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Evaluation of neck dissection with frozen section biopsy – Management of levels IV and V

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ABSTRACT

Introduction: Neck dissection is an essential component of oral cancer therapy. Based on a standardised approach to cervical lymph node management, we seek to define the relevance of neck dissection extension in cN + cases.
Material and methods: A retrospective analysis from January 2009 to February 2017 identified 84 patients with oral squamous cell carcinoma with a cN + neck or histologically proven lymph node involvement in intraoperative frozen sectioning and who received modified radical neck dissection according to the presented neck dissection algorithm.
Results: Overall 11 patients showed lymph node metastasis level IV or V, whereas 19 developed disease recurrence, of which 5 cases were neck recurrences. A total of 30 patients died within the time of observance (overall survival of n = 54). None of those patients with pN + status in levels IV and V reached a 5-year survival.
Discussion: With a look to the possibility of a 5-year survival in patients with a N+ status in level IV and V, the justification for a radical approach to the neck appears questionable. However, modified radical neck dissection appears to be a suitable for a high-risk oral cancer subgroup. A randomised controlled trial is needed to define guidelines for the neck dissection extent in c/pN + cases.

1. Introduction

The relevance of cervical lymph node dissection is an unquestionable treatment component in the therapy of oral squamous cell carcinoma (OSCC). First introduced by Jawdynski in the 19th century, treatment concepts followed radical procedures (radical neck dissection), resulting in great post-surgical impairment (Crile, 1987). An anatomical division of the neck into defined levels, as well as the awareness that mutilating surgery is not followed by improved patient outcome, led to moderate surgical concepts with preservation of non-lymphatic structures (modified radical neck dissection [MRND]) (Shah et al., 1981). The foundation of functional neck dissection was laid in Cordoba by Suarez,who introduced the idea of a fascia-guided lymphatic tissue removal (Suarez, 1963). Two decades later, the concept of supraomohyoid neck dissection (SOND) was introduced by Shah et al. (Lindberg, 1972; Shah et al., 1981).

To date, SOND is a standard in cN0 tumours and associated with improved survival (Guo et al., 2014; D'Cruz et al., 2015). However, the relevance of extending SOND in pN + situations remains the topic of an international debate, and no evidence-based guideline exists. In our previous work, we were able to show that an occurrence of lymph node involvement on the ipsilateral side in a cN0 neck is accompanied with an over 25% pN + status of the contralateral side (Koerdt et al., 2016). Furthermore, it has been proved that poorly differentiated tumours and extensive local disease are a predictor for contralateral neck failure (Iype et al., 2008; Scully and Bagan, 2009). Woolgar et al. found that 13% of OSCC patients had

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lymph node metastases in level IV and 3% in level V (Woolgar, 1997). An involvement of up to 20% for level IV and 4% for level V was reported by Shah et al. (1990). However, a meta-analysis stated no statistically significant differences in terms of overall and disease-free survival between treatment with SOND and MRND in cN + OSCC patients (Liang et al., 2015). Based on these findings, in 2016 we designed an individual surgical approach to a level-by-level dissection that clearly indicates the procedure in N+ situations (Fig. 1) (Koerdt et al., 2016). The advantages are a standardised and predictable surgical concept with less time-consuming surgery. This approach facilitates the training of young surgeons, enables the pathologist to make a more precise TNM classification, and provides better orientation for adjuvant radiation therapy (Upile et al., 2007).

Even though numerous studies have described lymph node management in oral cancer, the specific aim of this study was to evaluate a standardized clinical algorithm using frozen section biopsy intraoperatively. However, especially the treatment of the initially inconspicuous neck with the manifestation of positive nodes intraoperatively and the immediate extent of the neck dissection to levels further caudally seems of practical clinical relevance.

2. Materials and methods

The study was conducted in compliance with the current revision of the Declaration of Helsinki with regard to medical protocol and ethics. The Institutional Review Board of the Technical University of Munich (TUM), Germany, approved the study (Study-Number 2777/10). The records of all patients primarily diagnosed with OSCC and treated by surgical tumour resection and MRND from January 1, 2009, to April 1, 2017 in the Department of Oral and Maxillofacial Surgery of the Technical University of Munich, Germany, were reviewed retrospectively.

2.1. Patients and clinical data

The inclusion criteria were defined as follows: patients diagnosed with a histologically proven OSCC who were more than 18 years of age, had not received any treatment so far or suffered from any other tumour, and who were treated by radical tumour resection and neck dissection of the levels I–V.

Clinical records were screened for baseline data, staging documents, pre- and postoperative TNM status, tumour location, adjuvant therapy, recurrence, survival, and the availability of pathological and radiological diagnostics.

2.2. Surgical treatment and modified radical neck dissection

All patients received neck dissection of levels I–V followed by radical tumour resection and primary reconstruction. The decision to perform neck dissection was based on either cN + computed tomography staging or intraoperatively proven positive lymph node involvement on frozen sectioning of the levels II–III (Fig. 1). When tumour-positive frozen sectioning occurred, removal of levels I–V of the ipsilateral side and levels I–III of the contralateral side was performed. When the tumour affected the midline, both neck sides were treated by dissection of levels I–III, if histologically proven local metastatic disease occurred additionally levels IV and V were removed on the site of involvement. MRND was defined as the dissection of lymphatic tissue of the levels I–V without resection of the internal jugular vein, the carotid artery, the spinal accessory nerve, or the sternocleidomastoid muscle.

2.3. Statistical analysis

Data collection and evaluation were performed by the use of IBM SPSS for Mac (Version 24.0; IBM Corp., Armonk, NY). The statistics comprised means and standard deviations (SD), as well as significance test results. For all normally distributed values, a t-test was applied, and for non–normally distributed values the Mann–Whitney U test was used. Frequency tables of categorical data were analyzed by chi-square test, and the Yates correction was applied when the expected frequency reached less than 5. Statistical significance was defined as a two-sided p value of less than 0.05.

3. Results

3.1. Patients and clinical data

The study comprised 84 patients, 61 male and 23 female. The mean age was 61.1 years (median 59.03, minimum 34.58, maximum 87.82).

The most common tumour location was the floor of the mouth (n = 30), followed by the tongue (n = 26), the maxilla (n = 13), the alveolar crest of the mandible (n = 12), and the soft palate (n = 3) (Fig. 2). In terms of tumour location and pN+ in levels IV and V, no statistically significant difference could be found (Chi-squared test = 5.469, df = 6, $p = 0.243$). However, all tumours that showed a pN + status were primarily located in the lower third of the oral cavity (Fig. 2).

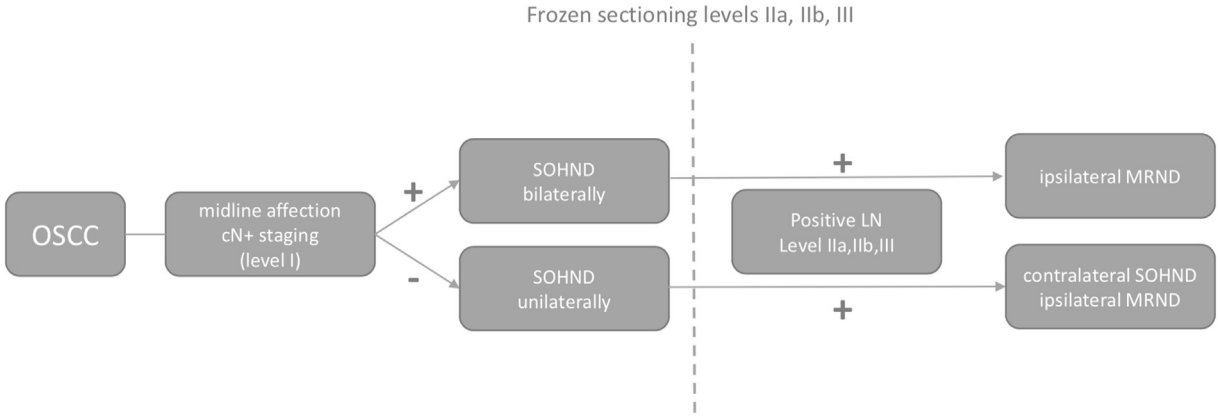

Fig. 1. Flow chart for the clinical algorithm of neck dissection.

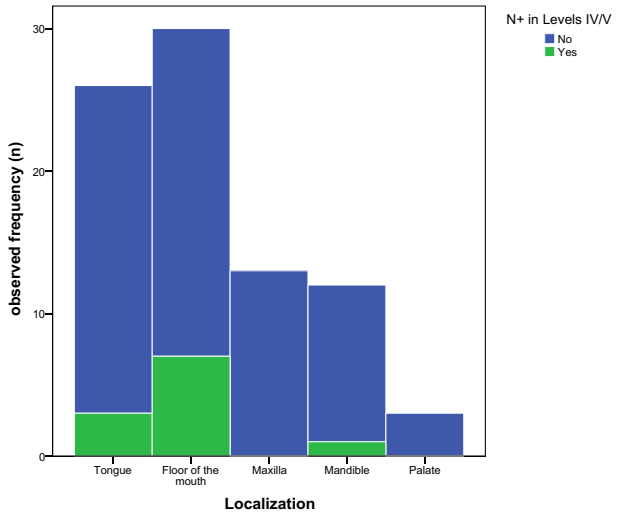

Fig. 2. Bar chart defining tumour localization and the corresponding frequency of pN+ in levels IV/V.

3.2. pTNM status

Postoperatively, 15 tumours were classified as T1, 30 as T2, 18 as T3, and 21 as T4. The N-status of patient necks was as follows: 3 patients were N0, 20 patients N1, 1 patient N2a, 27 patients N2b, 9 patients N2c, and 24 N3. The three patients who showed an N0 status on frozen sectioning revealed a pN + situation in the definitive histopathological statement. Fig. 3 visualizes the T-status in relation to overall survival. No statistically significant difference was found comparing the pT (Chi-squared test = 4.442, df = 3, $p = 0.217$) and G-status (Chi-squared test = 2.007, df = 3, $p = 0.571$) to pN+ in levels IV and V.

3.3. Neck dissection

The majority of patients received unilateral MRND (n = 45), in 39 cases MRND was performed bilaterally. Eleven patients showed lymph node metastases in level IV or V. The results in extracapsular extension (ECE) were well balanced with positive ECE-status (n = 41 necks) showing no ECE (n = 43 necks). The results considering the ECE status in relation to the pN status were not statistically significant (Chi-squared test = 2.339, df = 1, $p = 0.126$). The infiltration reached from 3 mm to 80 mm (mean 25.25 mm; median 22 mm) and did not reveal any significant correlation with the pN status (Chi-squared test = 1.768, df = 2, $p = 0.413$).

Overall, 4605 lymph nodes were dissected in 84 patients. A total of 283 lymph nodes were positive for nodal metastasis. According to the ND extent the following results were seen for the number of positive lymph nodes in each level.

Unilateral MRND right and SOND left (n = 20) showed 73 tumour -positive lymph nodes: Level Ia 0, Level Ib right 5, Level Ib left 0, Level IIa right 14, Level IIa left 1, Level IIb right 9, Level IIb left 1, Level III right 19, Level III left 0, Level IV/V right 24.

Unilateral MRND left and SOND right (n = 25) showed 70 tumour positive lymph nodes: Level Ia 3, Level Ib left 16, Level Ib right 0, Level IIa left 13, Level IIa right 1, Level IIb left 9, Level IIb right 0, Level III left 14, Level III right 3, Level IV/V left 11.

Bilateral MRND (n = 39) showed 140 tumour positive lymph nodes: Level Ia 9, Level Ib 41, Level IIa 28, Level IIb 19, Level III 31, Level IV/V 12.

Skip metastases were defined as pN + level III involvement that did not show any positive lymph nodes in levels I–II. Fourteen patients showed skip metastases in level III. Of these 14 patients, 3 also had a pN + status in levels IV and V. The majority of skip metastasis occurred in floor of the mouth cancer patients 10, followed by cases involving the tongue (n = 5), the lower jaw (n = 2) and the palate (n = 1).

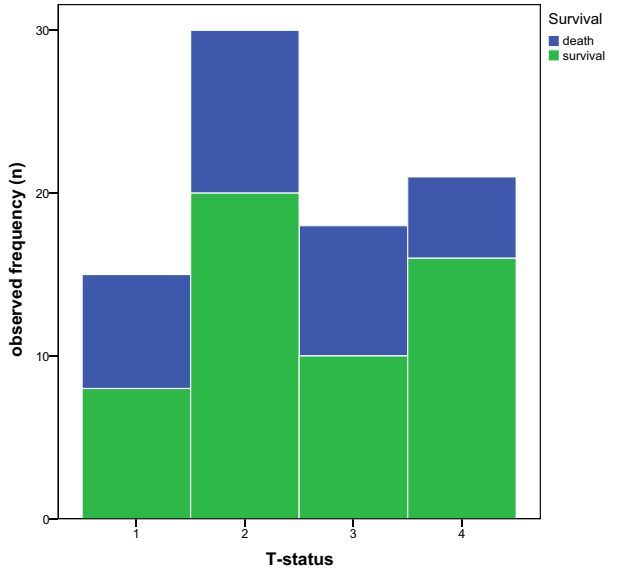

Fig. 3. Bar chart visualizing T-status in relation to overall survival.

3.4. Adjuvant therapy, recurrence and survival

According to interdisciplinary tumour conference statements, 4 patients were assigned to clinical control, 43 patients received adjuvant radiotherapy and 37 patients were allocated to adjuvant radiochemotherapy. The decision for adjuvant radiation was made according to the German "Guideline Program Oncology, S3, Guideline for diagnostics and treatment of oral cancer staging" for all tumors ≥ T3, close margin and ≥R1 resections, perineural tumor invasion, vessel invasion and lymphatic invasion (Wolff et al., 2012). Those four patients who did not undergo adjuvant treatment rejected the tumour board's recommendation or were excluded due to poor general condition.

Of 84 patients, 19 developed recurrent disease. Of all recurrent disease (n = 19), the most frequent recurrence was at the primary tumour site (n = 12), followed by nodal recurrence (n = 5). One patient suffered from distant metastasis and one further patient from secondary carcinoma. Recurrence occurred within 66–1146 days.

Overall, 30 patients died within the time of observance, resulting in an overall survival of 64.3% (n = 54 patients). Of those patients who showed a pN + status in levels IV and V (n = 11) none reached a 5-year survival (minimum 98 days, maximum 1276 days, median 289 days, mean 416.27 days) (Fig. 4). Five patients died before reaching 5 years, another 6 patients were still alive at the date of study closure but also did not reach a survival time of 5 years (Fig. 5). All causes of death were tumour associated and not due to further general illnesses. The hazard ratio for death when a pN + status in level IV and V occurred compared to a pN- status in levels IV and V was 2.253.

4. Discussion

The significance of SOND is an unquestionable component of oral cancer therapy (D'Cruz et al., 2015). However, active debate

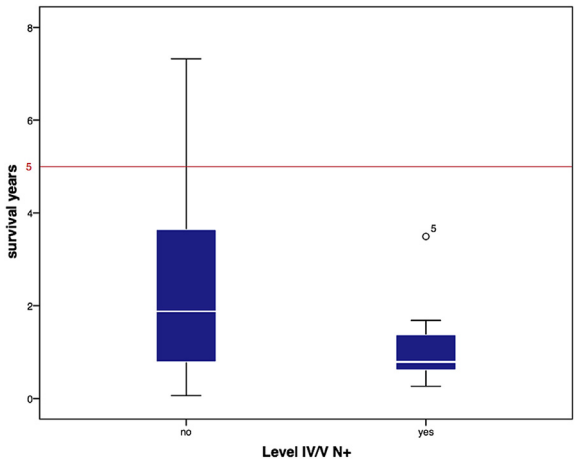

Fig. 4. Box plot visualizing pN status in levels IV/V in relation to years of survival.

exists on the relevance of MRND in patients with positive lymph node staging and pN + status in histopathological evaluation. Critical evaluation is needed to confirm the eligibility of a more radical approach in terms of recurrence, survival and postsurgical impairment.

All patients who received an MRND according to our treatment concept during the last 8 years were evaluated retrospectively. Three patients showed an N0 status on frozen sectioning; however, the definitive histopathological statement showed a pN + situation. Furthermore 12 patients showed a N+ status of level IIa to III of the contralateral neck but did not receive MRND of that side. This decision was due to the intraoperative condition of the patient or anatomical limitations (i.e. pre-existing vessel prothesis). A pN + status in levels IV and V occurred in 13.1% (n = 11) of all cases, which is slightly higher than the results of 3–10% in the literature (Shah et al., 1990; Crean et al., 2003; Mishra et al., 2010). The difference may be due to the inclusion of level V within our neck dissection workflow, as we remove the levels IV and V as one lymph node package in MRND. Additionally, the patient sample in this current study consisted of patients with N+ necks only.

The tumour location as well as the T, M and G status did not show any significant correlation with the pN + status. However, if a pN + status occurred in levels IV and V, the tumours were located in

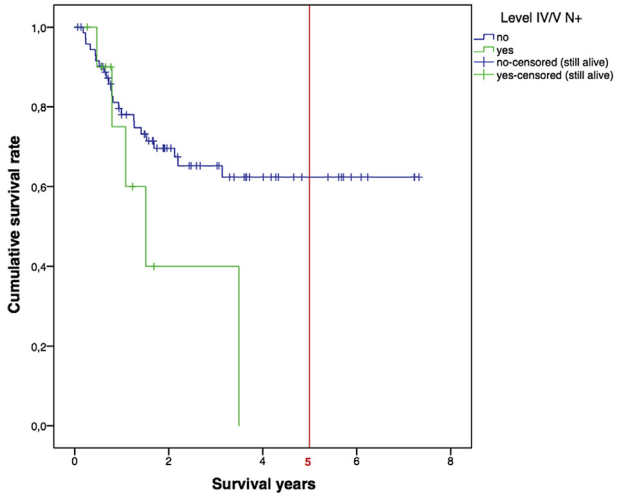

Fig. 5. Kaplan–Meier survival curve showing overall survival of patients in relation to pN status.

the lower third of the oral cavity (Fig. 2). These results are in line with earlier finding from Byers et al. (1997). The ECE status and the tumour invasion depth were not significantly associated with more frequent pN + results in levels IV and V. Still these results are in accordance with findings by Feng et al., who defined ECE as a sign of disease progression but not as an independent prognostic factor (Feng et al., 2014). The evidence of skip metastasis in pN + oral cancer cases is rare and ranges from 2% to 15.8% (Byers et al., 1997; Dias et al., 2006). At present, no larger studies concerning this issue are available. However, our findings of 14 cases showing skip metastasis is comparable to results provided by Byers et al., who found 15.8% skip metastasis in level III and IV (Byers et al., 1997). In our patient sample, more than 10 patients had cancer of the floor of the mouth. Adding the amount of oral tongue cases (n = 5) allows the conclusion that patients with disease affecting these specific areas of the oral cavity are at greater risk for skip metastasis compared to patients with cancers of other locations. Of those cases with skip metastasis in level III, 3 patients had positive lymph node involvement in levels IV and V.

According to the guideline for diagnostics and treatment of oral cancer all patients were assigned to adjuvant therapy. Four patients did not attend radio-chemotherapy due to personal rejection or limited general health conditions (Wolff et al., 2012). A total of 19 patients developed recurrent disease, which is consistent with the fact that lymph node invasion is significantly associated with relapse (Scully and Bagan, 2009). A total of 30 patients died within the time of observation, resulting in an overall survival of 64.3% (n = 54 patients).

With a view to those patients showing a pN + status in levels IV and V (n = 11), none reached a 5-years survival (minimum 98 days, maximum 1276 days, median 289 days, mean 416.27 days) (Fig. 4). Five patients died before reaching 5 years; another 6 patients were still alive at the date of study closure, but also did not reach a survival time of 5 years (Fig. 5). All causes of death were tumour associated and not due to further general illnesses. The hazard ratio for death when a pN + status in level IV and V occurred compared to a pN− status in levels IV and V was 2.253.

The results concerning the subgroup of patients with a pN + status in levels IV and V need to be discussed controversially. The need for extended ND in patients with oral tongue cancer has already been recommended in 1995 by Byers et al. and was redefined by Khalif et al., in 2001 (Byers et al., 1997; Khafif et al., 2001). The main factor that we consider a point of discussion is the result that a pN + status in level IV and V was associated with the death of the patient within less than 1 year after surgery (minimum 98 days, maximum 1276 days, median 289 days, mean 416.27 days) (Fig. 4). However, we rarely see heavy impairment such as chylus fistula, accessory nerve palsy or extensive wound healing disorders in patients receiving MRND compared to SOND. Hence, we consider postoperative weakness to pose a less significant risk for the well-trained surgeon and therefor reasonable for the patient. A randomised controlled trial is needed to examine whether the extension of SOND to MRND and adjuvant radiation is reasonable compared to SOND and adjuvant radiation alone in pN + cases.

Besides the directly patient-associated outcome, the data raises basic embryologic questions in association with tumour growth and metastasis. In 2000, Pfreudner et al. were able to show a systematic metastatic spread of head and neck carcinoma based on the anatomical development of the branchial arches and pouches (Pfreundner et al., 2000). Due to these findings, all present surgical concepts of the neck need to be discussed in regard to fundamental embryologic regularities. With a view to OSCC, the cancer-affected tissue arises from the first and third branchial arches and seems highly associated with metastasis in the submandibular and upper jugular lymphatic drainage. Hence, the question arises whether the

anatomic location of the tumour with regard to its embryologic origin is an additional important aspect to determine the extent of neck dissection. Further investigation is urgently needed to define the relevance of MRND in oral cancer treatment.

5. Conclusion

Due to the poor 5-year survival of patients with an N+ status in level IV and V, the justification for a radical approach to the neck appears to be questionable. A main interest for further research is the evaluation of a control group who received SOND only, even when a cN + status or frozen sectioning lymph node involvement is present. However, as a well-founded algorithm in neck management is still missing, we recommend a randomised controlled trial on the basis of the results of the current study. Especially, in patients with an N+ neck, the impact of the dissection of levels IV and V and the contralateral side with a view to post-surgical impairment, disease recurrence and long-term survival should be of further interest. Moreover, we refer to the importance of basic embryologic conditions and add these aspects to the discussion.

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