mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 17

Node micrometastases in upper aerodigestive cancer

Frédéric Michel[1], Jean-Michel Prades[1], Jean-Marc Dumollard[2], Caroline Martin[3], Mamadou Birame Faye[1], Andrei P. Timoshenko[1], Christian Martin[1].

[1] Service d'Oto-rhino-laryngologie, de chirurgie cervico-faciale et plastique, Hôpital Bellevue, CHU de Saint-Etienne - France.
[2] Laboratoire d'Anatomopathologie, Hôpital Bellevue, CHU de Saint-Etienne - France.
[3] Service de Santé publique et d'information médicale, Hôpital Saint Jean Bonnefonds, CHU de Saint-Etienne - France.

ABSTRACT

Introduction: Cervical lymph node involvement has a major impact on prognsois and treatment decisions in patients with squamous cell carcinoma of the upper aerodigestive tract (SCC-UADT). We investigated the rate of lymph node micrometastases (°‹10 mm) in neck dissection specimens.
Material and methods: From 1999 to 2003, 217 consecutive neck dissections in 152 patients with previously untreated SCC-UADT were studied. Excised nodes were counted, measured, serially cut at 2-mm intervals, subjected to standard staining, and examined under a light microscope.
Results: Mean number of nodes per dissection was 21.5. Among lymph node metastases (pN+), 45% were micrometastases, and among pN+ with extracapsular spread (pN+R+), 31% were micrometastases. Among pN+ patients, 66% had micrometastases and 18% had only micrometastases. In individual patients, the number of pN+ micrometastases was correlated with the number of pN+ metastases. Mean numbers of pN+ and of pN+R+ micrometastases were higher in N2 and N3 patients than in N0 and N1 patients.
Conclusion: The diagnosis of node micrometatases, which affects decisions regarding adjunctive treatments, requires painstaking dissection of the neck with pathological examination of all excised nodes. This procedure is feasible in everyday practice. A study of the prognostic significant of node micrometastases is ongoing at our center. *(Fr ORL - 2005 ; 86 : 17-22)*

Keywords: Cervical node metastases, Squamous cell carcinoma, Serial sections, Neck dissection, Micrometastases.

Submitted for publication: June 2004
Accepted for publication: November 2004
Corresponding author: Frédéric Michel
Service d'Oto-rhino-laryngologie, de chirurgie cervico-faciale et plastique
Hôpital Bellevue - CHU de Saint-Etienne
42055 Saint-Etienne Cedex 2 - France
e-mail: fredmichelorl@hotmail.com

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 18

ABBREVIATIONS

pN+ : histologically documented lymph-node metastasis
pN+R+ : histologically documented lymph-node metastasis with extracapsular spread
UICC : Union Internationale Contre le Cancer or International Union against Cancer (http://www.uicc.org/)

INTRODUCTION

Cervical lymph node metastases from squamous-cell carcinoma of the upper aerodigestive tract (SCC-UADT) has a major impact on the rates of regional recurrence, distant metastases, and survival. In addition, treatment decisions are influenced by the presence of cervical node involvement. Therefore, accurate staging of the neck is crucial. However, cervical lymph-node metastases frequently escape detection by palpation [1-3]. Ultrasonography has an about 20% diagnostic error rate when both false positives and false negatives are counted yet may be superior over computed tomography, magnetic resonance imaging, and positron emission tomography [4]. Node metastases 10 mm or less in diameter, known as micrometastases, are usually missed by imaging studies. Consequently, neck dissection followed by histologic examination is the reference method for detecting node metastases [1,3,5-7] and for evaluating their characteristics, such as location, size, number, and extracapsular spread, all of which have an impact on the prognosis and treatment decisions [2-3,5-6,8]. However, the effectiveness of neck dissection histology may vary with the procedure used for node removal and examination. The objective of this study was to determine the rates of node micrometastases with and without extracapsular spread detected by serial node section in patients undergoing routine neck dissection for previously untreated SCC-UADT.

MATERIEL ET METHODES

From 1999 to 2003, 217 consecutive neck dissections from 152 patients with a first and solitary SCC-UADT were entered into the study. There were 143 men and 9 women, with a mean age of 57 years (range, 35-89 years). Absence of distant metastatic disease was required for study inclusion. Location of the primary tumor was the oral cavity in 10% of patients, the oropharynx in 39%, the laryngeal margin in 10%, the hypopharynx in 20%, and the larynx in 21%. Table I shows the distribution by pretreatment TNM stage as defined by 1997 UICC criteria [9]. Computed tomography of the primary and neck was not obtained routinely; rather, T and N staging was based on physical findings. The neck dissection strategy was based on tumor location and lymph node status as evaluation preoperatively. Selective neck dissection was performed in N0 patients; levels I, II, and III were removed in patients with oral cavity carcinomas and levels II, III, and IV in those with lesions of the pharynx or larynx. In N1 patients and most N2 patients, we used modified radical neck dissection defined as preservation of at least one of the following three structures: spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein. Levels II through IV were removed, as well as level V nodes located in the lateral supraclavicular region; in addition, level I was removed in those patients with oral cavity primaries. Finally, in 8 N2 patients and all N3 patients, radical neck dissection was performed, with removal of levels II through V and, in patients with oral cavity primaries, of level I; Level VI nodes were removed with the tumor and were not counted in the study. In all, there were 112 selective neck dissections, 79 modified radical neck dissections, and 26 radical neck dissections. A single pathologist performed all histological studies. After fixation by immersion in Bouin's fluid for 24 hours, the nodes were counted, cut and measured along their major axis, and serially cut into 2-mm slices. Then, 5-µm slices were stained with hematoxylin-eosin-saffron and examined under a light microscope. Micronodes were defined as having a major axis no greater than 10 mm and macronodes as having a major axis greater than 10 mm. The estimated mean duration of the histological examination was 80 minutes per dissection.

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 19

Table I: Preoperative TNM stages based on 1997 UICC criteria (9) in the 152 study patients.

	T1	T2	T3	T4	Total	%
N0	3	47	19	5	74	50
N1	3	19	10	3	35	23
N2	0	7	14	4	25	16
N3	0	5	7	6	18	11
Total	6	78	50	18	152	100
%	**4**	**51**	**33**	**12**	**100**	

Table II: Node involvement and extracapsular spread in micronodes (°‹10 mm) and macronodes removed from the 152 study patients.

	nodes		**pN+ nodes**			**pN+R+ nodes**		
	N	%		n	%		n	%
Micro-nodes	4287	**92**	≤5mm	49	15	≤5mm	16	7
			>5mm	102	30	>5mm	52	24
			total	151	**45**	total	68	**31**
Macro-nodes	385	**8**	≤30mm	175	52	≤30mm	144	65
			>30mm	9	3	>30mm	9	4
			total	184	**55**	total	153	**69**
Total	4672	**100**	total	335	**100**	total	221	**100**

pN+: nodes with histologically documented metastases; pN+R+: nodes with histologically documented metastases extending beyond the capsule; n: number of nodes.

Table III: Micronode and macronode metastases in pN+ patients (n=89).

	pN+ micronodes only	pN+ macronodes only	pN+ micronodes and macronodes	Total
N0	9	9	3	21
N1	4	10	11	25
N2	1	8	16	25
N3	2	3	13	18
Total	16	30	43	89

Table IV: Micronode and macronode metastases in pN+R+ patients (n=75).

	pN+ micronodes only	pN+ macronodes only	pN+ micronodes and macronodes	Total
N0	4	4	3	11
N1	3	9	10	22
N2	1	7	16	24
N3	2	3	13	18
Total	10	23	42	75

Statistics

The mean number of lymph nodes per dissection was determined, as well as the proportions of nodes with micrometastases and with macrometastases. Among patients with histologically documented lymph-node metastases (pN+ patients), the mean numbers of micrometastases and macrometastases were compared across subgroups defined based on the preoperative N stage, using Student's t test. Correlations between micrometastatic and macrometastatic node involvement were evaluated, as well as the correlation between the number of micrometastases and the total number of node metastases. P values smaller than 0.05 were considered statistically significant.

RESULTS

The 217 neck dissections performed in the 152 study patients yielded 4672 lymph nodes, of which 4287 were micronodes and 385 were macronodes. The mean number of nodes per dissection was 21.5, with no significant difference according to the neck dissection protocol. Of the 4287 micronodes, 151 (3.5%) were involved ; among the 385 macronodes, 184 (48%) were involved (Table II). Among pN+ nodes, 45% (68/151) of micronodes and 82% (144/175) of macronodes no greater than 30 mm showed extracapsular spread (Table II). Among the 152 patients, 89 were pN+. Associations linking pN+ and pN+R+ micronodes and macronodes according to the preoperative N stage are shown in Tables III and IV. Among pN+ patients, 66% had involved micronodes, and 18% had micronodes as the only pattern of node involvement. Finally, among pN+ patients, 85% were pN+R+. The mean numbers of pN+ and pN+R+ micronodes was significantly greater in pN+ N2N3 patients (2.3 and 1.1, respectively) than in pN+ N0N1 patients (1.1 and 0.5, respectively). In individual patients, the number of pN+ micronodes was significantly correlated with the number of pN+ macronodes (coefficient of correlation, r=0.46).

DISCUSSION

Mean number of lymph nodes examined histologically

The mean number of lymph nodes examined per dissection in our study (21.5) was far greater than the

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 20

number required by the UICC for histological node staging (pN), namely, six nodes for selective dissection and ten nodes for modified radical or radical dissection [9]. Mean numbers in earlier reports have varied from 14 to 50 for selective dissection [1,2, 10-11] and from 26 to 67 for modified radical or radical dissection [1,2,11-13]. The relatively low mean examined node number in our study may be related to our use of selective dissection when indicated by tumor location.

Differences in procedures used for pathological node examination may contribute to the differences in mean examined node numbers across studies [2,13]. In our study, all lymph nodes visible to the naked eye were dissected out and examiend histologically. Higher examined node numbers, with longer examination times, have been obtained by radiography of the dissection specimen immersed in ethanol [2] or by embedment of the entire dissection specimen in paraffin [11] (43 and 67 nodes, respectively).

Node involvement and extracapsular spread

The main objective of routine serial section of excised lymph nodes is improved detection of micrometastases [11,14], most notably in micronodes [10,12], as compared to examination of one or two sections per node.

Routine serial node section in our study showed that only 3.5% of micronodes were involved but that metastases in micronodes accounted for 45% of pN+ nodes. Similarly, although only 1.5% of micronodes showed metastases with extracapsular spread, these nodes contributed 31% of all pN+R+ nodes. The UICC has not reached a consensus about the optimal number of sections per node [9]. In earlier studies, the serial section thickness ranged from 1 to 4 mm for neck dissection specimens [8,10,13-14] and from 1 to 2 mm for the sentinel lymph node [15-16].

Micronodes may be involved in patients classified as N0 based on preoperative physical findings. Among pN+ patients, the number of pN+ micronodes increased in our study with the preoperative N stage and with the total number of pN+ nodes.

We found a high rate of extracapsular spread, for both micronodes and macronodes, as compared to earlier work. Others have reported extracapsular spread rates of 20% to 23% for pN+ micronodes and of 53% to 65% for pN+ nodes measuring 20 to 30 mm in diameter [3,6,17]. In our study, extracapsular spread was documented in 85% of pN+ patients.

Implications for the preoperative workup, the treatment, and the prognosis

Physical findings and computed tomography imaging underestimate node involvement, most notably metastases to small nodes. A diameter of 10 mm or more is widely used as the CT criterion for defining a metastatic lymh node [2-3,12,17. In our study, however, 45% of metastatic lymph nodes measured 10 mm or less (Table II).

Micronodes must be excised during neck dissection. Among the 21 pN+ patients classified as N0 before surgery, 9 (43%), all positive nodes were micronodes. Furthernore, among the 43 N2 or N3 patients, 32 (75%) had positive micronodes (Table III). The detection of micronode involvement has an impact on treatment, as the choice of adjunctive treatments is based on the number of pN+ nodes and on the presence of extracapsular spread [1,6,18-19]. Thus, adjunctive radiotherapy may be offered to all pN+ patients [1,18] and adjunctive radiochemotherapy to all pN+R+ patients [6,19].

Nevertheless, controversy surrounds the prognostic significance of micronode metastases [10,12] and of microscopic extracapsular spread [5,20-21]. In patients with lung cancer initially classified as pN- based on standard pathological procedures, a statistically significant difference in survival was found between patients classified as pN+ or pN- after histological examination of thinner serial sections [21].

Conflicting data have been reported regarding the prognostic significance of gross and microscopic extracapsular spread [5,20].

CONCLUSION

Pathological examination is needed to reliably diagnose metastases in cervical lymph nodes no greater than 10 mm in diameter (micronodes). Painstaking dissection of neck regions draining the tumor followed by histological examination of all excised lymph nodes should be performed. Histological exa-

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 21

mination of 2-mm serial sections of all lymph nodes is feasible in everyday practice. In our study, 45% of all node metastases and 31% of those with extracapsular spread were located in micronodes. Among pN+ patients, 66% had metastases in micronodes. In addition, in pN+ patients the number of pN+ micronodes was correlated with the total number of pN+ nodes. Finally,, 85% of pN+ patients were pN+R+, and the mean numbers of pN+ and of pN+R+ micronodes were greater in N2N3 patients than in N0N1 patients. Detection of metastatic micronodes influences decisions regarding adjunctive treatment. A study of the prognostic significance of metastatic micronodes in patients with SCC-UADT is ongoing in our department.

REFERENCES

1. End results of a prospective trial on elective lateral neck dissection vs. type III modified radical neck dissection in the management of supraglottic and transglottic carcinomas. Brazilian Head and Neck Cancer Study Group. Head Neck 1999; 21: 694-702.
2. Van den Brekel MW, van der Waal I, Meijer CJ, Freeman JL, Castelijns JA, Snow GB. The incidence of micrometastases in neck dissection specimens obtained from elective neck dissections. Laryngoscope 1996; 106: 987-991.
3. Gillies EM, Luna MA. Histologic evaluation of neck dissection specimens. Otolaryngol Clin North Am. 1998; 31:759-771.
4. Stuckensen T, Kovacs AF, Adams S, Baum RP. Staging of the neck in patients with oral cavity squamous cell carcinomas: a prospective comparison of PET, ultrasound, CT and MRI. J Craniomaxillofac Surg. 2000; 28: 319-324.
5. Olsen KD, Caruso M, Foote RL, et al. Primary head and neck cancer. Histopathological preictors of recurrence after neck dissection in patients with lymph node involvement. Arch Otolaryngol Head Neck Surg. 1994;120: 1370-1374.
6. Myers EN, Fagan JJ. Management of the neck in cancer of the larynx. Ann Otol Rhinol Laryngol. 1999; 108: 828-832.
7. Kerrebijn JD, Freeman JL, Irish JC, Witterick IJ, Brown DH, Rotstein LE, Gullane PJ. Supraomohyoid neck dissection. Is it diagnostic or therapeutic? Head Neck 1999; 21: 39-42.
8. Hamakawa H, Takeruma K, Sumida T, Kayahara H, Tanioka H, Sogawa K. Histological study on pN upgrading of oral cancer. Virchows Arch. 2000;437: 116-121.
9. Sobin LH, Wittekind C. TNM classification of malignant tumors, 5th edition. Wiley, New York.1997.
10. Ambrosch P, Kron M, Fischer G, Brinck U. Micrometastases in carcinoma of the upper aerodigestive tract: detection, risk of metastasizing, and prognostic value of depth of invasion. Head Neck 1995; 17: 473-479.
11. Buckley JG, MacLennan K. Cervical node metastases in laryngeal and hypopharyngeal cancer: a prospective analysis of prevalence and distribution. Head Neck 2000; 22: 380-385.
12. Don DM, Anzai Y, Lufkin RB, Fu YS, Calcaterra TC. Evaluation of cervical lymph node metastases in squamous cell carcinoma of the head and neck. Laryngoscope 1995; 105: 669-674.
13. Van den Brekel MW, Stel HV, van der Valk P, Van der Waal I, Meyer CJ, Snow GB.. Micrometastases from squamous cell carcinoma in neck dissection specimens. Eur Arch Otolaryngol. 1992; 249: 349-353.
14. Jose J, Coatesworth AP, MacLennan K. Cervical metastases in upper aerodigestive tract squamous cell carcinoma: histopathological analysis and reporting. Head Neck 2003; 25: 194-197.
15. Stoeckli SJ, Steinert H, Pflatz M, Schmid S. Sentinel lymph node evaluation in squamous cell carcinoma of the head and neck. Otolaryngol Head Neck Surg. 2001; 125: 221-226.
16. Shoaib T, Soutar DS, Prosser JE, et al. A suggested method for sentinel node biopsy in squamous cell carcinoma of the head and neck. Head Neck 1999; 21: 728-733.
17. Friedman M, Roberts N, Kirshenbaum GL, Colombo J. Nodal size of metastatic squamous cell carcinoma of the neck. Laryngoscope 1993; 103: 854-856.
18. Ambrosch P, Kron M, Pradier O, Steiner W. Efficacy of selective neck dissection: a review of 503 cases of elective and therapeutic treatment of the neck in squamous cell carcinoma of the

mp ORL 86 ANGLAIS 207-275(new) 15/02/05 11:33 Page 22

upper aerodigestive tract. Otolaryngol Head Neck Surg. 2001; 124: 180-187.
19. Johnson JT, Wagner RL, Myers EN. A long-term assessment of adjuvant chemotherapy on outcome of patients with extracapsular spread of cervical metastases from squamous carcinoma of the head and neck. Cancer 1996; 77: 181-185.
20. De Carvalho MB. Quantitative analysis of the extent of extracapsular invasion and its prognostic significance: a prospective study of 170 cases of carcinoma of the larynx and hypopharynx. Head Neck 1998; 20: 16-21.
21. Ferlito A, Devaney KO, Devaney SL, Carbone A, Rinaldo A. Micrometastases: have they an impact on prognosis? Ann Otol Rhinol Laryngol. 1999; 108: 1185-1189.