# Relevance of perimarginal nodes for head and neck cancer

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## Abstract

**Objective** To estimate the prevalence of metastasis in the perimarginal nodes (PMNs) (also known as perifacial, preglandular and retroglandual nodes) in head and neck cancer.

**Methods** We recruited 136 patients affected by cancers of the oral cavity, lip, oropharynx, skin and by cáncer of unknown primary (CUP), who were candidates for level IB dissection. PMNs were identified and sent separately for histological analysis. Correlation between metastasis to the PMNs and characteristics of the primary tumour were reported.

**Results** The incidence of metastasis was 17% from oral cancer, 50% from lip cancer and 12.5% from skin cancer. No metastases were reported for oropharynx cancer or CUP. The only factor that correlated with the incidence of metastases was origin of the tumour from the upper part of oral cavity.

**Conclusion** PMNs represent a frequent site of metastasis in oral and lip cancers. In cancer of the oropharynx, their involvement has not been not reported, while their role in skin cancers remains to be clarified.

**Keywords** Perimarginal nodes · Perifacial nodes · Perimarginal lymph nodes · Perifacial lymph nodes · Neck dissection · Submandibular nodes · Submandibular lymph nodes · Level IB · Head and neck surgery

## Introduction

Head and neck cancers are estimated to be the 6th most common neoplasia in the world. Most of them are squamous cell carcinoma (90%), and metastatic spread to the lymph nodes is extremely frequent as a result of the rich representation of the cervical lymphatic drainage system [1]. Nodal status is considered the most important prognostic factor in head and neck cancer and the most significant factor in the treatment of these patients [2]. In cases where surgery is indicated, neck dissection (ND) represents the gold standard to remove cervical node metastases [3].

Nevertheless, few published studies have examined the issue of some nodes of the submandibular area (level IB according to Robbins) that are at risk of not being harvested when performing ND with the common surgical technique, and especially when performing the Hayes Martin manoeuvre [3, 4].

In a previous paper described of these nodes that we named perimarginal lymph nodes (PMN), due to their proximity to the marginal mandibular nerve (MMN) [5]. In our experience PMN could be identified in 84% of ND, ranging in number from 0 to 5, with a predominance of cases with two nodes, and they were found anterior and/or posterior to the anterior facial vein and/or to the submandibular gland. In a subsequent study, we analysed their involvement in oral cavity squamous cell carcinoma (OCSCC), finding metastases in 20.5% of patients [2, 6].

Usually, when metastases of PMN are evident (cN+) a complete ND of level IB is performed making mandatory the full exploration of the area. However, when level IB seems to be spared from nodal involvement (cN0), the risk of leaving unharvested the PMNs is high (69%) [2]. According to studies published in the 90 s, a threshold probability of occult metastasis of 20% represented an indication for

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elective treatment of the neck. More recently, this cut-off value was changed to 15% although some authors believe each center should adapt this value on the basis of its own case history [7]. Consequently, the prevalence of the pathological involvement of PMN in other head and neck cancers remains to be clarified.

The aim of this study was to estimate the prevalence of occult metastasis in PMNs and identify factors predictive of their involvement in a series of patients affected by head and neck squamous cell carcinoma (HNSCC) prone to metastasize to level IB nodes.

## Materials and methods

We recruited 137 consecutive patients, from April 2015 to December 2020, diagnosed with HNSCC and candidate to uni- or bilateral ND that included a cN0 level IB. The study was conduced at the ENT and Head and Neck Surgery Clinic of Trieste (Italy). We included patients affected by cancer of the oral cavity, the lips, the oropharynx (both HPV-driven and not) and squamous cell skin cancer of the head and neck, and carcinoma of unknown primary origin (CUP).

Preoperative evaluation and indications for ND followed the more recent version of the NCCN (National Comprehensive Cancer Network) guidelines. All patients underwent accurate physical examination by inspection and palpation of the neck. We have considered as cN0 all patients in whom level IB nodes were not identified as "pathological" on either neck palpation or imaging. The exclusion criteria were previous ND or other neck surgery, previous radiotherapy treatment of the head and neck and refusal to give consent to the study. All NDs were conducted with the aid of nerve integrity monitoring for identification of the MMN [8]. During the ND, the number of PMNs removed was noted, and the nodes were sent separately for histopathology examination.

In keeping with the aims of the study, we investigated the prevalence of PMN metastases in relation to the characteristics of the primary tumour and to the status of the neck. Characteristics of the primary tumour considered were: site, subsite, T stage, grade according to Broder's classification, depth of invasion (DOI), grade of keratinization (C), and bone infiltration [9]. The status of the neck was established by correlating the incidence of metastases with the pN stage, the presence of extracapsular extension (ECE), the number of nodes dissected, the number of nodes involved, and the lymph node ratio (LNR). Regarding the number of nodes dissected, number of nodes involved and LNR, we established cut off values according to the literature [10]. The oral cavity was divided into three zones: upper area (hard palate and superior alveolar ridge), middle area (buccal mucosa and retromolar trigone) and lower area (anterior and lateral floor and tongue). All analyses were carried out using IBM SPSS Statistics Software (IBM Corp.—Version 23 for Windows), with the Chi square test or Fisher test. Statistical significance was set at $p < 0.05$. This prospective study was approved by the local ethics committee (CRO Aviano National Cancer Institute, Institute for research and healthcare; Aviano, Italy) and all patients gave their signed informed consent.

## Results

### Population

Our population was composed of 136 patients: 52 women (38.2%) and 86 men (63.2%). The mean age, at the time of surgery, was 69 (range 36–85 years). A total of 180 NDs, 94 unilateral and 43 bilateral, were performed (Table 1).

### Primary tumour characteristics

The site of the primary cancer was the oral cavity in 86 patients (63.2%), the lips in 6 patients (4.4%), the oropharynx in 31 patients (22.8%) [14 (45.2%) of which HPV-driven]. The population also included eight patients with squamous cell skin cancer (5.7%) and five patients with CUP (3.7%). The subsites are reported in Table 1.

Histology was SCC in all cases. Concerning tumour staging (pT stage), there were 5 cases of CUP (3.7%), 19 cases of pT1 (13.9%), 48 cases of pT2 (35.3%), 30 cases of pT3 (22%) and 34 cases of pT4 (25%).

The primary tumour characteristics are summarized in Tables 1 and 2.

### Status of the neck

As for pathological nodal involvement (pN classification), 62 patients were diagnosed as pN0 (45.5%), 32 patients as pN1 (23.5%), 6 patients as pN2a (4.4%), 16 patients as pN2b (11.7%), 1 patient as pN2c (0.7%), and 19 as pN3b (14%). ECE was found in 37/136 (27.2%) patients. The status of the neck is summarized in Table 2.

### Characteristics of patients with oral cavity cancer

Among the 86 patients affected by oral cavity cancer, the anterior floor was the subsite in 14 cases (16.3%), the lateral floor in 14 cases (16.3%), the retromolar trigone in 14 cases (16.3%), the tongue in 27 cases (31.4%), the buccal mucosa in 6 cases (7%), the inferior alveolar ridge in 6 cases (7%), and the hard palate/superior alveolar ridge in 5 cases (5.7%) (Table 1). Considering the subdivision of the oral cavity into three zones, five patients were affected by an upper oral cavity tumour (5.8%), 20 patients by a middle

**Table 1** Characteristics of the population and of the primary tumour

| | TOT *n* (%) | PMN+ *n* (%) | *p* value |
|---|---|---|---|
| Tumour site/subsite | | | |
| Oral cavity | 86 (63.2) | 15 (17.4) | < 0.01* |
| Anterior floor | 14 (16.3) | 0 | |
| Lateral floor | 14 (16.3) | 4 (28.6) | |
| Retromolar trigone | 14 (16.3) | 2 (14.3) | |
| Tongue | 27 (31.4) | 2 (7.4) | |
| Buccal mucosa | 6 (7) | 0 | |
| Inferior alveolar ridge | 6 (7) | 3 (50) | |
| Hard palate/superior alveolar ridge | 5 (6) | 4 (80) | |
| Lip | 6 (4) | 3 (50) | |
| Inferior lip | 5 (83) | 3 (60) | |
| Labial commissure | 1 (17) | 0 | |
| Oropharynx | 31 (22.8) | 0 | |
| Base of tongue | 7 (22.5) | 0 | |
| Tonsil | 14 (45.1) | 0 | |
| Posterior pharyngeal wall | 6 (19.3) | 0 | |
| Soft palate | 4 (12.9) | 0 | |
| Skin | 8 (5.8) | 1 (12.5) | |
| CUP | 5 (3.6) | 0 | |
| pT | | | |
| I | 19 (14) | 2 (10.5) | N.S |
| II | 49 (36) | 5 (10.2) | |
| III | 33 (24.2) | 6 (18.1) | |
| IV | 35 (25.7) | 6 (17.1) | |
| Early stage (I–II) | 67 (49.2) | 7 (10.4) | N.S |
| Advanced stage (III–IV) | 69 (50.7) | 12 (17.4) | |
| Grading** | | | |
| G1–G2 | 73 (61.3) | 12 (16.4) | N.S |
| G3–G4 | 46 (38.6) | 7 (15.2) | |
| Grade of keratinization*** | | | |
| C1–C2 | 66 (73.3) | 9 (13.6) | N.S |
| C3–C4 | 24 (26.7) | 5 (20.8) | |

*PMN+* patients with perimarginal nodes involved by the tumour, *N.S.* not significant *CUP* cancer of unknown primary

*Oral cavity + lips VS others

**Data on 119 patients

***Data on 90 patients

**Table 2** Characteristics of cervical nodes in the population

| | TOT *n* (%) | PMN+ *n* (%) | *p* value |
|---|---|---|---|
| pN | | | |
| pN1 | 32 (23.5) | 7 (21.8) | N.S |
| pN2 | 23 (16.9) | 5 (21.7) | |
| pN3 | 19 (14) | 7 (36.8) | |
| ECE all | | | |
| ECE+ | 37 (50) | 6 (16.2) | N.S |
| ECE− | 37 (50) | 13 (48.1) | |
| Nodes dissected | | | |
| ≤ 15 | 18 (13.2) | 2 (11.1) | N.S |
| > 15 and ≤ 25 | 33 (24.3) | 8 (24.2) | |
| > 25 | 85 (62.5) | 9 (10.5) | |
| Nodes involved | | | |
| 1 | 35 (25.7) | 8 (22.8) | N.S |
| > 1 and ≤ 5 | 32 (25.7) | 9 (28.5) | |
| > 5 | 7 (5.1) | 2 (28.5) | |
| Lymph node ratio | | | |
| > 0 and < 0.05 | 34 (25) | 7 (20.5) | N.S |
| ≥ 0.05 and < 0.1 | 21 (15.4) | 6 (27.2) | |
| ≥ 0.1 | 19 (13.9) | 6 (31.5) | |

*PMN+* patients with perimarginal nodes involved by the tumour, *pN* regional lymph nodes-pathological, *ECE* extracapsular extension, *N.S.* not significant

oral cavity tumour (23.3%) and 61 by a lower oral cavity tumour (70.9%).

Regarding the T stage, 13 tumours were classified as pT1 (15.1%), 29 as pT2 (33.7%), 14 as pT3 (16.3%) and 30 as pT4 (34.9%). Bone involvement was present in 35 tumours (24.5%). The grading and the grade of keratinization are summarized in Table 3. Tumour DOI according to the oral cavity TNM 8th edition was less than or equal to 5 mm in 41 cases (47.7%), greater than 5 mm and less than or equal to 10 mm in 17 tumours (19.7), and greater than 10 mm in 28 tumours (32.6%). In particular, for the oral cavity primary tumours, 50 patients were classified as N0 (58.1%), 13 patients as N1 (15.1%), 1 patient as N2a (1.2%), 7 patients as N2b (8.1%), 1 patient as N2c (1.2%), and 14 patients as N3b (16.3%).

## Factors correlating with metastases to perimarginal nodes

A total of 19 patients with PMN involvement were identified; 15 (75%) of them had oral cavity tumour, 3 (15%) had lip tumour and 1 (5%) had skin carcinoma. The only factor that significantly correlated with PMN metastases was the site of the primary cancer, with a clear majority of OCSCC and lip cancer ($p < 0.01$). In particular, the prevalence of metastasis in PMNs in our population was 17.5% (15/86) in oral cavity cancer, 50% in lip cancer (3/6), 12.5% in skin cancer, and 0% in CUP and oropharyngeal cancer (0/5, 0/31) Fig. 1. Analysing the subpopulation of patients with OCSCC, we observed a significant correlation between PMN involvement and primary tumours arising from the upper zone of the oral cavity ($p < 0.001$). Other characteristics of the primary tumour or the status of the neck did not seem to influence the metastatic involvement of PMNs. The

**Table 3** Characteristic of oral cavity tumours

| | TOT *n* (%) | PMN+ *n* (%) | *p* value |
|---|---|---|---|
| pT | | | |
| I | 13 (15.1) | 0 | N.S |
| II | 29 (33.7) | 4 (13.7) | |
| III | 14 (16.2) | 4 (28.5) | |
| IV | 30 (34.8) | 7 (23.3) | |
| Early stage (I-II) | 42 (48.8) | 4 (9.4) | N.S |
| Advanced stage (III-IV) | 44 (51.1) | 11 (25) | |
| Depth of invasion | | | |
| < 5 mm | 41 (47.6) | 6 (14.6) | N.S |
| > 5 mm and < 10 mm | 17 (19.7) | 3 (17.6) | |
| > 10 mm | 28 (32.5) | 6 (21.4) | |
| Bone infiltration | | | |
| Yes | 35 (40.6) | 7 (20) | N.S |
| No | 51 (59.4) | 6 (11.7) | |
| Subsite | | | |
| Upper | 5 (5.8) | 4(80) | 0.003 |
| Middle | 20 (23.2) | 2 (10) | |
| Lower | 61 (70.9) | 9 (14.7) | |
| pN | | | |
| pN1 | 13 (15.1) | 6 (46.1) | N.S |
| pN2 | 9 (10.4) | 3 (33.3) | |
| pN3 | 14 (16.2) | 6 (42.8) | |
| Lymph node ratio | | | |
| > 0 and < 0.05 | 12 (13.9) | 8 (66.6) | N.S |
| > = 0.05 and < 0.1 | 7 (8.1) | 4 (57.1) | |
| > = 0.1 | 10 (11.6) | 3 (30) | |

*PMN+* patients with perimarginal nodes involved by the tumour, *pT* primary tumour-pathological, *N.S.* not significant

characteristics of patients with PMN involvement are summarized in Table 4.

## Discussion

Our group has recently described a cluster of lymph nodes (named perimarginal nodes, PMNs) belonging to all effects to level IB at risk of not being removed during classical submandibular triangle dissection [2, 6]. Prior to these studies, the literature was vague and contained no surgical description of these nodes or studies on their metastatic involvement. Several factors may account for this paucity of literature, including the fact that these nodes were often mistakenly regarded as a separate group not properly belonging to level IB, and, secondly, that their dissection was always considered unsafe due to their proximity to the MMN (Fig. 2). To protect the MMN, surgeons classically perform the Hayes Martin manoeuvre for a MMN-sparing

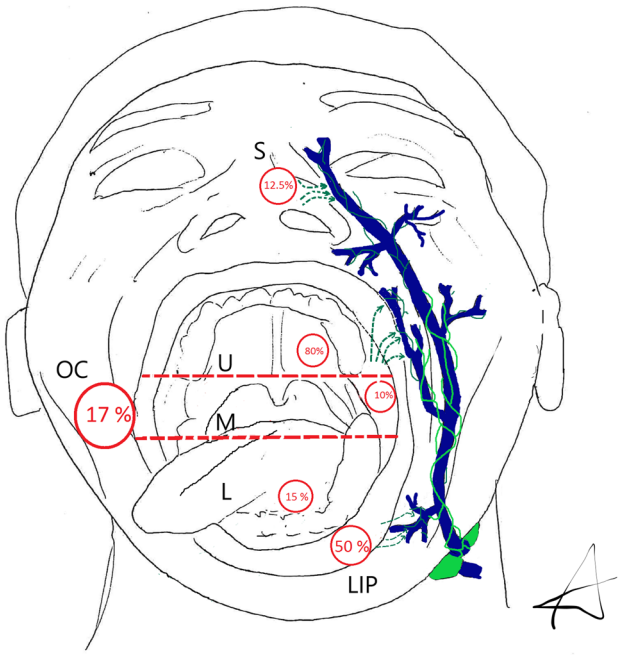


**Fig. 1** Incidence of perimarginal nodes metastasis from different tumor subsite. *OC* oral cavity; *U* upper part; *M* medial part; *L* lower part; *S* skin

dissection of level IB. The manoeuvre consists in interrupting and legating the AFV and then lifting the cranial portion of the vein to protect the MMN in a flap consisting of the trunk of the vein and the superficial cervical fascia, which is elevated and reflected superiorly. As demonstrated, performing this manoeuvre during level IB dissection can, in a large percentage of cases (59%), lead to leaving these lymph nodes in the operating field [2]. These nodes may be infiltrated by carcinoma in about 20% of cases of cancer of the oral cavity [6]. This finding prompted us to verify whether the PMNs could be involved in metastases from tumours originating from other head and neck locations. We therefore routinely removed these lymph nodes every time we approached level IB for oncological purposes; as already described in another paper, every time we performed this procedure the MMN was monitored with nerve integrity monitoring, with a very low incidence of damage to the nerve (4%) [8].

In our series, we did not find any cases of PMN metastases from oropharyngeal tumours; this is in agreement with the findings reported by Riffat et al. [11] In particular, in their series, no patients had level IB recurrence despite not having the perifacial lymph nodes (subgroup of PMN) removed [2, 11]. However, it should be emphasized that the patients in the study were fewer than in our group and they all underwent radiotherapic treatment on level IB [10]. Nonetheless, the prevalence of occult metastases to level IB from carcinomas of the oropharynx (both HPV-driven and not) is low and the utility of level I dissection in N0

**Table 4** Characteristics of the population with perimarginal nodes involved by tumour

| Pt | Sex | Age | No. PMNI / PMND | Site/Subsite | pT | DOI mm | Bone infiltration | pN | cN PMN | Other ipsilateral nodes involved | Contralateral nodes involved | ECE in PMN | ECE in other nodes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 67 | 1\1 | OC/floor | T3 | 7 | No | N3b | N0 | Yes, 5 | NA | Yes | Yes |
| 2 | M | 69 | 1\2 | OC/floor | T4a | 14 | No | N1 | N0 | No | NA | No | No |
| 3 | M | 77 | 1\3 | OC/inf alveolar ridge | T4a | 8 | Yes | N1 | N0 | No | No | No | No |
| 4 | M | 78 | 1\3 | OC/hard palate | T4a | 9 | Yes | N1 | N0 | No | NA | No | No |
| 5 | M | 53 | 1\1 | OC/trigone | T3 | 2.5 | No | N3b | N0 | Yes, 2 | NA | No | Yes |
| 6 | F | 74 | 1\4 | OC/inf alveolar ridge | T4a | 14 | Yes | N1 | N0 | No | No | No | No |
| 7 | F | 44 | 1\4 | OC/hard palate | T4 | 12 | Yes | N2c | N0 | No | Yes,1 | No | No |
| 8 | F | 66 | 2\2 | OC/trigone | T2 | 2.6 | No | N3b | N0 | Yes,2 | No | Yes | No |
| 9 | M | 74 | 1\2 | OC/tongue | T2 | 3.5 | No | N2a | N0 | No | NA | Yes | No |
| 10 | F | 71 | 2\2 | LIP/inf | T2 | 3.15 | No | N2b | N0 | Yes,1 | NA | No | No |
| 11 | M | 74 | 2\2 | OC/tongue | T2 | 3.5 | No | N3b | N0 | Yes,1 | NA | Yes | Yes |
| 12 | M | 53 | 1\2 | OC/sup alveolar ridge | T3 | 3.3 | No | N2b | N0 | Yes,1 | NA | No | No |
| 13 | F | 83 | 1\1 | OC/sup alveolar ridge | T4a | 10 | Yes | N1 | N0 | No | NA | No | No |
| 14 | M | 81 | 1\2 | OC/floor | T2 | 1.9 | No | N1 | N0 | No | NA | No | No |
| 15 | M | 72 | 1\1 | SK/nose | T3 | N/A | Yes | N1 | N0 | No | NA | No | No |
| 16 | F | 75 | 1\6 | OC/floor | T3 | 11 | No | N3b | N0 | Yes, 1 | no | No | Yes |
| 17 | M | 61 | 2\5 | LIP/inf | T2 | 4 | No | N3b | N0 | Yes,3 | NA | Yes | No |
| 18 | F | 70 | 1\1 | OC/inf alveolar ridge | T4a | 15 | Yes | N3b | N0 | Yes, 3 | NA | Yes | Yes |
| 19 | F | 67 | 1\1 | LIP/inf | T1 | 1.8 | No | N2b | N0 | Yes, 1 | NA | No | No |

*Pt* patient, *M* male, *F* female, *OC* oral cavity, *L* lip, *SK* skin, *no. PMNI/PMND* number of perimarginal nodes involved among all perimarginal nodes dissected, *DOI* depth of invasion, *ECE* extranodal extension, *PMN* perimarginal nodes, *NA* not applicable. *pT* primary tumour-pathological, *pN* regional lymph nodes-pathological

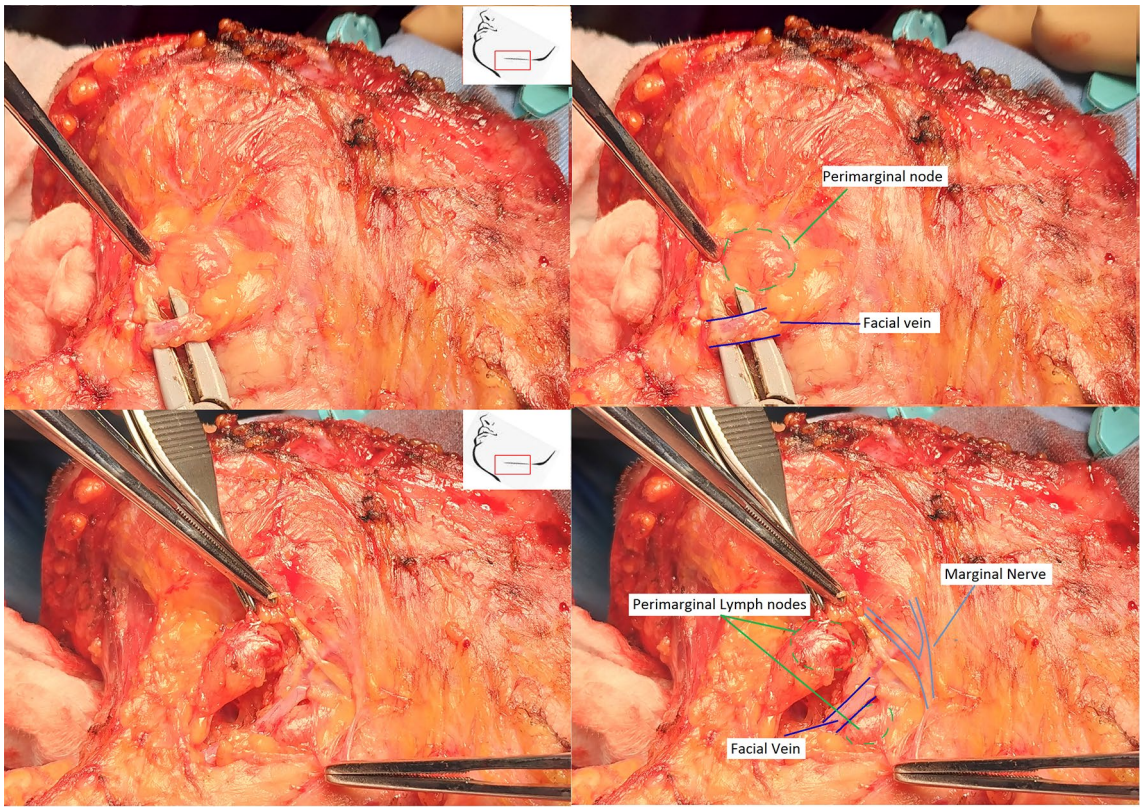


**Fig. 2** Dissection of perimarginal nodes. In the first sequence the surgeon identifies the facial vein; when the vein is dissected a second node appears (sequence). Note the close course of the marginal nerve in the last sequence

cases remains debated in the literature [12]. These considerations also justify the absence of PMN involvement in CUPs, whose origin is, in the vast majority of cases, the oropharynx [13].

In 17.5% of the OCSCC cases in our series, metastases to PMNs were found. This data are in agreement with what was found in our previous study on a smaller case series (20.5%) [6]. In that study, we did not identify intrinsic factors of the tumour that significantly correlated with the incidence of metastases. None of the parameters analyzed in the previous study were related to metastases to PMN even in our current series. The factor of greatest interest in our present series is the greater prevalence of metastases to PMNs in primary tumours located in the upper area of the oral cavity ($p < 0.001$). Given the location close to the oral floor, a greater spread of tumours starting from the floor, in particular from the anterior sector, would be expected. The literature does not contain reports that analyze the prevalence of metastases at level IB compared to the primary site of T within the oral cavity; however, there are studies that analyze the type of lymphatic drainage of the oral cavity [14, 15]. Werner et al. describe three areas of drainage from the oral cavity and, in particular, report that the anterior floor drains directly at level I [14]. This agrees with the findings of Abe et al., who identify a lymphatic drainage route between the oral floor and the pre-glandular lymph nodes (belonging to the PMN) in some lymphatics that cross the mylohyoid muscle [2, 15]. Neither of these findings were reflected in our series. No case of anterior floor carcinoma had metastasized to the anterior floor. An explanation for this can be found in studies that report metastases to PMNs from nasal and cutaneous tumours [16–18]. This lymphatic drainage follows the course of the facial vein and thus reaches directly the PMNs. It is reasonable to suppose that the hard palate, the trigone and the superior alveolar ridge drain in the facial vein lymphatic flow. This also explains our finding of a metastasis to the PMN in a patient with squamous carcinoma originating from the skin (wing of the nose) and the high prevalence found our labial carcinoma cases. None of the other factors related to T or N were found to be significantly linked to the presence of PMN involvement in our case series. This is in disagreement with the findings of Lym et al. that describe metastases to perifacial nodes from cancer of the tongue and oral floor. In their patients the tumours involving the nodes were all T3 or T4 [19]. Based on these data and on our previous work findings the message that we want to transmit it's that PMN removal should always been performed in cN0 cases in which the surgeon has decide to perform a selective

ND. The importance of dissection of "standard" level IB nodes is well noted, this work underline the importance of dissection also the PMN that are at high risk to be not harvest during ND.

A future goal of our group, once data relating to a significant follow-up become available, will be to verify whether the removal of PMN affects local recurrence and survival rates.

## Conclusions

PMNs represent a site of metastasis in oral and lip cancers and therefore their dissection should be mandatory during ND for cN0 cases. In cancer of the oropharynx, their involvement has not been reported so their removal may not be mandatory. The role of PMNs in skin cancers remains to be clarified. Further studies are needed to establish how their removal can affect local recurrence, survival and quality of life.

### Declarations

**Conflict of interest** No sponsorships or competing interests have been disclosed for this article.

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