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The importance of log odds of positive lymph nodes for locoregional recurrence in oral squamous cell carcinoma

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ABSTRACT

Objectives: Log odds of positive lymph nodes (LODDS) has been demonstrated as a very promising staging model for multiple cancer sites, as it avoids singularity and predicts prognosis significantly better than conventional nodal staging and lymph node ratio. However, published studies on the influence of LODDS for patients with OSCC are very seldom.

Material and methods: Retrospective chart review of 499 patients with treatment-naive oral squamous cell carcinoma. Exclusion criteria were neoadjuvant chemoradiotherapy, T4b classification, perioperative death, unresectable disease, synchronous malignancy, follow-up < 3 months and inadequate information to correctly determine nodal yield. Statistical analysis was performed using univariate and multivariate analysis.

Results: A significant correlation was found between locoregional recurrence and pathologic T classification (p=0.030), pathologic N classification p=0.013), extracapsular spread (p=0.034), grading (p=0.021), number of positive lymph nodes (p=0.042), lymph node ratio (p=0.009), LODDS (p=0.007) and treatment strategy (p=0.039). Multivariate analysis indicated lymph node ratio (p=0.029) and LODDS (p=0.015) as independent indicators for locoregional recurrence. Within the analyzed models, Nagelkerke R2 index and Someŕs D showed the strongest discrimination ability for LODDS.

Conclusion: For patients with oral squamous cell carcinoma, log odds of positive lymph nodes and lymph node ratio are independent indicators for locoregional recurrence. LODDS predicts locoregional recurrence better than conventional nodal staging system, lymph node ratio and the number of positive lymph nodes.

Introduction

Oral squamous cell carcinoma is one of the most common malignancies worldwide (OSCC) [1]. The annual incidence is 263.000 and 128.000 deaths are registered per year [1]. Despite major advances in diagnostic and therapeutic techniques, the prognosis of patients with oral squamous cell carcinoma has not improved in the last three decades and still remains below 50% [2,3].

An exact assessment of the cervical lymph node status is of utmost importance, as it represents one of the major indicators for poor prognosis and helps in decision-making for adequate treatment strategies [1,4,5]. In the daily clinical routine, the Union Internationale Contre le Cancer (UICC)/American Joint Committee on Cancer (AJCC) based N classification is frequently used to evaluate the nodal status [1,4]. It is based on the number and localization of positive lymph nodes and generally, prognosis deteriorates with advanced N classification [1,6]. Nevertheless, in recent years multiple studies indicated prognostic shortcomings of the conventional nodal staging system, mainly because it does not take the total number of retrieved lymph nodes into account [7–9]. Hence, a large number of studies investigated the ratio between the number of positive lymph nodes and total number of harvested lymph nodes (lymph node ratio (LNR)), and noticed LNR being a stronger independent prognostic marker than the conventional nodal staging system and number of positive lymph nodes [6,10,11]. However, several studies demonstrated, that the prognostic superiority of LNR might be confounded by a limited nodal yield, especially because approximately 40% of patients with OSCC do not have pathologically proven positive neck lymph nodes and

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therefore do not gain from the benefits of LNR [4,6,8,9]. Therefore, to overcome understaging and stage migration, log odds of positive lymph nodes (LODDS) has been demonstrated as a more recent and very promising staging model, especially for breast, gastric and colon cancer [12–14]. LODDS is defined as the log of the ratio between the probability of being a positive lymph node and the probability of being a negative lymph node when one lymph node is retrieved [14]. It avoids singularity and therefore enables discrimination between patients without positive lymph nodes [14]. For patients with OSCC there is a lack of data concerning the prognostic effect of LODDS. In 2016, Yildiz et al. compared pN staging, the number of positive lymph nodes, LNR and LODDS on 225 patients with head and neck cancer [5]. They concluded, that LODDS predicts overall survival better than pN classification, number of positive lymph nodes and LNR [5]. In 2017 Lee et al. reported on the prognostic value of LODDS for patients with OSCC in Taiwan in a cohort of 463 patients and suggested to incorporate LODDS into N classification, as it showed better discriminability than the AJCC pN classification [4]. However, their patient group consisted of 92.4% males, because in southeastern Asia betel quid is mainly chewed by men and represents the main risk factor for OSCC. To the best of our knowledge, further published studies investigating the importance of LODDS for patients with OSCC do not exist. Therefore, in light of these considerations, we aimed to evaluate, whether LODDS predicts locoregional recurrence in patients with OSCC better than pN classification, the number of positive lymph nodes and LNR. Hence, we performed a retrospective chart review of 499 patients, treated in our department between 2004 and 2014.

Material and methods

Patients and data collection

Our retrospective study followed the guidelines of the Helsinki Declaration. Inclusion criteria were patients with treatment-naive oral squamous cell carcinoma and primarily curative intended surgery with negative resection margins. Exclusion criteria were neoadjuvant chemoradiotherapy, T4b classification, perioperative death, unresectable disease, synchronous malignancy, follow-up <3 months and inadequate information to correctly determine clinicopathological characteristics. Thus our study consisted of 499 patients, who were diagnosed and treated between 2004 and 2014 at our Department for Oral and Craniomaxillofacial Plastic Surgery.

In accordance with existing literature, recurrence was defined as a tumor of similar histology appearing after 6 weeks of treatment and within the first 3 years after therapy of the primary tumor [15]. Regional recurrences were defined as recurrences within the lymph neck nodes and distant recurrences as metastasis outside the head and neck region.

Due to the retrospective nature of this study, it was granted an exemption in writing by the University Hospital IRB.

Clinicopathologic data were collected from medical records as well as pathology and surgery reports. Parameters were carefully reviewed and included gender, age, pathologic T-Classification, pathologic N-classification, UICC stage, extracapsular spread, lymphovascular invasion, blood vessel invasion, perineural invasion, grading, number of resected lymph nodes and number of positive lymph nodes. All cases were staged histopathologically according to l'Union Internationale Contre le Cancer (UICC) tumor, node, metastasis (TNM) Classification, 7th edition. The staging was updated retrospectively to the 7th edition by using the histopathological reports.

Treatment strategies

Treatment included radical surgery and neck dissection depending on the tumor stage. Patients, who were clinically classified as cN0 received selective neck dissection at least of the level I-III/IV. Patients with clinically positive cervical lymph node status (cN+) or histopathologically proven lymph node metastasis (pN+) were treated with a modified radical neck dissection of levels I-V. Whenever bilateral cervical lymph node metastasis was present, we performed a bilateral neck dissection.

All patients were treated with radical surgery including neck dissection. As this is a retrospective study, an interdisciplinary team of surgeons, radiation oncologists, medical oncologists, radiologists and pathologists determined the indications for adjuvant treatment individually so that some patients with stage without the risk factors of stage III and IV, positive or close margins, lymphangiosis carcinomatosa, extracapsular spread and poor histopathologic differentiation received a postoperative radiotherapy (RT) or radiochemotherapy (RCT), too. RT was delivered by 6-MV photons of a linear accelerator (LINAC) in daily fractions of 1.8 Gy five-times a week with a total dose 60–66 Gy. When chemotherapy was given it was administered in a concomitant setting during the first and fifth week of RT. Carboplatin was given as a short-term infusion 1 h before radi- ation at a dose of 70 mg/m^2/day.

Tissue samples

Histopathological analysis of lymph nodes was performed at the Institute of Pathology, University of Cologne. After fixation of the lymph nodes in 5% formaldehyde, they were embedded in paraffin. Longitudinal bisection and further sectioning were obtained if the thickness was larger than 2 mm. From each paraffin block, two-step sections were cut at 50 µm levels. Afterwards, staining was performed with hematoxylin and eosin, as well as periodic acid-Shiff, to histologically examine the presence or absence of metastatic disease. All specimens were evaluated by two independent, experienced pathologists.

Lymph node classification

We defined lymph node ratio as the ratio between positive lymph nodes and the total number of resected lymph nodes. LODDS was estimated by: log ((number of positive lymph nodes + 0.5)/(total number of resected lymph nodes − number of positive lymph nodes +0.5)).

Statistical analysis

Contingency tables and $\chi 2$-test were performed to analyze associations between clinicopathological features and recurrence. A p-value < 0.05 was considered as significant. The dependent variable was the presence of recurrence and the independent variable the clinicopathological parameters. The Kaplan-Meier analysis method was performed to estimate the events of interest for locoregional recurrence and the log-rank test was performed to determine differences. In multivariate analysis, the Cox proportional hazard model was performed to estimate the impact of significant patient and tumor-related factors from univariate analysis, on locoregional recurrence. Cutoff values for LNR and LODDS were obtained from ROC-curves and Youden index (Youden index = sensitivity + specificity - 1) [16]. To evaluate the goodness of fit of our regression models, we used the Nagelkerke R^2 index (R^2 N) [17]. This method summarizes the proportion of variance described by covariates in Cox regression models and provides values between 0 and 1 with larger R^2 N values indicating better predictive models