

The Impact of Adjuvant Radiotherapy on Survival in T1-2N1 Squamous Cell Carcinoma of the Oral Cavity

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Objective: To evaluate the survival impact of postoperative radiation therapy (RT) in patients with early T stage (T1-2) oral cavity squamous cell carcinoma (OCSCC) and a single positive lymph node.

Patients: Between 1983 and 2004, a total of 1539 patients were treated with surgery for T1-2N1 OCSCC.

Main Outcome Measures: The Surveillance, Epidemiology, and End Results database was used to determine whether postoperative RT improves survival in patients with T1-2N1 OCSCC.

Results: Postoperative RT improved the 5-year overall survival rate (41.4% for surgery alone vs 54.2% for surgery plus RT [$P < .001$]). Improvement in overall

survival in patients with T1N1 disease did not achieve statistical significance with the addition of RT in contradistinction to that in patients with T2N1 disease. Adjuvant RT improved survival in patients with T2 tongue and floor of mouth disease (52.3% vs 37.9% [$P = .002$] and 39.9% vs 17.7% [$P = .003$], respectively).

Conclusion: In cases involving T1-2N1 OCSCC in the Surveillance, Epidemiology, and End Results database, the use of RT is associated with statistically significant improved overall survival and cause-specific survival in patients with T2 disease, most strongly in the oral tongue and the floor of the mouth.

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ORAL CAVITY SQUAMOUS cell carcinoma (OCSCC) is a significant national and international public health issue and is responsible for more than 7000 deaths each year in the United States.^{1,2} Treatment protocols vary widely, depending on the stage of disease.³⁻⁵ Although the use of adjuvant radiotherapy (RT) and chemoradiotherapy in the setting of advanced-stage disease and the efficacy of single-modality therapy in early-stage disease are well documented, there are patients whose OCSCCs present a therapeutic dilemma. Many patients with OCSCC will develop symptoms or detect a lesion early in the course of their illness, thus presenting with T1 or T2 disease.¹ Many of these patients with no clinically or radiographically evident regional disease undergo staging neck dissections, in which subclinical nodal metastases are detected in approximately 34% of cases.⁶

There is little uncertainty regarding the role of adjuvant treatment when regional metastases are widespread, when nodal metastases are larger than 3 cm in size, or

when extranodal extension is present.⁷⁻¹¹ However, in patients in whom the metastases are limited to a single, ipsilateral positive lymph node not larger than 3 cm (ie, N1), the routine use of adjuvant therapy becomes more controversial. By TNM stage grouping rules for oral cavity cancers, cases that present with clinical or pathologic nodes are at least stage III. As a result, these cases have been included in clinical trials investigating RT and chemotherapy for advanced disease.⁵ However, limited regional spread may allow these cases to be treated with less intensive therapy, sparing the patients from significant additional treatment-related toxic effects.

Recently published Surveillance, Epidemiology, and End Results (SEER) data have shown a survival benefit with adjuvant RT for patients with node-positive squamous cell carcinoma of the head and neck.^{12,13} Subset analysis noted significantly improved survival for patients with N1 disease treated with RT.¹² To our knowledge, there is no cohort or population-based study assessing long-term survival and locoregional control rates following treatment protocols that routinely

Table. Number of Patients by Subsite, Stage, and Treatment^a

Stage and Subsite	RT	No RT
T1	442	123
Tongue	284	67
Floor of mouth	73	29
Other	85	27
T2	767	207
Tongue	450	107
Floor of mouth	122	48
Other	195	52

^aThe number of patients in each stage and subsite grouping was divided between the patients who received adjuvant radiation therapy (RT) and those who did not. Of note, there was no significant difference between treatment groups with respect to age or sex.

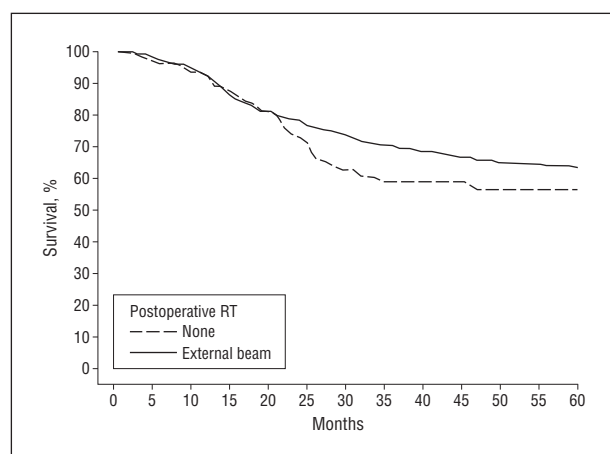


Figure 1. Overall 5-year survival for T1-2N1 oral cavity squamous cell carcinoma with and without postoperative radiotherapy (RT) ($P < .001$ at 60 months).

include or exclude routine postoperative irradiation for patients with T1-2N1 oral cavity cancer. Determining the benefit of postoperative RT in early primary oral cavity cancer with N1 disease from existing studies is difficult because these single-institution series are heterogeneous, do not always include patients with N1 disease or often group them with patients with N0 disease, report different outcomes, and include sites other than the oral cavity.

The primary objective of this study was to determine, using population-based data, whether the addition of postoperative RT provides an overall survival benefit in patients with early primary OCSCC with metastasis to a single regional lymph node. The secondary objective was to determine whether any survival benefit is subsite dependent.

METHODS

Cases of OCSCC diagnosed between 1983 and 2004 were extracted from the SEER-17 database. The SEER database is a population-based cancer registry that captures 17 distinct population groups in 198 counties in the United States. It represents approximately 26% of the overall United States population and contains information on 7 032 878 cases of cancer diagnosed since 1973.²

The data in this study were standardized according to schema-published second and third editions of the *International Classification of Disease for Oncology*. For the present review, cancers were limited to the oral cavity, which was defined as the oral tongue (C02.0-02.3, C02.8-02.9), upper and lower gingiva (C03.0-03.9), floor of mouth (C04.0-04.9), hard palate (C05.0, C05.8-05.9), buccal mucosa (C06.0), oral vestibule (C06.1), retromolar trigone (C06.2), and areas labeled *unspecified mouth* or *unspecified oral cavity* (C06.8-06.9). Lip cancers were excluded from the analysis.

Histologic type was limited to squamous cell carcinoma (M8052-8078 in the morphological codes of the second edition of the *International Classification of Disease for Oncology*). Verrucous carcinomas and carcinomas in situ were excluded. Tumors were limited to pathologic T1 and T2 primaries (>1 and ≤ 40 mm, without evidence of invasion), and only patients who were treated with primary surgery with or without postoperative external beam RT were included. Specific details regarding radiation dose and fractionation schedules, adjuvant chemoradiation therapy, and detailed pathologic information, such as extranodal extension, margin status, or vascular or perineural invasion, were not available in the SEER database during the period of interest for the study. Patients who were treated with brachytherapy and other adjuvant measures without RT were excluded. Patients with oral cavity tumors as second or third primary tumors were also excluded.

Data were analyzed using the SEER*Stat Limited Use software provided by the National Cancer Institute, Bethesda, Maryland. Both overall and disease-specific survival were the main outcomes of interest. The SEER data do not capture recurrence; therefore, local and regional control rates could not be determined. Survival rates were calculated using follow-up values, which were available from the database. Survival curves were determined using the Kaplan-Meier method. For the primary objective of the study, overall and cause-specific survival rates were compared at 60 months. Significance was defined as $P \leq .05$. For the secondary objective, significance was defined as $P \leq .005$ to provide some protection from multiple comparisons.

RESULTS

Between 1983 and 2004, a total of 13 767 new cases of early primary OCSCC were identified in the SEER database. Of these, 1539 also had a single pathologically positive lymph node after neck dissection and therefore served as the basis of our ensuing calculations. Three hundred thirty patients with T1-2N1 disease (21.4%) were treated with surgery alone; the rest underwent postoperative RT. There was no significant difference between the groups with respect to age and sex. These data are summarized in the **Table**.

OVERALL SURVIVAL

For all patients with early primary OCSCC and N1 regional disease, adjuvant RT was associated with superior overall survival at 5 years (54.2% vs 41.4% [$P < .001$]; **Figure 1**). This survival advantage was the largest in T2 primary tumors (48.8% vs 32.5% [$P < .001$]; **Figure 2**) and was present, but not statistically significant, in T1 primary tumors (63.4% vs 56.5% [$P = .25$]; **Figure 3**).

The various subsites of the oral cavity were analyzed separately for each T stage. No subsite with T1 disease revealed any significant survival advantage with the addition of adjuvant RT. In subsites with T2 disease, adjuvant RT significantly improved survival in patients with

tumors of the oral tongue (52.3% vs 37.9% [$P=.002$]) and floor of mouth (39.9% vs 17.7% [$P=.003$]). In all other subsites, improved overall 5-year survival was not associated with the addition of adjuvant RT.

CAUSE-SPECIFIC SURVIVAL

For the entire cohort, the 5-year, cause-specific survival rate in patients treated with surgery alone was 64.3%; after surgery and postoperative RT, it was 72.1% ($P=.12$). In patients with T2 disease of the oral cavity, the cause-specific survival rate improved from 57.0% to 69.5% ($P=.03$) with the addition of adjuvant RT, whereas in patients with T1 disease, the difference in cause-specific survival was not statistically significant (76.6% vs 75.3% [$P=.35$]). These differences were not maintained at a level of statistical significance when separated out by subsite. For T2 tongue cancer, the 5-year cause-specific survival rate in patients treated with surgery alone was 54.3%, and in patients treated with surgery and postoperative RT, it was 69.5% ($P=.32$). In patients with T2 floor of mouth cancer, the difference was 65.6% vs 66.8 ($P=.36$), respectively.

COMMENT

Carcinoma of the oral cavity presents a significant health concern, with approximately 35 000 new cases and 7500 mortalities each year.² Despite these numbers, it is often challenging to demonstrate large survival benefits with different treatment paradigms in these patients using data from single institutions. The SEER database is a publicly available database of all cancer diagnoses in 17 different population groups within the United States. Although the demographics of the patients within the database approximate, but do not exactly match, the overall demographics of the US population as a whole,¹⁴ the database does allow robust population-based analyses to be performed. We therefore used the available information within the SEER database to determine the effects of adjuvant RT in patients with early primary OSCC and a single positive node.

The treatment of patients with oral cavity cancer and advanced local and/or regional disease with surgery and RT is well documented. Retrospective series of head and neck cancer, single-arm prospective trials, and matched-pair analyses seem to suggest the superiority of combined-modality therapy in the achievement of locoregional control. Common indications for postoperative RT include advanced local disease, close or positive margins, perineural or vascular invasion, multiple positive lymph nodes, and extracapsular extension.

The role of adjuvant RT in the treatment of patients with T1-2N1 oral cavity cancer is less well defined.³⁻⁵ Although RT reduces the risk of regional recurrence, the absolute risk reduction is smaller in earlier-stage disease, possibly decreasing the potential for its impact on survival. However, studies have shown that RT reduces the risk of regional recurrence, and single-institution series suggest benefit even in patients with early primary OSCCs. As a result, most patients (78.6%) captured in the SEER database with T1-2N1 disease received adjuvant RT.

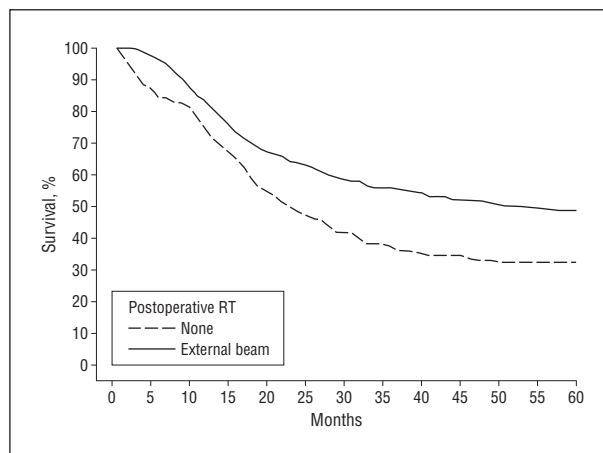


Figure 2. Overall 5-year survival for T2N1 oral cavity squamous cell carcinoma with and without postoperative radiotherapy (RT) ($P<.001$ at 60 months).

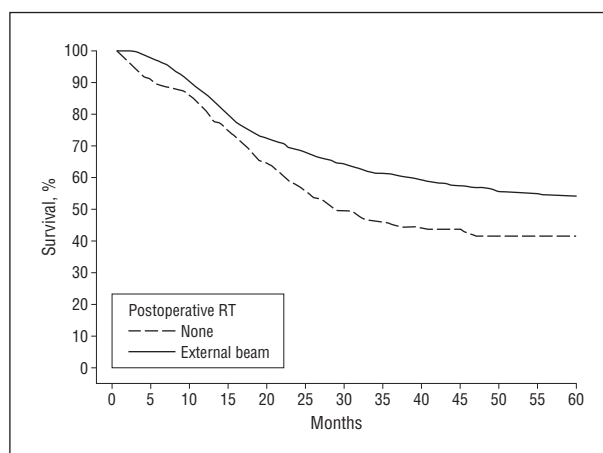


Figure 3. Overall 5-year survival for T1N1 oral cavity squamous cell carcinoma with and without postoperative radiotherapy (RT) ($P=.25$ at 60 months).

Our analysis demonstrated that the patients with T1 or T2 primary disease and a single positive lymph node who were treated with adjuvant RT also had improved survival compared with patients who did not receive RT. However, in subgroup analysis, this benefit was significant only among patients with T2 primary tumors of the oral tongue and floor of mouth. All patients with T1 disease and patients with T2 disease of other subsites did not have a statistically significant improvement in overall survival associated with the addition of RT.

The magnitude of benefit from adjuvant RT decreased when cause-specific survival was examined. Cause-specific survival was statistically significantly improved in patients with T2 OSCC, but the benefit was not significant in patient subgroups split by subsite within the oral cavity. Unfortunately, because a significant number of patients within the SEER database do not have a cause of death documented or are unavailable for follow-up, this population may not be powered enough to detect a difference in cause-specific survival that may ultimately be present.

Population-based studies are, by definition, retrospective and nonrandomized. Furthermore, only information entered into SEER by the cancer registrars throughout the

17 sites is included in the database. The data examined represent a relatively heterogeneous pool of patients from divergent sites within the United States. Treatment protocols obviously vary across institutions, and the reasons behind the withholding of RT from some patients are not evident. Although this allows for a modicum of bias, the bias is diluted by the size of the examined cohort and the variety of sites at which treatment is administered. If the extent of neck dissection was found to be important in only 1 particular institution, the generalizability of this statement could reasonably be called into question. However, the fact that our study incorporated a considerable amount of data from across various treatment sites, ethnic groups, socioeconomic classes, and ages lends credibility to the generalizability of its conclusions.

It must be recognized that the decision to administer postoperative RT to the patients in the present study may have been influenced by a variety of factors that themselves have an independent influence on outcome, separate from the benefits of RT. The use of RT in this study may be a surrogate for other adverse pathologic features that predispose to a worse prognosis. Specifically, perineural and lymphovascular invasion in the primary tumor and extracapsular extension in regional metastases all portend a worse prognosis with an expected increased use of RT in these patients.¹² This type of pathologic information, unfortunately, cannot be captured from SEER. The most recent iteration of the SEER database (patients diagnosed after 2004) will include data on extracapsular extension in patients with head and neck cancer. At this point, however, there is no meaningful follow-up in the database on these patients. Whether the prognostic power of these pathologic risk factors is borne out in population-based studies, and whether it affects the results presented herein, deserves future examination, as it remains a significant confounder to our results.

Also, in some cases, the decision not to use RT may, in theory, have been based on poor patient performance status and early death. The numbers do not bear this out: only 6 patients treated with surgery alone died within 3 months of treatment. A final caveat: nodal control in the neck cannot be measured using the data available in SEER. This is an important end point in head and neck cancer trials, as neck recurrences cause morbidity, often require the delivery of more therapy, and are salvageable in fewer than 40% of cases.^{15,16} Further well-designed prospective trials are warranted.

In conclusion, in cases involving T1N1 or T2N1 OSCCC, adjuvant RT was associated with a statistically significant improvement in overall survival in patients with T2 disease, with the most significant improvements in cancers of the oral tongue and floor of mouth. Improvements in cause-specific survival were also seen in patients with T2 disease. Further analysis with either large multi-institutional series or more detailed population-based registries needs to be performed with other prognostic pathologic factors controlled for.

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Author Contributions: Dr Shrime had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Shrime, Gilbert, and Goldstein. **Acquisition of data:** Shrime, Gullane, Kim, and Brown. **Analysis and interpretation of data:** Shrime, Dawson, Irish, and Goldstein. **Drafting of the manuscript:** Shrime and Goldstein. **Critical revision of the manuscript for important intellectual content:** Shrime, Gullane, Dawson, Kim, Gilbert, Irish, Brown, and Goldstein. **Statistical analysis:** Goldstein. **Obtained funding:** Gullane. **Administrative, technical, and material support:** Gullane and Irish. **Study supervision:** Gilbert, Brown, and Goldstein. **Financial Disclosure:** None reported.

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