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WILEY
Depth of Invasion Alone as a Prognostic Factor in Low-Risk Early-Stage Oral Cavity Carcinoma

Margaret M. Kozak, MD; Jennifer Shah, MD; Michelle Chen, MD; Kurt Schaberg, MD; Rie von Eyben, MS; Jie Jane Chen, BA; Timothy Bui, BS; Christina Kong, MD; Michael Kaplan, MD; Vasu Divi, MD; Wendy Hara, MD

Objectives: To evaluate the significance of increasing depth of invasion (DOI) as the sole risk factor for recurrence in patients with low-risk early-stage oral cavity squamous cell carcinoma (OCSCC).

Methods: We retrospectively reviewed 560 patients with OCSCC treated at our institution between 2003 and 2013. Patients were included if they had low-risk early-stage OCSCC treated with surgical resection ± neck dissection and no adjuvant therapy. Low risk was defined as absence of positive or close margins, lymphovascular invasion, perineural invasion, and positive lymph nodes. Patients with tumor (T)3-T4 disease were excluded. Pathology specimens were independently reviewed by two board-certified pathologists to confirm proper measurement of DOI. Kaplan-Meier and Cox proportional hazards regression analyses were performed to identify factors predictive for recurrence as well as progression-free survival (PFS) and overall survival (OS).

Results: A total of 126 patients with low-risk early-stage T1-2N0 OCSCC were included. Median follow-up time was 42.5 months and median DOI was 4 mm. There was no significant difference in incidence of local (P = 0.95), regional (P = 0.81), or distant recurrence (P = 0.96) among patients with DOI < 4 mm versus ≥4 mm. On multivariable analysis, DOI was significant for both PFS (P = 0.03) and OS (P = 0.002).

Conclusion: In this study, we show that in the absence of other high-risk pathologic features, DOI ≥ 4 mm does not portend for increased incidence of local, regional, or distant relapse in patients treated with surgery alone; however, increasing DOI is a marker for worse PFS and OS in patients with low-risk, early-stage OCSCC.

Key Words: Oral cavity cancer, early stage, depth of invasion, outcomes.

Level of Evidence: 4

INTRODUCTION

Oral cavity squamous cell carcinoma (OCSCC) is an aggressive head and neck malignancy with a high propensity for nodal spread. Initial surgical resection of the primary tumor is the standard of care for all stages of disease. The need for adjuvant treatment is determined by several well-established pathologic risk factors, including: lymphovascular invasion (LVI), perineural invasion (PNI), multiple positive lymph nodes, tumor (T)3 or T4 disease, close or positive margins, and extracapsular extension (ECE).1–5 Whereas depth of invasion (DOI) has been extensively studied as a marker for worse outcomes and has recently become incorporated into the newest American Joint Committee on Cancer (AJCC) 8th-edition staging,6 it is unclear whether this risk factor alone in patients with early-stage disease indicates a need for more aggressive treatment.

DOI assesses the invasiveness of a carcinoma regardless of its exophytic component.6 Its use as a prognostic factor and criterion for neck dissection (ND) in patients with OCSCC has been the topic of multiple clinical analyses, and DOI > 4 mm has been shown to be associated with worse outcomes.7–10 However, these studies have been heterogeneous and frequently included patients of any stage and with multiple risk factors for recurrence. In addition, patients often received adjuvant treatment in the form of chemotherapy and/or radiotherapy (RT), further confounding the results. Lastly, tumor thickness and DOI have been used interchangeably, and different methods have been used to determine these measurements.11–13 Tumor thickness can either overestimate or underestimate DOI depending on whether the tumor is exophytic or ulcerated.

The objective of our study was to determine whether DOI as a sole risk factor for recurrence influences disease control and overall survival (OS) in patients with low-risk, early-stage, lymph node negative (NO), T1-2 OCSCC.14 Whether these patients can be safely observed following surgical resection or whether they require adjuvant treatment is currently controversial.
MATERIALS AND METHODS

All patients were drawn from an institutional review board-approved database of OCSCC patients treated at a single academic institution between 2003 and 2013. A total of 560 patients were retrospectively reviewed. Patients were included in the final analysis if they had clinical or pathologic T1-2N0 OCSCC treated with surgical resection with or without ND. Clinical N0 was defined as no palpable neck lymphadenopathy on clinical exam and an absence of enlarged or positron emission tomography-avid lymph nodes on imaging. All oral cavity subsites were included. Staging was based on the seventh edition of the AJCC guidelines. Pathology specimens were independently re-reviewed by two board-certified pathologists. All patients included in this study had detailed clinical and pathologic information available for review. Patients were excluded if they received adjuvant treatment, chemotherapy for other cancer diagnoses in the follow-up period, or if other high-risk pathologic features were present, including LVI, PNI, positive lymph nodes, and close or positive margins. This yielded a homogenous patient population with DOI as the sole risk factor for recurrence. DOI was measured from the basement membrane of adjacent normal epithelium to the deepest extent of tumor. A DOI of ≥4 mm was used to stratify patients in keeping with published literature. All patients were followed with physical examination every 2 to 3 months for the first 2 years, then every 3 to 4 months the third year, every 6 months during year 4, then yearly; yearly chest imaging and additional imaging was performed as needed.

All statistical analysis was conducted using Statistical Analysis Software 9.4 (SAS Institute Inc., Cary, NC). Kaplan-Meier and Cox proportional hazards regression analyses were performed to identify factors predictive for progression-free survival (PFS), which was defined as recurrence or death. Competing risks analysis was performed using the Fine and Gray method to analyze cumulative incidence of local, regional, and distant failure. Hazard ratios were reported with a 95% confidence interval (CI). Overall survival was calculated using Kaplan-Meier and log-rank tests. Multivariable analysis was performed with Cox proportional hazards regression using select prognostic parameters identified as significant on competing risks analysis, as previously described. We applied the rule of 10s to prevent overfitting in the multivariable model. Statistical significance was determined as a two-sided P value of less than 0.05.

RESULTS

Patient Characteristics

A total of 126 patients with clinical or pathologic T1-2N0 OCSCC were included in our final analysis. Median age was 54 years (range: 31–94 years) and 55% (n = 69) of patients were male. Median follow-up for the entire cohort was 42.5 months (range 2–203 months). Median OS was 85 months, and 5-year OS was 74%. Table I details the clinical and pathologic characteristics of our patient population. All oral cavity subsites were included, and the majority (n = 79; 63%) of patients had oral tongue carcinoma. A total of 17 (13.5%) patients had a prior history of multiple head and neck cancers from which they were without evidence of recurrent disease at the time of diagnosis of the oral cavity OCSCC used for the purpose of this analysis. All patients were treated with surgical excision of the primary tumor ± ND. In total, 50 (42.9%) patients underwent ND with a median of 26 lymph nodes removed (range 4–60). Most patients (n = 46) underwent an ipsilateral ND, and four patients underwent bilateral ND. No patient received adjuvant chemotherapy or RT. Median DOI for all sites was 4 mm, with 60 (47.6%) patients with DOI < 4 mm and 66 (52.4%) patients with DOI ≥ 4 mm. A DOI cutoff of ≥4 mm was used for all analyses.

Local, Regional, and Distant Recurrence

In total, there were 18 patients (14.3%) with local recurrence (LR), 17 patients (13.5%) with regional recurrence (RR), and four patients (3.2%) with distant recurrence (DR). In a subset of patients with oral tongue carcinoma (n = 78), a total of 11 patients (14%) had LR, 11 patients (14%) had RR, and three patients (3.8%) had DR. With respect to RR, 15 of 17 (88.2%) patients...
recurred in the ipsilateral neck and 2 (11.8%) patients recurred in the contralateral neck. The 5-year local, regional, and distant control rates were 80%, 82%, and 96%, respectively. There was no significant difference in cumulative incidence of local ($P = 0.72$), regional ($P = 0.99$), or distant ($P = 0.82$) recurrence between patients with DOI < 4 mm and ≥ 4 mm (Fig. 1a-c). Similarly, for patients with oral tongue cancer, there were no significant differences in local ($P = 0.65$), regional ($P = 0.29$), or distant ($P = 0.60$) recurrence between patients with DOI < 4 mm ($n = 36$) and ≥ 4 mm ($n = 42$). Patients who underwent ND had less RR than those who did not: 17% versus 0% for patients with DOI < 4 mm and 24% versus 5% for those with DOI ≥ 4 mm. Detailed patterns of recurrence are depicted in Table II.

**Progression-Free and Overall Survival**

In total, 33 patients (26%) died. Of these, eight patients died due to disease progression, and seven died of unrelated causes. For the remaining patients, cause of death is unknown. The median age for those who died was 74 years (range: 32–94 years) with median DOI of 6 mm.

**TABLE II.**

Patterns of Recurrence for All Patients ($n = 126$) and Those With Oral Tongue Carcinoma Only ($n = 78$).

<table>
<thead>
<tr>
<th>All Patients</th>
<th>DOI &lt; 4 mm, no ND</th>
<th>DOI &lt; 4 mm, +ND</th>
<th>DOI ≥ 4 mm, no ND</th>
<th>DOI ≥ 4 mm, +ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>($n = 126$)</td>
<td>($n = 47$)</td>
<td>($n = 13$)</td>
<td>($n = 29$)</td>
<td>($n = 37$)</td>
</tr>
<tr>
<td>LR</td>
<td>6 (12.8%)</td>
<td>3 (23.0%)</td>
<td>6 (20.7%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>RR</td>
<td>8 (17.0%)</td>
<td>0 (0%)</td>
<td>7 (24.1%)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>DR</td>
<td>2 (4.3%)</td>
<td>0 (0%)</td>
<td>1 (3.4%)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Oral Tongue</td>
<td>Only ($n = 78$)</td>
<td>($n = 25$)</td>
<td>($n = 11$)</td>
<td>($n = 12$)</td>
</tr>
<tr>
<td>LR</td>
<td>3 (12.0%)</td>
<td>3 (27.3%)</td>
<td>2 (16.7%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>RR</td>
<td>5 (20.0%)</td>
<td>0 (0%)</td>
<td>3 (25.0%)</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>DR</td>
<td>1 (4.0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (3.3%)</td>
</tr>
</tbody>
</table>

DOI = depth of invasion; DR = distant recurrence; LR = local recurrence; ND = neck dissection; OT = oral tongue; RR = regional recurrence.

**Fig. 1.** Local (A), regional (B), and distant (C) failure for all patients by DOI < 4 mm and ≥ 4 mm. DOI = depth of invasion. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

**Fig. 2.** Progression-free (A) and overall (B) survival for all patients by depth of invasion (DOI) < 4 mm and ≥ 4 mm. DOI = depth of invasion. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

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**Fig. 2.** Progression-free (A) and overall (B) survival for all patients by depth of invasion (DOI) < 4 mm and ≥ 4 mm. DOI = depth of invasion. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
There was no significant difference in PFS among patients with DOI < 4 mm versus DOI ≥ 4 mm with 3-year PFS of 68% versus 63%, respectively (hazard ratio [HR] 0.62; 95% CI, 0.35–1.10; P = 0.13). However, patients with DOI ≥ 4 mm had significantly worse OS as compared to those with DOI < 4 mm, with 3-year OS of 74% versus 89%, respectively (HR 0.34; 95% CI, 0.19–0.75; P = 0.005) (Fig. 2A-B). Those with oral tongue carcinoma had significantly better PFS (HR 0.53; 95% CI, 0.29–0.97; P = 0.04) and OS as compared to all other oral cavity subtypes with median OS not reached versus 81 months, respectively (HR 0.36; 95% CI, 0.17–0.75; P = 0.006).

**Multivariable Analysis**

On multivariable analysis, DOI was significant for both PFS (HR 2.00; 95% CI, 1.07–3.73; P = 0.03) and OS (HR 3.86; 95% CI, 1.65–9.01; P = 0.002). Age was also significant for OS (HR 1.04; 95% CI, 1.02–1.07; P < 0.001), whereas ND was borderline significant for PFS (HR 0.52; 95% CI, 0.28–1.01; P = 0.052) and OS (HR 0.46; 95% CI, 0.21–1.02; P = 0.055) (Table III).

**DISCUSSION**

In this study, we evaluated a unique patient population comprised of low-risk early-stage OCSCC with DOI as the sole risk factor for recurrence. Our goal was to see whether these patients would benefit from escalation of therapy, such as the addition of chemotherapy and/or postoperative radiation treatment (PORT), or whether they can be safely observed following surgical resection of the primary tumor.

To our knowledge, our series is the first of its kind evaluating OCSCC patients with DOI as the sole risk factor for recurrence. The purpose of our study was to isolate this low-risk patient population and provide information on their outcomes because no data exist to guide clinical decision making in this context. Other high-risk pathologic features would likely have a dominating effect in our statistical models and were therefore excluded. This study is also unique in that every patient underwent detailed pathologic re-review of their specimen to ensure accurate DOI measurement. Our analysis reveals that DOI ≥ 4 mm alone does not portend for increased risk of local, regional, or distant recurrence but is a marker for worse PFS and OS. Patients with superficial disease appeared to benefit from ND, although this was only borderline significant on multivariable analysis.

Indications for adjuvant treatment for OCSCC are well established; however, a pressing question is whether DOI should be included as an indication for PORT in patients with early-stage OCSCC and no other pathologic risk factors for recurrence. Historical risk factors for which PORT is recommended include lymphovascular space invasion (LVSI), PNI, T3 or T4 disease, and advanced nodal disease (N2 or higher), whereas positive margins and ECE are indications for postoperative chemoradiation. Currently, DOI is not an indication for PORT, and DOI as a risk factor was not studied in the large randomized trials that determined what constitutes high-risk pathologic features. Retrospective series have evaluated the use of PORT in early-stage and recurrent OCSCC; however, whether DOI should be an indicator for PORT in the absence of other risk factors is unknown. Ganly et al. suggest that high rates of contralateral neck failure of 40% in their early-stage OCSCC population constitutes a need for PORT in patients with DOI ≥ 4 mm. However, patients in this series also had other high-risk pathologic features, such as LVSI, that increased the risk of neck recurrence.

Our data show a low rate of contralateral neck failure in only two patients (11%) and no increased risk of local, regional, or distant failure in patients with DOI ≥ 4 mm alone, suggesting that escalation of treatment for this patient population is not indicated. However, there is interest in the radiation oncology community to incorporate DOI as a risk factor for PORT recommendation. For example, Radiation Therapy Oncology Group (RTOG) 0920 is a PORT study that randomizes patients with intermediate risk factors to PORT alone versus PORT with concurrent cetuximab. The eligibility criteria include patients with T2N0 OCSCC with DOI > 5 mm as the sole intermediate risk factor for recurrence. There are no current trials randomizing patients with increasing DOI to observation versus PORT.

Some limitations to our analysis include its relatively small sample size, retrospective nature, and potential for selection bias. As a single institution study, our results may not be generalizable to the population at large but are hypothesis-generating nonetheless. Furthermore, approximately half of our patients did not receive an upfront ND because many had very superficial disease. However, our results suggest a benefit of ND even in those with superficial disease, as indicated by decreased rates of RR in patients with DOI < 4 mm and DOI ≥ 4 mm (Tables II and III). This benefit likely results from improved accuracy in staging and removal of tissues at risk of recurrence. In comparing our results to those of D’Cruz et al., which showed a 74% nodal recurrence in the therapeutic surgery group versus 30% in the upfront ND group, the rates of nodal recurrence in our study are lower (Table II), likely reflecting a lower risk patient

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>0.99–1.04</td>
<td>0.07</td>
</tr>
<tr>
<td>DOI ≥ 4 mm</td>
<td>2.00</td>
<td>1.07–3.73</td>
<td>0.03</td>
</tr>
<tr>
<td>ND</td>
<td>0.52</td>
<td>0.27–1.01</td>
<td>0.052</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.02–1.07</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DOI ≥ 4 mm</td>
<td>3.86</td>
<td>1.65–9.01</td>
<td>0.002</td>
</tr>
<tr>
<td>ND</td>
<td>0.46</td>
<td>0.21–1.02</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Cl = confidence interval; DOI = depth of invasion; HR = hazard ratio; ND = neck dissection.

TABLE III. Multivariable Analysis of Variables Predictive of Progression-Free Survival and Overall Survival.
population. In addition, we excluded higher risk patients who received adjuvant treatment, and as such our results may underestimate the true risk of recurrence in this patient group.

In conclusion, we have created a unique patient population comprised of early-stage OCSCC with DOI as the only pathologic risk factor for recurrence. The aim of our study was to ascertain whether increasing DOI in patients with early-stage OCSCC should be considered an independent risk factor for upfront aggressive therapy. Our analysis shows that surgery alone followed by observation is a reasonable option for these patients. We await the results of prospective trials, such as RTOG 0920, that will further shed light on the risks and benefits of more aggressive treatment for intermediate-risk patients.

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