Original article

# Influence of Nodal Yield in Individual Neck Dissection Levels on Survival of Patients With Oral and Oropharyngeal Cancer

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## Abstract

**Introduction:** Nodal yield (NY), or the number of collected and analysed lymph nodes in neck dissection, is one of the variables that could supplement the existing TNM classification in order to better stratify patients and their needs for further treatment. The purpose of this paper was to investigate the importance of NY in individual neck dissection levels and its relation to survival.

**Materials and methods:** A retrospective analysis of medical records of 133 patients regarding primary tumour excision and neck dissection from 2002 to 2013. Seventy-nine patients had a neck dissection divided by levels at the time of surgery and 54 patients had an en bloc resection.

**Results:** In the group of all patients, there was no correlation between NY and survival. In the group of patients who underwent a selective neck dissection, a NY above the median was an indicator of a better disease-specific survival (5-year DSS < median NY 70.6%, > median NY 95.2%, p = 0.037 log-rank test). The NY of specimens separated by level was significantly higher than the NY of specimens analysed en bloc (median 33 vs 16; p < 0.001, median test). In the group of specimens separated by level, the NY in levels I-II was not associated with survival, but a high NY in levels III-IV in selective neck dissections was an indicator of an improved overall survival (p = 0.05), disease-specific survival (p = 0.022) and disease-free survival (p = 0.05).

**Conclusion:** High NY in patients with specimens separated by levels could be caused by a more precise pathohistological analysis of a smaller sample. A high NY in levels III-IV can be an indicator of a well-performed selective neck dissection and sufficiently treated regional disease and therefore lead to better survival rates.

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## Introduction

Oral and oropharyngeal squamous cell carcinoma is one of the most prevalent malignancies of the head and neck[1,2]. Its treatment has changed significantly in the last decades, after the introduction of novel chemo-/chemoradiotherapeutic protocols, as well as a result of more sparing surgical procedures. It is well-known that oral and oropharyngeal cancer first metastasises in the regional lymph nodes of the neck (Figure 1).

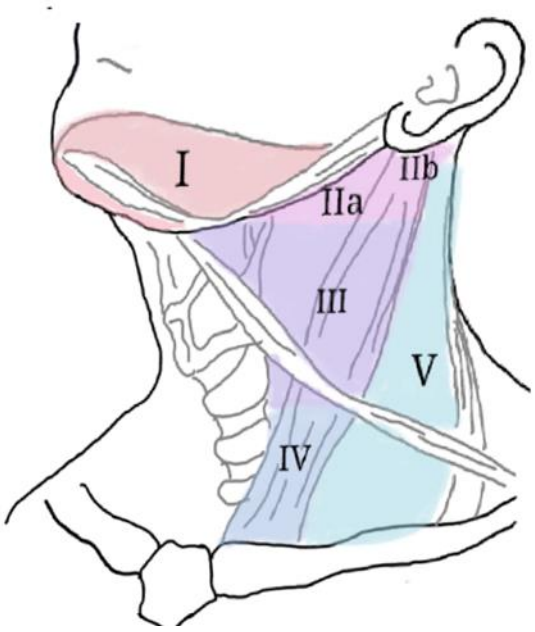


**Figure 1. Levels of neck dissection**

As metastases in the lower neck levels are quite rare, selective neck procedures have been developed. A sparing approach could provide a good postoperative recovery and minimal function impairment[3], but could also result in understaging of the disease due to the presence of an undetected metastasis or micrometastasis[4]. The question pertaining to the adequacy of the extent of neck dissection, especially when it comes to selective dissection, remains. Nodal yield (NY), or the total number of excised and pathohistologically examined lymph nodes, is a means of quantifying the extent of neck dissection, but it is still unclear whether it is also an independent criterion for survival. The value of nodal yield in clinical practice has been discussed in recent studies[5,6,7], but the results so far have been inconclusive. The aim of this study was to elucidate the connection between nodal yield and survival and the possibility of stratification of high-risk patients based on nodal yield.

## Materials and methods

A retrospective study of the influence of nodal yield on the outcome of patients treated surgically due to oral or oropharyngeal cancer was conducted. All patients were treated at the same department of the Clinical Hospital Centre from 1 January 2002 to the end of 2013 and their tumours were classified according to the 2002 TNM staging rules[8]. The study was approved by the Institutional Ethics Committee (number R2-:22512-6/2015 Clinical Hospital Centre Osijek, Ethics Committee).

Patients' medical records and the hospital's electronic database were analysed. General inclusion criteria were the following: pathohistological diagnosis of oral or oropharyngeal squamous cell carcinoma, surgical treatment including a radical or selective neck dissection and follow-up of at least two years or until death. From 229 patients diagnosed with oral or oropharyngeal carcinoma in this period, 133 were included in the study. There were 17 patients whose neck specimens had descriptive pathohistological terms such as "several", "a few" or "conglomerates" of lymph nodes and as such, they were unfit for statistical analysis. Thirty-one patients were treated only with transoral excision without neck dissection due to the early stage of the disease and were not included in the study. The remaining 48 patients were lost to follow-up or refused a proposed therapy. Nodal yield (NY) was defined as the total number of lymph nodes analysed in a neck specimen. If a patient underwent a bilateral dissection, NY was calculated as the sum of lymph nodes on both sides divided by two. Other variables noted and used in the statistical analysis were clinical and pathohistological N status, T status, loco-regional or distant recurrence and type of

dissection. Finally, the study included only the patients with regard to whom the absolute number of lymph nodes was indicated regardless of their quantity. Inclusion criteria were fulfilled by 133 patients on whom 149 neck dissections have been performed. Among them, 118 patients received postoperative radio- and/or chemoradiotherapy, while four patients received preoperative radio- and/or chemoradiotherapy. Due to a poor general condition, medical contraindications, a prolonged postoperative recovery or early stage of the disease, 10 patients did not receive any adjuvant radio-/chemoradiotherapy.

*Statistical analysis*

All statistical analyses were performed for the all-patients group and subgroups divided by surgical treatment, cN status and pN status. The above-mentioned groups were dichotomised by the median (due to the irregularity of spread of NY values) and cutoff point of 18 lymph nodes according to the recent report of Ebrahimi et al., who found a minimum NY of 18 to be a marker of a well-performed elective selective neck dissection and of a patient's outcome5,9. A separate statistical analysis was additionally made only for the patients (n = 79) whose neck specimens had been divided by levels at the time of surgery. Unfortunately, there was no consistency in the manner of division between various surgeons, e.g. some surgeons divided the upper neck levels (I and II) and lower neck levels (III and IV) as one sample, whilst others separated each level. In order to uniform our data, we presented the results regarding nodal yield in the regions of the upper neck and lower neck, while level V, present only in radical dissections, was analysed separately. We are aware that running multiple statistical analyses on a small data sample increases the probability of a chance finding, which is one of the major limitations of this study. However, it is our opinion that dividing patients into smaller groups was necessary in order to get the data that accurately portrays each specific group of patients.

The statistical analysis was performed using the SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA). Two-year and five-year overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS) were calculated using the Kaplan-Meier survival method (log-rank, Breslow and Tarone-Ware tests). OS was calculated as the time from the treatment to the last follow-up or death, DFS as the time from the treatment to the recurrence of carcinoma, either locoregional or as a metastasis, and DSS as the time from treatment to death due to oral or oropharyngeal SCC. A univariate analysis using the Pearson's chi-square test was made for OS, DFS and DSS. For the data with expected cell frequencies ≤ 5, the Fisher's exact test was performed. Medians were compared with the median test. Level of significance was defined as $p < 0.05$ and all statistical tests that were used in the calculations were two-sided.

## Results

From January 2002 to December 2013, 133 patients who were treated for oral or oropharyngeal cancer at the Clinical Hospital Centre Osijek met the inclusion criteria, of whom 122 (91.7%) were male and 11 (8.3%) were female. The mean age was 57.8 ± 8.6 years. The data regarding localisation, stage and treatment of the tumours is shown in Table 1 and Figure 2..

**Table 1. Demographical data regarding the study population**

| | | n | % |
|---|---|---|---|
| **Tumour site** | Oral | 89 | 66.9 |
| | Oropharyngeal | 44 | 33.1 |
| **Localisation** | Tongue | 45 | 33.8 |
| | Sublingual | 25 | 18.8 |
| | Tonsils | 20 | 15.0 |
| | Tongue base | 18 | 13.5 |
| | Mandibular gingiva | 5 | 3.8 |
| | Uvula | 7 | 5.3 |
| | Retromolar | 8 | 6.0 |
| | Oropharyngeal wall | 5 | 3.8 |
| **T** | T1 | 8 | 6.0 |
| | T2 | 49 | 36.8 |
| | T3 | 42 | 31.6 |
| | T4 | 34 | 25.6 |
| **N** | N0 | 54 | 40.6 |
| | N1 | 40 | 30.1 |
| | N2a | 10 | 7.5 |
| | N2b, N2c | 25 | 18.8 |
| | N3 | 4 | 3.0 |
| **Neck dissection** | Selective | 38 | 28.6 |
| | Radical | 95 | 71.4 |
| **Chemoradiotherapy** | Postoperative | 118 | 88.7 |
| | Preoperative | 5 | 3.8 |
| | No treatment | 10 | 7.5 |

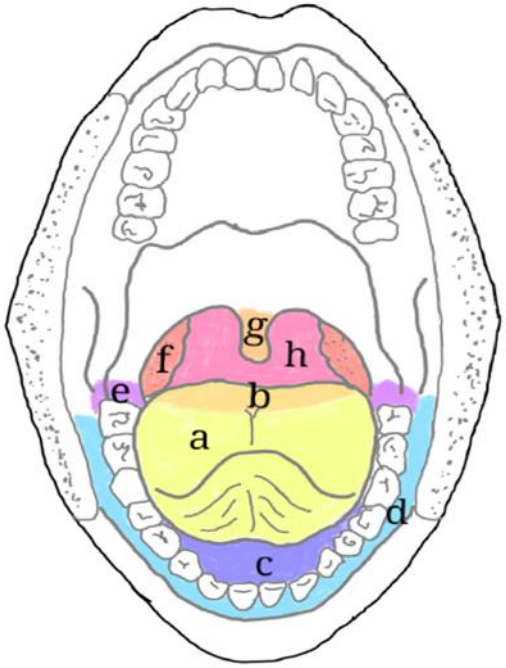


**Figure 2. Localisation of the primary tumour. a) tongue b) tongue base c) mouth floor d) mandibular gingiva e) retromolar f) tonsils g) uvula h) oropharyngeal wall**

*Neck dissection and nodal yield*

From 133 patients, 16 had a bilateral neck dissection, yielding a total of 149 dissections in this study. Median nodal yield for the entire study population was 25, with the lowest nodal yield being 4 and the highest being 75. Thirty-eight patients underwent a selective neck dissection, while 95 had a radical neck dissection. Median nodal yield was 25 for radical and 29 for selective neck dissection. There were 54 patients with the cN0 stage and 79 patients with cN+ neck specimens. In the cN0 group, the median nodal yield was 22 lymph nodes, and in the cN+ group, the median NY was 28 lymph nodes, which could have been a result of more sparing neck dissections being performed on patients with the clinically negative neck. We also analysed the patients according to the pathohistological N status. There were 32 patients whose cN and pN status did not match. Forty-six patients had the pN status with a median NY of 29, while 87 patients had the pN+ status with a median NY of 24. Nodal yield for each group can be found in Table 2..

**Table 2. Nodal yield in each group or dissection level**

| Group (n) | Median NY |
|---|---|
| **Overall (133)** | 25 |
| **Selective neck dissection (38)** | 29 |
| **Radical neck dissection (95)** | 25 |
| **cN0 (54)** | 22 |
| **cN+ (79)** | 28 |
| **pN0 (46)** | 29 |
| **pN+ (87)** | 24 |
| **Specimens en bloc (54)** | 16 |
| **Specimens separated by level (79)** | 33 |
| **Level I-II (79)** | 14 |
| **Level III-IV (79)** | 9 |
| **Level V (57)** | 8 |

*Nodal yield and separation of neck specimens by levels*

In 79 patients, the neck specimen was separated by levels at the time of surgery by two experienced surgeons. In this group, the median nodal yield was 33, while the group with en bloc resections had a median nodal yield of 16. The difference was statistically significant ($p < 0.001$, median test). See Table 2.

*Survival analysis*

Median survival for the entire group of patients was 33 (17-67) months after the surgery. In the first two years after the surgery, overall survival rate was 61.1% for patients with a NY below the median and 63.8% for patients above the median ($p = 0.298$; log-rank test). Disease-specific survival (the Kaplan-Meier curve in Figure 3) showed similar results ($p = 0,103$; log-rank test).

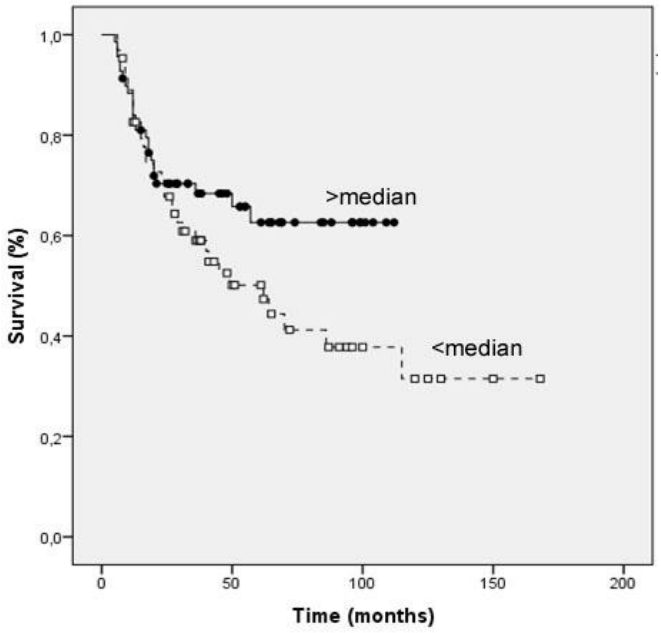


**Figure 3. Kaplan-Meier curves of disease-specific survival in the entire study population (N = 133); 2-year survival for NY > median group (n = 69) was 70.3%, and for NY < median group (n = 64) 67.7% (p = 0.103 log-rank test, p = 0.334 Breslow test, p = 0.206 Tarone-Ware test)**

For the purposes of survival analysis, we dichotomised all groups according to the nodal yield above and below the median and above and below 18 lymph nodes. There was no difference in survival below and above the cutoff point of 18 lymph nodes in either selective or radical neck dissection.

In the group of selective neck dissections (N = 38), the patients with a NY above the median had a statistically better disease-specific survival as opposed to those with a NY below the median (5-year DSS < median NY 70.6%, > median NY 95.2%, p = 0.037 log-rank test), as seen in Figure 4.

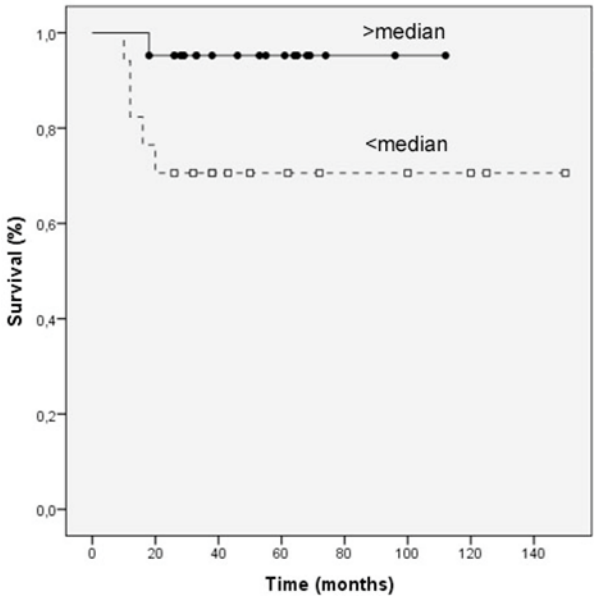


**Figure 4. Kaplan-Meier curves of disease specific survival for selective neck dissections; 2-year survival for NY > median group (n = 21) was 95.2%, and for NY < median group (n = 17) 70.6% (p = 0.037, log-rank test, p = 0.035 Breslow test, p = 0.036 Tarone-Ware test)**

However, in the group of radical neck dissections (N = 95), the Kaplan-Meier estimates did not confirm a statistical significance of nodal yield as an independent predictor of survival (5-year DSS < median NY 66.6%, > median NY 69.3%, p = 0.459).

We found no statistical difference of survival of patients with a higher and lower NY by dividing the patients into the cN- and cN+ group in any survival study, but a statistical significance was found when we analysed the pN- group. In patients with pathohistologically negative neck specimens, DSS was statistically higher in those patients whose NY was above the median (5-year DSS < median NY 38.4%, > median NY 67.4%, p = 0.045), while DFS was leaning towards a statistical significance (p = 0.057).

*NY by neck level and survival*

Median nodal yield was 14 lymph nodes in the upper neck (levels I and II) and 9 lymph nodes in the lower neck (levels III and IV). Level V, present only in radical dissections, yielded an average of 8 lymph nodes. We reviewed the upper neck NY separately for cN-, cN+, pN- and pN+ groups, selective dissection, radical dissection and the entire group, but no statistical correlation between survival and NY was found, only a tendency (p = 0.072) for a slightly better disease-specific survival of those with a NY above the median in the cN- group.

However, NY had interesting properties pertaining to the lower neck. In the group of selective dissections (n = 22), a NY above the median was related with a better OS (p = 0.05), DSS (p = 0.022), and DFS (p = 0.05). With regard to the radical neck dissection group (n = 57), findings were quite different. Interestingly, we found worse outcomes in patients with a NY above the median as compared to a NY below the median (OS p = 0.009, DSS p = 0.014, DFS p = 0.007). Kaplan-Meier plots can be seen in Figure 5.

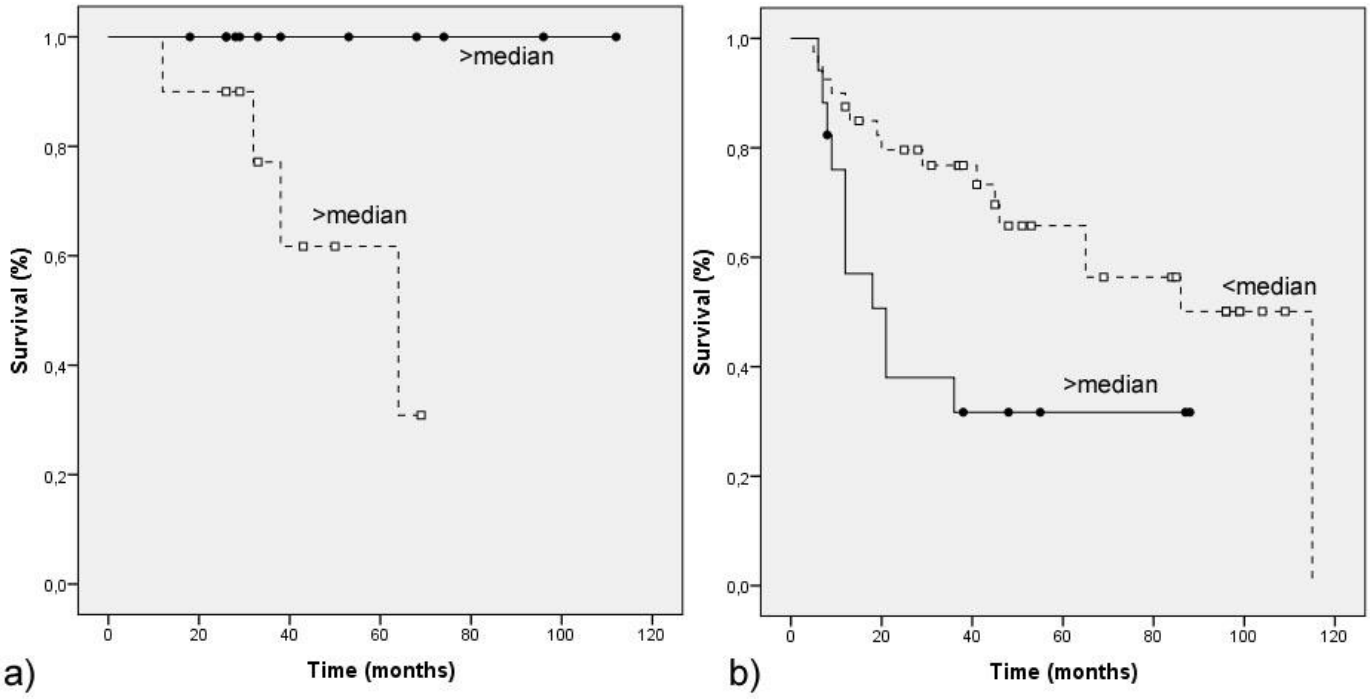


**Figure 5. Kaplan-Meier curves of disease-specific survival for NY in lower neck region (3 and 4) in a) selective neck dissections; 2-year survival for > median group (n = 12) was 100%, and for the < median group (n = 10) 30.9% (p = 0.022 log-rank test, p = 0.044 Breslow test, p = 0.029 Tarone-Ware test), and b) radical neck dissections; 2-year survival for > median group (n = 17) 38.0% and for < median group (n = 40) 56.8% (p = 0.014, log-rank test, p = 0.006 Breslow test, p = 0.007 Tarone-Ware test)**

With regard to level V, the results varied, with the lowest nodal yield being 0 and the highest being 27, which was not statistically significant for survival in any group of patients.

## Discussion

Even though the gold standard treatment for oral and oropharyngeal carcinoma includes a resection of the primary tumour followed by a neck dissection, the consensus pertaining to the width of the neck dissection has not been reached since its introduction in 1906. Squamous cell carcinoma usually metastasises in the upper neck levels (I, II, III), so the procedures have been shifting to a more sparing and selective neck dissection in order to preserve the function and cause minimal impairment to the patient. Since the introduction of adjuvant chemo- or chemoradiotherapy, surgical treatment options have become even more selective. However, neck dissection is not only vital for treatment, but also for correct staging. Consequently, an over-selective neck dissection could lead to understaging and loco-regional recurrence due to missed lymph nodes in the lower levels or due to micrometastases. The problem of the occult neck disease has been widely studied by Woolgar and Cho et al., who claim that comprehensive neck dissection is an important factor for finding micrometastases in lymph nodes of the neck that cannot be discovered by a routine pathohistological analysis[4,10]. This raises the issue of re-evaluating the margins of a well-performed neck dissection and determining how many levels are enough to ensure the best survival, the least regional recurrence rate and minimal impairment.

Recently, nodal yield has been proposed as a supplement to the standardised TNM classification, as well as a means of quantification of a performed dissection. Even though neck dissection is a standardised procedure, nodal yield in each neck dissection varies dramatically. This could be caused by its

dependence on the three following criteria: width of the dissection, the level of pathologists' scrutiny and individual differences in lymphatic tissue. Patel et al. reported a nodal yield of 2-104 (a mean of 39 ± 23) nodes[11], Ali et al. 7-140 (a mean of 42) nodes[12] and Ebrahimi reported a mean NY of 25.59, 276 and 305 in different studies. The median NY of 25 found in this study does not vary significantly compared to other studies. Nodal yield depends even on the type of surgical technique. Thus, Lörincz et al. [13] proved that a standardised horizontal dissection of the cervical fascia yields more lymph nodes than a caudal-to-cranial dissection. It is noteworthy to add that all our neck dissections have been performed in a standardised horizontal manner and included level I, both for oral and oropharyngeal cancer.

Several studies have tried to analyse NY and its impact on survival, but the results have so far been indecisive. Ebrahimi et al. [9] showed that a nodal yield above 18 is an independent prognostic factor for patients undergoing a selective neck dissection for cN0 oral squamous cell carcinoma. As this study population included patients undergoing both a radical and a selective neck dissection, in all N stages of the disease, we divided the patients into multiple groups in order to homogenise the sample. We found no statistically significant difference in survival of any group of patients with a cut-off point of 18, which could be explained by a higher T and N status at the beginning of the treatment, but also as an inter-institutional difference of overall NY between studies. Lemieux studied cN- patients, divided NY into quartiles and found an improved outcome in two higher quartiles (NY > 22)14. Our study used the median of each group as a cut-off point and showed similar results as Lemieux et al.[14] in the pN- group with a NY above the median having a better disease specific survival as compared to those with a NY below the median. These findings could support the theory that a higher NY increases the likelihood of finding neck metastases and allows for adequate clearance of occult metastases.

Nodal yield is also dependent on the manner of presenting the specimen to the pathologist. In a traditional radical neck dissection, en bloc specimen with non-lymphatic tissue such as the sternocleidomastoid muscle and jugular vein would be presented to the pathologist who was charged with dissecting the specimen by level and analysing it. This procedure was quite imprecise as the tissue of the sample is prone to shrinkage and the identification of level borders was often inaccurate, but this practice became even more imprecise with the introduction of selective neck dissections[15,16]. In selective neck dissection, samples did not have any anatomical structure that could be used for orientation. A correct analysis of each level is an important factor that provides information about the course of future treatment[17]. Dividing specimens by levels at the time of surgery is, therefore, the key to better and accurate staging; it reduces the manipulation of the tumour and tumour spillage. Smaller, more manageable samples could allow the pathologist to find and analyse more lymph nodes and to detect micrometastases if they are present[15,16]. This was confirmed by our data, with a much lower median NY of 19 in en bloc specimens, as compared with a median NY of 35 in specimens divided by levels. However, not all studies have come to the same conclusion; Kerawala[17] et al. found no significant difference between en bloc and divided specimens, while Marres et al.[18] noticed an increase in NY when specimens were examined by a pathological technician as compared to an examination by a pathologist.

To the best of our knowledge, no one has studied the importance of nodal yield in relation with survival on each level. Kerawala et al. [17] reported a median NY in each level as follows: I-3, II-9, III-7, IV-5 and V-9, while Norling et al.[19] studied nodal yield in cadavers as compared to other reports from literature. Both studies showed a notoriously wide range of nodal yield in each level (varying from 0 up to > 20). Our data, therefore, does not vary greatly from other reports. As described in the Materials and methods section, we presented nodal yield separately for the upper neck (levels I and II) and the lower neck (levels III and IV). The data regarding nodal yield in the lower neck levels was particularly perplexing, especially regarding radical neck dissections having a lower NY than

selective neck dissections. This difference might be caused by an imprecise separation, which led to lymph nodes from levels III and IV to end in level V specimens. It remains unclear why radical neck dissection overall had a slightly lower NY than selective dissection, but this could be due to differences in the number of samples (94 radical neck dissections as compared to 38 selective neck dissections).

Skip metastases, or metastases present only in the lower neck levels without involvement of levels I and II, remain a controversial topic and one of the arguments for a radical surgical treatment. While Feng et al.[20] report a rate of 1.1% for skip metastasis in level III and 3.2% in level IV, they concluded that supraomohyoid dissection does provide adequate care for patients with oral SCC. Khafif et al.[21] also argued that dissection of level IV is necessary only when there is intraoperative suspicion of metastatic involvement in levels II and III. Dias et al.[22] reported only 2% of skip metastasis, but 24.1% of occult neck metastases. It is, therefore, very important to correctly weigh the need to perform a selective or radical neck dissection. In this study, nodal yield in the upper neck showed no statistical significance pertaining to survival. This could be caused by easy surgical access and relatively uniform clearance of this level. A high nodal yield in the lower neck, however, proved to be an important predictor of outcome for node-negative and node-positive neck specimens treated by selective neck dissections. These findings are in consistence with other studies in which the positivity of the lower neck regions was found to be a predictor of a worse outcome[23] and could mean that by dissecting level IV, skip metastases, as well as occult metastases, have been cleared. The group of patients undergoing radical neck dissections showed quite an opposite result, where patients with a higher NY had a statistically worse outcome. Patients undergoing a radical neck dissection belonged to a group of a higher T and N stage. Therefore, it is logical that higher NY dissections would reveal more positive lymph nodes, which negatively affects the outcome. It is rather difficult to compare selective and radical neck dissections because of various other factors that affect a patient's prognosis, such as a more advanced disease, higher risk of perioperative complications and locoregional or distant failure, which are not directly linked with nodal yield. It is also important to evaluate the role of all healthcare providers who participated in the treatment of our patients, such as pathologists, whose impact on NY could not be assessed in detail in this study. However, the number of patients in whom neck specimens were divided into levels and who could partake in the statistical analysis was too small to make any definitive conclusions, but the conclusions that could be made raise some interesting questions and deserve further investigations in a larger cohort study.

## Conclusion

Our data showed improved outcomes of well-treated, high NY patients as compared with those with a lower NY. This could indicate the need to review the strategies of surgical approach to the neck metastasis, which has recently shifted towards a more selective approach. A better outcome in patients with a higher NY in the lower neck, even in the pN-group, could mean a higher probability of clearance of occult metastases, which have been linked to a worse outcome[10]. Even so, our data on the importance of NY in the lower neck must be treated with caution because of a small sample, but it could indicate a trend that should be studied in more detail in a larger study.

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