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de Ridder, M.

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CHAPTER 5

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

C.C.M. Marres
M. de Ridder
I. Hegger
M.L.F. van Velthuysen
M. Hauptmann
A. Navran
A.J.M. Balm

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ABSTRACT

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. 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.

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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.

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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 largestnumberof LNs (range: 1–89;mean34), 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).

Table 1 Patient demographics.

Variables	Before Oct' 07 N (%)*	After Oct '07 N (%)*	Total N (%)*	P Value
Age				
Average (SD)	61.16	62.60	61.75	0.073**
Range	35–88	28–89	28–89	
Sex				
Female	99 (26.5)	92 (34.8)	191 (29.9)	.028***
Male	275 (73.5)	172 (65.2)	447 (70.1)	
Site of carcinoma				
Lip	7 (1.9)	9 (3.4)	16 (2.5)	.011***
Oral cavity	137 (36.5)	130 (49.4)	267 (41.8)	
Oropharynx	87 (23.2)	47 (17.9)	134 (21.0)	
Nasopharynx	5 (1.3)	1 (0.4)	6 (0.9)	
Hypopharynx	40 (10.7)	19 (7.2)	59 (9.2)	
Larynx	98 (26.1)	58 (22.0)	156 (24.4)	
Type of neck dissection				
Level I-V	197 (52.7)	140 (53.0)	337 (52.8)	.112***
Level II-V	41 (11.0)	24 (9.1)	65 (10.2)	
Level I-IV	5 (1.3)	9 (3.4)	14 (2.2)	
Level I-III	63 (16.8)	56 (21.2)	119 (18.7)	
Level II-IV	68 (18.2)	35 (13.3)	103 (16.1)	
Preoperative treatment				
No treatment	245 (65.5)	168 (63.6)	413 (64.7)	.778***
Chemoradiotherapy	46 (12.3)	31 (11.7)	77 (12.1)	
Radiotherapy	83 (22.2)	65 (24.6)	148 (23.2)	
Total	374 (100)	264 (100)	638 (100)	

* Unless otherwise stated in the first column.
** Mann–Whitney U-test.
*** Exact Chi-square test.

Table 2. Total and positive number of LNs by type of neck dissection before and after October ‘07.

	Before Oct ’07*		After Oct ’07*		Total		p Value (Mann–Whitney)	
	LN Mean (SD)	Positive LNs (SD)**	LN Mean (SD)	Positive LNs (SD)**	LN Mean (SD)	Positive LNs (SD)**	LN Mean (SD)	Positive LNs (SD)**
Level I–V	29 (15.8)	2.7 (5.1)	41 (16.4)	2.8 (6.3)	34 (17.1)	2.8 (5.6)	<.001	<0.701
Level II–V	21 (12.1)	2.6 (2.9)	29 (15.3)	1.3 (1.9)	24 (14.0)	2.3 (2.7)	.027	<0.467
Level I–IV	22 (12.2)	1.0 (1.7)	27 (9.7)	1.0 (.8)	25 (10.4)	1.0 (1.1)	.257	<0.720
Level I–III	17 (8.9)	.38 (.9)	19 (9.6)	.81 (1.8)	18 (9.3)	.6(1.4)	.173	<0.085
Level II–IV	17 (9.4)	.57 (0.9)	17 (11.4)	1.0 (1.3)	17 (10.1)	.7 (1.0)	.738	<0.313
Total	24 (14.5)	1.9 (4.1)	32 (17.7)	2.1 (6.1)	27 (16.4)	2.0 (4.5)	<.001	<0.519

All LN means are completed on whole LNs.
* Before October 2007, nodal yield was determined by a pathologist compared with a pathology technician thereafter.
** All salvage patients were excluded in calculating the mean number of positive LNs.

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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).

Table 3. Lymph node ratio according to type of neck dissection before and after October ‘07.

	LNR (SD)			P Value (Mann–Whitney)
	Before Oct ’07	After Oct ’07	Total	
Level I–V	10.8 (14.6)	8.8 (13.3)	10.0 (14.1)	.075
Level II–V	21.3 (16.0)	5.5 (5.3)	18.4 (15.1)	.076
Level I–IV	21.4*	5.8 (2.9)	8.4 (6.9)	.143
Level I–III	10.7 (6.1)	10.1 (10.3)	10.3 (8.6)	.174
Level II–IV	8.7 (4.8)	6.7 (1.8)	8.1 (4.3)	.792
Total	11.3 (15.6)	8.7 (11.8)	10.2 (13.2)	.015

All salvage patients were excluded in calculating the lymph node ratio.
* With exclusion of salvage patients this group consisted of only one patient.

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 preoperative treatment. The variables age and sex, which might influence the LN yield, were also added. In multivariate linear regression none of the patient characteristics influenced the lymph node counting, whereas all the above mentioned factors showed a significant relationship with the number of LNs (P < .003, Table 5).

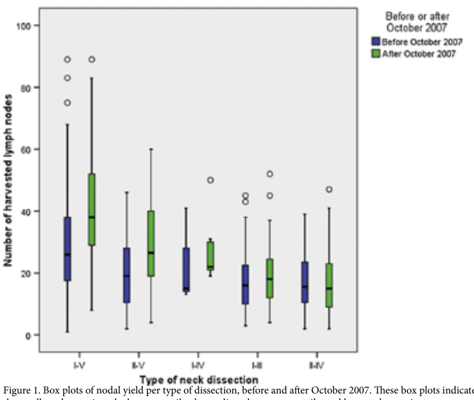

Figure 1. Box plots of nodal yield per type of dissection, before and after October 2007. These box plots indicate the smallest observation, the lower quartile, the median, the upper quartile, and largest observation.

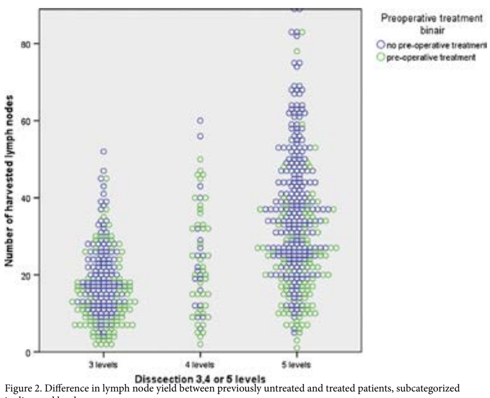

Figure 2. Difference in lymph node yield between previously untreated and treated patients, subcategorized in dissected levels.

Table 4. Nodal yield according to preoperative treatment.		
	LN mean (SD)	P Value
No treatment	31 (16.6)	<.001 (Mann–Whitney)
Radiotherapy	20 (13.5)	
Only radiotherapy	21 (14.0)	.099 (Kruskal–Wallis)
Chemoradiotherapy	18 (12.4)	
All LN means are completed on whole LNs.		

Table 5. Multivariate linear regression of LN.			
Variable	Coefficient B	95% CI	P value
Constant	39.1	32.8 to 45.5	
Sex, man vs. woman	-9.4	-1.9 to 2.7	.743
Age at diagnosis (per year)	-0.1	-.2 to .0	.060
After vs. before October 2007	8.5	6.1 to 10.3	<.001
Preoperative treatment vs. no treatment			
Chemoradiotherapy	-12.0	-15.3 to -8.7	<.001
Radiotherapy	-9.4	-12.1 to -6.8	<.001
Neck dissection vs. I–V			
II–V	-5.6	-9.4 to -1.9	.003
I–IV	-10.8	-17.9 to -3.7	.003
I–III	-17.2	-20.0 to -14.5	<.001
II–IV	-13.4	-16.4 to -10.4	<.001

DISCUSSION

This is the first report comparing LN harvesting from neck dissection specimens by pathologists and pathology technicians. Our study showed a significant increase of LN harvesting after the introduction of the pathology technician with the use of a standard protocol. In colorectal resection specimens it has already been demonstrated that the introduction of the pathology technician results in a significantly improved retrieval of LNs[14]. Kuijpers et al

showed that a pathology technician recovers more and, in particular, smaller LNs from colorectal resection specimens than the pathologist; 83% of the pathology technicians vs. 61% of the pathologists sampled more than 10 LNs per specimen.

This is most probably caused by the increased amount of time they can spend on harvesting lymph nodes, due to the nature of their job. In that study, after the introduction of pathology technicians for harvesting lymph nodes in colon specimens, the number of patients eligible for adjuvant chemotherapy reduced from 17% to 1% and diminished thereby the costs and morbidity. However, increased nodal yield will not only subject the LNR to shifting, it will also lower the risk of missing micro-metastases[15]. Ebrahimi et al[9] even suggest that nodal yield may be a surrogate quality control measure, with more thorough pathological analysis of the specimen leading to higher nodal yields and reducing the likelihood of under staging. Regarding the utility of the LNR in head and neck carcinomas, previous studies on LNR describe cutoff values for therapeutic decision making. These values vary between 2.5% and 20.0% (median:
6%) among the different studies[7–12]. In our study the LNR dropped from a mean of 11.4% to a mean of 8.7% after introducing pathology technicians (p = .016) (Table 3). It is obvious that such a change might have consequences for patients in determining the necessity of adjuvant treatment.

In contrast to other studies on LNR[7–9,11,12], we made a clear distinction between the extensiveness of neck dissections. As opposed to Friedman et al[16], we found a clear correlation between the number of harvested LNs and the extent of the dissection. Surprisingly, in SND I–III and II–IV there is no significant difference in LNs count before and after introducing pathology technicians, as opposed to the (M)RND and SND II–V, indicating that this difference was determined by the number of nodes harvested from level V. This could imply that level V entails a larger amount and more difficult to identify LNs compared to LNs in other levels. From our analysis it became apparent that the number of levels involved in the neck dissection and number of LNs are not directly linearly related. Recent studies show a very low prevalence of metastasis in level V[17,18]; nonetheless lymph node counts in level V significantly influence the LNR, with LNR ranging from 8.1% to 18.4% in the different type of neck dissections. It should therefore be emphasized that cutoff points for LNR are inextricably linked to the extensiveness of the neck dissection, demonstrated by the different mean LNR per type of dissection (Table 3). The prognostic impact of LNR could perhaps be more substantial if the type of neck dissection was taken into account [8,9,11,12].
The higher number of primary neck dissections before 2007 in our series may be due to the introduction of organ preserving chemo-irradation, which led to an increase of salvage super selective neck dissections[19]. All recent studies on LNR exclude patients treated with radiotherapy prior to surgery.

The known literature regarding preoperative RT or CRT and cervical LNs counts is conflicting with regards to the decrease of lymph node number in the specimen[20,21] as found by us (mean 31 vs. 20). This effect was even more pronounced in the group which received concurrent CRT (mean 18). In a small amount of cases it remains unclear if the radiation field included all the dissected levels, or if the radiation field was limited to fewer neck node levels, but even after we excluded these cases the outcome remained similar in both univariate and multivariate analyses. The negative influence of radiotherapy has also been described in patients who have been treated for rectal cancer[22,23]. Whether we are dealing with an actual decrease in number of lymph nodes or with a more difficult detection of lymph nodes by radiotherapy induced fibrosis remains to be elucidated[24]. If the LNR could have prognostic impact in patients, undergoing salvage neck surgery after (C)RT should be further investigated.

CONCLUSIONS

The results of this study show a significant increase in the number of harvested LNs, but a decrease in LNR after introducing pathology technicians for examination of the neck dissection specimen. We also found a clear correlation between the number of harvested LNs and the extent of the dissection. Based on our findings, it appears that in order for the LNR to become a reliable index, a standardized protocol in harvesting LNs and different cutoff points of LNR per type of neck dissection should be applied.

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