



Perimarginal lymph nodes: an undervalued entity in oral cancer

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Abstract

Purpose In a previous study, we gave a surgical description of a group of lymph nodes in the submandibular area at risk of remaining undissected during neck dissection (ND) for which we have proposed the term “perimarginal nodes” (PMNs) due to their proximity to marginal mandibular nerve (MMN). The aim of this study is to evaluate prevalence of PMNs involvement in oral cavity squamous cell cancer (OCSCC) and to verify if metastases are related to primary tumor characteristics or to the state of the neck.

Methods We recruited a total of 39 consecutive patients diagnosed with OCSCC candidate to ND. Histological characteristics of PMNs were analyzed and the incidence of metastases in relation to the primary tumor characteristics were noted.

Results PMNs were found to be involved with metastases in 8 patients (20.5%). No characteristic of the primary tumor seems to influence the metastatic involvement of the PMNs.

Conclusions PMNs represent a frequent site of micro-metastases in patients diagnosed with OCSCC regardless of other characteristics of the primary tumor.

Keywords Perimarginal nodes · Perifacial nodes · Submandibular nodes · Neck dissection · Oral cavity cancer

Introduction

In a previous study, we gave a description of a group of lymph nodes of the submandibular area that are strongly at risk of being left in the surgical field during neck dissection (ND). We have also reported how the classical Rouviere’s distinction between the subgroups of submandibular lymph nodes (pre/postglandular and perifacial) is not useful for describing the nodes at risk to be undissected. In our experience, in fact, these nodes at risk lie near the marginal mandibular nerve (MMN), that represents the essential anatomical landmark to be identified when approaching them (Fig. 1). For this reason, we have proposed the term “perimarginal nodes” (PMNs) [1]. Even though it is widely known that the involvement of cervical lymph nodes represents the most relevant prognostic factor in oral cavity squamous cell carcinoma (OCSCC), the pathological role of PMNs is scarcely described in literature due to the fact that

their classification has always been controversial and their removal hazardous [1, 2]. The primary aim of this study is to evaluate prevalence of PMNs involvement in OCSCC, secondly to ascertain whether PFM metastases are correlated with the size of the primary tumor, its subset, its histological characteristics and the status of the neck.

Materials and methods

This prospective study was approved by the local ethics committee and all patients gave their signed informed consent. We recruited a total of 80 consecutive patients diagnosed with OCSCC candidate to uni- or bilateral ND at the Otolaryngologic and Head and Neck surgery clinic of Trieste. Preoperative evaluation and indications to ND were made according to NCCN (National Comprehensive Cancer Network) guidelines. All patients underwent careful inspection and palpation of the neck. We included clinically negative (cN0) patients along with patients positive (cN+) for neck metastases. We consider as cN+, patients with palpable swelling with characteristics of malignancy and/or patients with suggestive radiological findings as main axis measurement of the node > 10 mm, necrosis or not recognizable

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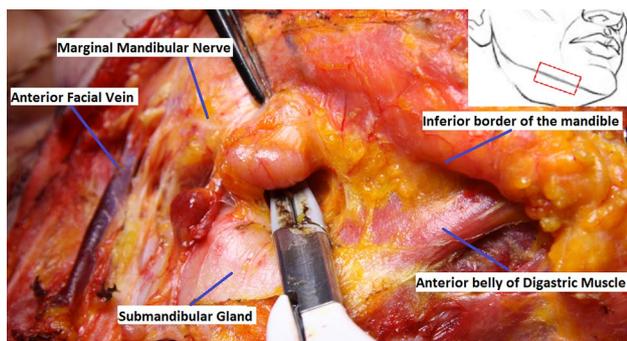


Fig. 1 Aspect of a perimarginal node and surrounding structures. Notice that the marginal mandibular nerve crosses the medial aspect of the node coming in close proximity to it

hilum. We excluded patients who underwent previous ND or other surgery of the neck, patients who had undergone radiotherapy treatment of head and neck and patients who denied consent to the study. All NDs were performed by the same two surgeons with the aid of nerve integrity monitoring (NIM) for the identification of MMN (electromyographic monitoring system: NIM-response 2.0; Xomed Medtronic, Inc, Jacksonville, Florida). The number of PMNs was noted and they were sent separately for histopathology examination. Finally, we analyzed incidence of PMN metastases in relation to the characteristics of the primary tumor and to the clinical and histopathological status of the neck. Characteristics of the primary that have been evaluated are the grade (T), the grading (G) (Broder's classification), the grade of keratinization (C) and the subset of the oral cavity. All analyses were carried out using IBM SPSS Statistics Software (IBM Corp.—Version 23 for Windows), with Fisher's exact test. Statistical significance was regarded as a $p < 0.05$.

Results

Population

A total of 39 patients met the inclusion criteria; 15 women (38.5%) and 24 men (61.5%), with a mean age of 67.7 years (range 44–86 years) at the time of surgery. Sixteen bilateral and 23 unilateral dissections were performed for a total of 55 ND.

Primary tumor characteristics

The anterior floor of the mouth was the sub-site of the primary cancer in 13 cases (33.3%), the lateral floor of the mouth in 8 cases (20.5%), the retromolar trigone in 6 cases (15.4%), the tongue in 5 patients (12.8), the buccal mucosa in 3 cases (7.7%), the inferior alveolar ridge in 2 cases

Table 1 Characteristics of primary tumor

	n° (%)
Subsite	
Anterior floor	13 (33.3)
Lateral floor	8 (20.5)
Retromolar trigone	6 (15.4)
Tongue	5 (12.8)
Buccal mucosa of the cheek	3 (7.7)
Inferior alveolar ridge	2 (5.1)
Superior alveolar ridge	1 (2.6)
Hard palate	1 (2.6)
pT	
Low (1–2)	16 (41)
High (3–4)	23 (59)
cN	
0	18 (46.2)
1	10 (25.6)
2	11 (28.2)
3	0 (0)
pN	
0	22 (56.4)
1	5 (12.8)
2	7 (17.9)
3	5 (12.8)

(5.1%), the hard palate in 1 case (2.6%) and the superior alveolar ridge in 1 case (2.6%) (Table 1).

Perimarginal nodes

A number variables from 0 to 3 of PMN per hemi-neck were identified. PMNs were found to be involved with metastases in 8 patients (20.5%), of these, metastases in other cervical lymph nodes were found in 3 cases (37.5%). No bilateral PMN metastases were found and in any cases there were more than 1 PMN involved. Extra-nodal extension (ENE) was present in 2 PMNs (25%), of these, in one case, the PMN was the only node involved and it measured less than 3 cm (pN2a, TNM 8th. edition). In the other case, ENE was present in other 5 lymph nodes of level IIa and III (pN3b) (Table 2).

Correlation with the primary tumor

The characteristics of the primary tumor do not seem to influence the metastatic involvement of the PMNs. In our population, patients with positive PMNs were equally distributed in relation to subsite of primary, grade of the tumor (T), grade of keratinization (C) and grade of cytological differentiation (G) (Table 3).

Table 2 Characteristics of patients with positive perimarginal nodes

Patient	Age	Sex	Subsite	cTNM	pTNM	No. of PMNs: involved with cancer/ total	Other ipsilateral nodes involved	Other con- tralateral nodes involved
1	67	M	Floor of the mouth (lateral)	cT2N2b	pT3N3b (ENE)	1/1	Yes	–
2	70	M	Floor of the mouth (lateral)	cT2N0	pT4aN1	1/2	No	–
3	76	M	Floor of the mouth (anterior)	cT4aN2b	pT4aN1	Left 1/2 right 0/1	No	No
4	77	M	Hard palate	cT4N0	pT4aN1	1/3	No	–
5	53	M	Left trigone	cT3N2b	pT3N2	1/1	Yes	–
6	74	F	Inferior alveolar ridge	cT4aN2b	pT4aN1	Right 1/3 left 0/1	No	No
7	44	F	Superior alveolar ridge	cT4aN2b	pT4aN2c	Left 1/3 right 0/1	No	Yes
8	74	M	Tongue	cT1N0	pT1N2a (ENE)	1/2	No	–

PMN perimarginal node, ENE extra-nodal extension

Table 3 Correlation between the primary tumor and involvement of perimarginal nodes

	n PMN + (%)	n PMN – (%)	p value
pT			
Low (1–2)	1 (2.5)	15 (38.5)	0.1
High (3–4)	7 (17.9)	16 (41)	
Grading*			
Low	5 (13.8)	18 (50)	1
High	3 (8.3)	10 (27.7)	
Grade of keratinization**			
Low	4 (8.5)	21 (61.8)	0.1
High	4 (8.5)	5 (14.7)	
Subsite			
Floor of the mouth	3 (7.7)	18 (46.1)	0.4
Other subsites	5 (12.8)	13 (33.3)	

*Data on 35 patients, **data on 34 patients, PMN: perimarginal nodes

Status of the neck

Eighteen patients presented clinically negative neck (46%); in 3 of these micro-metastases were reported on histological examination (16.7%). The neck stage was found to be variable from pN0 to pN3b (Table 1). Metastases in PMNs were found both in patients with pN0 and pN+. In 5 patients the PMN were the only lymph nodes of the neck with the presence of metastases, modifying the staging of the tumor from cN0 to pN1 or to pN2a/pN3b. All 3 cases classified as cN0 and subsequently classified as pN+ showed PMN involvement. In one patient, we found a PMN as the only metastatic lymph node on the left side, while the other involved cervical lymph nodes appeared on the right side.

Discussion

Presence of node metastases is the factor that majorly influence prognosis in OCSCC and is globally accepted that ND still the gold standard for the treatment [2]. In the last 40 years the treatment of the neck has evolved towards less invasive treatments. For cN0 oral cavity cancers, in particular, superselective ND has been proposed [3]. However, it is globally accepted that dissection of level IB is mandatory in OCSCC even if applying less invasive treatments. The submandibular lymph nodes, anatomically classified by Rouviere and then reviewed by DiNardo, comprise, by definition, all the lymph nodes within the boundaries of the anterior belly of digastric muscle, the stylohyoid muscle and the inferior border of the mandible. In literature, the lymph nodes closest to the mandibular margin and adjacent to the anterior facial vein (perifacial nodes) have often been considered as a separate group or confused with mandibular lymph nodes. Probably, the fact that their dissection is insidious because of their proximity to MMN accounts for this poor anatomic–surgical classification.

The maneuver of Hayes Martin, which according to some authors, is executable during the ND to protect the MMN, is oncologically unsafe, as we demonstrated in a previous work [1, 4]. While performing the maneuver, the ligation of the anterior facial vein and the overturning of the upper flap leads to the loss of the PMNs that remain wrapped up in the flap itself (59% of cases in our series). The submandibular lymph nodes represent the most common site of metastasis in cancer of the tongue and of the floor of the mouth (up to 39% of cases) and the relapses on N in this area are well reported in the literature [5, 6]. In addition, it should be considered that voluminous masses adjacent to the mandibular margin and treated as mandibular lymph nodes disease, are difficult to classify as it is not possible to exclude that they could be expression of grown metastases of the PMNs that have crossed the lower border of

the mandible. As a possible solution to the problem of submandibular recurrences, some authors proposed the concept of compartmental surgery. Conceptually this surgery provided for the removal of tumors of the tongue or the floor of the mouth in continuity with the lymph nodes of the neck. Subsequent works, however, have not shown the greatest efficacy compared to the T resection performed separately from the ND [7, 8]. While it is known that tumors of the oral tongue and floor of mouth most commonly metastasize to the submandibular nodes, evaluation of disease in submandibular subsites has apparently not been largely described in literature. Some authors have been focused on looking for possible metastatic involvement of the perifacial lymph nodes in head and neck cancer. McRackan describes perifacial nodes involvement in cases of carcinoma of the mastoid bone, Netterville and colleagues report their involvement in tumors related to midfacial area and Creighton et al. in studying possible sites of sentinel lymph nodes in cancer of the skin of the head [9–11]. However, all of these authors describe the peripheral lymph nodes as a separate group and not as lymph nodes of the IB level. In the literature we have only found three works that describe precisely the perifacial lymph nodes as submandibular lymph nodes and that selectively analyze the various groups of the IB level. Lym reports a 6% incidence of involvement of perifacial nodes in patients with carcinomas of the tongue/floor of the mouth and cN0 necks; he lately finds perifacial metastases in 35% of patients with OCSCC and clinically positive necks [6, 12]. DiNardo finds metastasis in 24% of perifacial nodes and 10% of preglandular nodes [5]. However, these authors do not specify which of these lymph nodes are at risk of remaining in the surgical field and can therefore be the site of relapse on N, above all the same authors slavishly follow the classification of Rouviere which, as previously shown, is not always useful during dissection of the lymph nodes of the IB level at risk [1]. In our opinion, is useful to the surgeon to know what is the incidence of metastases in the lymph nodes at the risk of remaining undissected performing ND for OCSCC. To our knowledge, this is the first work that selectively analyzes the incidence of metastasis in these lymph nodes. In our series the incidence is about 20% and seems to be influenced by the high T even if the sample is too low to obtain statistical significance. The degree of T was less than 3 in 1 patient. This finding can be compared with works of DiNardo and Agarwal, which showed a higher number of submandibular metastases with the growth of the grade of T [5, 13]. The number of cases in which PMNs represent the only site of cervical metastasis is also interesting (5/8–13% of total population, 62.5% of patients with positive PMNs). A similar situation has already been described by Agarwal et al. which reported 8% of isolated metastases of the perifacial lymph nodes in a fairly large series of patients with OCSCC [13]. Not only a clinically negative

neck, but even the absence of illness in other lymph nodes may hide micro-metastases in the PMNs. In our opinion, an increasingly complete approach to surgical treatment should include, in addition to the previously described histopathological parameters, the removal of PMNs regardless of the sub-site of the tumor [14]. In literature the most frequent objection to approach of this area is the risk of damage to MMN. In our experience, the use of NIM to map the course of the MMN before starting the dissection of the IB level is an effective solution to this problem. In our series in fact we have not reported permanent paralyses and, as demonstrated in a previous work, the use of NIM also reduces the incidence of temporary paralyses [15].

Conclusions

In our experience PMNs represent a frequent site of micro-metastases in patients diagnosed with OCSCC (20.5%), regardless of the subsite of the tumor or the state of the neck. In our opinion, PMNs must be accurately removed during ND for OCSCC.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest and this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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