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SFORL GUIDELINES

Initial staging of squamous cell carcinoma of the oral cavity, larynx and pharynx (excluding nasopharynx). Part I: Locoregional extension assessment: 2012 SFORL guidelines

S. Vergez[a,*], S. Morinière[b], F. Dubrulle[c], P.-Y. Salaun[d], E. De Monès[e], C. Bertolus[f], S. Temam[g], D. Chevalier[h], F. Lagarde[i], P. Schultz[j], J.-C. Ferrié[k], C. Badoual[l], M. Lapeyre[m], C. Righini[n], B. Barry[o], S. Tronche[p], D. De Raucourt[q]

[a] *Service d'ORL et de chirurgie cervico-faciale, hôpital Rangueil-Larrey, CHU de Toulouse, 24, chemin de Pouvourville, 31059 Toulouse cedex 9, France*
[b] *Service d'ORL et de chirurgie cervico-faciale, hôpital Bretonneau, CHRU de Tours, 37044 Tours cedex 9, France*
[c] *Service de radiologie, hôpital Claude-Huriez, 1, place de Verdun, 59037 Lille cedex, France*
[d] *Service de médecine nucléaire, CHU de Brest, avenue Foch, 29609 Brest cedex, France*
[e] *Service d'ORL et de chirurgie cervico-faciale, groupe hospitalier Pellegrin, CHU de Bordeaux, place Amélie-Raba-Léon, 33076 Bordeaux cedex, France*
[f] *Service de chirurgie maxillo-faciale, groupe hospitalier La Pitié-Salpêtrière — Charles-Foix, 47-83, boulevard de l'Hôpital, 75651 Paris cedex 13, France*
[g] *Service d'ORL et de chirurgie cervico-faciale, institut Gustave-Roussy, 39, rue Camille-Desmoulins, 94805 Villejuif cedex, France*
[h] *Service d'ORL et de chirurgie cervico-faciale, hôpital Huriez, CHRU de Lille, 1, place de Verdun, 59037 Lille cedex, France*
[i] *Service d'ORL et de chirurgie cervico-faciale, CHR d'Orléans, 1, rue Porte-Madeleine, 45032 Orléans cedex 1, France*
[j] *Service d'ORL et de chirurgie cervico-faciale, hôpital Hautepierre, CHU de Strasbourg, 1, avenue Molière, 67098 Strasbourg cedex, France*
[k] *Service de radiologie, CHU de Poitiers, 2, rue de la Miletrie, 86021 Poitiers cedex, France*
[l] *Service de pathologie, hôpital européen G.-Pompidou, AP—HP, 20, rue Leblanc, 75908 Paris cedex 15, France*
[m] *Service de radiothérapie, 58, rue Montalembert, BP 392, 63011 Clermont-Ferrand cedex 01, France*
[n] *Service d'ORL et de chirurgie cervico-faciale, hôpital A.-Michallon, CHU de Grenoble, boulevard de la Chantourne, 38043 Grenoble cedex 9, France*
[o] *Service d'ORL et de chirurgie cervico-faciale, hôpital Bichat-Claude-Bernard, 46, rue Henri-Huchard, 75877 Paris cedex 18, France*
[p] *SFORL, 26, rue Lalo, 75116 Paris, France*
[q] *Service d'ORL et de chirurgie cervico-faciale, centre François-Baclesse, avenue du Général-Harris, 14000 Caen, France*

* Corresponding author. Tel.: +33 05 67 77 17 88.
E-mail address: vergez.s@chu-toulouse.fr (S. Vergez).

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Summary
Objectives: To set out good practice guidelines for locoregional extension assessment of squamous cell carcinoma of the head and neck (excluding nasopharynx, nasal cavities and sinuses).
Materials and methods: A critical multidisciplinary review of the literature on locoregional extension assessment of squamous cell carcinoma of the head and neck was conducted, applying levels of evidence in line with the French health authority's (HAS) literature analysis guide of January 2000.
Conclusion: Based on the levels of evidence of the selected articles and on work-group consensus, graded guidelines are set out for clinical, endoscopic and imaging locoregional extension assessment of head and neck cancer.

Introduction

In head and neck as in any cancer, initial staging is crucial: it confirms diagnosis (histology) and assesses tumor stage (local, regional and any metastatic extension), and is essential for TNM staging and optimal therapeutic strategy.

It was decided that the present guidelines should concern initial staging of head and neck squamous cell carcinoma excluding nasopharynx, facial sinus and nasal cavity cancer.

The objective was thus to set out guidelines for locoregional extension assessment of squamous cell carcinoma of the head and neck.

Therapeutic strategy further involves remote extension assessment (notably including tracheobronchial and esophageal endoscopy) and general pre-treatment assessment, dealt with in separate reports.

Material and methods

The present guidelines were drawn up by a multidisciplinary expert group of ENT specialists and also radiologists, maxillofacial surgeons, radiotherapists, medical oncologists, pathologists, nuclear medicine specialists and anesthesiologists. They seek to specify locoregional extension assessment based on a critical literature analysis and, in the lack of firm evidence, to establish an expert consensus. They take full account of the 2012 French Society of Radiology (SFR) guidelines [1].

The individual guidelines were graded according to the level of evidence of each underlying literature report. Appendix A presents the levels of evidence and guideline grades, following the French health authority's (HAS) 2000 literature analysis and guideline grading guide, in turn inspired by the Sackett scoring system.

Clinical and endoscopic examination

Neck inspection and palpation and complete examination of the oral cavity, pharynx and larynx provide local extension assessment and also enable investigation of any synchronous mucosal location, which may concern the entire upper aerodigestive tract and also the tracheobronchial tree and esophagus. Secondary locations must be explored for in case of alcohol and nicotine intoxication, which is the prime risk factor in head and neck cancer. The incidence of synchronous cancer varies between reports:

- 2.4% in symptom-based exploration [2];
- 8.5% in systematic panendoscopic exploration [3];
- 66 out of 851 patients (7.7%) in a large-scale retrospective French study [4].

Clinical assessment: SFORL guidelines
Complete clinical examination of the oral cavity, oropharynx, laryngopharynx and neck should be included in initial staging in head and neck cancer. (Grade A)

Metastatic adenopathy is found in 10 to 50% of cases on initial examination, and represents an important prognostic factor [5]. Size, mobility and location (areas I to VI) should be investigated [6].

Endoscopic assessment: SFORL guidelines
Endoscopy under general anesthesia should be performed, associated to palpation, biopsies and a detailed report with a dated drawing and/or photograph or video. (Grade B)

Clinical TNM classification is based on endoscopy, ideally performed under general anesthesia if not contra-indicated. Techniques vary according to team and situation. Surgeon-anesthetist teamwork is essential. Assessment indicates lesion resection possibilities, and exposure options are detailed for possible transoral resection. Possible synchronous mucosal locations are explored. Biopsies are taken from within the tumor, outside of any necrotic or ulcerated area, and samples are sent for analysis accompanied by clinical data. If possible, a frozen fragment may, with the patient's consent, be delivered to the tumor bank, strictly observing good practice rules for sampling and conservation.

SFORL guidelines for cytology, histology and HPV exploration are published elsewhere.

Human papilloma virus (HPV): SFORL guidelines

HPV exploration should not be systematic in absence of therapeutic impact (professional consensus).

In the particular cases of oropharyngeal carcinoma and/or patients without alcohol/nicotine-related risk factors, immunohistochemistry with anti-P16 antibody is an option for epidemiological purposes (professional consensus).

Role of vital staining: SFORL guidelines

ENT-region vital staining is not recommended as part of initial staging in head and neck cancer (Grade A).

Toluidine blue (tolonium chloride) staining associated to acetic acid has been described essentially for oral cavity lesions, whereas Lugol can be used for the oral cavity, pharynx and esophagus. A recent systematic review [7] found no solid evidence in favor of diagnostic aids such as toluidine blue for early detection of oral cavity cancer. New controlled randomized cost/benefit studies are needed to assess these examinations in general population screening [7]. Moreover, being applied topically, these stains do not allow detection of submucosal lesions [7].

Role of novel endoscopy techniques: SFORL guidelines

Novel endoscopy techniques such as autofluorescence, narrow-band imaging or confocal endomicroscopy should be applied in research protocols (professional consensus).

New ''bioendoscopy'' techniques based on tissue composition and the physical properties of light are currently under evaluation. Tissue contains endogenous fluorophores, at concentrations varying between healthy and pathological tissue; excitation induces autofluorescence. Level 2 and 3 clinical studies reported greater sensitivity with autofluorescence than white-light endoscopy for early diagnosis of cancerous and precancerous laryngeal lesions; associating white light and autofluorescence enhanced diagnostic performance [8].

Narrow band imaging (NBI) endoscopy uses a series of emission wavebands specifically selected according to hemoglobin absorption spectra, improving visualization of microvascularization and tissue micro-architecture. It has been recommended for early diagnosis of cancerous and precancerous head and neck lesions, of the larynx but also the pharynx and oral cavity [9]. Preliminary studies also demonstrated applications in determining oncologic resection margins and exploring for the primary squamous cell carcinoma in precessive metastatic cervical adenopathy. NBI is currently associated to videoendoscopy, and considerably improves the resolution obtained with white light. Some preclinical and in vivo pilot studies have been performed in the oral cavity [10,11].

Confocal endomicroscopy is still in its experimental stages in ENT oncology; it produces in vivo cell-level tissue images. It is based on the principles of confocal microscopy, providing virtual optical cross-sections so that only those images showing fluorescence in a given optical plane may be recorded.

Imaging assessment

Imaging assessment: SFORL guidelines

Imaging assessment of head and neck carcinoma requires close teamwork between clinician and imaging specialist, with rigorous technique (professional consensus).

Information transmission should also enable full data analysis (various analysis windows, possibility of high-quality multiplanar reconstruction) and data storage in a picture archiving and communication system (PACS) (professional consensus).

Possible limitations for CT or MRI and contrast medium injection should be examined in advance and discussed with the radiologist. Transmission of clinical data and of available endoscopy and pathology results is essential to image interpretation. Exhaustive head and neck or thoracic CT or head and neck MRI examination should therefore be performed in line with the SFR quality guidelines [1]. Depending on tumor location, a second CT acquisition may be performed under dynamic maneuver: in phonation for laryngeal tumor staging; with Valsalva maneuver for hypopharyngeal tumor).

Imaging oral cavity and oropharynx cancer: SFORL guidelines

Cervicothoracic CT should be performed as part of initial staging in oral cavity and oropharynx cancer (Grade B).

MRI is the most effective means of local assessment of oral cavity and oropharynx cancer, and should usually be associated to cervicothoracic CT (Grade C).

CT and MRI are complementary explorations for assessing mandibular invasion (Grade C).

MRI is sensitive in deep lingual tumor extension assessment on gadolinium-enhanced T1-weighted and T2-weighted sequences [12]. Park et al. reported strong correlation (Pearson coefficient, 0.94) for lingual tumors on gadolinium-enhanced fat-suppressed T1-weighted sequences, but weaker correlation for tonsillar locations [13].

MRI is of great diagnostic value for mandibular invasion [14]. Van Cann et al., however, found no significant benefit of MRI over CT, although both were of greater diagnostic value than panoramic radiography [15]. Imaizumi et al. found no difference in sensitivity between MRI and CT in exploring mandibular invasion, although CT was much more specific in detecting incipient cortical invasion or mandibular canal

infiltration; they also stressed the high false-positive rate on MRI, associated with inflammatory dental remodeling or extraction [16].

Imaging laryngeal and pharyngeal cancer: SFORL guidelines

Cervico-thoracic CT should form part of initial staging in laryngeal and hypopharyngeal cancer (Grade B).

Cervical CT with dynamic maneuvers and optimized contrast enhancement is the most effective examination in local assessment of laryngeal and hypopharyngeal cancer (Grade C).

Indications for MRI are exceptional (professional consensus).

CT and/or MRI are the imaging techniques recommended in local assessment of deep tumor volume and extension. Some authors prefer CT, as being less sensitive to movement artifacts and allowing dynamic maneuvers and/or thoracic exploration in the same examination step [1]. In laryngeal and hypopharyngeal locations, CT and MRI provide detailed anatomic study, but overestimate local invasion, especially in the glottis, paraglottic region and cartilaginous structures (13.7 to 25% discordance with histology) [17—19]. Tumor volumes as contoured on CT and/or MRI are significantly greater than in reality or on fluorodeoxyglucose positron emission tomography (FDG-PET) [20], while superficial lateral and subglottic extension are underestimated [20,21].

Multislice helical CT provides fast multiplanar analysis of pharyngolaryngeal structures. In certain anatomic regions (larynx, piriform sinus), dynamic phonation or Valsalva maneuvers can enhance detection sensitivity (from 85 to 92%) [22]. Some authors consider that complementary acquisition under apnea or Valsalva is of interest only for exploration of the glottis [23].

MRI provides equally detailed anatomic study, but is longer to perform, and is more sensitive to movement artifacts, notably swallowing, and does not allow dynamic maneuver. According to Becker et al., it provides better tumor extension assessment within cartilage specimens, with overall sensitivity of 92% and overall specificity of 82% [24].

Whichever imaging technique (CT or MRI) is used, there is consensus as to the difficulty of precisely assessing cartilaginous extension and the need for strict semiological criteria in both CT (associated sclerosis, osteolysis and extra-laryngeal extension) and MRI (T1 hyposignal in invaded cartilage, with T2 and gadolinium-enhanced T1-weighted hypersignal indistinguishable from adjacent tumor) [21,24—26]. FDG-PET, while giving a more realistic estimate of tumor volume [20], contributes little to initial staging as its anatomic resolution is currently poorer than CT or MRI [27].

As a complement to clinical examination in initial head and neck cancer staging, the French national SFR guidelines recommend cross-sectional imaging to explore for regional lymph-node invasion [1]. Whatever the tumor location, cervical lymph-node extension should be assessed in the same step as local tumor assessment by CT (mean sensitivity, 81%; mean specificity, 76%) or MRI (mean sensitivity, 81%; mean specificity, 63%) [28]. There is no significant difference between the two techniques in terms of diagnostic value [28,29]. FDG-PET/CT also shows sensitivity (87—90%) and specificity (87—90%) as good as or better than CT and/or MRI, although the difference is not always significant, and the sensitivity of FDG-PET falls to 50% in clinically N0 patients [27,29—32]. Seitz et al. found no significant difference in overall diagnostic value between MRI and FDG-PET/CT in cervical lymph-node extension assessment [33]. A recent prospective study (n = 114 patients) comparing FDG-PET/CT and MRI or CT found significantly better sensitivity and specificity in FDG-PET/CT in detecting both ipsilateral (Se = 88% vs. 70%) and contralateral (Se = 52% vs. 36%) lymph-node metastasis. Negative FDG-PET/CT findings, however, do not rule out lymph-node invasion [34].

Cervical extension assessment: SFORL guidelines

Regional lymph-node extension should be assessed (from skull base to superior mediastinal orifice) as part of the local extension assessment, using contrast-injected cervicothoracic CT (Grade B).

MRI and FDG-PET/CT are effective in lymph-node extension assessment, but should not be the first-line examinations (Grade C).

Imaging assessment of metastatic adenopathy from squamous cell carcinoma without known primary: SFORL guidelines

Contrast-enhanced cervicothoracic CT and FDG-PET/CT should be performed as part of the diagnostic assessment of metastatic adenopathy from carcinoma without known primary. Imaging should ideally precede endoscopic assessment and biopsy (Grade B).

In suspected adenopathy, if cytologic and clinical findings point to lymph-node metastasis from a squamous cell carcinoma not found on initial assessment, FDG-PET/CT should logically precede panendoscopy with biopsies associated to ipsilateral tonsillectomy [35]. Performing endoscopy as a second step has the double advantage of not creating artifacts affecting FDG-PET/CT interpretation and of guiding biopsy. FDG-PET/CT performed before panendoscopy when cross-sectional imaging by CT or MRI was negative located 29% of primary tumors in Miller et al.'s series [36]; associating FDG-PET/CT to panendoscopy led to a detection rate of 45%. When both examinations were negative, the tumor was found during follow-up in fewer than 6% of cases [36]. Series reported in the literature do not seem to be easily comparable; it appears, however, that the sensitivity of FDG-PET/CT ranges between 27 and 87.5%, compared to 25—43.7% for conventional imaging, and that the positive predictive value of FDG-PET/CT ranges between 57 and 77%, compared to 62—75% for CT [37—40].

Time to treatment: SFORL guidelines

Staging should be organized as quickly as possible, so as to initiate treatment early. The interval between the first consultation with the team that is to manage the patient and the collection of data for decision-making and organization of treatment should be kept as short as possible: ideally 2 weeks, and not longer than 4 weeks (professional consensus).

Time to treatment

The literature on time to treatment focuses mainly on delayed diagnosis due to patient or health-care professional related factors (delayed specialist referral) or on the interval between diagnosis and implementation of treatment, mainly in the case of radiation therapy, and consists of retrospective cohort studies or meta-analyses.

Wyatt et al., in a theoretical study of the probability of tumor control by radiation therapy according to cell clone doubling time on the Poisson model, estimated that each extra week's delay before treatment initiation reduced tumor control by 1% [41]. Waaijer et al. compared CT scans for staging and for radiation therapy landmarking in 13 patients, with a mean interval of 56 days between the two; the mean increase in tumor volume was 70%, impacting staging in 23% of patients [42]. Chen et al.'s meta-analysis found an increased relative risk of local recurrence after radiation therapy of 1.15 per month between diagnosis and treatment initiation (95%CI: 1.02—1.29) [43], and Huang et al.'s meta-analysis of 4 studies found a 1.17 increase in RR of local recurrence (95%CI: 0.96—1.44) for an interval greater than 1 month [44].

Fortin et al.'s retrospective study found increased risk of local or regional recurrence and reduced survival when the interval to initiation of radiation therapy exceeded 40 days [45]. This finding is in contradiction with, for example, Caudell et al.'s study, which found no impact of interval to initiation of radiation therapy on results [46]. Schlienger, in a literature review, retrieved five studies reporting negative impact of late treatment initiation and eight reporting none; they recommended a ceiling of 2 weeks for initial staging [47].

Conclusion

Locoregional extension assessment in head and neck cancer should determine patients' individual tumor stage and resection possibilities. It should then be discussed, in the light of the general health assessment and remote extension assessment, in the multidisciplinary team meeting to determine a treatment option in line with the validated guidelines, which will be presented, along with any alternatives, in a dedicated consultation with the patient. In collaboration with the patient's family physician, the treatment proposal should be made as described in the French health authority (HAS) circular DHOS/SDO/2005/101 (February 22, 2005) concerning care organization in oncology and national guidelines for the implementation of the cancer diagnosis disclosure system in health establishments [48].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Correspondence between levels of evidence in the literature and guideline grades (from the French health authority (HAS) guide to literature analysis and guideline grading, January 2000, in turn derived from the Sackett scoring system)

Level of evidence provide by the literature EXPLANATION	Strength of recommendation RECOMMENDATION
LEVEL 1 Randomized comparative trial with strong power Meta-analysis of randomized comparative trials Decision analysis based on well-conducted studies	**GRADE A** **Good scientific evidence**
LEVEL 2 Randomized comparative trial with weak power Well-conducted non-randomized comparative trial Cohort study	**GRADE B** **Fair scientific evidence**
LEVEL 3 Case-control study Retrospective comparative trial	**GRADE C**
LEVEL 4 Comparative study with significant bias Retrospective study Case series Descriptive epidemiological study (transversal, longitudinal)	**GRADE D** **Low level of scientific evidence**
Any other publication (Expert opinion, etc.) No publication	**Professional consensus**

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