

Abstract

This study evaluated lymphovascular invasion (LVI) as an independent predictor for overall survival (OS) in patients with oral cavity squamous cell carcinoma (OCSCC). This retrospective cohort study drew from multi-center, population-based facilities reporting to the National Cancer Database (NCBD). A multivariate Cox proportional hazards model was used to analyze the association between presence of LVI and OS. LVI predicted reduced OS in patients with SCC of the oral tongue, floor of mouth, and buccal mucosa. Patients with LVI treated with surgery and adjuvant radiotherapy or chemoradiotherapy had improved survival compared to those treated with surgery alone.

Introduction

It has been well demonstrated that factors such as nodal metastases, extranodal extension (ENE), surgical margins and depth of invasion (DOI) are associated with decreased OS in OCSCC. However, certain histologic factors and their association with OS remain less understood. Lymphovascular invasion is defined as tumor cell invasion into the endothelium-lined lumina of lymphatic or blood vessels. Several studies have reported an association between the pathologic feature LVI and worse OS in patients with OCSCC.^{1,3–8} For example, Cassidy et al. and Fives et al. found that LVI was an independent predictor for decreased OS among cohorts at their institutions.^{3,4} Additionally, the European trial EORTC 22931 established LVI as one of two features signifying high-risk disease, warranting chemotherapy or radiotherapy following definitive resection for OCSCC.⁹ However, others have found no significant association linking LVI with OS.^{10,11} For example, Chen et al. studied a cohort of 442 patients and found that LVI was not a significant risk factor for worse OS in OCSCC.¹⁰

The aim of this study was to evaluate LVI as an independent predictor for OS in patients with OCSCC. To further investigate this, a comprehensive review of the National Cancer Database was performed.

Methods

Cohort Selection

16,992 adult patients (>18 years of age) who underwent primary surgery for OCSCC between 2010-2015 were included.

Outcomes

The primary outcome measured was OS measured after the time of initial diagnosis of OCSCC. In the NCDB, this was defined as the duration of time after diagnosis at which the patient was deceased. Secondary outcomes included 2-and-5-year OS. Subgroup analyses were performed among groups of patients with T1/2 versus T3/4 tumors, N0/1 versus N2/3 neck disease, overall stage I/II disease versus overall stage III/IV disease. Subgroup analyses was also performed to evaluate for differences amongst treatment modalities, including treatment with surgery alone vs surgery + PORT vs surgery + POCRT.

Statistical Analysis

A multivariate cox proportional hazards model was built to analyze the association between LVI and OS, while controlling for covariates including the following: age (≤ 64 vs. > 64), sex, race, treatment facility type (academic vs. nonacademic/community center), presence of positive margins, T-classification, N-classification, treatment modality (surgery alone, surgery + PORT, and surgery + POCRT), Charlson/Deyo score and various oral cavity subsites.

Subgroup analyses were performed among specific oral cavity subsites (tongue, alveolar ridge/mandible, buccal mucosa, retromolar trigone, hard palate and floor of mouth), T-classification, N-classification, overall clinical stage and treatment modality (surgery alone, surgery + PORT, surgery + POCRT). Analysis was performed in Stata (StataCorp, LLC, College Station, Texas), and statistical significance was considered at p values < 0.05 .

Results

LVI and OS

The presence of pathological LVI was associated with significantly reduced OS (relative hazard 1.30, 95% CI: 1.22, 1.38, $p<0.001$) among all patients (Figure 1). When stratifying for each treatment modality, LVI was associated with significantly reduced OS in patients treated with surgery alone (relative hazard 1.39, 95% CI: 1.26, 1.54, $p<0.001$), with surgery plus PORT (relative hazard 1.24, 95% CI: 1.11, 1.39, $p<0.001$), and with surgery plus POCRT (relative hazard 1.16, 95% CI: 1.05, 1.29, $p=0.004$).

TNM, Staging, and Subsite

LVI was associated with significantly reduced OS among patients with T1/T2, T3/4, N0/N1, and N2/3 classifications; as well as stage I/II and stage III/IV ($p<0.001$). LVI was associated with significantly reduced OS in patients who specifically had SCC of the oral tongue subsite (relative hazard: 1.27, 95% CI: 1.17, 1.39, $p<0.001$), floor of mouth subsite (relative hazard: 1.33, 95% CI: 1.17, 1.52, $p<0.001$), or buccal mucosa subsite (relative hazard: 1.44, 95% CI: 1.15, 1.81, $p=0.001$).

Interestingly, LVI was not independently associated with altered OS in patients with SCC of the alveolar ridge ($p=0.511$), hard palate ($p=0.971$) or retromolar trigone ($p=0.298$).

LVI and OS by Treatment Modality

Patients with LVI who underwent surgery + PORT had significantly improved OS compared to those who underwent surgery alone (relative hazard 1.79, 95% CI: 2.03, 1.58, $p<0.001$). Those treated with surgery + POCRT experienced an even greater improvement when compared to those treated with surgery alone (relative hazard 2.0, 95% CI: 2.26, 1.79, $p<0.001$).

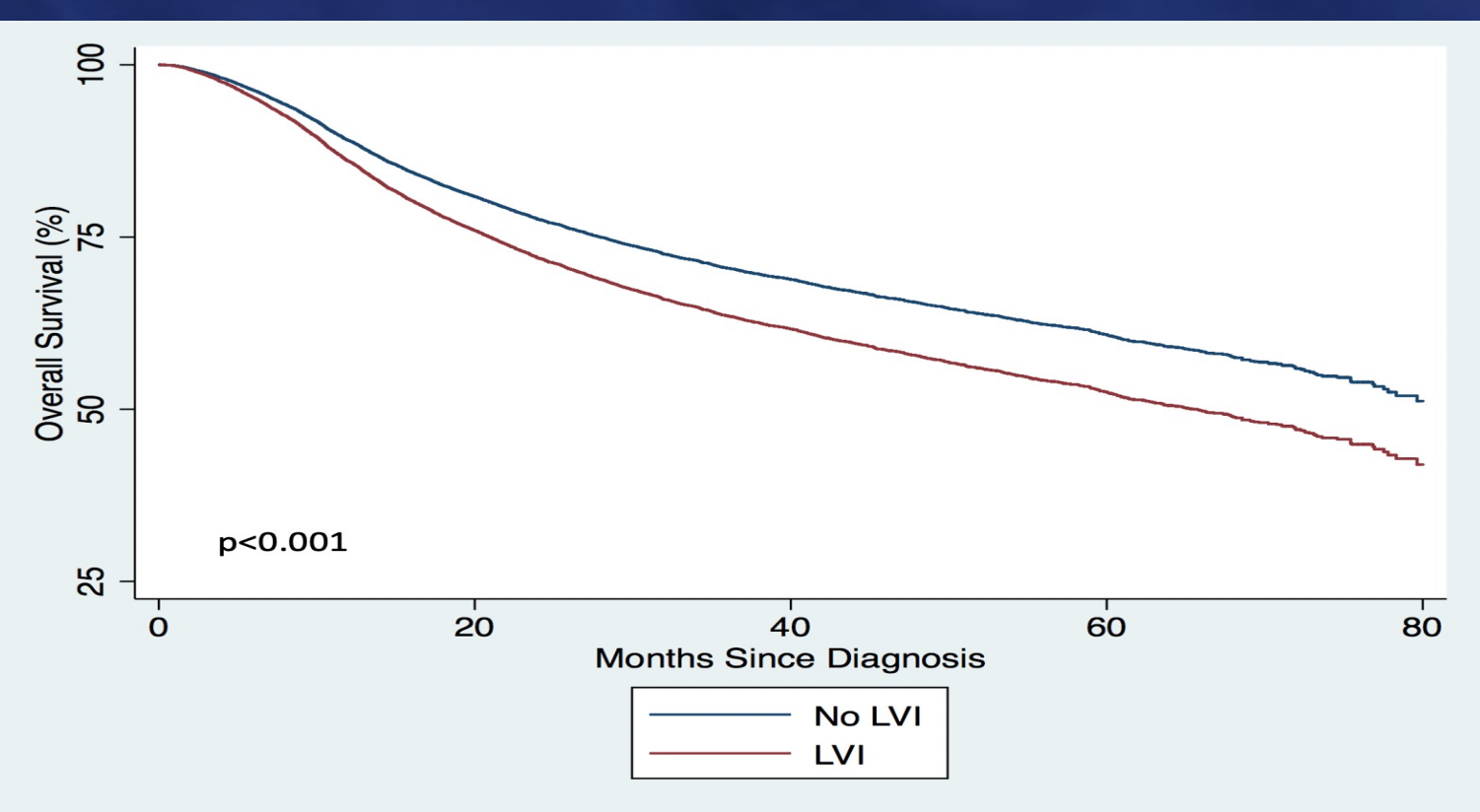


FIGURE 1. Cumulative Survival Stratified by Presence of LVI. Inverse Cox proportional hazard plotted at average values for all covariates. Probability of overall survival is shown on the Y axis, time since diagnosis (months) on the X axis.

Discussion

1. LVI occurs in 19% of nodal negative and 51% of nodal positive OCSCC patients.¹³ Studies have found mixed results as to the feature's prognostic value in OCSCC.^{1,3–8,10,14}. There is no clear consensus regarding which adverse pathologic features should guide management decisions. The European trial EORTC 22931 identified LVI and PNI as adverse features, while the Radiation Therapy Oncology Group identified ENE and positive margins.^{1,9} Given the adverse effects associated with PORT, it is important to determine the most appropriate scenario for its use in patients by examining the value of individual factors as prognostic indicators.¹
2. Chen et al. found no significant difference in OS between early stage OCSCC patients with and without PNI or LVI.¹⁰ In contrast, Jardim et al. showed reduced survival. Huang et al. proposed that tumor emboli are more likely to form in wider lymphatics found in deep tissue than in the narrow lymph vessels of superficial tissue, a theory that may explain the negative prognostic value of LVI in late stage.⁶
3. Limitations of the current study include its retrospective nature and the data in NCDB reflecting the American Joint Committee on Cancer's 7th edition, which does not include ENE or PNI. Strengths include the large sample size of patients collected from a multi-center national database.

Conclusions

1. LVI appears to be an independent predictor of OS.
2. Patients with LVI may benefit from PORT.

References

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