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SFORL GUIDELINES

Initial staging of squamous cell carcinoma of the oral cavity, larynx and pharynx (excluding nasopharynx). Part 2: Remote extension assessment and exploration for secondary synchronous locations outside of the upper aerodigestive tract. 2012 SFORL guidelines

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KEYWORDS
Squamous cell carcinoma;
Oral cavity;

Summary
Objectives: This report presents the French Society of ORL (SFORL) guidelines for exploration for remote metastasis and synchronous second cancer in initial staging of head and neck squamous cell carcinoma.

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Initial staging;
Metastasis;
Synchronous secondary location;
CT;
MRI;
FDG-PET/CT;
Flexible endoscopy of the esophagus

Materials and methods: An exhaustive literature review was analyzed by a multidisciplinary work-group.
Results: The thorax is the most frequent location of remote metastases and synchronous second cancer outside of the upper aerodigestive tract. Thoracic CT is recommended as first-line examination in all cases (grade B). 18-FDG PET/CT is recommended when the thoracic CT image is doubtful or in case of high metastatic risk (grade B), for the detection of non-pulmonary remote metastasis. Esophageal exploration is recommended in case of significant risk of synchronous esophageal cancer (hypopharyngeal or oropharyngeal tumor, chronic alcohol intoxication) (grade B). The reference examination is flexible endoscopy of the upper digestive tract (grade B).
Conclusion: The present grade B recommendations rationalize the roles of the various first-line radiological and endoscopic examinations for remote metastasis and synchronous second cancer, so as to limit the number of examinations performed, thereby reducing the time needed for initial staging.

Pre-treatment assessment of squamous cell carcinoma of the oral cavity, larynx and pharynx (excluding the nasopharynx) is controversial. Part 1 of the present guideline dealt with initial local and cervical lymph-node assessment. Part 2 deals with assessment of remote extension and synchronous second cancer outside of the upper aerodigestive tract.

The first section presents the main anatomic locations of remote metastasis and means of detection. Section 2 presents the two most frequent synchronous tumor locations: lung and esophagus. Frequencies, risk factors and means of detection are analyzed.

Guidelines based on levels of evidence are presented for each entity; when the level of evidence is insufficient, a professional consensus is put forward.

Remote extension assessment (exploration for remote metastasis)

Exploration for remote metastasis: SFORL guidelines:

- systematic thoracic CT (Grade B);
- 18FDG-PET/CT in elevated metastatic risk (stages III and IV with multiple or low-lying adenopathy) or in case of inconclusive thoracic CT image (professional consensus);
- chest X-ray is not recommended in these indications (Grade B);
- systematic liver US scan, bone scintigraphy or cerebral CT scan are not recommended. (professional consensus).

There have been no studies clearly determining the rate of metastasis at the time of discovery of the primary tumor, but the incidence would appear to be fairly low. Remote metastasis generally leads to palliative treatment adapted to a poor prognosis. Thus, discovery of remote metastasis at the time of diagnosis impacts management of the primary tumor. If there is any risk of metastasis, exploration should be implemented.

Between 7% and 10% of patients show metastatic evolution during treatment [1—4]. Data from these studies were analyzed to assess relative risk according to metastatic location and to determine diagnostic strategy.

The main risk factors for remote metastasis are well-established [1,2,4—10]:

- regional lymph-node extension, regardless of T stage, with risk correlating to N stage;
- tumor volume, with metastasis risk correlating to T stage;
- head and neck location, with higher risk associated with hypopharyngeal tumor.

The most frequent remote metastatic location is the pulmonary parenchyma (45—55%), followed by bone (3—10%) and liver (< 5%) [2,4,11]. In almost a third of cases, metastasis involves several locations at once.

In the literature, pulmonary metastasis and a possible synchronous second pulmonary primary are often explored for in a single analysis. These two different pathologies may present in the same form, as rounded parenchymatous nodules. The existence of several synchronous pulmonary nodules does not always prove metastasis: several primary pulmonary tumors may coexist, sometimes with differing histology [12]; histology fails to differentiate between the two entities in the case of squamous cell carcinoma [13]. Thoracic CT has consistently proved better than plain chest X-ray in terms of sensitivity and specificity in detecting suspect pulmonary nodules [14—21]. Not all pulmonary nodules are cancerous, even when synchronous with head and neck cancer. Several studies have shown the interest of 18FDG-PET coupled to CT (18FDG-PET/CT) in differentiating suspect images found on CT alone [22,23].

Extra-pulmonary metastasis is not systematically associated with pulmonary metastasis. In case of high metastatic risk (stages III or IV with multiple or low-lying adenopathy), 18FDG-PET/CT is recommended whatever the thoracic CT findings, to avoid subjecting the patient to potentially tiring, toxic or mutilating treatment not adapted to disease extension (heavy surgery, potentialized radiation therapy). 18FDG-PET/CT has the advantage of providing full-body exploration with excellent sensitivity. In a meta-analysis comprising 1276 patients, mean sensitivity and specificity

of 18FDG-PET/CT in detecting extra-cervical locations during initial head and neck cancer staging were respectively 88% and 93.3% [24]. 18FDG-PET/CT is further recommended by the National Comprehensive Cancer Network in stages III or IV or if detection of remote locations will impact local treatment (NCCN 2011); if extra-pulmonary metastasis is suspected on imaging, targeted exploration should be undertaken: biological, radiological (plain X-ray, ultrasound, MRI, CT, bone scintigraphy), histology.

Exploration for secondary locations outside the upper aerodigestive tract

''Synchronous'' refers to second cancers diagnosed at the same time as or within 6 months of the primary; ''metachronous'' refers to those diagnosed later than 6 months. Most head and neck squamous cell carcinomas are associated with chronic nicotine and/or alcohol intoxication, and such patients are at increased risk of second cancer with the same risk factors. By order of frequency, second locations are upper aerodigestive tract, lung and esophagus.

Incidence of metachronous second cancer at whatever location is estimated at 4% to 7% per year [25]. In a large-scale analysis of 13 registries totaling 99,257 patients, the main risk was onset in another head and neck location, with cumulative risk of 36% over 20 years, the second being the development of a primary bronchial cancer, with cumulative risk of 13% over 20 years [26].

Pre-treatment assessment concerns diagnosis of synchronous cancer to the extent that discovery may impact management of the first.

Exploration for a synchronous second pulmonary location

Exploration for a synchronous second pulmonary location: SFORL guidelines:

- systematic thoracic CT (Grade B);
- 18FDG-PET/CT in case of inconclusive thoracic CT image (Grade B);
- in case of suspected primary bronchopulmonary carcinoma on thoracic CT, a pneumologist's opinion should be sought. Systematic tracheobronchial flexible endoscopy is not recommended (professional consensus).

Incidence of primary bronchial cancer synchronous with head and neck squamous cell carcinoma is estimated at 0.3% to 3% [27—30].

Primary bronchial cancer is the third most frequent form of cancer, after colorectal and breast cancer, but is associated with the highest mortality: 30,651 new cases and 26,624 deaths in 2005 in France [31]. Risk factors are well-established:

- active smoking is the main risk factor: in 2000, 85% of primary bronchial cancers implicated smoking [32];
- the role of passive smoking has been known since the 1980s; in 1998, a meta-analysis found 26% elevation of risk of bronchial cancer in non-smokers living in contact with smokers [33];
- other risk factors have been identified, mainly implicated in occupational cancer: exposure to asbestos, silica, nickel, hexavalent chromium, cadmium, paint or radon [34].

Some patients develop primary bronchial cancer without displaying any identified or known risk factors. Bronchial cancer in non-smokers is the seventh most frequent cause of cancer death [35]. It is an entity in itself, characterized by female predominance, adenocarcinoma and fairer prognosis [36,37].

There are several arguments in favor of systematic screening for primary bronchial cancer in at-risk populations:

- systematic radiological lung cancer screening in at-risk populations would enable early stage detection [38,39];
- the smaller the lesions detected, the less risk of mediastinal lymph-node extension [40];
- lung cancer tumor size is an independent prognostic factor [41].

The impact of systematic screening on overall survival in at-risk populations, however, is not clear [42]. Primary bronchial cancer is of poorer prognosis when synchronous than metachronous [43].

As in exploration for pulmonary metastasis, the first-line examination is thoracic CT, being more effective than chest X-ray in detecting parenchymatous nodules and mediastinal adenopathies [14—21]. As in exploration for pulmonary metastasis once again, 18FDG PET/CT should be performed in second line when the thoracic CT image is suspect [22,23].

Tracheobronchial flexible endoscopy is of limited interest: most pulmonary parenchymatous nodules diagnosed on thoracic CT go undetected [44—46]. Its usefulness lies in detecting early-stage proximal bronchial tumor invisible on X-ray; incidence, however, is rare [47].

Exploration for a synchronous second esophageal location

Prevalence of second primary esophageal cancer in patients treated and followed for head and neck squamous cell carcinoma (oral cavity, oropharynx, larynx, hypopharynx) is estimated at 0—21.9% [47—52], a variability explained by that of the populations studied in terms of cancer risk factors, head and neck locations and esophageal lesion detection techniques.

The relative risk of preneoplastic lesion of esophageal cancer in patients treated and followed for head and neck squamous cell carcinoma varies between patients. Two risk factors have been identified:

- head and neck squamous cell carcinoma location, with elevated risk associated with hypopharynx and lowest risk

Exploration for a synchronous second esophageal location: SFORL guidelines:

- systematic esophageal exploration as part of the pre-treatment work-up in at-risk patients (hypopharynx and oropharynx and/or chronic alcohol intoxication) (Grade B);
- recommended reference examination: flexible esophageal white-light video endoscopy, with targeted biopsies of all suspect mucosal lesions (Grade B);
- role of vital staining, such as Lugol: diagnoses more early-stage preneoplastic and neoplastic lesions, with better definition of local extension of more advanced tumors; optional but recommended. Narrow-band imaging (NBI) seems promising, but remains to be validated (Grade B);
- alternative: rigid esophagoscopy with rigid endoscope, performed during panendoscopy. This examination, however, does not explore the lower esophagus, entails a risk of perforating the esophagus (especially when irradiated) and is difficult to associated to vital staining (professional consensus).

with oral cavity and larynx; results for the oropharynx are less clear [47—49,51]: T stage in head and neck cancer is not a risk factor at all, even in the hypopharynx;
- chronic alcohol intoxication, which is a risk factor independent of smoking [51], and increases with the degree of intoxication.

There are two main arguments in favor of early diagnosis of synchronous esophageal cancer:

- discovery of a synchronous esophageal cancer may impact respective management approaches for both cancers. Late diagnosis after treatment of the head and neck cancer could hinder that of the esophageal cancer due to treatment sequelae or restrictions on the therapeutic arsenal (radiation therapy used for the head and neck cancer might exclude reutilization because of field overlap, especially in the cervical esophagus). Strategy should therefore be global, so that treatment of one cancer is not to the cost of the other;
- early stage preneoplastic or neoplastic esophageal lesions may benefit from endoscopic surgery, whereas more advanced forms will typically be managed by chemo-radio-therapy. Endoscopy has the advantage of lighter treatment of superficial early-stage lesions, without compromising the treatment of the head and neck cancer. Lugol vital staining during flexible esophageal endoscopy is very useful in detecting early stage esophageal lesions especially amenable to endoscopic management [50].

The impact of screening on survival remains in suspense: no reports have so far proved any positive survival impact of early diagnosis of esophageal lesions.

Incipient neoplastic esophageal lesions are often asymptomatic and go undetected on CT work-up and also on 18FDG PET-CT [30,53], requiring meticulous mucosal exploration. Lacking sensitivity, imaging is not recommended as a means of exploring for an asymptomatic synchronous second esophageal location.

The reference screening examination is flexible white-light endoscopy, also known as esophageal video-endoscopy (French Society of Digestive Endoscopy (SFED) guideline, and professional consensus). It may be performed under local anesthesia, with or without premedication, or under general anesthesia. It provides a macroscopic aspect of the esophageal mucosa, enabling targeted biopsy of suspect areas (SFED guidelines for digestive biopsy indications, and professional consensus).

Lugol staining significantly enhances the sensitivity of flexible endoscopic detection of preneoplastic lesions (mucosal dysplasia), and provides a more precise account of the peripheral superficial extension of macroscopic lesions [48,51,54—56]. Lugol vaporization during flexible esophageal endoscopy may induce usually moderate and transient side-effects: bradycardia, cough, agitation, esophageal spasm or burning sensation [49]. The presence of large or numerous areas of Lugol non-uptake represents a risk factor for metachronous esophageal cancer [57,58]. Lugol vaporization identifies a patient subgroup requiring subsequent flexible esophageal endoscopic monitoring.

Rigid esophagoscopy is in our opinion a second choice, being less sensitive and with higher morbidity [59]. The risk of iatrogenic esophageal perforation is higher in case of previous cervicomediastinal radiation therapy [60].

Conclusion

The present grade B guidelines rationalize the respective roles of the various first-line radiological and endoscopic explorations for remote metastasis and synchronous second cancer. Thoracic CT is reinforced by 18FDG-PET/CT in patients at high risk of remote metastasis. Flexible tracheobronchial endoscopy is no longer recommended as a first line examination. Endoscopic exploration of the esophagus is recommended in certain at-risk patients. This rationalization should limit the number of examinations and thus reduce the time needed for initial staging.

Disclosure of interest

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

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