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SFORL Guidelines

Cystic form of cervical lymphadenopathy. Guidelines of the French Society of Otorhinolaryngology - Head and Neck Surgery (SFORL). Part 1: Diagnostic procedures for lymphadenopathy in case of cervical mass with cystic aspect

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ABSTRACT

Objectives: The authors present the guidelines of the French Society of Otorhinolaryngology - Head and Neck Surgery Society on diagnostic procedures for lymphadenopathy in case of a cervical mass with cystic aspect.

Methods: A multidisciplinary work-group was entrusted with a review of the scientific literature on the topic. Guidelines were drawn up, then read over by an editorial group independent of the work-group, and the final version was drawn up. Guidelines were graded as A, B, C or expert opinion, by decreasing level of evidence.

Results: In adults presenting a cystic cervical mass, it is recommended to suspect cervical lymphadenopathy: in order of decreasing frequency, cystic metastasis of head and neck squamous cell carcinoma, of undifferentiated nasopharyngeal carcinoma, and of thyroid papillary carcinoma (Grade C). On discovery of a cystic cervical mass on ultrasound, architectural elements indicating a lymph node and a thyroid nodule with signs of malignancy should be screened for, especially if the mass is located in levels III, IV or VI (Grade A). Malignant lymphadenopathy should be suspected in case of cervical mass with cystic component on CT (Grade B), but benign or malignant status cannot be diagnosed only on radiological data (CT or MRI) (Grade A), and 18-FDG PET-CT should be performed, particularly in case of inconclusive ultrasound-guided fine needle aspiration biopsy (Grade C).

1. Introduction

In the following guidelines, "lymphadenopathy" refers to lymph-node metastasis from a malignant tumor, excluding all other causes of adenomegaly (i.e., abnormally large lymph node), including other tumoral malignancy such as lymphoma.

Purely cystic cervical lymphadenopathy (i.e., with exclusively liquid or fluid contents) seems infrequent, although exact incidence is not known. Clinical and radiological presentation, however, is sometimes similar to a benign pathology, making diagnosis challenging.

Broadening the topic to cervical lymphadenopathy with cystic aspect (rather than purely cystic) was intended to include more

common clinical situations. Cystic aspect refers to lymphadenopathy with mainly liquid or fluid content on clinical examination and/or fine-needle aspiration and lymphadenopathy with mainly necrotic-like content on imaging.

The aim of this study was to update the state of knowledge on clinical and paraclinical diagnosis of lymphadenopathy, to review the etiologies of cervical lymphadenopathy with cystic aspect in adults and the main differential diagnoses, and to formulate good practice guidelines. Guidelines on identification of the primary carcinoma underlying cervical lymphadenopathy with cystic aspect are presented in a separate article.

2. Epidemiology and etiologies of cervical lymphadenopathy with cystic aspect in adults

Overall prevalence of cervical lymphadenopathy with cystic aspect compared to cervical lymphadenopathy in general is unknown. Prevalence in series presenting with cervical mass of cystic aspect, on the other hand, has been reported. In a study of 196 patients presenting with supposedly benign cystic cervical mass, 3.6% of lesions turned out to be malignant, with 3.1% metastases of squamous cell carcinoma and 0.5% metastases of papillary thyroid carcinoma [1] (level of evidence, 4). In a retrospective study of 136 cervical cystic metastases of unknown primary, work-up and follow-up identified 87 lingual or palatine tonsillar primaries (64% of cases) and 11 nasopharyngeal (8%) [2] (level of evidence, 4). In another series of 67 patients presenting with cystic lateral cervical mass presumed to be a congenital branchial cleft cyst, 10% proved in fact to be lymphadenopathies (7% squamous cell carcinoma and 3% papillary thyroid carcinoma), especially in patients aged > 40 years [3] (level of evidence, 4).

Thus, adult cervical lymphadenopathy with cystic aspect is mainly related to head and neck squamous cell carcinoma (HNSCC) (oropharyngeal or nasopharyngeal), and more rarely to thyroid carcinoma.

2.1. HNSCC

In over-40 year-olds, the first diagnosis to be suspected in case of cystic lateral cervical mass is cystic lymph-node metastasis of non-keratinizing HPV-induced oropharyngeal squamous cell carcinoma [3] (level of evidence, 4), [4] (level of evidence, 4).

A literature review of cystic cervical metastasis found that epidemiology differed from that of non-cystic lymphadenopathy: rates of concomitant alcohol abuse and smoking were lower, age was younger, and prognosis better. The primary was either unknown or tonsillar (43–64%), basilingual (37–60%) or nasopharyngeal (1.3–3%) [5] (level of evidence, 4).

2.2. Undifferentiated nasopharyngeal carcinoma

Cystic lymphadenopathy is found in 1.3–13.6% of nasopharyngeal carcinomas [2–11] (level of evidence, 4). Incidence of nasopharyngeal carcinoma varies geographically, with high risk (30–80/100,000) in South-East Asia, intermediate risk (10/100,000) in North Africa, the Middle East and in Greenland and Alaska Inuits, and low risk (0.5–2/100,000) in North America, Europe in general and France in particular [12] (expert opinion). Nasopharyngeal origin should always be suspected in case of no clear oropharyngeal primary.

2.3. Thyroid carcinoma

Metastatic lymphadenopathy from differentiated papillary thyroid carcinoma may be cystic [13] (level of evidence, 4), [14] (level of evidence, 2), [15] (level of evidence, 4). In a study of 167 papillary thyroid microcarcinomas, 13 cases were revealed by cervical lymphadenopathy, and preoperative ultrasound scan found a totally or partially cystic lymph-node mass in 6 out of 11 cases [16] (level of evidence, 4). In a series of 75 papillary thyroid carcinoma patients, ultrasound found cystic lymphadenopathy in 6.7% of cases, all of which proved metastatic on histology [17] (level of evidence, 4). Several cases of cystic cervical lymphadenopathy of thyroid origin mimicking congenital branchial cleft cyst have been reported [17–21] (level of evidence, 4).

2.4. Other tumors

More rarely, cervical metastasis with cystic aspect may originate from lung cancer, skin carcinoma [22] (level of evidence, 4), melanoma [23] (level of evidence, 4) and, exceptionally, lymphoma [24] (level of evidence, 4).

Guideline 1

In central or lateral compartment cystic cervical tumoral lymphadenopathy, the following should be suspected, in decreasing order of frequency:

- cystic metastasis of HNSCC, preponderantly (90%) oropharyngeal (tongue base or palatine tonsil) (Grade C);
- cystic metastasis of undifferentiated nasopharyngeal carcinoma, which shows 8% incidence in non-endemic countries and more in South-East Asia and North Africa (Grade C);
- cystic metastasis of papillary thyroid carcinoma (2% of cases) (Grade C).

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3. Differential diagnoses for cervical lymphadenopathy with cystic aspect

The main differential diagnoses for cervical lymphadenopathy with cystic aspect are non-cancerous cystic lymph-node and non-lymph cystic cervical mass.

3.1. Non-cancerous cystic lymph-node

3.1.1. Lymph-node tuberculosis

Lymph-node tuberculosis is frequent in endemic zones, accounting for 40% of cases of cervical mass in a series of 630 Turkish patients [25] (level of evidence, 4). The ultrasound and CT aspect may mimic cystic lymph-node metastasis, with thicker walls. Cervical levels IIB and V are principally involved [26,27] (level of evidence, 4). Diagnosis is founded on *Mycobacterium tuberculosis* detected directly or in culture from liquid aspirated from the lymphadenopathy or, if necessary, from an adenectomy specimen. Tuberculin skin test by intra-dermal reaction (IDR) and interferon-gamma release assay (IGRA) is highly contributive but cannot distinguish between latent and active infection; moreover, the specificity of IDR is greatly impaired by previous vaccination. IGRA shows 90.4% sensitivity and 70.5% specificity in diagnosing non-pulmonary lymph-node tuberculosis [28] (level of evidence, 2). Gene amplification (PCR) enables rapid identification of tubercular bacilli, excluding other mycobacterial species, with greater sensitivity than direct examination [29] (level of evidence, 4).

3.1.2. Atypic mycobacterial adenitis

Atypic mycobacterial adenitis is more frequent in 3-5-year-old immunocompetent children, with female predominance. Progression is chronic. Location is submandibular. Diagnosis uses the techniques referred to above: prolonged culture and PCR [30] (level of evidence, 4).

3.1.3. Bartonellosis

Bartonellosis is induced by Bartonella henselae (BH) from cat scratches or bites, and mainly involves children. Lymphadenopathies appear 2 weeks after inoculation and may last several weeks. Location is submandibular [31] (level of evidence, 4). Definitive diagnosis is founded on BH serology or PCR performed on aspiration of biopsy samples [32] (level of evidence, 1).

3.1.4. Tularemia

Tularemia is induced by Francisella tularensis. It is a zoonosis most frequently encountered in the Balkans, Turkey and Scandinavia, transmitted by lagomorphs and rodents via direct contact or ingestion of contaminated water or food. The cervical lymphadenopathies show a hypoechogenic ultrasound aspect, with presence of septa. Standard diagnosis is based on sample culture, although serology and PCR are more frequently used [33] (level of evidence, 4).

3.2. Medial non-lymph cystic mass

3.2.1. Thyroglossal duct cyst (TDC)

Thyroglossal duct cyst is a deformity caused by involution of the thyroid migration pathway from the tongue toward the anterior cervical space during the first weeks of gestation [34] (level of evidence, 4), occurring mainly in children and young adults [25] (level of evidence, 4). It presents as a soft midline tumefaction at or just below the hyoid bone in 75% of cases [35,36] (expert opinion). The ultrasound aspect is a thin-walled medial avascular hypo- or an-echogenic mass close to the hyoid bone. CT shows a hypodense medial mass with parietal contrast uptake, increased in case of infection. In case of associated thyroid carcinoma, the aspect may be atypic, with calcifications within the cyst [35–37] (expert opinion). Thyroid position should be systematically checked on imaging to rule out ectopic thyroid [37] (expert opinion).

3.2.2. Bronchogenic cyst

Bronchogenic cyst is rare, at < 1% of cystic cervical lesions [34] (level of evidence, 4). Onset is in the first years of life, mainly in under-18 year-old boys. Cervical locations are suprasternal and medial [34,38] (level of evidence, 4). CT finds a mass without contrast uptake, of variable density depending on levels of protein debris and mucus. MRI allows differentiation from tissular mass in case of atypic CT aspect, finding thin walls and a homogenous hyperintense aspect on T2-weighted sequences [36] (expert opinion).

3.2.3. Dermoid cyst

Dermoid cyst is a benign embryonic tumor comprising several type of tissue. Location in 1–7% of cases is head and neck: periorbital or oral cavity. More than 50% of cervical locations are on the midline [39,40] (level of evidence, 4). Ultrasound shows a hypoechogenic subcutaneous lesion in 50% of cases, in the mandibular or sublingual space, hypodense on CT, with a moderately thin wall showing contrast uptake. There may be a "sack of marbles" aspect. MRI finds a heterogeneous cystic mass, iso- or hypo-intense on T1 and hyper-intense on T2, with visible walls [35,40] (expert opinion; level of evidence, 4).

3.3. Lateral non-lymph cystic mass

3.3.1. Branchial cleft cyst

Branchial cleft cyst is the second most frequent congenital cervical deformity after TDC. It is caused by branchial cleft involution during gestation [25,41] (level of evidence, 4). The embryological origin determines clinical presentation: 2nd cleft or tonsillar cyst is the most frequent, situated along the anterior edge of the sternocleidomastoid muscle close to the mandibular angle; 1st cleft cysts are located in contact with the parotid gland; 3rd cleft cyst is rarer, connected to the oro- or hypo-pharyngeal wall; 4th cleft cysts originate from the piriform sinus floor and extend toward the thyroid region. Presentation is in the form of a mobile, soft and painless mass with progressive growth [25] (level of evidence, 4). A fistular opening in the skin (especially in 1st and 2nd cleft cysts) or mucosa should be screened for. Ultrasound finds a hypo- or an-echogenic, avascular, compressible tumefaction. CT finds a hypodense homogeneous thin-walled mass. In case of infection, differential diagnosis with abscess or cystic lymphadenopathy can be difficult to make due to thickening of the cystic walls and a hyperdense aspect. In 1st cleft cyst, MRI is recommended to assess parotid gland contact [35] (expert opinion).

3.3.2. Cystic cervical lymphangioma

Cystic cervical lymphangioma accounts for 5% of benign cystic tumors in children [35,42] (expert opinion). A macrocystic presentation may mimic cystic lymphadenopathy. Location is in the posterior cervical triangle or subclavicular region [34] (level of evidence, 4). Presentation is in the form of a painless soft tumefaction of variable size. Diagnosis may be established antenatally. Ultrasound finds a multilocular cystic mass with septa of variable thickness. CT finds a hypodense multilocular mass centered on the posterior cervical region and submandibular space. MRI is contributive in analyzing contact between the cystic lymphangioma, hypo- or iso-intense on T1 and hyper-intense on T2, and neighboring structures [35,37] (expert opinion).

3.3.3. Thymic cyst

Thymic cyst may be congenital or acquired. It accounts for less than 1% of cystic cervical masses [34] (level of evidence, 4). Diagnosis is made before 10 years of age, mainly in boys [34,43] (level of evidence, 4). Location is mainly in the left neck, forward of the sternocleidomastoid muscle, between the jugular and carotid axes. Growth is progressive and painless, sometimes accompanied by symptoms of digestive or respiratory tract compression due to superior mediastinal involvement in 40–50% of cases [43,44] (level of evidence, 4). CT finds a thin-walled hypodense cystic mass with homogeneous uptake. MRI can screen for associated thymic lesions [44] (level of evidence, 4).

3.3.4. Cystic cervical schwannoma

Cystic cervical schwannoma is a neural tumor, long remaining asymptomatic and painless, composed of cells from the neural crest. Cervical locations are mainly parapharyngeal, but all nerves, whether motor or sensory, may be involved. Cystic transformation is rare, reported in 4% of cases. CT and MRI find a thin-walled cyst with septa [45] (level of evidence, 4).

3.3.5. Ranula

Ranula is an oral floor mucocele, originating from a sublingual salivary gland. It may cross the oral floor muscles and appear as a cystic cervical mass. Ultrasound finds a hypo-echogenic cystic mass. CT finds a well-delineated hypodense lesion [37] (expert opinion).

3.3.6. Cystic form synovial sarcoma

Cystic form synovial sarcoma is a rare malignant tumor found in children and young adults, sometimes presenting as a cystic mass in various spaces of the neck. Ultrasound finds a hypo-echogenic aspect, thin walls and septa. CT finds a hypodense lesion with walls showing moderate contrast uptake, a central septum and sometimes calcifications [46] (level of evidence, 4).
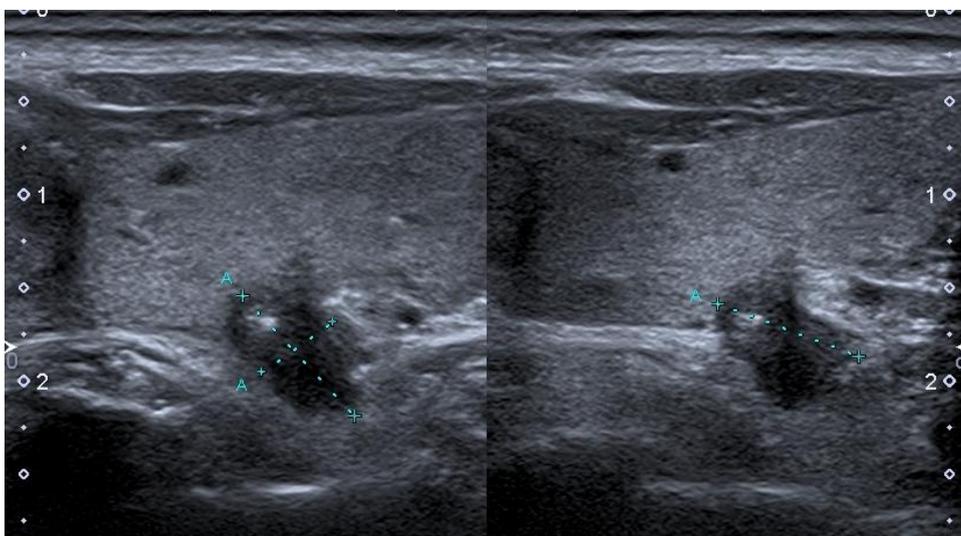
Fig. 1. Ultrasound image of EU-TIRADS 5 thyroid nodule, transverse (left) and longitudinal slice (right). The nodule has a non-oval form, with irregular contours and a marked hypo-echogenic zone.

4. Contribution of imaging

Two types of cystic mass are to be considered: tissular mass with cystic components, and "pure" cystic mass: i.e., with peripheral wall and purely liquid content, or sometimes with rare septa. The latter type raises problems of differential diagnosis with respect to branchial cleft cyst and benign cystic mass.

4.1. Ultrasound

Ultrasound clearly plays a role in determining the nature of a cystic cervical mass, but cannot be interpreted without reference to clinical context and notably history. It can also guide fine needle aspiration, if required.

Ultrasound elements suggestive of a lymph node are primarily architectural [47] (level of evidence, 2), [48] (level of evidence, 4):

- solid oval mass with regular contours;
- hilum, showing as a central or sometimes peripheral echogenic line, or an echogenic area surrounded by a thin hypoechogenic radiolucent line corresponding to the cortex;
- arborescent vascularization pattern.

In metastatic lymph nodes, the last two of these features may often be lacking, and it is necessary to screen for:

- single or multiple presentation, the latter strongly indicating lymph node metastasis;
- in the thyroid, primary carcinoma; mass location in level III, IV or VI or, more rarely II, is suggestive [49] (level of evidence, 1).

Thyroid ultrasound is used to detect and characterize nodules. Features suggesting thyroid carcinoma liable to lead to cystic metastasis are: nodule ipsilateral to the lymph node, and ultrasound malignancy risk stratification on the European-Thyroid Imaging and Reporting Data System (EU-TIRADS) [50] (level of evidence, 1). Nodules are ranked 1 to 5 by increasing risk of malignancy: 1, normal ultrasound aspect; 2, pure cyst and entirely iso-echogenic spongiform nodule; 3, oval, regularly contoured nodule with solid component entirely iso- or hyper-echogenic (malignancy risk < 4%); 4, oval, regularly contoured nodule but with moderately hypo-echogenic component (intermediate risk, 6–17%); and 5, high risk (> 25%) with at least 1 strongly suggestive
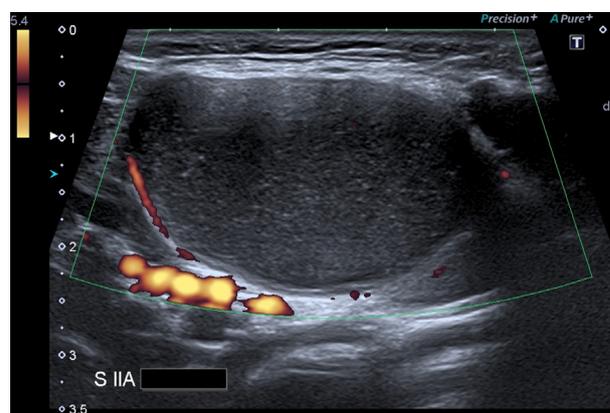

Fig. 2. Ultrasound image of left cervical level IIA branchial cleft cyst. Oval, with regular contours. Hypoechogenic but avascular, suggesting a purely cystic form.

sign: non-oval form, irregular contours, microcalcifications and/or clear hypoechogenicity.

Cystic metastasis of thyroid origin thus corresponds to EU-TIRADS 4 or more often 5 (Fig. 1). Nodules with microcalcification are at greater risk of local lymph-node involvement [51] (level of evidence, 2), [52] (level of evidence, 3).

Ultrasound is not contributive for other etiologies of cystic metastasis. Certain minor signs may be suggestive. Metastases are hypervascularized in case of renal origin; very hypoechogenic in case of melanoma [23] (level of evidence, 4); and predominantly level II, heterogeneous with low-intensity anarchic vascularization in case of head and neck squamous cell carcinoma, where the cystic component may then suggest an HPV-positive form. Tuberculosis shows vary variable, sometimes cystic, aspects [53] (level of evidence, 4), and socioeconomic context and/or immunodepression are then highly suggestive.

Conversely, other features may suggest that a cystic cervical mass is not a lymphadenopathy (differential diagnosis): longstanding lesion, isolated, without signs of head and neck or renal cancer, melanoma or suspect thyroid nodule. The main differential diagnosis is 2nd branchial cleft cyst: suspected in level IIA location, oval and well-delineated, with variable but homogeneous echogenicity, and strictly avascular (Fig. 2) [54] (level of evidence, 4).
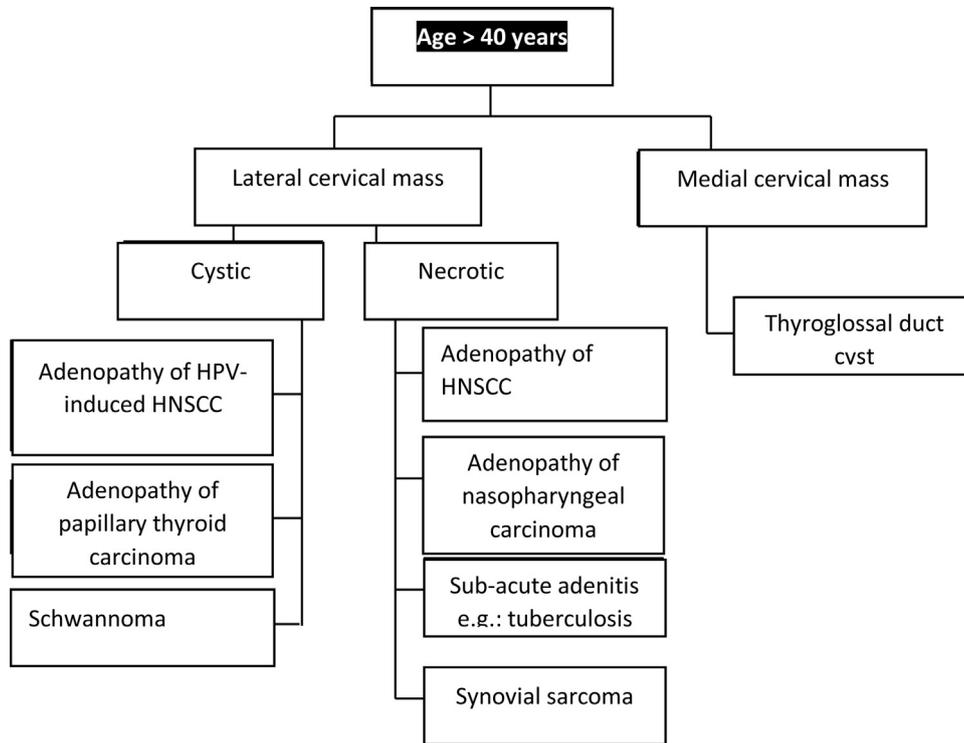
Fig. 3. Diagnostic tree in case of cervical mass with cystic aspect in an adult over 40 years of age. HNSCC: head and neck squamous cell carcinoma.
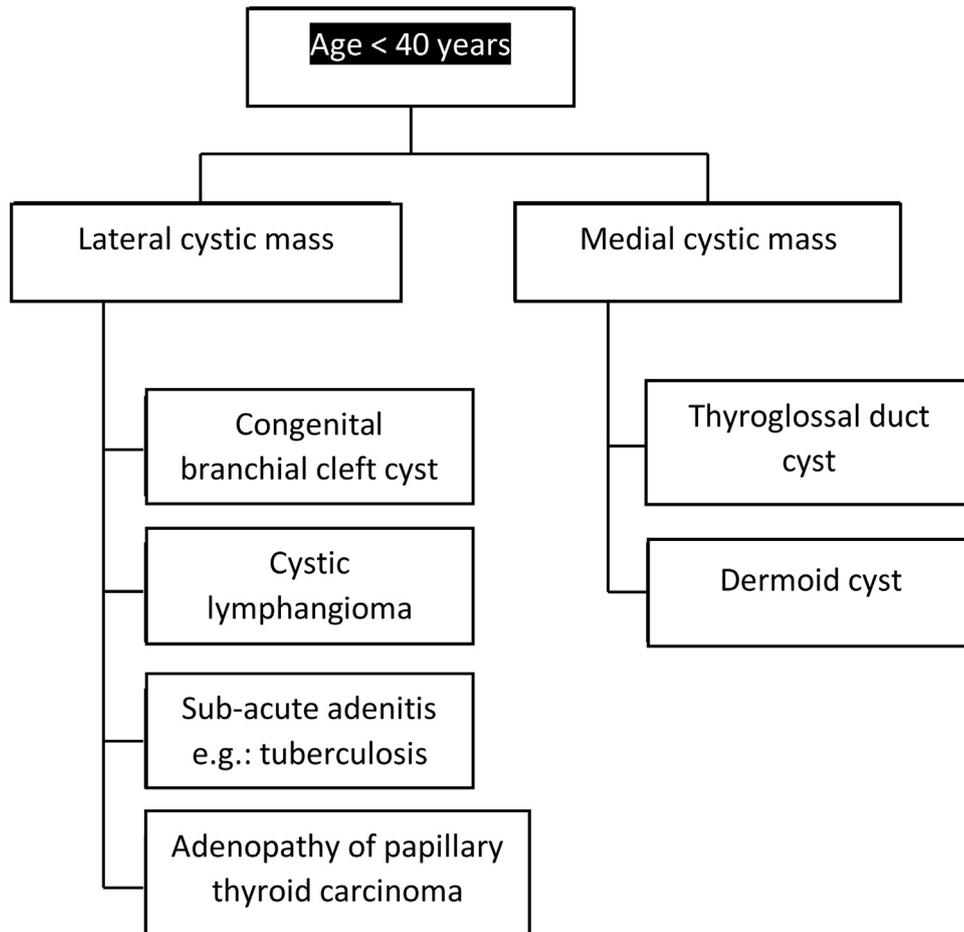

Fig. 4. Diagnostic tree in case of cervical mass with cystic aspect in an adult under 40 years of age.

Guideline 2

In case of cystic cervical mass, ultrasound should screen for architectural elements suggestive of lymph node and thyroid nodule showing suspected malignancy, especially if the mass is located in levels III, IV or VI. Grade A

4.2. CT

A tissular mass with cystic components is immediately highly suspect. The cystic aspect often corresponds to necrosis and, in a structure identified as being a lymph node, is strongly suggestive of malignancy. The necrosis presents as an area of lower density than the lymph node cortex, without contrast uptake [55] (level of evidence, 2). Except in a context of acute or chronic infection, necrosis in a lymph node almost systematically indicated metastasis [55,56] (level of evidence, 2). Other signs are also suggestive of malignancy [55,56] (level of evidence, 2):

- small axis > 10 mm (or > 15 mm in level II);
- rounded form;
- extra-capsular extension;
- > 3 contiguous hypertrophic nodes in a given drainage area.

Guideline 3

Malignant lymphadenopathy should be suspected in priority in case of tissular mass identified as a lymph node on CT and presenting a cystic component. Grade B

Diagnosis is more difficult for a pure cystic mass. Certain signs are often said to correspond to malignancy: parietal asymmetry or parietal tissular nodular component; but the evidence is not clear.

Only two CT signs significantly differentiate branchial cleft cyst from cystic lymphadenopathy [8] (level of evidence, 4):

- size, branchial cleft cyst having a longer short axis than cystic lymphadenopathy (mean: 22 mm versus 14 mm);
- parietal thickness: mean 2.4 mm versus 2.7 mm, respectively.

These signs, however, are not practically useful, there being no relevant threshold for size, and scatter is much narrower than inter- and intra-individual variability on CT for thickness.

4.3. MRI

MRI is comparable to CT in semiology, but with better soft-tissue contrast. Cystic components within a lymph node, showing hypointensity on T1, hyperintensity on T2, without contrast uptake and with elevated apparent diffusion coefficient (ADC), are strongly associated with metastasis except in case of infection [57] (level of evidence, 4). There is no evidence for signs differentiating between a benign cystic mass and a pure cystic lymphadenopathy. In necrotic lymphadenopathy, assessing ADC in the necrotic part can differentiate between metastasis lymphadenopathy and lymphomatous lymphadenopathy or tuberculous adenomegaly [58] (level of evidence, 2).

Guideline 4

Benign/malignant status in a pure cystic cervical mass should not be diagnosed on CT or MRI data alone. Grade A

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5. 18-FDG PET-CT

A recent retrospective study by Abadie et al. assessed 18-FDG PET-CT in differential diagnosis between benign cystic cervical mass and malignant necrotic lymph-node lesion [59] (level of evidence, 4). In 58 patients with isolated cystic cervical lesion, 20 lesions were found to be of malignant origin. 18-FDG PET-CT suggested malignancy in 34 patients (19 true, 15 false positive), and benign status in the other 24 (23 true, 1 false negative). Sensitivity, specificity, diagnostic precision and positive and negative predictive values were respectively 95%, 61%, 72%, 56% and 96%. Median SUVmax was significantly higher in malignant than benign cystic lymph nodes: 7.42 vs. 1.86 ($P < 0.0001$). This contribution of quantitative 18-FDG PET-CT analysis in diagnosing malignancy agreed with Haerle et al.'s report of 34 oropharyngeal squamous cell carcinomas [60] (level of evidence, 4), where mean SUVmax in malignant lymph node lesions was 8.5 ± 4.1, with negative correlation between SUVmax and necrosis grade on pathology (r = −0.44; $P = 0.011$). The authors advocated a contribution of 18-FDG PET-CT for guiding new biopsy in high-fixation areas in case of initial inconclusive findings.

Guideline 5

18-FDG PET-CT is recommended for differential benign/malignant diagnosis in cystic cervical lesions, notably when ultrasound-guided fine-needle aspiration biopsy is inconclusive. Grade C

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6. Conclusion

This part of the guidelines updates the literature on the etiologies and ranking of complementary examinations for diagnosis of suspected lymphadenopathy with cystic aspect. At present, cystic and necrotic lymphadenopathy in adults suggest oropharyngeal carcinoma, often implicating HPV. Thus, any clinical presentation of tonsillar cyst in an over-40-year-old should first suggest malignant lymphadenopathy from an HPV-related squamous cell carcinoma unless proved otherwise, in which case other cancer etiologies, and notably the nasopharynx and thyroid, should then be considered (Fig. 3). In under-40-year-olds, benign etiologies predominate (Fig. 4). Resort to imaging is guided by history-taking and the clinical characteristics of the lymphadenopathy.

Disclosure of interest

The authors declare that they have no competing interest.

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