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Prognostic impact of perineural invasion and lymphovascular invasion in advanced stage oral squamous cell carcinoma

J. F. Jardim[1], A. L. N. Francisco[2], R. Gondak[3], A. Damascena[4], L. P. Kowalski[2]

[1]Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), São Paulo, Brazil; [2]Department of Head and Neck Surgery and Otorhinolaryngology, AC Camargo Cancer Centre and the National Institute of Science and Technology in Oncogenomics (INCITO), São Paulo, Brazil; [3]Department of Pathology, Federal University of Santa Catarina, Santa Catarina, Brazil; [4]International Centre for Cancer Research (CIPE), AC Camargo Cancer Centre, São Paulo, Brazil

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Abstract. Perineural invasion (PNI) and lymphovascular invasion (LVI) have been associated with the risk of local recurrences and lymph node metastasis. The aim of this study was to evaluate the prognostic impact of PNI and LVI in patients with advanced stage squamous cell carcinoma of the tongue and floor of the mouth. One hundred and forty-two patients without previous treatment were selected. These patients underwent radical surgery with neck dissection and adjuvant treatment. Clinicopathological data were retrieved from the medical charts, including histopathology and surgery reports. Univariate analysis was performed to assess the impact of studied variables on survival. Overall survival was negatively influenced by six tumour-related factors: increasing T stage ($P = 0.003$), more than two clinically positive nodes ($P = 0.002$), extracapsular spread of lymph node metastasis ($P < 0.001$), tumour thickness ($P = 0.04$), PNI ($P < 0.001$), and LVI ($P = 0.012$). Disease-free survival was influenced by PNI ($P = 0.04$), extracapsular spread of lymph node metastasis ($P = 0.008$), and N stage ($P = 0.006$). Multivariate analysis showed PNI to be an independent predictor for overall survival ($P = 0.01$) and disease-free survival ($P = 0.03$). Thus the presence of PNI in oral carcinoma surgical specimens has a significant impact on survival outcomes in patients with advanced stage tumours submitted to radical surgery and adjuvant radiotherapy/radiochemotherapy.

Keywords: squamous cell carcinoma; oral cancer; perineural invasion; vascular invasion; prognosis; survival.

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Oral squamous cell carcinoma (OSCC) is the sixth most common human cancer, accounting for over 500,000 new cases annually worldwide, and more than 50% of all patients have advanced disease at the time of diagnosis.[1] With the advent of multimodality treatment programmes that include surgery, radiotherapy, and chemotherapy, several reports have shown that patients with stage III and stage IV OSCC are more often surviving.[2–4] However, mortality rates reported in population-based registries have remained nearly unchanged, motivating the search for prognostic factors that can be used to

tailor the individual management of patients.[5–7]

Many variables have been identified in the search for prognostic factors in oral carcinoma; these can broadly be placed into the categories of tumour-related, patient-related, and treatment-related factors.[8] Of the known prognostic factors, the TNM stage, histological grade, and tumour thickness are almost universally recognized; however, the prognostic value of other clinicopathological factors is often uncertain and controversial.[7–9] Among the various parameters used to predict the outcome of malignant disease in OSCC, lymphovascular invasion (LVI) and perineural invasion (PNI) are both widely used as indicators of aggressive behaviour.[1,5,10]

PNI is a tropism of tumour cells for nerve bundles in the surrounding tissues. PNI is well known as an independent predictor of a poor outcome in colorectal carcinoma and salivary gland malignancies. However in OSCC there is no consensus among authors about the real prognostic impact.[10–12] LVI is classified according to the presence or absence of neoplastic cells located in the wall or lumen of blood or lymphatic vessels. LVI has been demonstrated to be a good prognostic tool, and has been found to be correlated with low rates of survival and a high risk of recurrence.[13] However, due to difficulty in defining and recognizing this parameter with certainty, some grading systems have omitted this factor.[5]

The aim of this study was to evaluate the prognostic impact of histopathological features, with emphasis on PNI and LVI, on the survival of patients with advanced stage OSCC.

Patients and methods

A retrospective review of the medical records was performed for 142 patients with advanced stage (clinical stage III and IV) SCC of the oral tongue and floor of the mouth treated primarily with surgery at the cancer centre in São Paulo, Brazil. To be eligible for inclusion, the patient had to have been submitted to treatment at the institution between 1998 and 2009 and not to have been treated previously. This study was approved by the institutional ethics committee on research.

All patients had received primary surgical tumour resection with simultaneous neck dissection and adjuvant radiotherapy/radiochemotherapy. Patients with distant metastases (M1) at the beginning of treatment were not included in this study, nor were those with unresectable tumours and those who had had any prior treatment. TNM restaging was reviewed in accordance with the International Union Against Cancer Criteria (UICC, 2002).[14]

For all cases, the medical and pathology charts were examined for demographic data (age, gender, and race) and clinicopathological information (clinical stage, invasion of adjacent structures, LVI, PNI, histological grade, pattern of invasion, tumour size, nodal status, and margins). All slides were re-examined in a blinded manner by a pathologist with experience in oral cancer.

Twenty-three variables were analyzed by univariate analysis to assess their influence on survival. Survival calculations were done by Kaplan–Meier method and compared using the log-rank test. Overall survival was defined as the time from the beginning of primary therapy to death from any cause. For multivariate analysis, the Cox proportional hazards model was used to estimate the independent prognostic impact of patient- and tumour-related factors on survival. All statistical analyses were performed using R, version 3.0.1 (R Development Core Team (2010), Vienna, Austria; www.R-project.org). *P*-values less than 0.05 were considered statistically significant.

Results

Among 142 eligible patients, 109 (76.8%) were male and 33 (23.2%) were female. Most of the patients reported smoking (113 patients, 79.6%) and drinking alcohol (89 patients, 62.7%). The mean age of the study patients was 57 years. The tongue was the primary site in 97 cases (68.3%), while the tumour had arisen in the floor of the mouth in 45 (31.7%). Ninety-two (64.8%) patients had their histological grade defined as well differentiated, whereas 50 (35.2%) were classified as moderately/poorly differentiated. The clinicopathological data are summarized in Table 1.

Of the 142 patients, 38 (26.8%) were node-negative, 53 (37.3%) had N1 disease, 22 (15.5%) were classified as N2a, 15 (10.6%) as N2b, 10 (7.0%) as N2c, and four (2.8%) as N3. A total of 68 (47.9%) patients were classified in stage III, whereas 74 (52.1%) were classified in stage IV. LVI was present in the primary tumour in 58 (40.8%) cases, while PNI was present in 71 (50%) cases in our sample. Of the 93 patients with positive nodes at pathological examination (pN+), there were 47 with LVI and 50 who exhibited PNI. Therefore, the percentages of LVI and PNI with positive nodal disease were 50.5% and 53.8%, respectively. There were 104 (73.2%) recurrences, and 48 of these (46.2%) had LVI. Only 10 (9.6%) patients with LVI did not show recurrence. Concerning PNI, 59 patients (56.7%) with invasion had recurrences, while 10 (9.6%) continued to have no evidence of disease.

The median follow-up was of 31.2 months (range 2–176 months). The disease-free survival was estimated at 25% for 5 years. Overall survival at 5 years was 42.2% and at 10 years was 28.8%.

On univariate analysis, the overall survival rate was negatively influenced by six tumour-related factors: increasing T stage ($P = 0.003$), more than two clinically positive nodes ($P = 0.002$), extracapsular spread of lymph node metastasis ($P < 0.001$), tumour thickness ($P = 0.04$), PNI ($P < 0.001$), and LVI ($P = 0.012$). The disease-free survival rate was influenced by PNI ($P = 0.04$), extracapsular spread of lymph node metastasis ($P = 0.008$), and N stage ($P = 0.006$). Figures 1 and 2 show the overall survival and disease-free survival curves in relation to PNI and LVI.

In addition, LVI was found to be correlated with histological grade ($P = 0.03$) and lymph node capsular rupture ($P = 0.034$), while PNI was correlated with pathological lymph node metastasis ($P = 0.019$) and recurrence ($P = 0.04$). The association between LVI/PNI and clinicopathological parameters is shown in Table 2.

Results from the survival analysis using the Cox proportional hazard model showed PNI to be a significant independent predictor for overall survival ($P = 0.01$) and also for disease-free survival ($P = 0.03$), whereas LVI did not reach significance in the multivariate analysis of survival outcomes (Tables 3 and 4).

Discussion

In agreement with the literature, our findings showed that advanced stage OSCC cases are most often diagnosed in males older than 55 years of age.[9,15] However, the incidence appears to be increasing in women, especially those who smoke and who are heavy consumers of alcohol.[16]

The TNM system is used to categorize the malignancy at all body sites; 'T' relates to the ability of the tumour to grow and invade tissue locally, 'N' relates to its ability to metastasize to regional lymph nodes, and 'M' relates to its ability to metastasize to distant sites.[14] In the oral cavity, these three criteria are independent indicators of the prognosis, although they are inter-related. Increasing size by T stage leads to an increase in the rate of