Impact of Treatment Sequence of Multimodal Therapy for Advanced Oral Cavity Cancer with Mandible Invasion

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Impact of Treatment Sequence of Multimodal Therapy for Advanced Oral Cavity Cancer with Mandible Invasion

Larry L. Myers, MD¹, Baran D. Sumer, MD¹, John M. Truelson, MD¹, Lucien Nedzi, MD², Steve Perkins, MD³, Randall S. Hughes, MD⁴, and Chul Ahn, PhD⁵

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Abstract
Objective. To determine the effect of treatment sequence of multimodal therapy for clinically advanced squamous cell carcinoma (SCC) of the oral cavity (OC) with mandible invasion.

Study Design. Case series with chart review.

Setting. University-based, tertiary care hospitals.

Subjects and Methods. The authors retrospectively analyzed 70 patients presenting between January 2000 and January 2010 with newly diagnosed, previously untreated SCC of the OC with mandible invasion that we deemed resectable (stages IVa, b). Patients with evidence of distant metastases or a second primary malignancy were excluded. All patients were presented at a multidisciplinary tumor board for prospective planning of trimodality therapy (surgery, radiation therapy, chemotherapy). When performed, surgery included segmental mandibulectomy. Radiotherapy was delivered using standard intensity-modulated radiation therapy technique. Study patients were divided into 2 groups: group 1 received induction chemotherapy and/or concurrent chemoradiation followed by surgery, and group 2 was treated with primary resection followed by chemoradiation.

Main Outcome Measure. Progression-free survival (PFS).

Results. Eighteen patients (26%) comprised group 1, and 52 patients (74%) comprised group 2. The groups were matched in oral cavity subsite, tumor differentiation, tumor characteristics of aggressiveness (perineural and lymphovascular invasion), extent of mandible invasion, and cervical node status. The 5-year PFS for group 1 (33.3%) was not significantly different from that for group 2 (32.3%; P = .643).

Conclusion. Advanced OC cancer with mandible invasion is an ominous disease. Although treatment must be individualized, our data suggest no clear advantage to any specific sequence of multimodality therapy affecting PFS.

Keywords
oral cavity cancer, oral composite resection, mandible invasion, chemotherapy, radiation therapy

Althought oral cavity (OC) cancers are the most common head and neck cancers in the United States,¹ many patients present to large referral centers with advanced disease.² When oral cancers become large or display aggressive behavior, they can invade the mandible via clefts on the mandible surface at the site of mucosal attachment of the bone.³ Patients with locally advanced, operable oral cancer present a particular therapeutic challenge because these cancers are at high risk for treatment failure, ranging from local recurrence to regional lymphatic spread to systemic metastasis.⁴ To effectively combat each pattern of failure requires the use of multimodal
therapy (surgery, radiation, and chemotherapy). Surgical resection remains the cornerstone of treatment of oral squamous cell carcinoma (SCC). The evidence favoring postoperative chemoradiation (CRT) over postoperative radiation (RT) alone for patients with poor-prognosis SCC has already been established by large phase III trials. On the other hand, there are recent reports supporting the use of CRT protocols alone as viable treatment options for patients with advanced oral SCC. Despite the progress made in treating oral cancer through use of multiple modalities, no significant improvement in overall survival (OS) rates have been seen.

The impact of the sequence of multimodal therapy on patients with advanced oral SCC with mandible invasion has not been established. The purpose of this study is to compare the OS and progression-free survival (PFS) of 2 cohorts of patients with differing sequences of treatment.

**Patients and Methods**

The Institutional Review Board of the University of Texas Southwestern Medical Center approved this study. We retrospectively analyzed 70 patients presenting between January 2000 and January 2010 with newly diagnosed, previously untreated SCC of the OC with radiographic evidence of mandible invasion that we deemed resectable (stages IVa, b). We excluded patients with evidence of distant metastases or a second primary malignancy. We excluded all patients for whom treatment was deemed palliative even if there was no evidence of distant metastasis. We presented all patients at a multidisciplinary tumor board for prospective planning of trimodality therapy (surgery, radiation therapy, chemotherapy). When performed, surgery included segmental mandibulectomy. Radiotherapy was delivered using standard intensity-modulated radiation therapy technique. We divided study patients into 2 groups: group 1 received induction chemotherapy and/or concurrent CRT followed by surgery, and group 2 was treated with primary resection followed by CRT.

For most patients, we planned for 3 treatment modalities (surgery, radiation therapy, chemotherapy) a priori. Per our institution’s philosophy, we performed an oncologic segmental mandibulectomy when patients underwent surgery. We did not perform marginal or sagittal mandibulectomies. We planned mandible reconstruction with an immediate osseous or osteocutaneous free tissue transfer.

Standard chemotherapy agents were administered according to National Comprehensive Cancer Network (http://www.nccn.org) guidelines. Induction chemotherapy was given at the discretion of the treating medical oncologist and was generally a platinum/taxane–based regimen with or without 5-fluorouracil (5FU). Agents used for concurrent chemoradiotherapy protocols included either 5FU/platinum or single-agent platinum. In certain patients with inadequate renal function, cetuximab was given in place of platinum with concurrent radiotherapy.

We treated all patients with intensity-modulated radiotherapy to primary cancer site and cervical lymphatics. We treated all involved lymph nodes and all uninvolved at-risk nodal groups. In general, we delivered preoperative and postoperative doses to 68 Gy and 63 Gy, respectively, divided in 1.2 Gy daily.

All patients had at least computed tomography (CT) of the neck and the chest with intravenous contrast for radiographic workup. We used the neck CT to grade the radiographic extent of mandible invasion as follows: grade 1, involving lingual cortex only; grade 2, involving entire lingual cortex; grade 3, involving mandible medullary space and lateral cortex; and grade 4, involving both cortices of mandible with extension into the lateral soft tissue. Patients had a chest CT to evaluate for lung metastasis.

All patients were presented at a multidisciplinary tumor board composed of head and neck oncologic and reconstructive surgeons, radiation oncologists, medical oncologists, and other allied health care professionals dedicated to the treatment and prevention of head and neck cancer.

For those patients undergoing surgery, we recorded specimen volume, margin status, and aggressive histopathologic features (perineural and lymphovascular invasion) of the final pathologic specimen.

Patients were further subdivided into groups 1a and 2a (those patients receiving at least 2 forms of therapy) and groups 1b and 2b (those patients receiving all 3 forms of therapy). PFS and OS were calculated by the Kaplan-Meier product limit estimate. OS was measured from the date of diagnosis to the date of death or the date of the last follow-up visit.

Patients who had not died or who were lost to follow-up were censored for OS when they were last known to be alive. PFS was measured from the date of diagnosis to first evidence of disease recurrence, death due to complications of the disease, or the last follow-up. Patients who were alive and who had not experienced disease progression or were lost to follow-up were censored for PFS at the date that they were last known to be alive and progression free.

Statistical analysis was performed using commercially available SAS (Cary, NC) software. Fisher exact tests or $\chi^2$ tests were used for categorical variables, and Student $t$ tests were used for continuous variables. Statistical significance was reached when $P$ values were less than .05.

**Results**

We evaluated 70 patients in this study. Eighteen patients (26%) comprised group 1, and 52 patients (74%) comprised group 2. See Table 1 for a comparison of clinical features between groups. The groups were evenly matched in age, gender, ethnicity, OC subsite, tumor differentiation, tumor characteristics of aggressiveness (perineural and lymphovascular invasion), extent of mandible invasion, and cervical node status.

The average ages (±standard deviation) of groups 1 and 2 were 58.9 years (±14.1 years) and 60.4 years (±10.2 years), respectively ($P = .620$). The groups were composed of 72% and 75% men, respectively ($P = 1.00$). Of the groups, 72% and 63% were white, respectively ($P =$ ...
In group 1, 11 patients (61%) had N1 disease, and in group 2, 22 patients (42%) had N1 disease \((P = .168)\). Two patients of group 1 (11%) had stage IVb disease, and no patients in group 2 had stage IVb disease \((P = .063)\). The percentages of patients per OC subsite were floor of mouth (33% and 50%, respectively), tongue (17% and 8%, respectively), alveolar ridge (39% and 35%, respectively), and other (11% and 8%, respectively; \(P = .601)\). Most patients in each group (89% and 87%, respectively) had moderately differentiated invasive SCC \((P = 1.000)\).

Radiology

<table>
<thead>
<tr>
<th>Radiology</th>
<th>Group 1 (n = 18)</th>
<th>Group 2 (n = 52)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal medial cortex</td>
<td>5 (28%)</td>
<td>15 (29%)</td>
<td></td>
</tr>
<tr>
<td>Medial cortex</td>
<td>5 (28%)</td>
<td>14 (27%)</td>
<td></td>
</tr>
<tr>
<td>Lateral cortex</td>
<td>4 (22%)</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>Lateral soft tissue</td>
<td>4 (22%)</td>
<td>20 (38%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FOM, floor of mouth; N+, N1-N3.

\(^a\)P value based on Student t test.

\(^b\)P value based on Fisher exact test. Other \(P\) values based on \(\chi^2\) test.

.500). In group 1, 11 patients (61%) had N+ disease, and in group 2, 22 patients (42%) had N+ disease \((P = .168)\). Two patients of group 1 (11%) had stage IVb disease, and no patients in group 2 had stage IVb disease \((P = .063)\). The percentages of patients per OC subsite were floor of mouth (33% and 50%, respectively), tongue (17% and 8%, respectively), alveolar ridge (39% and 35%, respectively), and other (11% and 8%, respectively; \(P = .601\)). Most patients in each group (89% and 87%, respectively) had moderately differentiated invasive SCC \((P = 1.000)\).

In groups 1 and 2, 28% and 29%, respectively, had grade 1 mandible involvement; 28% and 27%, respectively, had grade 2 mandible involvement; 22% and 6%, respectively, had grade 3 mandible involvement; and 22% and 38%, respectively, had grade 4 mandible involvement \((P = .203)\). The average specimen volume for group 1 was 205.7 cm\(^3\) (range, 122.8-336 cm\(^3\)) and that for group 2 was 187.1 cm\(^3\) (range, 30-855 cm\(^3\)). The average radiation dose for group 1 was 68 Gy, and that for group 2 was 63.5 Gy.

The median follow-up was 1.2 years (range, 0.46 months to 9.36 years). At the time of analysis, 27 patients (39%) were alive, 26 patients (37%) died with disease, and 17 patients (24%) died of other causes \((Table 2)\). Thirty patients (61%) had recurrent disease. Of these, 18 patients (26%) had local/regional disease only and 12 patients (17%) had either distant disease alone or combined local/regional and distant disease. Six patients each from group 1 (33%) and group 2 (12%) developed distant metastatic disease \((P = .084)\). Of all the patients who died, respectively, 11 patients (92%) who died with disease were from group 1, and 15 patients who died with disease (48%) were from group 2 \((P = .014)\).

The 5-year OS for groups 1 and 2 was 31.1% and 32.3%, respectively \((Figure 1)\). The 5-year PFS was 33.3% and 32.3%, respectively \((Figure 2)\). The 3-year OS was 31.1%
and 38.8%, respectively. The 3-year PFS was 33.3% and 38.8%, respectively. The 1-year OS was 61.1% and 60.2%, respectively. The 1-year PFS was 55.6% and 56.4%, respectively. Log-rank test shows that there were no significant differences in OS ($P = .596$) and PFS ($P = .643$) between groups.

In group 1, there were no significant differences in OS ($P = .083$) and PFS ($P = .231$) between local/regional and distant disease (by log-rank test). In group 2, there were no significant differences in OS ($P = .160$) and PFS ($P = .134$) between local/regional and distant disease (by log-rank test).

In group 1, there was no significant difference in OS between patients who died with disease and without disease ($P = .931$). In group 2, there was no significant difference in OS between patients with disease and without disease ($P = .734$).

From group 1, 8 patients (44%) had chemotherapy and/or radiation followed by surgical resection (group 1a), and 6 patients (33%) had all 3 planned therapies (group 1b). From group 2, 41 patients (79%) had postoperative radiation (group 2a) and 10 patients (19%) completed full CRT therapy postoperatively (group 2b). The subgroups were also matched in age, gender, ethnicity, OC subsite, tumor differentiation, tumor characteristics of aggressiveness (perineural and lymphovascular invasion), extent of mandible invasion, and cervical node status. The log-rank test showed no significant differences in OS ($P = .855$) and PFS ($P = .826$) between groups 1a and 2a or in OS ($P = .160$) and PFS ($P = .134$) between groups 1b and 2b.

**Discussion**

For many years, the treatment of advanced OC cancer was primary ablative surgery followed by postoperative radiation therapy. Both the European Organisation for Research and Treatment of Cancer (EORTC)$^4$ and the North American Intergroup$^7$ trials compared adjuvant postoperative CRT to standard postoperative RT alone in patients with resectable, poor-prognosis SCC of the head and neck. Both trials

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<table>
<thead>
<tr>
<th>Extent of disease at recurrence</th>
<th>Group 1 (n = 18)</th>
<th>Group 2 (n = 52)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local/regional</td>
<td>5 (28%)</td>
<td>13 (25%)</td>
<td>.084$^a$</td>
</tr>
<tr>
<td>Distant</td>
<td>6 (33%)</td>
<td>6 (12%)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>7 (39%)</td>
<td>33 (63%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Died with disease</th>
<th>Group 1 (n = 18)</th>
<th>Group 2 (n = 52)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local/regional</td>
<td>1 (6%)</td>
<td>16 (31%)</td>
<td>.025</td>
</tr>
<tr>
<td>Distant</td>
<td>11 (61%)</td>
<td>15 (29%)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>6 (33%)</td>
<td>21 (40%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Died with disease (died only)</th>
<th>Group 1 (n = 18)</th>
<th>Group 2 (n = 52)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>12</td>
<td>31</td>
<td>.014$^a$</td>
</tr>
<tr>
<td>No</td>
<td>1 (8%)</td>
<td>16 (52%)</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>11 (92%)</td>
<td>15 (48%)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$P value based on Fisher exact test; other P values based on $\chi^2$ test.
resulted in substantial and significant increase in local/ regional control with postoperative adjuvant CRT. Both trials also demonstrated a substantial short-term increase in survival, but only the EORTC showed a significant increase in survival. These studies established a foundation that multimodal therapy (surgery, radiation therapy, and chemotherapy) plays an increased role in this patient population.

The main finding of our study is that there is no clear advantage of any specific sequence of multimodality therapy affecting PFS. Patients with advanced OC cancers with mandible invasion pose a unique therapeutic challenge because outcomes tend to be poor, treatment-related complications are frequent, and patients are frequently in a catabolic state. Although patients were placed in groups with the intent of completing a particular therapeutic course, most patients were unable to complete all 3 forms of therapy.

CRT protocols and major ablative surgery with free tissue reconstruction each has its respective complications. The efficacy of CRT protocols must be weighed against the expected toxicities, some of which are life threatening or lethal. Likewise, the benefits of surgical procedures must be weighed against the possibility of devastating postoperative complications, such as poor wound healing and breakdown, infection, fistula formation, and free tissue partial or total failure. The physiologic toll of undergoing all 3 forms of therapy is of critical importance when carrying out such a treatment plan.

In the large phase 3 trials assessing the value of postoperative concurrent CRT versus postoperative radiation alone, not all of these patients were able to complete the prescribed chemotherapy dose. In the North American Intergroup study, a total of 157 patients of 459 (61%) were able to receive all 3 planned cycles of cisplatin. Similarly, in the EORTC study, only one-half of the patients received the planned 3 chemotherapy courses without any delay or dose reduction.

A somewhat less aggressive approach than scheduling 3 forms of treatment upfront was reported by Cohen et al. They performed a retrospective review of 4 multi-institutional phase 2 studies. They reviewed 39 patients with T4 OC cancers to determine the efficacy and safety of treating with primary CRT. All CRT protocols used 5FU, hydroxyurea, and a third added agent (cisplatin or paclitaxel). CRT cycles were repeated every 14 days to complete a total RT dose of ≥70 Gy. After a median follow-up of 83 months, 29 patients (74%) died. The 5-year survival probability was 56%. Of the 29 deaths, 10 (34%) died of recurrence or progression of disease. These authors reported 16 patients (41%) had mandible involvement.

Our study population yielded a 5-year survival probability of 31.1% for group 1, nearly one-half of Cohen et al. The reason for this disparity in similar treatment groups is unclear. All of the patients in our study population had mandible invasion, in contrast to the 41% of the study population of Cohen et al, which may indicate that our study patients presented later in their disease or that the disease may have behaved more aggressively, thus negatively affecting prognosis.

In a larger, follow-up study, Stenson et al evaluated the role of curative CRT for 111 patients with advanced (stage III and IV) OC cancer. They demonstrated a favorable 5-year OS of 67% and a PFS of 65% for this relatively heterogeneous population. They further analyzed a subset of 27 patients who underwent surgical resection followed by CRT. They reported a 5-year OS of 53% and PFS of 54%. They compared the larger study group with the subgroup and found no statistical difference in OS and PFS. This study differs from our study in that we analyzed only patients with stage IVa and IVb OC cancer.

Liao et al addressed the issue of whether stage IVb disease of the OC is surgically resectable. These investigators compared 58 patients with stage IVa cancer to 45 patients with stage IVb cancer. They observed no statistical difference in the 5-year local control, neck control disease-free survival, or OS between stage IVa and b. In multivariate analyses, pathologic lymph node status (N0-1 versus N2+) was found to be the sole independent predictor for OS (P = .008).

Although mandible conservation surgery has been advocated, our practice has been to perform a segmental mandibulectomy. Patel et al analyzed 111 patients, with a median follow-up of 44 months, with oral SCC undergoing marginal (78 patients) or segmental mandibulectomy (33 patients). They found pathologic mandible invasion in 46% of marginal mandibulectomy specimens and in 96% of segmental mandibulectomy specimens. They reported that the 5-year OS was 71%, and this correlated with bone invasion and involved margins (P < .05) but not with extent of mandible invasion or resection.

Munoz Guerra et al reviewed 106 patients with oral cancer undergoing marginal (50 patients) or segmental (56 patients) mandibulectomy. Their observed 5-year survival rate was 60.4%. They found that bone resection >4 cm, advanced stage, positive soft tissue, or bone margins showed a statistically significant lower survival rate. However, no statistically significant differences were found between patients treated by marginal or segmental mandibulectomy. Our study differs from these 2 reports in that we specifically evaluated only stage IV disease.

In our study, most patients from group 1 (61%) died with persistent, progressive, distant or second primary disease. This was in contrast to only 29% of group 2 who died of similar causes.

The limitations of this study are those inherent to retrospective reports. We acknowledge the surgeons’ selection bias and statistical trend to place stage IVb patients in group 1 (P = .063). However, group 1 did not undersurvive its group 2 counterparts. Patients in group 1 did not have strict uniformity in chemotherapy protocols, although platinum-based combination regimens are generally viewed as equivalent. A greater number of advanced head and neck cancer patients are typically referred to tertiary, university-based medical centers for treatment. Data from this study may not necessarily be transferable to other large academic centers or non-university-based institutions. Nevertheless, we believe these data generated from our study are useful for this select group of patients.
Conclusion

Advanced OC cancer with mandible invasion is an ominous disease. Although treatment must be individualized, our data suggest that there is no statistical disadvantage in any particular sequence of multimodal therapy affecting PFS. Future investigations will explore the effect of treatment sequence on functional and therapeutic outcome, quality of life, and successful completion of all planned treatment.

Author Contributions

Larry L. Myers, corresponding author, substantial contribution to study concept/design, analysis and interpretation of data, drafting manuscript, critically revising manuscript, final approval; Baran D. Sumer, substantial contribution to study concept/design and analysis and interpretation of data, revising manuscript, final approval; John M. Truelson, substantial contribution to data acquisition/analysis and interpretation of data, drafting manuscript, final approval; Lucien Nedzi, substantial contribution to data acquisition/analysis and interpretation of data, drafting manuscript, final approval; Steve Perkins, substantial contribution to analysis and interpretation of data, critically revising manuscript, final approval; Chul Ahn, substantial contribution to analysis and interpretation of data, critically revising manuscript, final approval.

Disclosures

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