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The influence of nodal yield in neck dissections on lymph node ratio in head and neck cancer

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SUMMARY

Objectives: Recent studies suggest that lymph node ratio (LNR) is a strong prognostic factor in head and neck cancer. This study aims to determine if the yield of harvested lymph nodes (LNs) influences the LNR.
Methods: The study included 522 head and neck cancer patients, undergoing 638 primary and salvage (selective) neck dissections between 2002 and 2012. Before 2007 the neck dissection specimens were macroscopically and microscopically examined by pathologists and after 2007 the macroscopic examination was performed by pathology technicians. For comparison of mean LN yields, univariate and multivariate analyses were performed.
Results: The mean number of LNs among 374 specimens examined by pathologists was 24 (range 0–89) vs. 32 (range 2–89) among 264 specimens examined by pathology technicians ($P < .001$). This caused the mean LNR in the non pre-treated patient group to drop from 11.4% to 8.7%. The counts of LNs per type of neck dissection were significantly different and increased with the number of levels involved. However, there was no linear relationship and the higher yields could be mostly ascribed to LNs in level V. The LNR varied from 8.1% to 18.4% among the different types of neck dissections.
Conclusions: A significant increase in the number of harvested LNs, but a decrease in LNR was observed after introducing pathology technicians for macroscopic examination. A clear association between the extent of the dissection and the number of harvested LNs was observed. LNR appears to be strongly dependent on the harvesting protocol and the extent of the dissection.

Introduction

Head and neck cancer tends to metastasize to cervical lymph nodes (LNs) and the presence of lymph node metastases is an important prognostic indicator [1]. The probability of distant metastases is dependent on the extent of lymph node disease in the neck and determines overall survival. Although the TNM classification – where N status is based on the diameter, bilateral occurrence and number of positive nodes – has developed into an important instrument for determining the prognostic impact, other 'lymph node associated factors', such as the exact number of positive nodes, the total number of harvested nodes and the presence of extra-capsular growth [2,3] also play an important role and are not included in the current TNM classification.

The lymph node ratio (LNR), a possible alternative for prognostication, represents the fraction of metastatic nodes among all harvested nodes. This ratio determines the extent of cancer spread and extent of clearance. In stomach-, bladder- and esophageal cancer, the LNR has been proven to be a reliable prognostic factor and has been used as an indicator for adjuvant treatment [4–6]. Evidence has emerged showing that the LNR also seems to be a strong prognostic factor in head and neck cancer, outweighing the TNM classification in multivariate analysis [7–12]. Nevertheless, before introducing the LNR as a reliable prognostic index, standardization of harvesting the LNs from the neck dissection specimen and accurate classification of the extent of neck dissection is of utmost importance. In the literature on this subject, uniformity of analysis is lacking.

In order to lower the workload of pathologists in our institution, pathology technicians were introduced for taking over certain routine activities, including harvesting LNs. Since October 2007 pathology technicians asses neck dissection specimens in accordance with a standardized protocol.

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The aim of this study is to determine if the yield of harvested lymph nodes (LNs) influences the lymph node ratio, by determining the nodal yield after introducing pathology technicians for examining the specimen and by investigating the influence of the extensiveness of the neck dissection on nodal yield.

Material and methods

Patients

All patients who underwent primary and salvage (modified) radical neck dissections [(M)RND] and selective neck dissections (SND) for primary tumors of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and lip, between 2002 and 2012 in our institute, were selected. We excluded patients who received a super selective neck dissection (SSND) (two levels or less, or three levels separately) or those with a previous ipsilateral neck dissection. In total, 638 (selective) neck dissections were performed in 522 patients, of which 104 bilateral procedures, as well as fourteen patients who underwent a subsequent operation at the contralateral side were considered as separate cases. Patients, who underwent previous (chemo) radiation targeted at the neck, were excluded from calculating the LNR analyses.

(Selective) neck dissection specimen processing

All neck dissections, either SND or (M)RND were performed in a standardized manner by experienced Head and Neck Surgeons. Operation specimens were fixated in neutral buffered formaldehyde. From 2002 to 2007, neck dissection specimens were both macroscopically and microscopically examined by a pathologist and from 2007 to 2012 the macroscopic examination was done by a pathology technician. Over the whole period three technicians did the macroscopic lymph node counting according to a strict protocol (see below). Microscopic examination was still done by a pathologist. The macroscopic examination was done in accordance with a standardized protocol, based on the international level classification of the neck [13]. The protocol started with orientation of the specimen based on beads, indicating the separate neck node levels, applied by the surgeon, and the identification of the sternocleidomastoid muscle, salivary glands and the internal jugular vein. Subsequently, a macro photo was made and the levels were designated in the photograph; submandicular–submental (I), high jugular (II), mid jugular (III) low jugular (IV) posterior triangle V and sometimes the anterior triangle/paratracheal (VI). Thereafter, the specimens were accurately manually palpated for LNs and all identified LNs were counted, embedded in paraffin and stained with hematoxolin–eosin.

Statistical analysis

Univariate analysis was based on Mann–Whitney *U*-tests, Kruskal–Wallis tests and Jonckheere–Terpstra tests. Multivariate analysis was based on linear regression.

A *p*-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 20.0 software (SPSS Inc, Chicago, IL).

As stated in the previous section, 118 of the 522 patients (23%) contributed two neck dissections, which could have introduced dependence among our observations. However, we believe that for the outcomes studied here, i.e. the number of LNs and the LNR, little or no correlation remains among neck dissections from the same patient, given the factors included in the multivariate linear regression. We therefore did not perform clustered analysis.

Results

Patient demographics

The study population of 522 head and neck squamous cell carcinoma patients consisted of 449 men and 189 women with a mean age of 62 (range 28–89). Relevant patient demographics are summarized in Table 1.

Neck dissections

The type of neck dissection included 337 (53%) (modified) radical neck dissection (M)RND (level I to V), 119 (19%) selective neck dissection (SND) including level I to III, 65 (10%) SND level II to V, 103 (16%) SND level II to IV and 14 (2%) SND level I to IV. Sixty-four percent of patients received no treatment before surgery. Twelve percent received chemoradiotherapy prior to surgery and 24% radiotherapy.

Table 2 shows the mean number of LNs found, before and after October 2007, by type of neck dissection. Overall, the (M)RND (level I–V) produced the largest number of LNs (range: 1–89; mean 34), followed by SND level II–V (range:2–60; mean 23), SND level I–III and SND II–IV, (respectively range: 3–52; mean 18 and range: 2–47; mean 17). We included both salvage patients as well as non treated patients. In the group of previously untreated patients there were 17 specimens containing <10 lymph nodes. Fifteen of those specimens were processed before 2007, i.e. according to the old protocol. The remaining specimens (both SND) were processed after 2007, yielding 4 and 7 lymph nodes. [Fig. 1] The mean number of LNs differed significantly by type of dissection. ($P < .001$). Node counts increased significantly by number of neck levels involved. ($P < .001$).

A clear dichotomy could be discriminated between the number of lymph nodes harvested from specimens before 2007 and thereafter (Table 2). The 374 (M) RND and SND specimens before 2007 had a mean of 24 and a median of 20 LNs (range 0–89). The 243 (M) RND and SND specimens after October 2007 had a mean of 32 and a median of 29 LNs (range 2–89) ($P < .001$). Between the SND I–III and SND II–IV no differences were found in lymph node counts after introducing pathology technicians (2002–2007 vs. 2007–2012). However, in specimens of (modified) RND, as well as the SND II–V significantly more lymph nodes were found after October 2007, respectively 29 vs. 41 and 20 vs. 29 ($P < .001$), indicating that this difference was determined by the extra number of nodes found in level V (Fig. 2).

The LNR is calculated as the ratio of positive lymph nodes to the total number of lymph nodes removed (Table 2) multiplied by 100. The LNR dropped from a mean of 11.4% to a mean of 8.7% after introducing pathology technicians ($p = .016$) (Table 3).

Radiotherapy or chemoradiotherapy

In the salvage (selective) neck dissections, both preoperative radiotherapy (RT) and chemoradiotherapy (CRT) had a significant influence on the number of harvested LNs compared to the untreated neck dissections (Table 4). In total, 76 neck dissection specimens, from patients who underwent preoperative CRT had a mean of 18 LNs (range 2–83). 146 specimens from patients who received only RT had a mean of 20 LNs (range1–78). The 413 neck dissections from patients receiving no treatment had a mean of 31 LNs (range 4–89). The differences between pre-treated and untreated neck dissection specimens were statistically significant ($P < .001$).

Multivariate analysis

In the multivariate analysis we included all above-mentioned variables; before or after 2007, type of neck dissection and