. After the proposed procedure was explained to the patient, a separate informed consent was obtained prior to the interstitial implantation.

In preparation for the implant, the photographs, operative findings, and sometimes the gross specimen were rereviewed as necessary to determine the location and size of the target volume. The procedure was performed using a Mick applicator (Mick Industries, Bronx, NY) and 3M/Mediphysics (Arlington Heights, Illinois) $^{125}\text{I}$ sources and was designed to administer a cumulative lifetime dose of 120–160 Gy (9) to the high-risk target volume. The average activity implanted was 7.78 millicurie (range 2.9–21.5 millicuries; standard deviation—4.36 millicuries). Details of the procedure have previously been published (22).

$^{125}\text{I}$ implantation was performed as an ambulatory procedure under general anesthesia in the operating theater, and after implantation the patient had simulation films, and surveys for levels of emitted radiation.

**RESULTS**

Clinical results appear in Table 2. Local control was 93%, and the two local recurrences occurred 9.5 and 11.9 months after initial surgery (see Fig. 1). One developed metastases 2 weeks after documentation of local failure, and both local failure patients died of disease.

By approximately 12 months, six patients developed metastatic disease (see Fig. 2).

**Complications**

One patient sustained a fractured mandible during intubation for the $^{125}\text{I}$ implant. The procedure was aborted and $^{125}\text{I}$ implant was never performed. The patient died with eventual local failure and is not included in our clinical results.

A second patient who had a postoperative orocutaneous fistula, redeveloped the fistula after $^{125}\text{I}$ implant. The fistula was surgically resected and the patient remains free of disease 24 months after the original surgery.

<table>
<thead>
<tr>
<th>Table 1. Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td>Squamous</td>
</tr>
<tr>
<td>Primary site</td>
</tr>
<tr>
<td>Tonsil</td>
</tr>
<tr>
<td>Larynx</td>
</tr>
<tr>
<td>Tongue</td>
</tr>
<tr>
<td>Floor of mouth</td>
</tr>
<tr>
<td>Retromolar</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Alveolar</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Clinical results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Local control</td>
</tr>
<tr>
<td>Local failure</td>
</tr>
<tr>
<td>Mets</td>
</tr>
<tr>
<td>New primaries</td>
</tr>
<tr>
<td>Intercurrent</td>
</tr>
<tr>
<td>Dead or AWD</td>
</tr>
<tr>
<td>Alive and NED</td>
</tr>
</tbody>
</table>

![Fig. 1. Local control.](image1)

![Fig. 2. Distant metastases.](image2)
A third patient had persistent edema after supraglottic laryngectomy, external radiation, and $^{125}\text{I}$ interstitial implantation. She was treated with systemic steroids then the "excessive" soft tissue was resected. She has since returned to the operating room for deep biopsies, which revealed necrosis, which has necessitated a tracheostomy. She is free of cancer 20 months after her initial, definitive surgery.

A fourth patient with an extensive floor of mouth cancer and a continued unhealthy lifestyle, developed a fistula 34 months after initial surgery and underwent reconstruction 6 months later. A month after reconstruction she fractured her mandible while yawning. She has no evidence of cancer 53 months after her initial surgery.

A patient developed an ulcer of her tongue, which was biopsied 12 months after implantation. The biopsy fragments showed radiation reaction, and though difficult to interpret, were signed out as positive for superficial squamous cell cancer. The patient underwent resection of a 6.0 \times 5.0 \times 5.0 \text{cm} specimen that contained a 3.5 \times 2.5 \times 1.0 \text{cm} ulcer. Despite submitting the entire specimen for microscopic analysis, and despite the best efforts of six attending pathologists, no tumor was found in the large specimen. The pathology report that prompted the resection was amended, taking into account the large surgical specimen subsequently provided. The amended reports states that the biopsy fragments, although suspicious for cancer, were not diagnostic due to the marked radiation changes. This patient is considered to have retained local control and has been without evidence of disease for 42 months since her initial surgery.

**DISCUSSION**

An adequate margin of resection has not been precisely defined, and specimen shrinkage, pathological processing artifacts, and difficult anatomy complicate the problem. Looser, Shah, and Strong (16) studied 62 of 1775 patients with positive margins, and found that invasive cancer at the margins, in situ cancer at the margins, premalignant change, and tumor within 0.5 cm of the margin all had an equally high risk of local recurrence and increased mortality. Overall 71% of these patients developed a local recurrence and 31% survived 5 years. Amdur et al. (1) reviewed 134 patients who underwent radical surgery and found that the evaluable positive margin group (n = 13) suffered worse local control than the clear margin group. Patients with close margins (n = 19) or carcinoma in situ (n = 3) at the margins did not suffer local-regionally when compared to the group with clear margins.

Within the head and neck cancer population, larynx patients with positive margins fare better (18% local recurrence) (2) and we hypothesize that this may be the result of the many perilyngeal barriers to tumor spread (3). Forty-nine percent of the evaluable patients in the Amdur series had primary carcinomas in the supraglottic or glottic larynx, compared to only 8% in the Looser series, and this may explain the differing results and conclusions.

Intergroup Study 0034 mandated frozen sections be obtained if the margin was < 2 cm (13). Frozen sections were taken from the patient and not the resected tumor and if both the permanent section from the specimen and the frozen section from the patient were positive, the patients were ineligible for randomization. Patients with < 5 mm margins, carcinoma in situ at the margins, or extracapsular nodal extension received 60 Gy because of high risk. When the high-risk group was compared to the low-risk group that received only 50–54 Gy, the high-risk group suffered more (p = 0.016) local-regional failure (26%, 69 of 270) than the low-risk group (15%, 27 of 176). Although the definitions of positive and close margins are peculiar to this study, and therefore must be interpreted with caution, it would appear that margins < 5 mm as well as carcinoma in situ are risk factors for increased local failure. The patients who were excluded from the study because of positive margins from both the tumor and the operative bed suffered a 21% recurrence rate at the primary site alone. The regional prognostic importance of extranodal extension has been independently verified (20).

It has been said that "One of the chief tenets of surgical management of advanced head and neck squamous cell carcinoma is the imperative to obtain negative surgical margins (11)." Zelefsky et al., on the other hand felt that "... with postoperative doses of \( \geq 60 \) Gy excellent local control was achieved in patients with inadequate margins of resection." Though the Zelefsky group appropriately emphasized the importance of anatomic subsite to their results, looking at the entire group, 4 of 25 patients with positive margins and 11 of 41 patients with close margins failed locally. This would imply a local failure rate in the oral cavity and oropharynx of 23% (15 of 66) despite a median of 60 Gy of external radiation therapy (see Fig. 3).

In our series distant metastases became clinically de-
tectable by roughly 1 year from the initial surgery and may well represent subclinical disease present before the $^{125}$I implant was performed. It is unlikely that this technique will impact on freedom from metastatic disease in the 20% of our population that developed distant disease. However, the absence of late distant metastases when the primary was controlled was encouraging.

The appropriate postoperative dose of radiation for each patient is not precisely known. Postoperative dose of 60 Gy in 30 fractions were described by the 2nd edition of Dr. Fletcher's textbook (6). An early paper from Gainesville (17) recommended 65 Gy using 1.7-1.8 Gy fractions, but for the oral cavity and oropharynx, 70 Gy was recommended, particularly when the margins were positive. Randomized data from MD Anderson (20) failed to justify external beam dose escalation, and that group recommended a minimum dose of 57.6 Gy with a boost of 63 Gy to areas of increased risk.

$^{125}$I for unrespectable neck disease (8) and for tumor adherent to the carotid artery (19) and recurrent cancers (14) has been described. One Stanford report (18) suggested no local failure in the irradiated volume; however, only 18 of the 48 patients were treated for cure. A later report (7) noted 79 and 71% local control in the implanted volume and in all head and neck sites, respectively. Many of the Stanford patients had gross residual disease or recurrent tumors after prior treatment, and certainly their tumor burdens were heavier than ours. All our patients have been treated with curative intent.

We believe that inadequate margins continue to represent a challenge to local control in the head and neck population treated with postoperative external radiation therapy alone. Our technique appears to improve local control (see Fig. 3), but this conclusion is limited by the nature of a nonrandomized study and the number of patients in our study population. Obviously, our gains must be weighed by the risk of serious complication, and tissue necrosis is of concern.

This technique requires a bit of detective work, and particularly close collaboration between radiation oncologists, surgeons, pathologists, and physicists. In some cases anatomic uncertainty may necessitate bringing a member of the surgical team to optimize seed placement.

Because of the operator dependent nature of the $^{125}$I implantation procedure, a multinstitutional randomized trial does not seem practical at present. In the future, when PCR (4) or other technologies can reliably localize residual microscopic disease, a multicenter randomized trial should be initiated. We plan to continue the present treatment approach for close or positive margins.

REFERENCES


