Quality indicators in head and neck oncology

de Ridder, M.

Publication date
2017
Document Version
Other version
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CHAPTER 6

A critical evaluation of lymph node ratio in Head and Neck cancer

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M . de Ridder
C.C.M. Marres
L.E. Smeele
M.W.M. van den Brekel
M. Hauptmann
A.J.M. Balm
M.L.F. van Velthuysen

Virchows Archiv. 2016; 469: 635-641

ABSTRACT
In head and neck squamous cell carcinoma (HNSCC), the search for better prognostic factors beyond TNM-stage is ongoing. Lymph node ratio (LNR) (positive lymph nodes/total lymph nodes) is gaining interest in view of its potential prognostic significance.

All HNSCC patients at the Netherlands Cancer Institute undergoing neck dissection for lymph node metastases in the neck region between 2002 and 2012 (n = 176) were included. Based on a protocol change in specimen processing, the cohort was subdivided in two distinct consecutive periods (pre and post 2007). The prognostic value of LNR, N-stage, and number of positive lymph nodes for overall survival was assessed.

The mean number of examined lymph nodes after 2007 was significantly higher (42.3) than before (35.8) (p = 0.024). The higher number concerned mostly lymph nodes in level V. The mean number of positive lymph nodes before 2007 was 3.3 vs. 3.6 after 2007 (p = 0.745). By multivariate analysis of both pre- and post-2007 cohort data, two factors remained associated with an increased hazard of dying: N2 [HR 2.1 (1.1–4.1) and 2.4 (1.0–5.8)] and >3 positive lymph nodes [HR 2.0 (1.1–3.5) and 3.1 (1.4–6.9)]. Hazard ratio for LNR >7 % was not significantly different: pre 2007 at 2.2 (1.3–3.8) and post 2007 at 2.1 (1.0–4.8, p = 0.053).

In this study, changes in specimen processing influenced LNR values, but not the total number of tumor positive nodes found. Therefore, in HNSCC, the number of positive nodes seems a more reliable parameter than LNR, provided a minimum number of lymph nodes are examined.

Keywords Prognosis .Lymph nodemetastases . Lymph node ratio . Staging . Head and neck cancer

INTRODUCTION

Lymph node metastases are among the most important independent prognostic factors in head and neck carcinoma[3, 17, 21] and, as a consequence, N-stage has a significant influence on treatment choice. In addition, the number of metastatic lymph nodes, contra-lateral lymph node status, level (s) involved, and extracapsular extension (ECE) are independent prognostic parameters and contribute to further tailoring of treatment[3, 21]. However, the value of N-stage as prognostic indicator is under discussion, in particular for patients after postoperative radiotherapy [2, 22, 28]. Bernier et al compared the results of two trials (EORTC #22931 and RTOG #9501) which studied postoperative chemo-radiotherapy of locally advanced head and neck squamous cell carcinoma[2]. They found as a prognostic factor, for both loco-regional recurrence and survival, involvement of resection margins and ECE is more significant than N-stage. Others reported similar findings in patients who had undergone complete surgical excision and postoperative radiotherapy[7, 22, 28]. In a recent study, however, ECE lost its prognostic significance in patients who had undergone postoperative radiotherapy[10]. For malignancies other than head and neck cancer, the lymph node ratio (LNR), the proportion of lymph nodes with metastases relative to the total number of examined lymph nodes, has emerged as an important prognostic parameter in surgically treated patients[1, 11, 18, 19, 38]. In colorectal cancer, LNR is a significant prognostic factor for a 5-year overall survival (OS) and disease-specific survival (DSS)[1]. For gastric cancer, by multivariate analysis, LNR but not N-category emerged as an independent prognostic factor for overall survival[18]. Data on the prognostic influence of LNR in head and neck cancer predominantly focus on surgically treated oral cavity carcinomas (Table 1), and show poor prognosis in patients with higher LNR values[6, 8, 12–16, 23–25, 29–32, 34, 36, 37]. In a recent multi-institutional study on oral cavity carcinoma, reliability and applicability of the LNR were assessed in predicting outcome[23]. An LNR above 7 % was associated with a significantly increased risk of death from oral cancer [multivariate HR 1.62 ($p = 0.004$)]. In a multivariate model, TNM with LNR (TLNRM) stage was superior to TNM stage. However, LNR is a derivative of two variables which are both related to the lymph nodes "harvested" from surgical specimens. To investigate the effect of these two variables, we compared in two consecutive time frames, which differed in the method of processing of neck dissection specimens, the prognostic impact of LNR, traditional N-stage, and the number of positive lymph nodes found.

PATIENTS AND METHODS

Patients

Medical records of all 522 head and neck cancer patients, undergoing a (modified) radical [(M) RND] or selective neck dissection (SND) for squamous cell cancer of the larynx, hypopharynx, oropharynx, and oral cavity between 2002 and 2012, were retrieved. We did not include patients with a stage pN0 or pN3 (the latter often representing clusters of metastatic lymph nodes) and patients with a prior neck dissection or prior radiotherapy, as the number of lymph nodes in these specimens is influenced by previous treatment (s) or cannot be reliably counted[20]. In total, 176 patients were included in the study.

Specimen processing

All neck dissections were performed in the same institute by experienced head and neck surgeons. Levels of dissection were classified according to the guidelines of the American Head and Neck Society[26]. Between 2002 and 2007, pathologists performed macroscopic examination of the specimen.

From 2007 to 2012, pathology technicians processed the specimens according to a standard protocol, which included a more thorough examination of the neck dissection specimen and yielded a higher number of examined lymph nodes [20]. Cutoff value for high and low LNR was set at 7 %, based upon a large international series of >4000 patients[23].

Statistical analysis

Median overall survival (OS) was calculated using the Kaplan-Meier method. OS was defined as time between surgery and death.We evaluated the prognostic effect of T-stage, N-stage, ECE, LNR and number of positive nodes, sex, age, adjuvant therapy, and number of evaluated nodes. Univariate significant factors were retained in the final multivariate Cox regression model. Analyses were done separately for the time periods before and after 2007. Outcome analyses were done for individual patients. Categorical data were analyzed using chi-square test or Fisher's exact, normally distributed continuous data using t test. Trend tests were based on the p value of the coefficient for the continuous variable. Significance levels were set at <0.05. All analyses were done by PASW statistics 20.0 (SPSS Inc. Chicago).

Table 1. Literature overview: lymph node ratio as survival predictor in head and neck cancer							
Author	Year	Site	n	N+	Ntot	LNR cut off	OS / DSS
Shrime[14]	2009	Oral cavity	2955	3	26 (N1) 32 (N2)	0% - 6%, 6% - 12.5%, >12.5%	OS
Gil[18]	2009	Oral cavity	386	3	35	6%	OS/DSS
Suslu[23]	2010	Larynx, hypopharynx, oral cavity, oropharynx, skin	142	2	n.a.	4%	OS / DSS
Ebrahimi[17]	2010	Oral cavity	313	3	27	2.5% - 7.5%, 7.5% - 20%, >20%	OS / DSS
Kim[19]	2011	Oral cavity	211	2	25	6%	DSS
Liao[20]	2011	Oral cavity	148	I-III 3, I-V 5	I-III 40. I-V 57	4.8%	OS/DSS
Rudra[21]	2013	Oropharynx, Oral cavity, CUP, Larynx Hypo-pharynx	38	n.a.	n.a.	2%	OS/DFS
Künzel[26]	2013	Oropharynx	384	4	4	10%	DSS
Sayed[22]	2013	Oral cavity	1408	3	3	8.8%	OS / DSS
Patel[16]	2013	Oral cavity	4254	3	3	7%	OS/DSS
Wang[24]	2014	Hypopharynx	916	2	2	R0 – 0, R1 - <5%, R2 – 5-30%, R3 - >30%	CSS/OS
Künzel[25]	2014	Oral cavity	374	3	3	5% - 7%	DSS
Wang[29]	2014	Larynx	1963	2	2	R1 - <9%, R2 – 9-20%, R3 - >20%	OS
Prabhu[27]	2014	Larynx, oral cavity	350	n.a.	n.a.	20%	LRR
Reinisch[28]	2014	HNSCC	291	n.a.	n.a.	6%	OS, LRR
Künzel[30]	2015	Larynx	202	3	3	5%, 7%, 9%	DSS

Abbreviations: OS – overall survival, DSS – disease specific survival, DFS – disease free survival, LNR – lymph node ratio, CSS – cause specific survival, LRR – locoregionall recurrence. N+ – mean number of positive LN found, Ntot – mean total number of LN examined, n.a. – not available, HNSCC – head and neck squamous cell carcinoma, CUP – carcinoma of unknown primary

RESULTS

Patient characteristics (Table 2)

Of the 176 patients who met the inclusion criteria, 118 (67 %) were male and 58 (33 %) were female. Of the patients, 13 % had laryngeal, 3 % hypopharyngeal, 19 % oropharyngeal, and 64 % oral cavity cancer. Of the 33 oropharyngeal tumors, 17 (52 %) were HPV positive. The pre-2007 period contained 30 oropharynx carcinoma patients, of whom 15 were HPV positive. The majority of patients (135; 77 %) underwent a (Modified) Radical Neck Dissection [(M)RND] and 41 (33 %). a selective neck dissection. Details about the different types of neck dissection are listed in Table 3. The majority of patients (61 %) underwent postoperative radiotherapy and 21 % were treated with postoperative concurrent cisplatin-based chemo-radiotherapy. Less than half of the patients (40 %) suffered from recurrent disease. Of those, 20 % had a loco-regional recurrence without distant metastases and 20% had distant metastases (some in addition to locoregional recurrent disease). Patient characteristics did not significantly differ between the periods before and after October 2007, except for tumor site, as after 2007, there were significantly less oropharyngeal carcinomas (27 vs. 5 %, p = 0.004). Patient, tumor, and treatment characteristics were equally distributed between both groups.

Lymph node parameters

The mean number of examined lymph nodes was 38.1 (range 7–100; median 36). Mean LNR was 8 % (range 1—77 %; median 5 %) (Table 2). There was no difference in LNR between SND and (M) RND (p = 0.757). The mean number of examined lymph nodes in the period after the change in protocol was significantly higher (35.8 before and 42.3 after October 2007; p = 0,024) (Table 2). The increased number was notably on account of more lymph nodes in level V (Table 3). The mean number of detected lymph node metastases was not significantly different between the two periods (3.6 vs. 3.3 nodes; p = 0.745) (Table 2). Also, N-stage distribution was similar (p = 0.740).

Table 2. Demographic distribution

	Total		Pre 2007		Post 2007		p-value
	n	%	n	%	n	%	
Age							
<65	116	66	73	65	43	68	0.624
≥65	60	34	40	35	20	32	
Sex							
Male	118	67	79	70	39	62	0.279
Female	58	33	34	30	24	38	
Tumor site							
Larynx	24	14	17	15	7	11	0.004
Hypopharynx	6	3	5	4	1	2	
Oral cavity	113	64	61	54	52	83	
Oropharynx	33	19	30	27	3	5	
HPV+	17	52	15	50	2	67	
HPV-	11	33	10	33	1	33	
HPV doubtful	3	9	3	10	-	-	
HPV n.a.	2	6	2	7	-	-	
T-stage							
T1-2	90	51	58	51	32	51	0.867
T3-4	71	40	40	35	31	49	
Tx	15	9	15	13	-	-	
N-stage							
N1	64	36	37	33	27	43	0.740
N2a	12	7	11	10	1	2	
N2b	78	44	48	43	30	48	
N2c	22	13	17	15	5	8	
ECE							
Absent	90	51	49	43	41	65	0.554
Present	82	47	61	54	21	33	
Unknown	4	2	3	3	1	2	
Additional therapy							
None	24	14	8	7	16	25	0.070
Radiotherapy	108	61	75	66	33	52	
Concurrent chemo-radiation	37	21	25	22	12	19	
Other	7	4	5	4	2	3	
Type of dissection							
MRND	135	77	90	80	45	71	0.151
SND	41	24	23	20	18	29	
Level II-V	9	22	7	6	2	3	
Level I-IV	6	15	1	1	5	8	
Level I-III	14	34	6	5	8	13	
Level II-IV	12	29	9	8	3	5	
Vital status							
Alive	93	53	57	50	36	57	
Death	83	47	56	50	27	43	
LNR (Mean (range)	10.2 (1.2-90.9)		10.8 (1.5-90.9)		9.0 (1.2 -66.7)		0.382
Number of positive nodes (Mean (range)	3.5 (1-45)		3.6 (1-45)		3.3 (1-22)		0.745
Lymph node yield (Mean (range)	38.1 (7-100)		35.8 (9-100)		42.3 (7 -83)		0.024

Abbreviations: HPV – human papilloma virus, n.a. – not available - ECE –extracapsular extension, MRND – modified radical neck dissection, SND – selective neck dissection, LNR – lymph node ratio

Overall survival (Table 4)

Median overall survival of the cohort was 71 months (95%CI 45–97 months), in which 83 events occurred. There was no significant difference in overall survival between the two time periods (p = 0.270). Cox regression analysis of the period before October 2007 yielded as significant prognostic factors for overall survival LNR >7 % HR 2.2 (95 % CI 1.3–3.8), T3–4 HR 2.0 (95 % CI 1.1–3.6), N2 HR 2.1(95 % CI 1.1–4.1), and the number of positive lymph nodes >3 HR 2.0 (95 % CI 1.1–3.5). For the period after October 2007, these were N2 HR 2.4 (95 % CI 1.0–5.8), ECE HR 2.5 (95 % CI 1.1–5.3), and number of positive nodes >3 HR 3.1 (95 % CI 1.4–6.9). After exclusion of patients with HPV-positive oropharyngeal carcinoma, HRs were similar except for T-stage which was no longer significant. Adding individual lymph node parameters in a multivariate model did not change the outcome of the analysis. Since LNR and number of positive lymph nodes are continuous variables, a similar multivariate model introducing step-wise LNR and number of positive nodes as continuous variables was performed, indicating trend p values of positive lymph nodes and LNR as listed in Table 4.

Table 3. Number of examined and positive nodes by level and year

	Mean examined nodes		Mean positive nodes	
	Pre 2007	Post 2007	Pre 2007	Post 2007
MRND				
Level I-V	36.0	47.2	3.5	3.4
SND	34.1	51.5	5.0	2.5
Level II-V	14.0	25.6	3.0	1.4
Level I-III	34.0	24.8	3.5	4.3
Level II-IV	38.9	37.3	3.0	3.7
Total	35.8	42.3	3.6	3.3

Abbreviations: MRND: Modified radical neck dissection, SND: selective neck dissection

Table 4. Multivariate Cox regression analysis for overall survival

	Before October 2007				After October 2007			
	HPV + included		HPV + excluded		HPV + included		HPV + excluded	
	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value
T-classification								
T3–4 vs. T1-2	2.0 (1.1–3.6)	0.023	1.7 (0.9 – 3.2)	0.09	1.6 (0.8-3.5)	0.216	1.7 (0.8 – 3.6)	0.18
Extra capsular extension								
ECE + vs. ECE -	1.4 (0.8-2.4)	0.253	1.3 (0.7 – 2.4)	0.35	2.5 (1.1-5.3)	0.024	2.5 (1.1 – 5.3)	0.02
LNR								
>7% vs. < =7%	2.2 (1.3-3.8)	<0.001*	1.9 (1.1 – 3.2)	0.03	2.1 (1.0-4.8)	0.086*	2.0 (0.9 – 4.4)	0.07
Positive nodes								
>3 vs. <=3	2.0 (1.1-3.5)	<0.001*	1.6 (0.9 – 3.0)	0.12	3.1 (1.4-6.9)	0.037*	3.2 (1.5 – 7.1)	0.004
N-classification								
N2 vs. N1	2.1(1.1-4.1)	0.026	2.1 (1.1 – 4.1)	0.03	2.4 (1.0-5.8)	0.044	2.4 (1.0 – 5.6)	0.05

Abbreviations: HR: hazard ratio, LNR: lymph node ratio, ECE: extra capsular extension, HPV: human papilloma virus, CI: confidence interval

* Trend tests were based on the p-value of the coefficient for the continuous variable

DISCUSSION

LNR is a ratio, based upon the number of tumor-positive lymph nodes in a neck dissection specimen as numerator and the total number of lymph nodes as denominator. The potential advantage of LNR relative to the number of metastatic nodes only is that LNR takes into account both parameters. Studies on the prognostic value of LNR are part of an international search for accurate and objective staging methods. The prognostic value of LNR has been demonstrated in a variety of cancer types[1, 11, 18, 19, 38], including head and neck cancer (see Table 1)[6, 8, 12–16, 23–25, 29–32, 34, 36, 37]. Several authors[15, 23, 36] have suggested that LNR might be added to the current TNM staging. Based upon a series of more than 4000 oral cancer patients, Patel et al. reported that LNR is superior to the current N-stage[23] and suggested to include LNR as a rule in TNM staging.

In a recent paper, however, Roberts et al[27] questioned the role of LNR as a prognostic factor for HNSCC on a multivariate analysis of 12,437 patients. They did not confirm prognostic significance of LNR, whereas the prognostic value of pN and AJCC stage was confirmed. Gleisner et al[9] also questioned the value of the total number of examined lymph nodes in a SEER database study on a series of 154, 208 colorectal cancer patients and found that outcome for patients with the same LNR could be completely different. As an example, a patient with one metastasis in a single examined lymph node (LNR = 1) had a better prognosis than a patient with 12 metastases in 12 lymph nodes (LNR = 1). Examination of a single lymph node probably represented serious under-sampling. Their conclusion was that the number of positive lymph nodes is a better indicator of survival than the LNR. We have previously shown that the total number of examined nodes varies significantly between different methods of neck dissection specimen processing[20].

The present study documents that a more detailed protocol applied by pathology technicians resulted in a significantly higher number of harvested lymph nodes, while the lower mean LNR (from 10.8 to 9.0 %) and range (from 1.5–90.9 % to 1.2–66.7%) were not statistically significant. The latter may be due to the low number of cases collected since 2007. Many of the additional lymph nodes were found in level V, where lymph nodes as a rule are rather small. It is unlikely that the higher number of lymph nodes can be attributed to a change in surgical technique as this has not changed being performed by a stable group of surgeons in our institution. It is more likely that the difference in the number is due to the introduction of a stricter protocol executed by pathology technicians. The observation that the mean number of positive lymph nodes did not change significantly lends credibility to this assumption. Our data show that the prognostic value of three lymph node statusassociated prognostic factors, total number, number of nodes with metastases, and LNR, is influenced by variations in pathology
specimen processing.We document intra-institutional variation but contend that this can be extrapolated to interinstitutional variations in specimen processing. Why LNR does not emerge uniformly as valuable prognostic factor is clarified by the results of our study in that different lymph node procurement protocols result in different yield with an effect on LNR. The finding that prognostic significance of LNR was not different between the two time frames while that of the number of positive lymph nodes appeared stronger after 2007 merits some comments. A higher yield of lymph nodes not accompanied by more lymph node metastases only dilutes LNR importance. The importance of LNR is that it provides insight into the quality of lymph node dissection/sampling. For other cancer types, this problem has been addressed by requiring examination of a minimum number of lymph nodes, resulting in a quality indicator of at least 10–12 evaluated lymph nodes in colon cancer [4]. A recent paper on lymph node sampling in colon cancer showed that a higher yield of lymph nodes does not necessarily increase the number of nodes with metastases or of lymph node-positive cases[35]. The UICC guideline states that selective neck dissection ordinarily includes 6, and (modified) radical neck dissection ordinarily includes 10 lymph nodes^ and Bif lymph nodes are negative, but the number ordinarily examined is not met, they have to classify as pN0^ [33]. This statement does not clarify what the minimum number of lymph nodes is to qualify sampling of a neck dissection specimen as sufficient. The numbers stated in the UICC guideline seem to be very low, as in the literature reviewed; for our study, we found 23 as the lowest number of sampled lymph nodes (Table 1).

We argue that a minimum number of lymph node samples from a MRND should be 20 rather than the 10 required by the UICC. A limitation of our study is that several important elements differ from previously published studies on the subject. The majority of our patients underwent a modified radical neck dissection. This is important, since MRND includes level V lymph nodes but SND does not, which dilutes LNR significantly. Furthermore, changes in the treatment protocol, such as inclusion in 2010 of postoperative chemo-radiotherapy in cases with positive tumor resection margins and ECE, might have influenced impact of lymph node-related prognostic factors. A final issue is that we included all head and neck squamous cell carcinomas and not only oral cavity cancer as most other studies[6, 8, 12, 14, 16, 23, 29, 31], which we consider justified because lymph node staging and its prognostic value are not different between head and neck subsites. However, for HPV-positive tumors, TNM stage is less predictive[5], and therefore, we performed the multivariate analyses twice, including HPV-positive tumors and excluding HPV-positive tumors.

In conclusion, we show that LNR is prognostic in head and neck cancer. However, as LNR varies according to the protocols applied for processing of neck dissection specimens which may vary between institutions and in time, it is subject to important variability.We find that the number of positive lymph nodes is as least as good as LNR but less susceptible to variation, provided that lymph node sampling is adequate. The requirement for the minimum number of lymph nodes to be examined in an MRND specimen should be increased from the presently UICC required number of 10 to 20.

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SUPPLEMENTAL MATERIAL

Supplement table 1.						
	Model 1		Model 2		Model 3	
	<okt2007	>okt2007	<okt2007	>okt2007	<okt2007	>okt2007
Sex	0.836 (0.622)	1.109 (0.797)	0.817 (0.576)	1.016 (0.968)	0.890 (0.746)	0.886 (0.765)
T_group	1.752 (0.076)	1.374 (0.424)	1.970 (0.025)	1.644 (0.205)	1.880 (0.038)	1.688 (0.180
ECE	1.345 (0.289)	1.712 (0.242)	1.190 (0.540)	2.259 (0.042)	1.261 (0.407)	1.971 (0.111)
Pos LN	1.832 (0.089)	2.973 (0.008)	*	*	*	*
LNR	*	*	2.184 (0.011)	2.150 (0.050)	*	*
N_group	*	*	*	*	1.957 (0.074)	2.538 (0.037)
Abbreviations: ECE: extra capsular extension, LN: lymph node, LNR: lymph node ratio						

Supplement table 2. Univariate analysis						
	<2007			>2007		
	HR	95% CI	P	HR	95% CI	P
Sex	1.025	0.574-1.831	0.925	1.059	0.486-2.305	0.854
T_group	1.993	1.100-3.613	0.018	1.622	0.754-3.489	0.204
ECE	1.375	0.797-2.373	0.274	2.453	1.126-5.344	0.031
Pos LN	1.985	1.119-3.520	0.010	3.134	1.421-6.911	0.002
Pos LN_cont	1.113	1.065-1.162	<0.001	1.072	1.005-1.143	0.021
LNR	2.165	1.250-3.751	0.006	1.978	0.921-4.249	0.080
LNR_cont	1.044	1.026-1.062	<0.001	1.029	1.006-1.052	0.011
N_group	2.121	1.096-4.107	0.018	2.436	1.026-5.782	0.031
Nodal yield	0.992	0.977-1.008	0.280	1.003	0.982-1.024	0.650
Abbreviations: HR: hazard ratio, ECE: extra capsular extension, LN: lymph node, LNR: lymph node ratio						