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Clinical and histopathological staging in oral squamous cell carcinoma – Comparison of the prognostic significance

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ABSTRACT

Background: In oral cancer the prognostic significance of clinical staging (cTNM) is regarded inferior to histopathologic staging (pTNM) after surgery. This is mainly due to the point that the quality of the cTNM strongly depends on the clinical and radiological examination techniques applied and the physician's experience. The aim of this study was to evaluate the prognostic quality of cTNM and pTNM in a single center cohort.

Methods: This retrospective study included 392 patients with treatment-naive oral squamous cell carcinoma (OSCC). All patients received primary surgery including a neck dissection. According to tumor stage and histopathologic risk factors patients received adjuvant radiotherapy (RT) or radiochemotherapy (RCT). Prognostic factors were identified in univariate analysis by using the log rank test and in multivariate analysis through Cox regression.

Results: Clinical and histopathologic staging showed concordance in 62% for the primary tumor and 59% for cN- and pN-classification. In 58% of the cases of discordance the primary tumor was overstaged. In case of discordance of metastatic spread to the cervical lymph nodes, lymph node involvement showed overstaging in 78%. In univariate analysis cT-, cN-, cT- and pT-classification had a significant impact ($p < 0.05$) on overall survival (OS). In multivariate analysis only pT- and pN-classification had a significant impact on OS.

Conclusion: Despite advances and modern radiologic techniques, pTNM has a higher prognostic quality than cTNM. Discordance between clinical and histopathologic staging was observed in up to 40%. When discordance was observed overstaging for clinical T-stage and clinical N-stage was more likely than understaging.

Introduction

With an annual incidence of 263.000 newly diagnosed cases and 128.000 annual casualties worldwide, oral squamous cell carcinoma (OSCC) constitutes one of the most common malignancies with an increasing incidence [1–3]. A slight improvement in survival has been reported for the last decade, many patients with advanced stage tumors however still die because of locoregional treatment failure [4]. Although molecular and histological features of the tumor play an increasingly important role in the prognostication of OSCC, the anatomic extent described by size of the primary tumor (T-classification), by the lymphatic spread (N-classification) and by distant metastases (M-classification) is still considered as the most important prognostic factor [5,6]. Tumors must be classified before treatment (clinical staging, cTNM) and after resection (pathologic staging, pTNM). The pre-therapeutic anatomic extent (cTNM) of the tumor is derived from clinical and radiologic examinations such as MRI and CT and determines the choice of primary treatment. The decision for adjuvant radiotherapy (RT) or radiochemotherapy is based on the pTNM, which is determined by histologic analysis of the resected tumor and the neck dissection specimen. While pTNM is considered to have a highly significant impact on survival the prognostic quality of clinical TNM remains unclear [7,8]. For patients, who do receive a

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definitive RT of neoadjuvant treatment followed by surgery, no pTNM is available. This highlights the importance of an accurate clinical staging [9]. Accurate staging of oral cancer is challenging. It usually includes MRI or CT of the head and neck region to determine the extent of the primary tumor and cervical lymph node metastases [10]. The addition of neck ultrasound enhances detection of cervical lymph node metastases [10]. Additionally it involves CT of the chest to detect distant metastases [11]. There are only few studies comparing the prognostic quality of clinical and histopathologic TNM for oral cancer [10,12]. The largest study so far included patients from all different head and neck sites and did not focus on carcinoma of the oral cavity [12].

The aim of this study was to compare the prognostic significance of cTNM and pTNM in patients with OSCC treated with primary surgery. Additionally we analyzed the concordance between cTNM and pTNM.

Materials and methods

Patients and specimens

The retrospective study included 392 treatment-naive patients with biopsy proven OSCC of advanced stages I–IVb, who were treated with curative intend at the Department for Oral and Craniomaxillo-Facial Plastic Surgery at the University of Cologne between 2003 and 2010. The patients' clinical characteristics are listed in Table 1. Clinical and histopathologic staging was conducted according to the 7th edition of the UICC for carcinoma of the oral cavity. Patients with distant metastases were excluded from our study. All patients received MRI- and CT-scan, ultrasound of the head and neck region and a three-phase bone scintigraphy using 99mTc to detect bone invasion and distant metastases. Clinical staging data were obtained using the results from clinical examinations and the CT, MRI, and sonographic and scintigraphic pretreatment reports from the Department of Radiology. Lymph nodes of a diameter >1.5 cm were considered as positive. Apart from size other criteria such as uptake of contrast medium with a diameter >1 cm, round shape and central necrosis were considered, too [13]. To detect distant metastases chest X-ray and abdominal ultrasound were conducted. No PET-CT data were available. Histopathologic staging data were gathered from pathologic reports.

The specimens were obtained from the operation theatre were formalin-fixation occurred after orientation of the specimens by the surgeon. Further processing occurred at the Department of Pathology where the specimens were embedded into paraffin. Resection specimens were analyzed macroscopically according to tumor localization and tumor and nodal stage. Cross sectioning was performed and tissue was embedded into Paraffin. Paraffin blocks were sliced into 4 μm thick sections and analyzed by senior pathologists.

Treatment

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 RT or 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 radiation at a dose of 70 mg/m^2/day.

Statistical analysis

The Kaplan-Meier survival analysis method was used to estimate the events of interest for overall survival (OS, time interval from beginning of primary therapy until death. Patients who were alive at the last date of follow up were classified as censored observations) and disease specific survival (DSS, time interval from beginning of primary therapy until death caused by the tumor. Patients, who were alive at the last date of follow up or died of other reasons than oral cancer, were classified as censored observations) [14]. The log rank test was used to compare survival times among patients with different characteristics. *P*-values of less than 0.05 were considered as statistically significant and printed in bold. For multivariate analysis, two Cox proportional hazard models, one for the clinical staging and one for the histopathological staging, were calculated to estimate the prognostic impact of patient and tumor related factors on OS [15]. The log likelihood was used to compare the model fir between both models. Sensitivity for clinical staging was defined as the number of patients with concordant clinical and histopathological staging (correct test result) divided by the number of patients with concordant clinical and histopathological staging plus the number of patients with clinical understaging in comparison to the results of the histopathological staging (false negative test result).

Results

Patient and tumor characteristics

Table 1 shows the patient and tumor characteristics. At the time of diagnosis, the patients' age ranged from 25 to 90 years with an average age of 61.8 years and a median age of 62 years. The average follow-up time for patients alive was 46.1 months (median 39 months). Out of the patients alive, 28 patients had a follow up of less than 12 months. The mean nodal yield was 24.8 (median 20.0, standard deviation 18.2).

Univariate analysis

At the time of analysis, 83 patients had died. None of our patients died because of treatment-related complications. Five-year OS was 73%. Univariate analysis revealed that clinical as well as pathological T-stage and N-stage of the 7th edition of the UICC are feasible predictors for OS ($p < 0.001$, Table 1). The 5-year OS rate (Fig. 1) decreased from pT1 (96%) to pT4b (28%). Patients with no histological evidence of cervical lymph node metastases had a significantly higher 5-year OS rate (pN0, 85%) in comparison to patients with cervical lymph node metastases. While patients with pN1 status had a 5-year OS rate of 68% the 5-years OS rate dropped to 25% for patients with pN3-status (Fig. 2, $p < 0.001$). Similar results were found for DSS: in univariate analysis, cT-, cN-, pT- and pN-classification had a highly significant impact on DSS ($p < 0.001$). Out of the patients with histologically confirmed metastases 18 patients (12%) were staged as cN0 without clinical or radiological signs of the disease spread but had metastases in the neck dissection specimen (cN0pN+). Compared to the patients with cN0pN0-status, they had a significantly poorer 5-year overall survival rate (61% vs. 80%, $p = 0.004$, Fig. 3). When comparing cN0pN0 and cN + pN0 no significant differences were observed between both groups for OS (5-year OS 81% vs. 90%, $p = 0.463$) and for DSS (5-year DSS 88% vs. 92%, $p = 0.726$).