Retromolar Trigone Carcinoma Treated by Primary Radiation Therapy

An Alternative to the Primary Surgical Approach

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Objectives: To review our experience in the treatment of retromolar trigone carcinoma with radiotherapy as the primary modality and to evaluate the different factors affecting locoregional control and survival.

Design: We retrospectively examined 46 patients with squamous cell carcinoma of the retromolar trigone treated primarily with radiotherapy from January 1, 1973, to June 31, 2002. Four had T1, 21 had T2, 17 had T3, and 4 had T4 lesions; 25 had N0, 15 had N1, 5 had N2, and 1 had N3 disease. The overall stage was I in 3, II in 18, III in 18, and IV in 7 patients. All patients received conventional once-daily fraction radiotherapy as the primary modality of treatment. Three patients received chemotherapy. Overall survival, cause-specific survival, and locoregional control were estimated using the Kaplan-Meier method. Log-rank statistics were used to identify significant prognostic factors for overall survival and locoregional control.

Results: The median follow-up was 43 (range, 5-217) months overall and 78 (range, 26-188) months for living patients. The 5-year overall survival and cause-specific survival rates were 47% and 78%, respectively. Favorable prognostic factors for cause-specific survival were a lower tumor stage (univariate and multivariate analysis) and a lower nodal stage (multivariate analysis). The 5-year local control rate was 49% after radiotherapy and 67% after salvage surgery. The 5-year regional control rate was 88%. Favorable prognostic factors were a lower nodal stage and a lower overall stage (univariate analysis). The 5-year locoregional control rate for all patients was 42% after radiotherapy and 70% after salvage surgery.

Conclusions: Given the surgical salvage rate in our series and previous published experience, radiation therapy can be used with curative intent for small retromolar trigone carcinomas (T1-T2 lesions). For advanced stages without bone invasion, consideration for concurrent chemotherapy and radiation therapy might increase previous historical locoregional and survival rates.


The retromolar trigone (RMT) is a small triangular subsite of the oral cavity. It is the portion of mucosa that lies behind the third molar tooth covering the anterior ramus of the mandible. The base of the triangle is posterior to the last inferior molar tooth; the apex is in continuity with the tuberosity of the maxilla behind the last upper molar tooth. It is bounded laterally by the gingival buccal sulcus and medially by the anterior tonsillar pillar. Cancerous lesions involving the RMT are almost always squamous cell carcinomas. Minor salivary gland tumors are sometimes diagnosed. Because of its continuity with the oral cavity mucosa and its close relation to the mandible, spreading to adjacent structures can easily occur.

Little information has been published concerning this rare tumor. Treatment options for RMT carcinoma include surgery, radiation therapy, and chemotherapy. To our knowledge, there are no clear guidelines concerning the initial treatment. There is no randomized-controlled study comparing surgery with radiation therapy, but only retrospective studies with a few patients. In some larger studies, RMT carcinomas are grouped together with tumors originating from the anterior tonsillar pillar.

Surgery has been used as a standard treatment. Wide excision is necessary, even in the absence of bone invasion. Soft tissue deficits generally necessitate reconstruction with at least local or regional flaps and sometimes free tissue transfer. When bone is involved, marginal or segmental mandibulectomy with bone free flaps is required. Radiation therapy could be an acceptable alternative treatment to surgery, with the advantage of being less morbid.
However, few studies have evaluated its efficacy. Our objectives are to assess the locoregional control (LRC) and survival rates of patients with RMT carcinomas treated by radiation therapy at Notre-Dame Hospital. We also evaluated the different factors affecting LRC and survival.

**METHODS**

**DATA COLLECTION**

We reviewed the medical records of all patients with RMT carcinoma referred to the radiation oncology department at Notre-Dame Hospital between January 1, 1973, and June 31, 2002. Follow-up data were obtained for all patients using the clinical record notes and correspondence with the referring physician, the patient, or the patient’s family. Before initiation of treatment, all patients were examined by a radiotherapist (M.G. and P.F.N.-T.) and a head and neck surgeon (L.G., D.L., J.-C.T., and M.-J.O.). Patients were reexamined a few days before treatment to confirm the tumor staging. After March 1, 1986, 13 patients underwent computed tomography (CT) of the head and neck. Lesions were retrospectively staged according to the American Joint Committee for Cancer Staging 1998 guidelines using all the information available, including the physical findings and the imaging study results.

**PATIENT CHARACTERISTICS**

Fifty-one patients received radiation therapy as the primary modality of treatment. The following eligibility criteria were used for inclusion in this study: (1) patients with a biopsy-proved RMT squamous cell carcinoma, (2) patients who underwent radiotherapy as the primary modality of treatment or combined with chemotherapy, and (3) patients with a minimum follow-up of 2 years. We excluded from our study the following patients: (1) those with tumors from an uncertain initial localization and (2) those who underwent surgery at the primary site as part of the initial treatment plan. Considering these criteria, 46 patients were included in our study. All patients completed their treatments.

There were 31 male and 15 female patients. The median age at diagnosis was 62 (range, 38-87) years. The median follow-up for all patients was 43 (range, 5-217) months, and for living patients was 78 (range, 26-188) months. Six patients died of their primary RMT carcinoma in the first 2 years of their follow-up. All living patients had been followed up for longer than 2 years, and 93% (43/46) had been followed up for longer than 5 years. Of the 3 patients with a follow-up of less than 5 years, all were alive at the last visit. Two had follow-up at the time of analysis, and 1 was lost to follow-up at 40 months, without relapse.

The distribution of patients according to tumor and nodal stage is shown in Table 1. Of the 46 patients, 21 (46%) showed clinically positive neck nodes at presentation, and 2 (4%) of them having contralateral neck metastases. Repartition of patients according to overall staging was as follows: I, 3 patients (7%); II, 18 patients (39%); III, 18 patients (39%); and IV, 7 patients (15%). Histopathological reports showed 11 patients (24%) with a well-differentiated carcinoma, 17 (37%) with moderate differentiation, and 3 (7%) with poor differentiation. The histological grade was not reported in 13 patients (33%). (Percentages do not total 100 because of rounding.) Thirty-seven patients (80%) had initial extension of the RMT carcinoma to other oral or oropharyngeal subsites. From these 37 patients, 4 (11%) had extension to 2 subsites and 33 (89%) had extension to 3 or more subsites. Extension of the primary tumor involved the anterior tonsillar pillar most frequently (37 patients [80%]). Then, in decreasing order, the subsites involved by the cancer were as follows: soft palate, 27 patients (59%); lower gum, 17 patients (37%); floor of the mouth, 14 patients (30%); cheek mucosa, 12 patients (26%); tongue base, 11 patients (24%); tonsillar fossa, 6 patients (13%); hard palate, 5 patients (11%); mobile tongue, 4 patients (9%); mandible, 3 patients (7%); and upper gum, 1 patient (2%).

**TREATMENT OF PRIMARY TUMORS**

The recommendation for treatment took into account the general medical condition of the patient, the extent of the disease, and the patient’s preferences. Patients with a clinical or radiological suggestion of mandible involvement were usually treated with surgery followed by radiation therapy. All patients in our study received radiation therapy as the primary treatment. Patients with neck disease had definitive radiation therapy. Neck dissection was planned for residual neck disease. Salvage surgery was also considered for local failures. Three patients underwent chemotherapy: 2 underwent neoadjuvant chemotherapy, and 1 underwent concurrent chemotherapy. The chemotherapeutic regimen was platinum based. Two patients had stage IV and 1 had stage III carcinoma. These 3 patients refused surgery as the initial treatment modality.

Radiotherapy was delivered with megavoltage beams using either linear accelerators or telecobalt machines. In most patients, external beam radiotherapy was delivered via a parallel-opposed field technique to cover the primary site and the upper neck nodes. The lower neck and the supraclavicular field were treated with a matched anterior field. The patients received conventional once-daily fractions of 2 Gy/d to a median dose of 66 Gy (range, 60-70 Gy). The median delay between diagnosis and initiation of treatment was 34 (range, 2-56) days.

**STATISTICAL ANALYSIS**

Estimates of local control, regional control, LRC, overall survival, and cause-specific survival were computed with the Kaplan-Meier product-limit method. Outcomes were measured from diagnosis to the date of failure for control analysis and to the last date of follow-up for survival analysis. For LRC, the first locoregional failure was scored. Patients who died of intercurrent diseases were censored from the analysis the day before their death. For overall survival, all causes of deaths were considered. Specific data were evaluated as possible prognostic factors using univariate (log-rank test) and
multivariate (Cox proportional hazards regression model) analyses: age, sex, tumor stage, nodal stage, overall stage, histological tumor grade, radiotherapy dose, and delay between diagnosis and treatment.

RESULTS

SURVIVAL

The 2- and 5-year overall survival rates for all patients were 73% and 47%, respectively. We found no significant prognostic factors on univariate or multivariate analysis.

The 2- and 5-year cause-specific survival rates were 84% and 78%, respectively. Figure 1 shows estimates of cause-specific survival for all patients. The favorable prognostic factor on univariate analysis for cause-specific survival was a lower tumor stage (T1 or T2) \( (P = .02) \). Favorable prognostic factors on multivariate analysis were a lower tumor stage (T1 or T2) and a lower nodal stage (N0 or N1) (Figure 2).

The contribution to overall deaths (25 patients) was as follows: death of RMT cancer, 10 patients (40%); death of a secondary head and neck malignancy, 9 patients (36%); and death of other causes, 6 patients (24%). One patient died of pulmonary metastases from his RMT cancer.

LOCAL CONTROL

The 2- and 5-year local control rates for all patients after radiation therapy were 68% and 49%, respectively. The local control rate after radiation therapy according to tumor stage is given in Table 2. The local control rate after salvage surgery is also given in Table 2. No salvage surgery was attempted on patients with T4 tumors. Nineteen patients had local relapse or nonresponse to radiation therapy, of whom 12 underwent surgical salvage. Salvage was successful in 9 of these patients, leading to an ultimate 5-year local control rate of 67%. No significant prognostic factor was found.

REGIONAL CONTROL

The 2-year regional control rate for all patients was 88%, and remained identical the following years. The regional control rate according to nodal stage was 100% (25/25) for N0, 80% (12/15) for N1, 80% (4/5) for N2, and 0% (0/1) for N3. One patient with N1 disease and 2 patients with N2 disease received chemotherapy. Five
patients experienced neck relapse, and none underwent surgical salvage. Two had advanced disease and were not candidates for salvage surgery. Three refused further curative treatments. Favorable prognostic factors on univariate analysis were a lower nodal stage (N0 or N1) \((P = .04)\) and a lower overall cancer stage (I or II) \((P = .02)\). No significant prognostic factors were found on multivariate analysis.

**LOCOREGIONAL CONTROL**

The 2- and 5-year LRC rates for all patients after radiation therapy were 59% and 42%, respectively (Figure 4). The LRC rate after radiation therapy according to overall staging is given in Table 3. The LRC rate after salvage surgery is also given in Table 3. No salvage surgery was attempted on patients with stage IV disease. The ultimate 5-year LRC rate was 70% after salvage surgery. Of the 3 patients who underwent radiation therapy and chemotherapy, 2 showed no evidence of disease at the 5-year follow-up.

**LOCOREGIONAL AND DISTANT FAILURES, TIME TO LOCOREGIONAL RECURRENCE, AND SECOND MALIGNANCY**

Of the 23 failures following radiation therapy, 19 were local and 5 were regional. One patient showed local and regional failure. Metastases to a distant site were seen in one patient (lungs) with concomitant regional failure. All regional relapses concerned patients initially classified as having N1 to N3 disease. All nodal recurrence occurred in the ipsilateral neck.

Twenty-three patients had locoregional failures; 78% (18/23) occurred within 2 years of treatment. All regional failures (5/23) occurred within 2 years of treatment.

Fifteen patients developed a second malignancy: 1 (2%) in the lung and 14 (30%) in a new head and neck site. Three of them developed a third head and neck cancer later in the follow-up.

**IMAGING**

All patients underwent pretreatment mandible radiography. Thirteen patients underwent a pretreatment CT scan. There was a good correlation between clinical examination and CT scan results for tumor staging when we reviewed the medical records of these 13 patients. Clinical and radiological tumor stages were the same for these patients. None revealed a clinically unsuspected bone invasion. Two confirmed bone invasions were suspected on clinical examination.

**COMPLICATIONS**

There was no treatment-related death. Four patients required a nasogastric tube for feeding because of severe mucositis leading to significant weight loss. Three patients developed osteoradionecrosis of the mandible within 1 year after radiotherapy. This condition resolved in all of them with conservative treatment, and none required surgical intervention. Two of these patients had T2 and T4 cancer. One underwent concomitant chemotherapy.

**COMMENT**

The oral cavity is by far the most predominant location for head and neck cancers. In the Western world, RMT carcinoma is a rare tumor at large and as a subsite of the oral cavity. However, in areas of the world where chewing of tobacco and betel nut is more frequent, RMT is the most common site of the oral cavity where cancers arise, along with the buccal mucosa.1 As for the rest of the oral cavity, the lesions are predominantly invasive squamous cell carcinoma. The RMT area is peculiar in many instances. Its finite location makes cancers confined to this area the exception rather than the rule. Retromolar trigone cancers tend to spread to 1 or more adjacent sites in 73.7% to 84.5% of cases.2-4 In our study, the 3 most common sites involved are the anterior tonsillar pillar (80%), the soft palate (59%), and the lower gum (37%). This is also the same order of frequency that Byers et al5 and Huang et al4 reported.

Another specificity of the RMT is its proximity to the mandible and its continuity with the tuberosity of the maxilla, making osseous invasion a matter of concern when evaluating these cancers. Reported rates of pathologi-
clearly determined. This can be explained in part by the ever, the optimal treatment of RMT carcinomas is not yet

2- and 5-year local control rates for all patients after radiation therapy were 68% and 49%, respectively. Of the 12 patients who underwent surgical salvage, 9 were ultimately free of disease, leading to an ultimate 5-year local control rate of 67%. After salvage surgery, the control rate was 75% for T1 lesions, 90% for T2 lesions, and 65% for T3 lesions, and the rate remained the same for T4 lesions (no salvage surgery was tried). We found that salvage surgery is beneficial for primary failures, which is consistent with other studies. In the study by Lo et al, the 5-year local control rate after radiation therapy was 71% for T1 lesions, 70% for T2 lesions, 76% for T3 lesions, and 60% for T4 lesions. After salvage surgery, the local control rate increased to 100% for T1 lesions, 94% for T2 lesions, 92% for T3 lesions, and 80% for T4 lesions. Barker and Fletcher found comparable local control rates after salvage surgery in 204 irradiated patients: 96% for T1 lesions, 93% for T2 lesions, 97% for T3 lesions, and 79% for T4 lesions. The local control rate found in these 2 studies is superior to ours. However, these studies grouped together tumors originating from the RMT and those originating from the anterior tonsillar pillar, which could explain the differences. Locoregional failures occurred within 2 years of treatment in 78% of the cases in our study. The literature shows similar timing of failures for RMT carcinomas and oral cancers in general. Given the fact that most radiotherapy failures are salvageable by surgery, the necessity for close follow-up for these patients is warranted in that period.

The regional control rate for all patients was 88% in our study. This compares well with studies using neck dissection as the primary treatment of the neck, with a regional control rate of 89.5%. This result is also concordant with other studies using radiation therapy as the primary treatment modality. Nodal metastases rarely occur in the contralateral neck. In our study, no regional metastases occurred in patients with an initial stage of N0.

The ultimate 5-year LRC rate was 70% after salvage surgery. In series using surgery as the initial treatment sometimes followed by radiotherapy, reported LRC rates
are 44.8%\(^3\) (3-year follow-up) and 64%\(^1\) (5-year follow-up). Huang et al\(^1\) reported 5-year LRC rates ranging from 56% to 90%, depending on the treatment, with preoperative radiotherapy leading to the best results.

The difficulty lies in discriminating patients who will not likely respond to radiation therapy and who would be better treated with surgery as the primary modality. We found no significant prognostic factor predicting for LRC on multivariate analysis. Surprisingly, the tumor stage did not correlate well with local control in our study. This is a constant finding in the literature with RMT carcinomas.\(^1\,3\) This could be explained by the superficial growth of RMT carcinomas.\(^1\,3\) In fact, cancer growth in this area is limited in deeper planes by the periosteum and bone. As a consequence, for each tumor stage, cancers arising and spreading in this area contain proportionately fewer cells than cancers that grow spherically (eg, tongue or tonsillar fossa tumors). As stated by Barker and Fletcher, \(^1\,3\) “the stage according to diameter of the lesion is not a reflection of the volume of the cancer.” Moreover, tumors of the RMT are associated with areas of leukoplakia and erythroplasia in adjacent mucosa. If underestimated, these lesions could be excluded from the radiation field.\(^1\,3\) Another potential contributing factor to the discrepancies observed in local control and tumor stage is the erroneous staging of the disease. Small lesions can involve minimal foci of osseous invasion that may be missed by physical examination or imaging. Stage understimation can result in inappropriate treatment, and local control rates for a particular stage will no longer reflect the true evolution of this disease. We found a surprising rate of local failure in 3 of 4 patients with T1 tumors of the RMT. There was no difference in the treatment compared with other patients. The techniques used were similar and the doses administered were within the same range. However, on review, none of these 4 patients had the benefit of a pretreatment CT scan because it was not available at the time. Computed tomography of the head and neck was available at our center starting in 1986. It is possible that the tumors of these patients were understaged. We believe that patients with RMT cancers should systematically undergo a CT scan of the head and neck to assess the integrity of the mandible, even for small lesions.

Retromolar trigone cancer is responsible for 40% of the deaths in our study, the remaining being secondary to death of a secondary head and neck malignancy (36%) and death of other causes (24%). Other studies\(^2,4\) also show that secondary head and neck malignancies and concurrent diseases represent a considerable burden. Given this high incidence of death of a secondary head and neck malignancy, strategies looking at preventing secondary malignancies in this patient population are warranted.

Mandibular osteoradionecrosis is a feared complication of radiation therapy for RMT carcinomas. It happens spontaneously after radiation therapy, or it can be associated with recurrent disease, dental extractions, and trauma. The literature\(^3,13,15,16\) shows rates of osteoradionecrosis ranging from 7% to 30% after radiation therapy administered for RMT carcinomas. Conservative treatment is successful in nearly half of the cases.\(^16\) Mandibular osteoradionecrosis occurred in 7% of our patients, and all responded to medical treatment.

Concurrent chemotherapy and radiation therapy has gained widespread acceptance as an alternative for advanced stage head and neck carcinoma.\(^17\-19\) Although most of these studies have few RMT primary tumors, the survival advantage of concurrent radiation therapy and chemotherapy over radiation therapy alone has led us to adopt that approach for extensive lesions (T3 or T4 tumors without bone invasion). However, primary surgery followed by radiation therapy is still the modality of choice at our institution for patients with bone invasion. Smaller lesions (T1 and T2) can be treated by radiation therapy if the clinical examination and CT scan show no bone invasion. Neck treatment is warranted for patients with NO disease, considering a 15.0% rate of occult metastases in RMT cancers.\(^1\) At our institution, neck dissection after radiotherapy is performed on patients with N3 disease or patients with clinical or radiological residual neck disease.\(^20\)

In conclusion, there are no definitive guidelines for the treatment of RMT carcinomas. However, given the surgical salvage rate in our series and previous published experience, radiation therapy can be used with curative intent for small RMT carcinomas (T1-T2). For advanced stages (T3 or T4 tumors without bone invasion), consideration for concurrent chemotherapy and radiation therapy might increase previous historical locoregional and survival rates. For patients with bony invasion, we recommend surgery followed by radiation therapy.

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Disclaimer: The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES


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**Correction**

Error in Byline. In the original article titled “Preventing Labyrinthitis Ossificans: The Role of Steroids” by Hartnick et al, published in the February 2001 issue of the *ARCHIVES* (2001;127:180-183), there was an error in the byline. Hank Y. Kim, MD, should have been listed by his correct name, Harold H. Kim, MD.