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Review

Head and neck carcinoma of unknown primary

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ABSTRACT

In adult cervicofacial pathology, carcinoma of unknown primary is defined as lymph-node metastasis the anatomic origin of which is not known at the time of initial management. It constitutes up to 5% of head and neck cancers. Presentation may suggest benign pathology, delaying and confusing oncologic treatment. Diagnostic strategy in cervical lymph node with suspicion of neoplasia requires exhaustive work-up to diagnose malignancy and, in 45% to 80% of cases, depending on the series, to identify the primary site. Histologic types comprise squamous cell carcinoma, thyroid carcinoma, adenocarcinoma, neuroendocrine carcinoma and undifferentiated carcinoma. Association is sometimes found with human papilloma virus or Epstein Barr virus, guiding treatment. The objective of the present study was to provide clinicians with the necessary diagnostic tools, based on the current state of clinical, imaging and pathologic knowledge, and to detail treatment options.

1. Introduction

Metastasis of unknown primary is defined as metastasis the anatomic origin of which is not known at the time of initial management [1]. In the head and neck region, it concerns lymph-node structures, and accounts for 1.5–5% of tumors [2,3]. Rigor is needed to diagnose head and neck cancer of unknown primary (CUP). When the work-up succeeds in identifying the primary site, the term "lymph-node metastasis without known primary" is inappropriate. Head and neck CUP is a diagnostic challenge, due to unusual presentation, delaying treatment [4,5], and liable to sow confusion leading to therapeutic error.

The present study aimed to review the literature on histologic type, diagnostic strategy and treatment options in cervical CUP.

2. Discussion

2.1. Histopathology of cervical CUP

2.1.1. Squamous cell carcinoma: general considerations

Squamous cell carcinoma accounts for 53% to 77% of cervical CUPs. The most frequent form is common squamous cell carcinoma, accounting for 58% of cases; the other 15% are variants: verrucous, papillary, spindle-cell, adenosquamous, undifferentiated or basaloid [4].

There would seem to be a link between human papillomavirus (HPV) and CUP. American series show up to 80% oropharyngeal primary locations on diagnostic work-up including robotic surgery, with up to 90% correlation between HPV and squamous cell CUP [6–8]. However, results from published or forthcoming studies on primary rates or therapeutic de-escalation are to be interpreted with caution, due to the geographic variability of ENT HPV. The Papillophar study, conducted between 2009 and 2012 in 14 French hospitals, found only 27% association between HPV and oropharyngeal cancer, which was much lower than the American findings [9]. In France, the prevalence of HPV in squamous cell CUP is not known.

One explanation for how oropharyngeal cancer takes the form of CUP concerns the histologic structure of tonsillar tissue, which is composed of lymphoid and epithelial tissue [10]. The superficial epithelium in continuity with the mucosa of the oropharynx is strewn with crypts involved in the tonsillar immune function. During HPV infection with high oncogenic risk, the virus infecting the Malpighian epithelium basal cells induces tumor in the crypt floor. Tonsillar crypt epithelium lies on a discontinuous basal membrane bordered by intraepithelial blood vessels, enabling millimeter-sized tumors to metastize without acquiring the genetic alterations required for stromal invasion (thus, the term "in situ carcinoma" is

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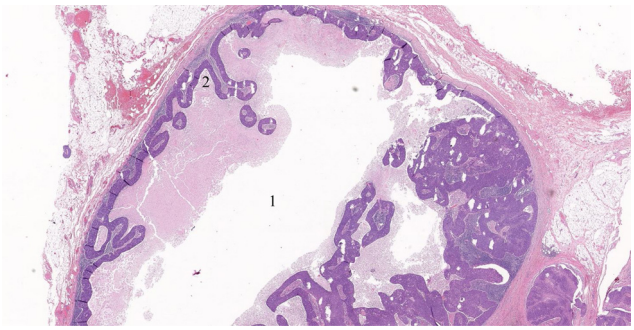

Fig. 1. Lymph-node metastasis from HPV-induced non-keratinizing squamous cell carcinoma. Hematoxylin-eosin staining; low magnification (Pr V. Costes). Morphologic analysis shows lymph node with cystic cavity (1) surrounded by poorly or non-keratinized epithelial proliferation (2), comprising oval or slightly spindle-shaped cells with fuzzy cytoplasmic boundaries and high nucleo-cytoplasm ratio.

inappropriate to tumor localized in the lingual or palatine tonsils) [11]. This poorly differentiated metastatic tissue migrates into the lymphatic system at an early stage, often accompanied by necrotic remodeling leading to metastatic cyst formation (Fig. 1).

2.1.2. Nasopharyngeal squamous cell carcinoma

Nasopharyngeal squamous cell carcinoma comprises keratinizing, non-keratinizing and basaloid forms. The non-keratinizing form is subdivided as differentiated and non-differentiated, and is almost systematically associated with Epstein Barr virus (EBV) [12].

Squamous cell carcinoma associated with EBV should thus be seen as an occult nasopharyngeal primary [13].

2.1.3. What markers to screen for in squamous cell CUP?

Screening for association with HPV or EBV has been part of the CUP work-up procedure since the 2017 8th edition of the American Joint Committee on Cancer (AJCC)'s Tumor Node Metastasis (TNM) classification (Tables 1–3) [13]. This classifies unknown primaries associated with HPV as being of oropharyngeal origin and those associated with EBV as of nasopharyngeal origin, to guide treatment and notably to select target mucosa volumes in radiation therapy. The decision-tree shown in Fig. 2 indicates the situations in which tests should be made according to the College of American Pathologists' guideline (Fig. 2) [14].

Cystic metastasis of HPV-induced squamous cell carcinoma can be confirmed on lymph-node fine-needle biopsy by detection of: deoxyribonucleic acid (DNA) of high-risk HPV (HR-HPV) on polymerase chain reaction (PCR); HR-HPV DNA on in-situ hybridization (ISH); or E6/E7 ribonucleic acid (E6/E7 RNA) on ISH. Anti-p16 immunolabeling is insufficient on fine-needle biopsy material alone.

The HPV origin of metastasis in levels II or III of a non-keratinizing squamous cell carcinoma can be confirmed on the lymph-node resection specimen by screening for p16 protein alone: intense diffuse expression in > 70% of cells on nuclear and cytoplasm labeling.

For keratinizing squamous cell carcinoma or adenopathies outside levels II and III, complementary HPV-specific testing (ISH or PCR) is required. Association with EBV is best screened for on ISH detection of Epstein-Barr-encoded RNA-1 (EBER1).

2.1.4. Differential diagnoses of p16+ squamous cell CUP without oropharyngeal primary

Cervical lymph-node metastases of cutaneous squamous cell carcinoma express p16 in 20% of cases, without association with HR-HPV [15,16]. HPV-associated squamous cell carcinoma has been reported in the nasopharynx [17], oral cavity and larynx [18]. Whatever the primary site, spontaneous regression can result in the primary disappearing: i.e., authentic T0 on the TNM classification [19].

2.1.5. Differentiated thyroid carcinoma

Differentiated thyroid carcinoma mainly comprises papillary carcinoma, where lymph-node metastasis is more frequent than in the vesicular subtype. In the series of 167 papillary microcarcinomas reported by Garrel et al. [20], 4.4% of patients ($n = 15$) showed lymph-node metastasis of a papillary carcinoma not seen on imaging. Diagnosis is confirmed by papillary cells detected on lymph-node aspiration biopsy or elevated thyroglobulin in the biopsy needle rinse liquid [21,22]. Thyroid medullary carcinoma should also be screened for; serum calcitonin assay is contributive, but needs to take account of a false-positive rate that was as high as 69% in some series [23,24].

2.1.6. Neuroendocrine carcinoma

Morphologic criteria associated with chromogranin A and synaptophysin expression suggest neuroendocrine carcinoma [25]. The most common head and neck location is the supraglottic larynx, where progression may be submucosal. Merkel carcinoma should be suspected in neuroendocrine carcinoma positive for cytokeratin 20, suggesting metastasis from an occult or spontaneously regressing cutaneous primary [26].

2.1.7. Salivary gland adenocarcinoma

In lymph-node metastasis of level I, II or III adenocarcinoma, a salivary gland primary should be investigated [27].

2.1.8. Carcinoma of subclavicular origin

Cervical lymph-node metastasis involves a non-head and neck primary in almost 1% of cases, mainly adenocarcinoma. Locations in decreasing order of frequency comprise the breast, lung, kidney, testicle and uterus [28]. Tumor profiling is based on cytokeratin CK7 and CK20, identifying a group of possible primary sites, completed by immunohistochemistry [25].

2.2. Diagnostic procedure

2.2.1. Clinical assessment

The mean interval between discovery of a cervical mass and diagnosis of CUP ranges from 2 to 5 months [4,5]. The usual clinical presentation is of a cervical mass with 3–4 weeks' progression. In the series reported by Grau et al. [29], this was the only symptom in 94% of cases ($n = 352$); pain and weight-loss were found in only 9% and 7% of cases, respectively. The procedure in case of chronic or cyst-like cervical adenopathy was set out by the French Society of ENT guidelines of 2010 and 2018 [30,31], as shown in Fig. 3. The clinician's prime objective is to rule out neoplastic pathology by tracing history of cutaneous carcinoma with metastatic potential (squamous cell carcinoma, melanoma or Merkel carcinoma) or head and neck or thyroid primary. Particular attention should be paid to diagnosis of 2nd branchial cleft cyst (tonsillar cyst); this is a thin-walled isolated anterolateral cervical mass with thick "milk chocolate" liquid on aspiration, without malignancy criteria on imaging. Revelation may be late, in adulthood, secondary to infection. After 40 years of age, such cysts should be considered metastatic unless proved otherwise [32–34]. In Pietarinen-Runtti et al.'s series [35] of 196 patients with radiologically benign 2nd-cleft cysts, the rate of cystic metastasis of squamous cell carcinoma was 3.1% ($n = 6$) and that of cystic metastasis of occult thyroid papillary carcinoma 0.5% ($n = 1$). Cystic lymph nodes may also suggest a papillomavirus-induced primary in the oropharynx (palatine or lingual tonsils) [3,36,37]. The location of the metastatic lymph node indicates the possible primary site (Fig. 4) [38]. Lymph-node levels mainly involved in cervical CUP are, in decreasing order of

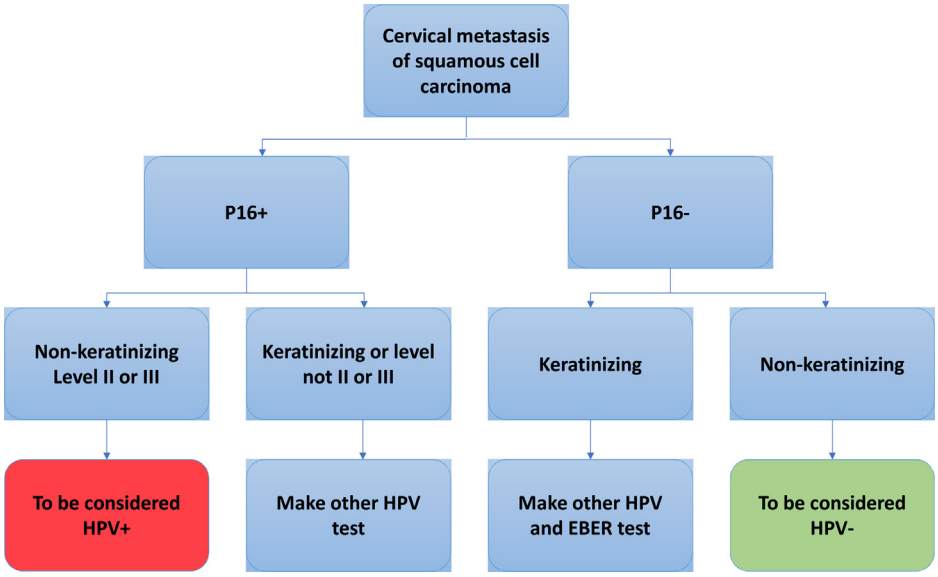

Fig. 2. Decision-tree for screening of HPV and EBER status.

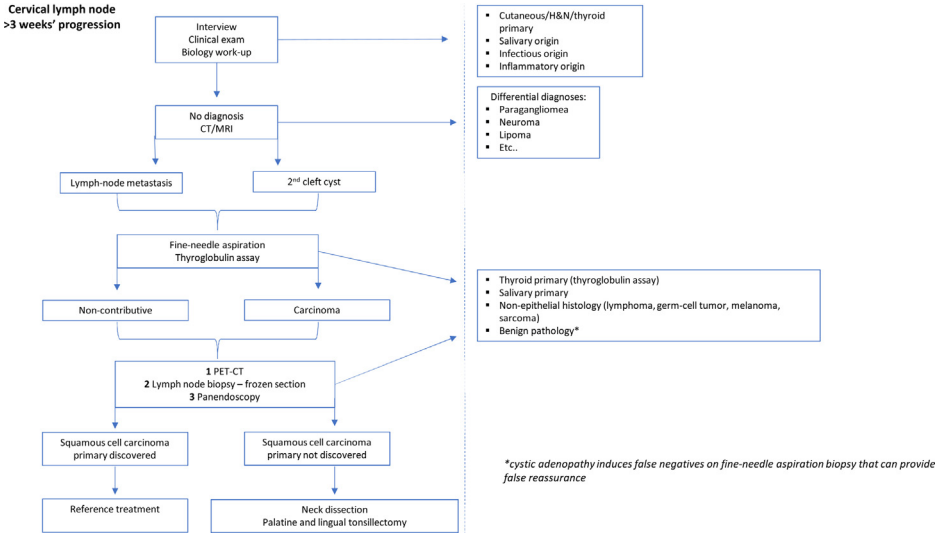

Fig. 3. Decision-tree in case of cervical lymph-node metastasis.

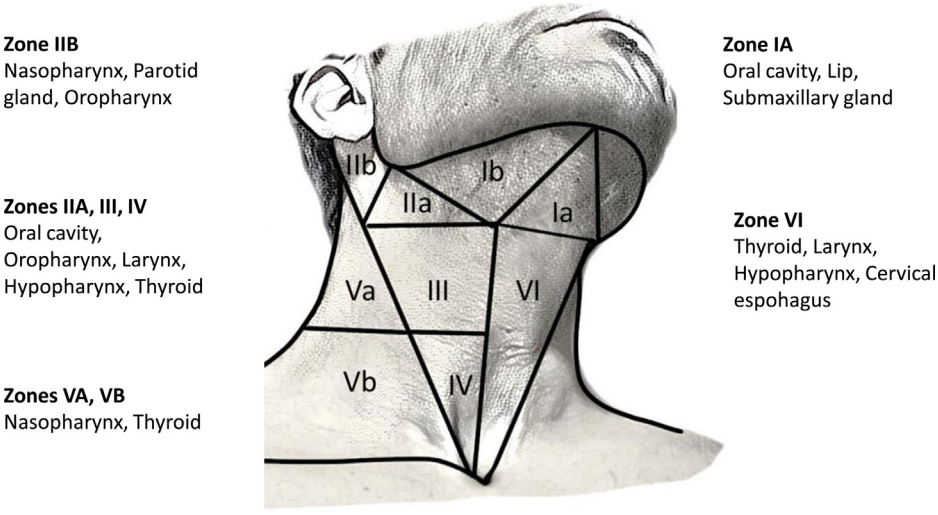

Fig. 4. First levels of lymphatic drainage according to head and neck site [38].

Table 1
HPV-associated oropharyngeal cancer of unknown primary: AJCC/UICC 2017 TNM classification.

Tumor (T)	
T0	No primary identified, but association to papillomavirus found in lymph node
Cervical lymph nodes (N)	
Clinical classification (cN)	For patients managed without neck dissection
cNx	Lymph nodes cannot be assessed
cN0	No lymph-node metastasis
cN1	One or more ipsilateral lymph nodes, none larger than 6 cm
cN2	Contralateral or bilateral lymph nodes, none larger than 6 cm
cN3	Lymph nodes larger than 6 cm
Pathological classification (pN)	For patients managed with neck dissection and histologic analysis
pNx	Lymph nodes cannot be assessed
pN0	No lymph-node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes
Distant metastasis (M)	
MX	Distant metastasis not assessed
M0	No distant metastasis
M1	Distant metastasis

Prognostic stages

T	N	M	Stage
T0	N1	M0	I
T0	N2	M0	II
T0	N3	M0	III
T0	All N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; HPV: human Papillomavirus.

Table 2
Nasopharyngeal cancer of unknown primary: AJCC/UICC 2017 TNM classification.

Tumor (T)	
T0	No primary identified, but association to EBV found in lymph node
Cervical lymph nodes (N)	
Nx	Lymph nodes cannot be assessed
N0	No lymph-node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below caudal border of cricoid cartilage
Distant metastasis (M)	
MX	Distant metastasis not assessed
M0	No distant metastasis
M1	Distant metastasis

Prognostic stages

T	N	M	Stade
T0	N1	M0	II
T0	N2	M0	III
T0	N3	M0	IV A
T0	All N	M1	IV B

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; EBV: Epstein-Barr Virus.

frequency, II, III and IV [29]. Bilateral lymph-node metastasis suggests mid-line tumor: oral floor, nasopharynx, tongue base, larynx. Metastases of nasopharyngeal carcinoma are located mainly in levels IIb or V, and those of occult thyroid cancer mainly in level IV [20]. In case of level IV (left = Virchow-Troisier node) or Vb involvement, a digestive, pulmonary or mammary primitive is suggested [39]. This distribution may, however, lead to confusion, as in 10-15% of cases lymph-node metastases of the oral cavity and oropharynx are located in level III or IV [40].

2.2.2. Computer tomography (CT) and magnetic resonance imaging (MRI)

Contrast-enhanced cervical CT from skull-base to clavicles coupled to thoracic CT is the reference imaging technique for extension assessment. Sensitivity is between 49% and 94% and specificity between 78% and 98% for lymph-node malignancy; the examination determines the anatomic situation in relation to neurovascular structures, and assesses extracapsular extension and presence of retropharyngeal or contralateral adenopathies [41]. MRI provides better tissue analysis for the skull base and palatine tonsils, which are the main sites for cervical CUP [42,43]. However, MRI has not been shown to be more sensitive than CT to occult head and neck cancer [44].

2.2.3. Cytology

Lymph-node fine-needle aspiration, preferably under ultrasound control, is the first-line examination. The risk of disseminating cells along the way is negligible [45]. It is an operator-dependent

Table 3
Head and neck squamous cell carcinoma of unknown primary, without HPV or EBV association: AJCC/UICC 2017 TNM classification.

Tumor (T)	
T0	Primary tumor cannot be assessed
Cervical lymph nodes(N)	
Clinical classification (cN)	For patients managed without neck dissection
cNx	Lymph nodes cannot be assessed
cN1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENEc(−)
cN2a	Metastasis in a single ipsilateral lymph node, > 3 cm, ≤ 6 cm, ENEc (−)
cN2b	Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENEc (−)
cN2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENEc (−)
cN3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENEc (−)
cN3b	Metastasis in any node(s) and clinically overt ENEc (+)
Clinical capsule rupture (ENEc) is defined by skin lesion, fixation to underlying muscular or vascular structures, clinical signs of neural involvement (cranial nerve(s), brachial plexus, phrenic nerve, sympathetic nerve trunk)	
Pathological classification (pN)	For patients managed with neck dissection and histologic analysis
pNx	Lymph nodes cannot be assessed
pN0	No lymph-node metastasis
pN1	Ipsilateral lymph node metastasis ≤ 3 cm and ENEp (-)
pN2a	Single ipsilateral lymph node metastasis ≤ 3 cm and ENEp(+) or Single ipsilateral lymph node metastasis > 3 cm, ≤ 6 cm, ENEp (−)
pN2b	Ipsilateral lymph node metastasis ≤ 6 cm, ENEp (−)
pN2c	Bilateral or contralateral lymph node metastasis ≤ 6 cm, ENEp (−)
pN3a	Lymph node metastasis >6 cm, ENEp (−)
pN3b	Single ipsilateral lymph node metastasis > 3 cm and ENEp (+) or Single contralateral lymph node metastasis ≤ 3 cm and ENEp (+) or Multiple ipsi-, contra- or bi-lateral lymph node metastases with ENEp (+) regardless of size
Capsule rupture on histology (ENEp) is classified as minor (ENEmi) for extension ≤ 2 mm or major for > 2 mm. ENEmi and ENEma are considered ENE(+) in the pN classification	
Distant metastasis (M)	
MX	Distant metastasis not assessed
M0	No distant metastasis
M1	Distant metastasis

Prognostic stages

T	N	M	Stade
T0	N1	M0	III
T0	N2	M0	IVA
T0	N3	M0	IVB
T0	All N	M1	IVC

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; HPV: Human Papillomavirus; EBV: Epstein-Barr Virus; ENE: extra-nodal extension (capsule rupture).

examination; for an experienced team, sensitivity is 83–97% and specificity 91–100% for metastatic cell detection [45–47]. Negative findings do not rule out metastatic lymph nodes, especially in case of cystic presentation, where the false-negative rate may be as high as 42% [48]. Aspiration targeting the cyst walls enhances positivity [49]. A simple means of confirming differentiated thyroid cancer is to assay thyroglobulin in the rinse liquid. Even in the absence of tumor cells, elevated thyroglobulin confirms neoplasia of thyroid origin [21,22]. Trocar biopsy may be considered in case of negative findings; the risk of dissemination is no more than 0.001% [50]. Partial lymph-node resection is not recommended due to risk of local complications and systemic dissemination [51]. However, these techniques were reported to be harmless when complementary surgery and/or radiation therapy is performed for malignant pathology [52,53].

2.2.4. Positron-emission tomography (PET)

18-fluorodeoxyglucose positron-emission tomography (18-FDG PET) is currently recommended in diagnostic work-up for cervical lymph-node metastasis. PET/PET-CT resolution encounters a limit for tumors less than 8–10 mm [42,54]. The lympho-epithelial tissue of Waldeyer's ring and the salivary glands are physiological fixation sites for FDG, causing false positives. Hypermetabolic activity is detected at the surgical site up to 6 weeks after biopsy or tonsillectomy [55]. PET coupled to CT (PET-CT) shows better diagnostic efficiency than PET alone, and is now the reference technique [2]. According to Miller [56], PET-CT detects 29% of primaries when CT and MRI proved negative; linking PET-CT to panendoscopy gave a detection rate of 45%. When the paired examination identified no primary, the tumor was identified during follow-up in fewer than 6% of cases. In the meta-analysis by Rusthoven et al. [54], including 16 studies (302 patients) between 1994 and 2003, detection of hypermetabolic activity gave false-positive rates of 39.3% in the palatine tonsils, 21% in the tongue base, and 8% in the hypopharynx. The examination identified unknown cervical lymph-node metastases in 15.9% of cases and remote distant metastases in 11.2%. The main problem with these studies and their findings lies in the definition of CUP, as inclusion criteria varied from physical examination alone to CT/MRI+panendoscopy preceding PET/PET-CT [57]. The sensitivity of PET/PET-CT thus ranged from 27% to 87.5%, with positive predictive values ranging from 57% to 77% for primary detection [58–60].

2.2.5. Panendoscopy-tonsillectomy-biopsy

Sequential panendoscopy-tonsillectomy-biopsy is used for squamous cell CUP. Head and neck panendoscopy including

nasopharyngeal endoscopy under general anesthesia is systematic. It screens for sometimes millimeter-sized submucosal lesions, notably in the tonsillar and tongue-base regions, with the help of finger palpation. If panendoscopy and PET-CT fail to guide biopsy, palatine tonsillectomy ipsilateral to the metastatic lymph node coupled to tongue-base biopsy is performed. The aim is to detect submucosal cancer or cancer in the palatine and lingual tonsil lymphoepithelial crypts; these sites account for up to 90% of unknown primaries emerging during follow-up [61]. The interest of this surgical technique is to determine the optimal target volume in case radiation therapy is indicated, limiting radiation dose to other head and neck mucosa sites, and to improve post-treatment follow-up [62,63]. Histologic analysis of tonsillar tissue should use fine slices every 2 mm, to screen for sub-centimeter-sized tumors. Tonsillectomy ipsilateral to the metastatic lymph node provides between 18% and 44.6% detection of primaries [61,64,65]. The variability of diagnostic efficiency between studies is due to differences in preoperative imaging, with varying use of CT and PET-CT. The diagnostic efficiency of palatine tonsillectomy is greater than that of deep biopsy: 29.5% versus 3.2% ($P = 0.0002$) [66]. A recent technique consists in transoral robotic-assisted or laser resection of tongue-base lymphoepithelial tissue. A literature review reported 80% primary detection when transoral palatine tonsillectomy was associated to lingual tonsillectomy; primaries were located in the lingual tonsils in 56% of cases [8]. The usefulness of bilateral palatine tonsillectomy is a subject of discussion. Two studies reported respectively 10% (4/41) [67] and 23% (5/22) [68] primary detection in the contralateral palatine tonsil. Bilateral palatine tonsillectomy has other interests: morbidity is low; it resolves clinicians' doubts in case of contralateral tonsillar fixation on follow-up PET-CT; and serendipitous discovery of synchronous primaries has been reported [69].

2.2.6. Lymph-node biopsy and neck dissection

Lymph nodes suspected of neoplasia or benign branchial cyst aspect on imaging should be checked histologically. The entire mass is resected, under general anesthesia if possible, to associate frozen-section biopsy and neck dissection in a single step in case of squamous cell carcinoma metastasis or tumor necessitating lymph-node surgery [30]. In non-operable advanced stages, chemoradiotherapy may be proposed [70].

2.2.7. TNM staging of squamous cell CUP

The 2017 update to the AJCC TNM classification [13] includes head and neck squamous cell carcinoma of unknown primary, distinguishing 3 entities. Forms associated with papillomavirus are of oropharyngeal origin, those associated with EBV of nasopharyngeal origin, and p16- EBV- forms cannot be assigned to any specific head and neck mucosal site (Tables 1–3).

The p16+ status is to be considered with caution, due to the differential diagnoses of oropharyngeal primaries, as seen above.

2.3. Treatment of head and neck CUP

2.3.1. General principles for adenocarcinoma, neuroendocrine carcinoma and undifferentiated of unknown primary

Neck dissection usually follows diagnosis on frozen section analysis if there are no subclavicular metastases and the lymph node is resectable.

In adenocarcinoma of suspected salivary gland origin (levels I, II, III), the problem is that the tumor is high grade, due to the lymph-node metastases, and resistant to radiation therapy.

Initial neck dissection allows screening for a primary in the submaxillary and sublingual glands. Panendoscopy should be associated to screen for accessory salivary gland lesions. If no primary is found, secondary parotidectomy is a good option [70]. Postoperative adjuvant radiation therapy is implemented according to histologic findings.

In undifferentiated carcinoma of non-thyroid origin, EBV status determines therapy. EBV+ carcinoma is considered to be of nasopharyngeal origin (Table 2), treated by chemoradiotherapy. EBV- forms are treated as for squamous cell carcinoma. Neuroendocrine carcinoma suggestive of Merkel carcinoma on immunohistochemistry is treated by neck dissection associated to radiation therapy according to histologic findings, with dermatologic follow-up.

2.3.2. Treatment of squamous cell CUP: surgery

The diagnostic sequence for operable squamous cell CUP includes I-IV neck dissection. The procedure is adequate treatment for squamous cell carcinoma with N1 lymph node metastasis (previous 7th edition AJCC TNM classification) without macroscopic capsule rupture, with or without HPV association, as adjuvant radiation therapy seems not to improve local control or overall survival [71,72]. Discovery of the primary during diagnostic transoral surgery (palatine and/or lingual tonsillectomy) results in T1 classification, but is not enough to achieve oncologic margins. Purely surgical management requires completing resection with supplementary muscular margins: pharyngectomy including the middle pharyngeal constrictor for the palatine tonsil and the lingual muscle for the lingual tonsil. Including these margins in initial diagnostic surgery, however, increases morbidity and the risk of surgical complications. Complementary radiation therapy can be avoided only in case of satisfactory margins and no negative criteria on histology [70].

2.3.3. Treatment of squamous cell CUP: radiation therapy

Conformational intensity-modulated radiation therapy (CIMRT) is now the technique of choice [68,73,74].

Iganej [75] found an 81% rate (13/16) of local control in pN1 and pN2 without capsule rupture (AJCC TNM 7th edition) de 81% (13/16) with surgery alone, versus 89% (8/9) with surgery and adjuvant radiation therapy in early stages ($P = 0.94$). For stages N2b, N2c and N3 (AJCC TNM 7th edition) and lymph node metastasis with capsule rupture, adjuvant radiation therapy provided better overall and specific survival than isolated surgery or isolated radiation therapy [76]. None of these studies took account of HPV status. When tumor site is unknown, choice of uni- versus bi-lateral cervical radiation therapy cannot be guided with precision in unilateral metastasis. Ligey et al. [77] found no difference in 5-year overall survival and locoregional control between uni- versus bi-lateral radiation therapy in a series of 95 patients. The Swedish study by Hemminki et al. [78] suggested better locoregional control after bilateral than ipsilateral radiation therapy; this did not improve survival, and may be due to effective salvage radiation therapy and surgery in patients having undergone unilateral lymph-node radiation treatment. These retrospective data suggest that unilateral lymph-node radiation therapy is sufficient as a first step when involvement is not bilateral, histologic grade is favorable and EBV is negative [79]. Irradiation of the mucosa reduces both subsequent emergence of the primary (estimated at 20% [29]) and locoregional recurrence, but does not seem to improve survival [80,81]. There are several protocols: extensive irradiation from nasopharynx to larynx, or more focalized on the oropharynx or nasopharynx; no superiority has been demonstrated, due to lack of therapeutic trials, but sequelae are greater after extensive radiation therapy. There are at present no guidelines for selective irradiation of mucosal sites in case of HPV or EBV association [13].

2.3.4. Treatment of squamous cell CUP: chemotherapy

No randomized trials in cervical CUP have shown benefit for chemotherapy. Indications are based on results for squamous

cell carcinoma of known head and neck primary. Capsule rupture and positive margins on histology are of poor prognosis, and chemotherapy associated to postoperative radiation therapy may improve overall survival, recurrence-free survival and locoregional control [82].

2.3.5. Prognosis in squamous cell CUP

A recent American study, with 978 patients treated between 2010 and 2013, analyzed prognostic factors for CUP. Three-year survival in HPV-associated CUP ($n = 746$) was 94.8%, compared to 80.3% in HPV-negative cases ($n = 232$). There was no difference in survival according to treatment modality in HPV-associated CUP. Isolated radiation therapy in cN2/N3 HPV-negative patients was associated with significantly poorer survival than multimodal chemoradiotherapy or surgery with chemoradiotherapy [83].

3. Conclusion

Head and neck carcinoma of unknown primary is a rare condition in which management has recently progressed with the demonstration of HPV or EBV association in some cases, impacting clinical presentation. In future, likely further studies will enable "therapeutic de-escalation" to be proposed, promising improved quality of life. Caution is, however, called for, and de-escalation should not be extended to CUP unassociated with HPV, at the risk of jeopardizing oncologic results.

Disclosure of interest

The authors declare that they have no competing interest.

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