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Lymph node metastases

Lymph node ratio predicts the benefit of post-operative radiotherapy in oral cavity cancer

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ABSTRACT

Background: The standard treatment for non-metastatic oral cavity squamous cell carcinoma (OCSCC) is surgical resection followed by post-operative radiotherapy (PORT) with/without chemotherapy in high risk patients. Given the substantial toxicity of PORT we assessed lymph node ratio (LNR) as a predictor of PORT benefit.

Design: By using the Surveillance, Epidemiology and End Results (SEER) database, we analyzed all node positive OCSCC patients diagnosed between 1988 and 2007 who underwent neck dissection. LNR was categorized into three groups: <6%, 6–12.5% and >12.5%.

Results: In 3091 subjects identified, median survival was 32, 25 and 16 months for LNR Groups 1, 2 and 3, respectively. On multivariate analysis, survival was associated with age, race, grade, tumor size, nodal stage, extra-capsular extension, use of PORT and LNR. When stratified by LNR group, PORT was associated with a survival benefit only in Group 3 (LNR > 12.5%): 2 year survival 25% vs 37%. No benefit to PORT was seen when the LNR ⩽ 12.5%: 2 year survival 51% vs 54%.

Conclusion: A low LNR is associated with extended survival in LN positive OCSCC. The survival benefit associated with PORT in this disease appears to be limited to those with a LNR > 12.5%. Validation is required prior to the clinical implementation of our findings.

Oral cavity squamous cell carcinoma (OCSCC) is diagnosed in over 39,000 Europeans per year, leading to over 13,000 deaths [1]. Approximately 40–50% of cases present with locally advanced disease [2]. The primary treatment of OCSCC is resection. The most common pattern of disease recurrence is loco-regional and the recommended use of adjuvant radiotherapy is broadly based upon perceived risk of loco-regional failure. Low-risk individuals (e.g. small primary tumors and no lymph node metastases) typically receive no adjuvant treatment. Post-operative radiotherapy (PORT) is currently based on risk of relapse and is indicated in patients with a medium–high likelihood of loco-regional failure [3] including those with large or deeply penetrating tumors, advanced nodal disease (AJCC 6th ed. N stage 2–3), positive surgical margins and extra-capsular extension (ECE) [4]. The latter two factors, which place individuals at a very high-risk of loco-regional and distant failure, are indications for post-operative chemo-radiation based upon the results of phase III trials and a subsequent meta-analysis [5–7].

The use of PORT in oral cavity cancer involves substantial acute toxicity, and even more concerning, a significant risk for late effects [8,9] that might impair the patients' quality of life [10,11] yet is not based upon randomized evidence [4]. Some studies have failed to demonstrate a benefit for PORT in head and neck squamous cell carcinoma (HNSCC) [12,13]. More precise predictive variables are needed to define accurately who benefits from PORT, and conversely which patients may be spared this toxic treatment.

Lymph node metastases are a negative prognostic factor in nearly all-solid malignancies. The current AJCC TNM system incorporates the absolute number of lymph nodes involved irrespective of the extent of nodal dissection. The lymph node ratio (LNR) has been proposed as a more effective metric since it incorporates both the number of pathologically positive lymph nodes (LNs) and the number of LNs examined. The LNR has been shown to be prognostic in multiple malignancies including breast cancer [14,15], colon cancer [16], bladder cancer [17], melanoma [18] and OCSCC [19–24].

The purpose of this study is to challenge our hypothesis that LNR predicts the benefit of PORT in node positive OCSCC.

Materials and methods

The SEER Program is a comprehensive source of population-based data in the United States (US) that includes stage of cancer at the time of diagnosis, patient demographics, primary tumor site and histology, surgical and/or radiation treatment as a first treatment; the database includes comprehensive survival data. In

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2001 the database was expanded to include new regions of the US, covering approximately 26% of the population.

Inclusion criteria were patients registered within SEER diagnosed with squamous cell carcinoma of the oral cavity between the years 1988 and 2007 who underwent surgical neck dissection with pathological lymph node involvement. The oral cavity was defined as 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) and areas labeled "unspecified mouth" or "unspecified oral cavity" (C06.8–06.9). Because the pathophysiology of cancers of the lip is felt to be different to that of cancers of the remainder of the oral cavity, lip subsites were excluded in this study. The histology was limited to squamous cell carcinoma as defined by the ICD-03 codes 8051–8053/03, 8070–8078/03.

Exclusion criteria were: multiple primary tumors, unknown stage at diagnosis, no lymph nodes examined, unknown number of positive lymph nodes, distant metastases and those diagnosed at autopsy. Patients with unknown radiotherapy use, unknown sequence of RT and surgery, pre-operative RT, or the use of radioisotopes and radioactive implants alone were also excluded. Data on patient demographics, disease characteristics, RT received, and survival until death or follow-up as of December 31, 2007 were extracted. Data were not available regarding use of chemotherapy, and any salvage/subsequent therapies.

LNR was defined as the number of pathologically positive LNs divided by the number of LNs examined. LNR categories were based upon previously defined groups [24]. Group 1 was defined as LNR $\leqslant$ 6.5%, Group 2 as LNR 6.5–12.5%, and Group 3 when LNR > 12.5%.

Statistical analyses were performed using the Stata Statistical package (version IC 11.1, Texas). Chi-square tests were used to assess correlations between categorical variables. Overall survival was defined from the time of initial diagnosis to the date of death and was calculated using the Kaplan–Meier method. The effects of demographic, pathologic, and treatment variables and multivariate analyses were tested using the Cox proportional hazards model. Patients who had missing data were excluded from the multivariate analysis. A two sided p-value <0.05 was considered statistically significant.

Results

A total of 3091 patients with lymph node (LN) positive OCSCC were included in the analysis. The demographic characteristics are summarized in Table 1. The median age at diagnosis was 60 years (range 14–99). Males comprised 65% of patients. The most common primary site was the tongue (43%).

Surgical neck dissection

The median number of lymph nodes examined was 27 (range 1–90), with a median number of positive LNs of 2 (range 1–68). In the absence of the extent of surgical dissection and the anatomical nodal levels removed in the SEER registry recorded for the entire study period, we used the yield of lymph nodes as a surrogate for extent of lymph node dissection [25]. The extent of lymph-node dissection (i.e. the number of LNs examined) was divided into three groups: Group 1 <10 LNs, Group 2 with 10–19 LNs and Group 3 $\geqslant$20 LNs. An inadequate lymph node dissection was defined as less than 10 LNs removed, based upon the recommendations of the Royal College of Pathologists [26].

PORT

Seventy-six percent of patients received PORT. Patients receiving PORT were more likely to be younger, have a higher N stage and a higher LNR (all p < 0.001; Table 1). Eighty percent of patients with a LNR > 12.5% were treated with PORT compared to 74% of patients with a LNR $\leqslant$ 12.5% (p < 0.001) and 79% vs 69% of those with N3 compared to N1 disease received PORT (p < 0.001). T size, number of LN examined and grade were not associated with the use of PORT.

Survival

Thirty-five percent of patients were alive at last follow up. The median survival of the entire cohort was 21 months; 2- and 5-year survival was 46% and 31%, respectively. The factors associated with survival by univariate and multivariate analysis are provided in Table 2. Fig. 1 illustrates the prognostic value of well-established prognostic factors. Due to collinearity, the year of diagnosis was omitted from multivariate analyses. Factors associated with survival on multivariate analysis were age, race, marital status, grade, T stage, N-stage, LNR, extracapsular extension (ECE) and PORT (all p < 0.05). The use of RT was associated with an improvement in overall survival within the population as a whole (HR 0.83, CI 0.75–0.91, p < 0.001). There was no association between the number of lymph nodes evaluated and overall- (Group 3 vs Group 1 HR = 1.03 CI 0.90–1.18 p = 0.65) or cancer-specific survival (Group 3 vs Group 1 HR = 1.18 CI 0.95–1.5 p = 0.14).

LNR and outcome

The number of patients in LNR Groups 1, 2 and 3 was 1060 (34%), 863 (28%) and 1168 (38%), respectively. LNR was associated with overall survival (OS) and cancer specific survival (CSS) (Fig. 2) on both univariate and multivariate analyses, with a higher LNR associated with a poorer outcome (Table 2). This association remained true whether or not N-stage was included in the multivariate analysis model. In addition, LNR was prognostic in both patients who received PORT and those who did not.

LNR appears to be prognostic in patients with both more limited and those with more extensive LN dissections. When looking at patients who had a few vs many LNs examined (<10 LNs vs $\geqslant$10 LNs), LNR was significantly prognostic in the 2703 patients with 10 LNs or more removed (LNR Group 3 vs Group 1 HR = 2.0, CI 1.78–2.23, p < 0.001) and a trend to significance in the 368 patients with less than 10 LNs examined (Group 3 vs Group 2 HR = 1.45, CI = 0.99–2.12, p = 0.06, of note, by definition, there were no patients with LNR Group 1 who had less than 10 LNs examined). In addition, LNR was also prognostic in patients with only one pathologically involved LN (HR 1.16, CI 1.05–1.28, p = 0.003) or 2 pathologically involved LN (HR 1.13, CI 1.00–1.28, p = 0.046).

Stratifying by LNR group on multivariate analysis, the use of PORT was significantly associated with an improved OS and CSS, only in the LNR > 12.5% group (OS HR = 0.37 CI 0.23–0.57 p < 0.001, see Fig. 3; CSS–HR 0.48 CI 0.24–0.98 p = 0.04). In contrast, PORT was not associated with an OS or CSS in LNR Groups 1 (OS HR = 0.86 CI 0.54–1.37 p = 0.5) and 2 (HR = 0.73 CI 0.43–1.25 p = 0.3). Within the subgroup of patients with ECE, the benefit of PORT was also limited to patients with a LNR greater than 12.5% (Table 3). Within the subgroup of patients with an adequate LN dissection, the OS benefit of PORT was limited to LNR > 12.5% (LNR Group 1 HR = 0.81 CI 0.51–1.27, p = 0.35; LNR Group 2 HR = 0.74 CI 0.43–1.27 p = 0.27; LNR Group 3 HR = 0.36 CI 0.22–0.59 p < 0.001). Given only 369 patients underwent an inadequate LN dissection and of these only 49 had a LNR < 12.5%, it was not possible to accurately establish the lack of benefit of RT in this subgroup. However, those with an inadequate LN dissection with a LNR > 12.5% did benefit from RT (OS HR = 0.66 CI 0.45–0.96 p = 0.03).