European Archives of Oto-Rhino-Laryngology (2023) 280:869–876
https://doi.org/10.1007/s00405-022-07647-6

HEAD AND NECK

Lymph node metastasis in level IIb in oropharyngeal squamous cell carcinoma: a multicentric, longitudinal, retrospective analysis

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Received: 1 January 2022 / Accepted: 5 September 2022 / Published online: 14 September 2022

Abstract

Introduction Nowadays, 70% of patients in Europe and the USA are affected by a p16 +, potentially HPV driven oropharyngeal squamous cell carcinoma. However, despite the improved survival rate in this group, the quality-of-life remains low in cases which neck dissection took place. In this vein, in recent years, some surgeons have considered to avoid dissection of level IIB, proposing a supra-selective non-IIb neck dissection.

Materials and methods A retrospective, longitudinal, multicentric study was conducted, including patients with pathologically confirmed primary HPV + or HPV − OPSCC who went through surgical treatment for the primary lesion and neck dissection.

Results 141 patients were included. Among them, 99 (70.2%) were male and 42 (29.8%) were female. The mean age was 62 ± 9 years (range 36–81). The most frequent anatomical location was the tonsil in 63 (44.7%) of patients. The most common approach was the classic transoral oropharyngectomy in 51 (36.2%) patients. Immunohistochemistry for p16 was positive in 62 (44%) patients. One-hundred and five (74.5%) patients received a unilateral ND, and a 36 (25.5%) a bilateral ND. Of those, a 12.8% (18/141) of patients were level IIb LN +. According to our results, level IIb ND should be considered in patients underwent therapeutic ND with positive LN metastasis in level IIa (OR = 9.83; 95% CI 3.463–27.917) or III (OR = 6.25; 95% CI 2.158–18.143), advanced (T3/T4) oropharyngeal primary tumors (OR = 3.38; 95% CI 1.366–8.405), and patients with ENE (OR = 6.56; 95% CI 2.182–19.770), regardless of p16 status.

Conclusions According to our results, level IIb ND should be considered in patients who underwent therapeutic ND with positive LN metastasis in level IIa or III, advanced oropharyngeal primary tumors, and patients with ENE, independently of p16 status. Prospective data are necessary to definitively ensure the safety of omitting ipsilateral or contralateral level IIb ND in cN − patients with early stage disease.

Keywords Oropharynx · Neck dissection · Shoulder syndrome

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Introduction

Cervical lymph node (LN) metastasis represents a well-known prognostic factor in head and neck (H&N) squamous cell carcinoma (SCC). It is well-known that chances of survival drop by almost 50% when the tumor involves the cervical LN [1, 2]. Clinically detectable LN metastasis in HPV negative oropharyngeal SCC (OPSCC) ranges from 40% to > 80%, and the rate of occult LN metastasis goes up to 30% [3–7]. LN metastasis in Human papillomavirus (HPV-p16 +) driven OPSCC, which is considered a distinct disease from tobacco associated HPV-OPSCC, is frequently reported [8, 9], while cervical LN involvement affects nearly 44% of clinically N0 necks and more than 80% of patients clinically N + after histological analysis [10].

Historically, H&N surgeons agree that in a patient with a risk of occult LN metastasis > 15–20% the neck should be treated either by surgery or radiotherapy (RT) [11]. This concept pushed forward the evolution of the surgical treatment of neck metastasis in the last century, leading to better oncological results, while minimizing the surgical morbidity.

The traditional radical neck dissection (ND) [removal of level I–V cervical LNs, Spinal accessory nerve (SAN), internal jugular vein (IJV), and sternocleidomastoid muscle (SCM)]) was associated with a dramatic morbidity [12], which has been evolving in the past five decades, thanks to a better understanding of the specific lymphatic spread in the H&N region, looking for procedures with equal oncologic efficacy and lower morbidity rates [6, 13–17].

Level IIb dissection is defined as the dissection of LN packed into the fibrofatty tissue confined in the triangle bounded by the posterior belly of digastric muscle and the skull base superiorly, SAN inferiorly and anteriorly, the SCM posteriorly and deep to the plane of the SAN over the e*levator scapulae muscle* and *splenius capitis* muscles. Level IIb neck dissection is commonly associated with SAN traction and devascularization.

The postoperative shoulder syndrome (SS), is defined as those anatomical changes, such as shoulder drop, muscle atrophy and winged scapula, accompanied by a decreased activity of the arm and associated with shoulder pain exacerbated by arm abduction [18], all of them, proportionally correlated with the extent of ND [19–22].

Despite the evolution of ND techniques, SS continues to be a complication, even with functional selective ND, with an incidence of at least 40% when the nerve is preserved [20–23]. This high rate is probably secondary to SAN traction, during the technically difficult level IIb dissection, whose procedure is in closed proximity of important structures, such as the SAN, IJV, internal carotid artery (ICA) or the occipital artery (OA).

In recent years, surgeons have considered to not dissect the level IIb, proposing a supra-selective non-IIb ND, supported by a less degree of SS in these patients [24–26], expecting to decrease the incidence of SS. The aim of the current study is to determine the distribution of positive LN metastasis in the level IIb in patients affected by an OPSCC (HPV + and HPV −) as well as to evaluate the potential oncological safety through the exclusion of level IIb dissection, to hypothetically preserve the SAN integrity in the HPV driven OPSCC era.

Methods

A retrospective, longitudinal, multicentric study (2 Spanish and 3 Italian Tertiary University Hospital) was conducted. Patients over 18 years with pathologically confirmed primary HPV + or HPV − OPSCC who underwent surgical treatment for the primary lesion and neck dissection between January 2016 and January 2021 were considered eligible for this study. Case identification was made throughout review of each department's databases using the International Classification of Diseases (ICD-9–10). Institutional review board was obtained.

The patients' medical histories were reviewed to obtain information about demographic data, clinical presentation, preoperative assessment, diagnosis, and surgical management. Factors potentially correlated with LN metastasis such as TNM classification, level of LN dissected and those involved in pathological analysis (at least level II–IV), age, sex, smoking history (defined as > 10 pack per years), alcohol consumption history, primary tumor site were investigated. Tonsil, Soft Palate or Base of Tongue (BOT) and pathological microscopic or gross extranodal extension (ENE) were revised.

Patients with incomplete clinical data, previous or primary non-surgical treatment, recurrent or persistent disease, distant metastasis, non-SCC etiology or unresectable disease (vertebral bone or tumor surrounding the ICA) were excluded. Unknown primary cases were left out, to decrease the risk of bias.

Before surgery, each patient was evaluated in the cancer clinic and underwent neck and chest computed tomography scan (CT) or Magnetic Resonance imaging (MRI) for preoperative evaluation of the neck and staging (N0 or N +). All patients were discussed in a multidisciplinary H&N tumor board with H&N surgeons, medical oncologists, radiation oncologists, radiologists, and pathologists. Is this phase, recommendation about the best option for each patient was assessed. OPSCC staging was updated in old cases and determined according to the Union for International Cancer Control (UICC) system and the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines. Positive p16 immunohistochemistry (IHC) was used as a surrogate marker to determine HPV-driven disease. Contralateral neck dissections were performed in case of primary tumor midline involvement or in case of clinical and radiologically suspected contralateral metastases. Following resection, the neck dissection specimens were separately stored according to each neck level included for histopathological analysis. Pathological reports were reviewed to determine the frequencies of nodal metastasis. All specimens were divided according to the levels (affected and unaffected levels). The number of dissected lymph nodes and prevalence of level IIb metastasis in each group were then determined and compared. After surgery, once it was recommended by the tumor board, patients received adjuvant radiotherapy or chemo-radiotherapy.

Quantitative and continuous variables are expressed as the mean ± standard deviation (SD). Results are expressed as both total and percentage. In the statistical analysis, Fisher's exact test was used to assess comparisons of the different outcome measures. Univariate association was calculated and multivariate association with level IIb LN metastasis was determined with a logistic regression model. Statistical analyses were performed using JASP (Version 0.11.1. University of Amsterdam, Netherlands) (https://jasp-stats.org/). A *p* value of 0.05 was considered statistically significant.

Results

A total of 141 patients benefited from surgery due to an OPSCC (p16 + or −). Among them, 99 (70.2%) were male and 42 (29.8%) were female. The mean age was 62 ± 9 years (range 36–81). Other demographic and clinical variables are described in Table 1.

The most common anatomical location was the tonsil in 63 (44.7%) patients, the BOT in 33 (23.4%), the soft palate in 10 (7.1%) with the remaining patients having disease in more than one sublocation (Table 1). The most frequent approach was the classic transoral oropharyngectomy, performed in 51 (36.2%) patients. IHC for p16 was positive in 62 (44%) patients. The primary tumor (pT) and pN classification is described in Table 1. Overall staging according to p16 immunohistochemistry is expressed in Table 2.

105 (74.5%) patients received a unilateral ND, and 36 (25.5%) a bilateral ND. Of the 177 dissections, 18 (9.6%) were positive for level IIb LN metastasis, meaning that 12.8% (18/141) of patients were level IIb LN +. These included two (3.3%) of the 61 cN0 dissections, confirmed as micro-metastasis, one p16 + and one p16 −, and 16 (13.8%) of the 116 cN + dissections, 5 p16 (+) and 10 p16 −. The mean number of LN dissected were 32 ± 20 (Min: 4/Max: 123) and the mean number of pathologically positive LN were 2 ± 2 (Min: 0/Max: 8). Among the 18 dissections with at least one positive LN in level IIb, one (5.5%) had at least one positive LN in level I, 14 (77.7%) in level IIa, 12 (66.6%) in level III, 3 (16.6%) in level IV, one (5.5%) in level V. There were just one (5.5%) dissection with one positive LN in level IIb only and just one case (5.5%) had a contralateral level IIb LN metastases with positives LN in both sides. All the data regarding ND and the overall distribution of level IIb metastasis according to stage and p16 immunohistochemistry are described in Tables 3 and 4, respectively.

The univariate analysis reveals a correlation between the presence of advanced T stage (T3/T4), positive LN in level IIa and III and ENE with LN metastasis in the level IIb (Table 5). The multivariate analysis confirms a correlation between the presence of level IIa LN metastasis, level III LN metastasis, advanced primary tumor stage, and ENE, as factors significantly associated with level IIb LN metastasis (Table 5). The multivariate analysis did not show that positive neck metastasis at other neck levels or HPV + OPSCC to be a risk or protective factor per se for level IIb metastasis.

Discussion

Nowadays, 70% of patients in Europe and the USA are affected by a p16 +, potentially HPV driven OPSCC [27]. The majority of them will be younger patients, who presented p16 + at early stages, and occupy median higher socioeconomic groups [28], compared to historically non-HPV associated OPSCC (p16 −). However, despite the improved survival in this group of patients, quality-of-life (QoL) remains lower in those cases, where ND was performed [29]. In this vein, and aiming for a decrease in ND-related morbidity, previous studies have been published suggesting to avoid level IIb dissection in clinical negative neck patients [24, 25]. Therefore, UK guidelines recommendations remain that level IIb may be omittable in T1–2 tumors if clinical disease in level IIa is absent, with heightened suspicion in tonsillar tumours [28, 30].

According to our results, 18 (12.8%) patients presented metastatic disease in the sub-level IIb. Moreover, factors such as the presence of level IIa or level III LN metastasis, an advanced primary tumor stage or the presence of ENE, were significantly associated with level IIb LN metastasis. Regarding P16 IHC status, 9.7% of p16 + cases have a positive LN in level IIb, and 15.1% of p16 cases have a positive LN in level IIb.

The debate is still ongoing as whether we can we omit level IIb ND in OPSCC regardless of the p16 status (+ or −). In general, it is known that level IIb is not a typical anatomic drainage site for primary tumors originated in the oropharynx. For this reason, some studies support the oncologic safety of selective ND for clinical neck disease, although

Table 1 Demographic variable

Variable	*N* (%)	IIb positive (%)	p^b
Sex			
Male	99 (70.2)	–	0.356
Female	42 (29.8)		
Age	62 ± 9(Min:36/Max:81)	–	
Tobacco consumption			
> 10 packs per year	76 (53.9)	–	0.890
< 10 packs per year	20 (14.2)		
No	45 (321.9)		
Alcohol consumption		–	
> 70 g per day	57 (40.4)		0.744
< 70 g. per day	84 59.6)		
HTA	70 (49.6)	–	0.270
DM	21 (14.9)	–	0.785
Cardiovascular disease	16 (11.3)	–	0.318
COPD	7 (5)	–	0.882
Anatomic location			0.295
Tonsil	63 (44.7)	–	
Base of tongue	33 (23.4)		
Tonsil + base of tongue	9 (6.4)		
Soft palate	10 (7.1)		
Tonsil + soft palate	13 (9.2)		
Tonsil + pharyngeal wall	6 (4.3)		
Tonsil + soft palate + pharyngeal wall	7 (5)		
Side			NC
Left	70 (49.6)	–	
Right	71 (50.4)		
Surgical technique			NC
Classic transoral oropharyngectomy	51 (36.2)	–	
Co2 TOLMS of the Pharynx	15 (10.6)		
TORS	47 (33.3)		
TOUSS	6 (4.3)		
Open approach	22 (15.6)		
Immunohistochemistry p16			0.684
Positive	62 (44)	6 (9.6)	
Negative	79 (56)	12 (15.2)	
p16 Positive previous smokers	22 (35)	–	NC
T Stage(including all cases)[a]			0.020
T1	58 (41.1)	3 (5.2)	
T2	63 (44.7)	8 (12.7)	
T3	14 (9.9)	4 (28.6)	
T4	6 (4.2)	3 (50%)	
Clinical N stage (including all cases)[a]		Histological result	0.014
N0	41 (29.1)	2 (4.9)	
N1	51 (26.2)	1 (1.9)	
N2a	15 (10.6)	3 (20)	
N2b	19 (13.5)	8 (42.1)	
N2c	12 (8.5)	2 (16.6)	
N3a	1 (0.7)	0 (0)	
N3b	2 (1.4)	2 (100)	
M stage			NC
M0	141 (100)		–

HTA arterial hypertension; *DM* diabetes mellitus; *COPD* chronic obstructive pulmonary disease; *TOLMS* transoral laser microsurgery; *TORS* transoral robotic surgery; *TOUSS* transoral ultrasonic surgery

[a]Data correspond to pathological T and N stage independent of IHC status and Univariate analysis

[b]*P* comparison about clinical and demographic variables in patients with and without level IIb metastasis; *NC* not calculated

Table 2 Overall stage and level IIb metastasis according to p16 immunohistochemistry

Overall stage	p16 negative (%)	p16 positive (%)	p^a	Level IIb (p16 negative)	Level IIb (p16 positive)	p
I	10 (12.6)	42 (68.8)	0.01	0	2	0.585
II	11 (13.9)	18 (29)		2	3	0.080
III	20 (25.3)	2 (3.2)		4	1	0.01
IVa	35 (44.3)			6		N/A
IVb	3 (3.8)			0		N/A
Total	79	62		12	6	

N/A Not apply

[a]Statistical significance of the difference in stage distribution between p16+and p16−Oropharyngeal Squamous Cell Carcinoma

Table 3 Data regarding neck dissection

Variable	N	%
Mean number of lymph nodes dissected	32 ± 20 (Min: 4/Max: 123)	
Mean number of pathologic lymph nodes	2 ± 2 (Min: 0/Max: 8)	
Number of neck dissections		
Unilateral	105	74.5
Bilateral	36	25.5
Total	177	100
Type of neck dissection		
Radical	20	11.3
Functional	58	32.7
Selective	65	36.7
Comprehensive	23	13
Modified radical	11	6.2
Levels included		
I–V	76	43
II–IV	101	57
Positives Lymph Node		
Level I	17	7.3[a]
Level IIa	90	50.8
Level IIb	18	9.6
Level III	62	35
Level IV	28	15.8
Level Va	14	6.2[a]
Level Vb	10	4.5[a]
IIb Pathological/clinical lymph nodes correlation		
cN−	2/61	3.3
cN+	16/116	13.8
Extranodal extension	25	14.1

[a]Percentage regarding patients underwent level I–V neck dissection

this issue remains controversial [31–33]. In general, our data are consistent with previous studies reporting frequencies of LN metastasis of 76–90% for level II (IIa and IIb), 22–50% for level III and 9–14% for level IV including all cases [31, 34–37]. When we merely considered level IIb metastasis, rates were 3.3% in cN−ND, and 13.8% in cN+ND. These data are consistent with the literature, that described rates between 2.5% and 20% for cN−patients and 5–50% cN+patients [3, 28, 38–41]. Our results highlight the importance of treating level IIb in a cN+patients and question the relevance of level IIb neck dissection in a cN−patients. Our data analysis according to p16 status is still consistent with the literature, with no significant differences between both groups. In this vein, previous authors

Table 4 Factors associated with Level IIb positive metastasis—univariate analysis

	N	*p*	OR (95% CI)
Positives lymph node			
Level I	0/17[a]	1.000	1.0 (0.018–53.282)
Level IIa	9/90	0.0001	1.19 (1.052–1.321)
Level III	7/62	0.0001	1.26 (1.073–1.447)
Level IV	1/28	0.506	3.0 (0.117–76.793)
Level Va	1/14[a]	0.656	3.0 (0.112–79.918)
Level Vb	0/10	1.000	1.0 (0.018–55.271)
Immunohistochemistry p16			
Positive	6/62	0.393	0.63 (0.226–1.793)
Negative	12/79		
T Stage (p16 negative)			
T1/T2	2/12	0.05	3.0 (0.642–13.885)
T3/T4	10/12		
T Stage (p16 positive)			
T1/T2	2/6	0.505	2.0 (0.260–15.381)
T3/T4	4/6		
T stage (overall)			
T1/T2	4/18	0.05	1.28 (0.078–1.437)
T3/T4	14/18		
N stage (including all cases)			
N –	2/61	0.06	4.20 (0.936–18.8987)
N +	16/116		
Extranodal extension			
Present	8/25	0.004	4.72 (1.614–13.848)
Absent	10/152		

OR Odds ratio

[a]Patients underwent level I–V neck dissection

Table 5 Factors associated with Level IIb positive metastasis—multivariate analysis

Factor	*p*	OR (95% CI)
Level IIa metastasis	0.001	9.83 (3.463–27.917)
Level III metastasis	0.0007	6.25 (2.158–18.143)
Advanced primary tumor stage (T3/T4)	0.008	3.38 (1.366–8.405)
Extranodal extension[a]	0.0008	6.56 (2.182–19.770)

OR odds ratio

[a]Microscopic or gross extranodal extension was considered

such as Amsbaugh et al., compared nodal frequencies per neck level in p16 + and p16 – OPSCC disregarding the N status and established similar distributions in both cases, after comparing the historical Lindbergh study examining overall distributions in OPSCC [35, 36].

One case of isolated level IIb metastases was found in our cohort. This finding is consistent with previous data published about H&N anatomical sub-sites, where authors described that level IIb metastasis are most often found with occult or gross pathologic nodes at other levels [41–43]. Regarding the need of contralateral dissection, definitive recommendation based in our results for contralateral IIb level dissection are difficult to establish, since just one patient had a positive contralateral NM in level IIb in a patient with a BOT tumor, with bilateral positive NM. This is consistent with the study recently published by Last et al. [44] which demonstrated a rate of occult contralateral NM in 21.4% of patients with HPV-related BOT OPSCC. The risk is considered higher when the tumor crosses the midline. In both situations, our data suggest that omitting level IIb dissection in a cN – case would be possible if the patients are appropriately staged and the tumor does not cross the midline in case of BOT primary.

In this vein, when an elective ND is planned, in a N0 neck, our results suggest that the risk of occult level IIb nodal metastasis will be lower than the usual threshold considered in ND (15–20%) for potential micro-metastasis, and therefore, we should advocate for level IIb sparing, regardless of p16 status. By contrast, in a N + neck treated by therapeutic ND, the radiosensitivity of the cancer according to the p16 status should be considered to decide the necessity to dissect level IIb. In the same vein, and despite the increasing ability to diagnose ENE radiologically, pathologic ENE is known just postoperatively in many cases. Being difficult for surgeons to decide on the need for level IIb neck dissection. However, based in our results, hypothetically, this might help in the decision of adjuvant treatment of level IIb if a neck dissection has not yet been performed.

Regarding potential confounding risk factors in OPSCC p16 + patients, tobacco consumption was the most common in our cohort, corresponding to 35% of patients. This is lower than what Amsbaugh et al. [36] reported (67%) but higher than Plonowska et al. (27%), being this group of patients considered as intermediate risk [34].

Concerning SS, multiple techniques have been described to reduce ND morbidity so far. However, this continues to be a surgical procedure associated with multiple sequelae that can impact the patient's QoL. In addition, the anatomical preservation of the SAN is not always associated with normal shoulder function. Anatomically, the SAN has its cranial origin in two parts: an accessory portion from the medulla and a spinal part from the lateral portion of the ventral column. The SCM and trapezius muscles will receive motor innervation from the SAN. However, the cervical plexus (C2–C4) also innervates the trapezius, providing some motor input in approximately 20% of the population [45, 46]. According to the indexed literature, 40% of patients who underwent a nerve sparing ND will suffer a SS [19, 47]. This is most probably caused by the clearance of the submuscular recess associated with mechanical traction and ischemic trauma on the cranial portion of the spinal accessory nerve running from the skull base to its entrance into the sternocleidomastoid muscle. Moreover, the vascular supply to the SAN usually originates from the surrounding fibrofatty tissue in the levels IIa/IIb making it difficult to avoid the ischemic consequences of dissection. Moreover, SAN injury can cause long-term complications such as adhesive capsulitis and fibrosis of the glenohumeral joint secondary to the limitation in the mobility of the shoulder.

Finally, we need to highlight the limitations of our study such as the retrospective and descriptive nature of the study design, the absence of neurophysiologic studies regarding SAN function, the lack quality of life questionnaire, the risk of neck-level misclassification given the different operative techniques of multiple surgeons, the lack of standardization of HPV testing methods among centers and the necessity to omit the type of technique such as in situ hybridization and polymerase chain reaction from the final analysis. Further prospective studies are needed to analyze possible risk factors for occult lymph nodes and recurrence for OPSCC independent of p16 status, the neurophysiologic rate of SAN injury, the value of positron emission tomography combined with computed tomography scanning in the preoperative assessment and the QoL of those patients who underwent ND. Moreover, unknown primary cases (IHC p16 +) need to be analyzed in future studies.

Conclusions

According to our results, level IIb ND should be considered in patients who underwent therapeutic ND with positive LN metastasis in level IIa or III, advanced oropharyngeal primary tumors, and patients with ENE, independently of p16 status. Prospective data are necessary to definitively ensure the safety of omitting ipsilateral or contralateral level IIb ND in cN − patients with early stage disease.

Funding No funding was used for this research.

Declarations

Conflict of interest Authors declare don't have any conflict of interest.

Ethical approval IRB approval—Code: HUD2105.

Informed consent Informed consent was not required due to the retrospective nature of data collection.

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