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SFORL Guidelines

# Guidelines update: Post-treatment follow-up of adult head and neck squamous cell carcinoma: Screening for metastasis and metachronous esophageal and bronchial locations

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ABSTRACT

*Objective:* The present article is an update of the guideline of the French Society of Otorhinolaryngology and Head and Neck Surgery (SFORL) on the post-treatment follow-up of adult head and neck squamous cell carcinoma concerning screening for metastasis and metachronous esophageal and bronchial locations.
*Methods:* A multidisciplinary work-group was entrusted with a review of the literature on the above topic. Guidelines were drawn up, based on the articles retrieved and the work-group members' own experience. These were then reviewed by an editorial group independent of the work-group. A coordination meeting then finalized the guidelines. Guidelines were graded A, B, C or "expert opinion" according to decreasing level of evidence.



## 1. Head and neck cancer and metachronous bronchopulmonary and esophageal locations

Neoplasia is said to be metachronous with respect to a head and neck tumor when diagnosed at least 6 months after the primary diagnosis; earlier than this, it is said to be synchronous [1,2].

Patients managed for head and neck carcinoma are exposed to a risk of locoregional recurrence and/or onset of second cancer. Two periods can be roughly distinguished:

- the first 2 or 3 years following primary treatment show elevated risk of locoregional recurrence and metastasis;
- thereafter, the risk of second (metachronous) cancer predominates, mainly in the head and neck region but also remotely, notably in the lung or esophagus [1,3].

Risk of second cancer is higher in patients who continue active smoking and/or alcohol abuse after primary treatment [1]. This risk persists to a lesser extent after smoking cessation, with a high rate of persistent high-grade precancerous lesions (severe dysplasia, which in 40–80% of cases progresses toward an invasive lesion or in situ carcinoma) found on bronchoscopy in patients who have given up smoking [4]. The risk is not to be taken into account in those who have never smoked [4].

The risk of metachronous cancer during follow-up of head and neck cancer is well known [1–3,5–7], with an annual rate of 3–7%.

No correlation has been found between primary tumor stage and rate of onset of metachronous cancer.

A laryngeal primary location increases the risk of bronchopulmonary metachronous cancer [1], and oral or pharyngeal location that of esophageal metachronous cancer.

Risk persists over time [6,7].

### 1.1. Bronchopulmonary metachronous locations

Three histologic types are found, in decreasing order of frequency: squamous cell carcinoma, adenocarcinoma, and small-cell carcinoma [8]. Squamous cell carcinoma accounts for 50–65% of pulmonary metachronous cancers in males and 20–25% in females [9]. Adenocarcinoma is more frequent in females than males [10].

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More than 95% of lung cancers are discovered in the absence of clinical signs [3]. Squamous cell carcinoma is the most frequently symptomatic, due to anatomic location: central, para-hilar, major bronchial axes [9]. This underscores the need for paraclinical examinations in screening for such cancers.

*1.1.1. Role of biological markers*

There are no validated biological markers in bronchopulmonary cancer screening [11].

*1.1.2. Role of cytology*

Bronchopulmonary cancer screening by cytological sputum analysis in high-risk populations is not considered contributive [11,12].

*1.1.3. Role of lung X-ray*

In high-risk populations, the contribution of chest X-ray in bronchopulmonary cancer screening was the focus of several reports, including 2 prospective randomized studies [11,13]. Radiologic screening was found to increase the rate of early-stage detection, feasibility of surgery and overall survival. This gain in survival, however, is dependent on discovery and diagnosis of slowly progressive lesions: no studies have reported reduction in mortality specific to lung cancer.

These studies established that bronchial cancer screening by chest X-ray in high-risk populations is non-contributive [11].

Several studies [7,14,15] focused on chest X-ray follow-up of head and neck cancer patients: none found improved survival in patients screened for second bronchopulmonary cancer.

Head and neck cancer follow-up by routine iterative lung X-ray has not proved contributive.

*1.1.4. Role of CT*

CT screening for bronchopulmonary cancer in high-risk patients shows high sensitivity but poor specificity. It enables early-stage diagnosis, increases surgical feasibility, and increases survival in patients screened for bronchopulmonary cancer by 20% at 5 years [16,17].

The rate of bronchopulmonary cancer found on screening is 0.7% for chest X-ray and 2.7% for low-dose spiral CT [18].

A 2011 randomized trial including 53,454 smokers aged 55-74 years with > 30 pack-years compared 3 years' annual bronchopulmonary cancer screening by chest X-ray versus low-dose CT without contrast enhancement [19]; there was a significant 20% reduction in death from bronchopulmonary cancer (95% CI: 6.86–26.7; $P = 0.004$) and overall mortality (6.7%; 95% CI: 1.2–13.6; $P = 0.020$) in the CT group. This was the first study to show a survival impact of bronchopulmonary cancer screening in high-risk patients.

A 2014 meta-analysis of 9 randomized studies confirmed these findings [20].

These results led several international learned societies to recommend individual screening of bronchopulmonary cancer in high-risk subjects alongside anti-smoking campaigns [21–23].

All publications on low-dose CT bronchopulmonary cancer screening report false positives in the form of non-cancerous nodules. In case of nodule discovered on chest CT, the work-group recommends the attitude shown on Figs. 1 and 2, following the guidelines of the French-Language Thoracic Oncology Intergroup, Society of Thoracic Imaging and French-Language Oncology Group [24].

*1.1.5. Role of autofluorescence bronchoscopy*

Screening and treatment of precancerous bronchial lesions by autofluorescence bronchoscopy has been the focus of several studies in high-risk subjects [25–28], with discordant findings.

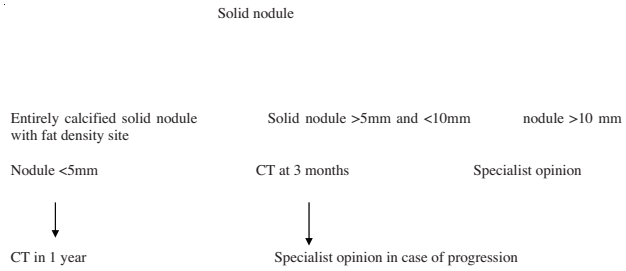


**Fig. 1.** Decision tree in case of isolated solid pulmonary nodule on CT.

Autofluorescence improved detection and follow-up of precancerous and in situ lesions, but the impact on specific mortality is not known. The examination is not widely available, and in the present state of knowledge is reserved to controlled assessment protocols.

*1.2. Esophageal metachronous locations*

The severity of esophageal metachronous cancer mainly implicates frequently late diagnosis [2], whence in principle the interest of early screening, if possible at an asymptomatic stage [1,29,30] when relatively non-invasive curative treatments are feasible: phototherapy, $CO_2$ laser, endoscopic resection [30].

*1.2.1. Epidemiology*

Mean annual incidence is 2.3% (range, 0.6–4.7%) [31,32]. The variation in reported incidence is due to differences in sample size and follow-up time and variable risk factors according to primary location.

The risk of esophageal cancer after treatment for head and neck cancer is 15–20-fold greater than in the general population [30].

Time to onset ranges between 1 and 5 years in 58% of cases, 6 and 10 years in 25% and more than 10 years in 17% [1].

The mid-third of the esophagus is the most frequent location [31], but several others are not exceptional (27.3%) [33].

The predominant 50–60-year age bracket corresponds to the mean age at onset of head and neck cancer plus mean time to onset of esophageal metachronous cancer.

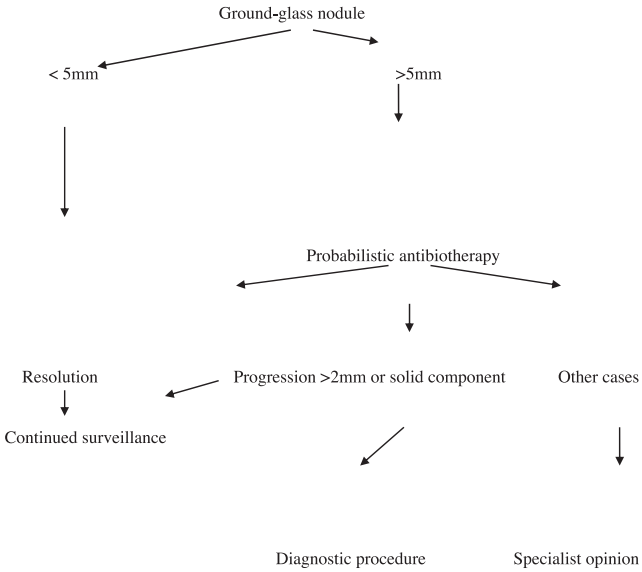


**Fig. 2.** Decision tree in case of ground-glass pulmonary nodule on CT.

*1.2.2. Clinical alerts*

Clinical signs, when present, indicate a stage that is already fairly advanced, whence the importance of informing the patient about alarm signals [29].

Dysphagia is the first symptom, often in the form of a simple sensation of food "getting stuck". It may be associated with chest pain.

Impairment of good esophageal voice should also be reported.

*1.2.3. Means of diagnosis*

*1.2.3.1. Imaging.* Barium sulfate contrast transit time, with or without radiocinematography [34], no longer plays a role in early diagnosis.

CT and MRI are contributive only to pre-treatment assessment and not to diagnosis.

*1.2.3.2. Abrasive esophageal cytology [32,35].* Abrasive esophageal cytology is a frequent means of screening for several teams: notably in certain Chinese provinces, Iran and South Africa.

It is, nevertheless, no longer recommended except for controlled prospective clinical studies.

*1.2.3.3. Fiberoptic endoscopy [30,31].* Fiberoptic endoscopy is indicated:

- in first-line in case of alarm signs;
- secondarily, to complement positive or uncertain esophageal cytology results in organized screening programs;
- in programmed surveillance, for certain teams.

Conventional fiberoptic endoscopy is insufficient to diagnose superficial cancerous lesions in asymptomatic patients [36].

Videoendoscopy has given a new lease of life to chromoendoscopy, which enhances endoscopic diagnostic performance by helping diagnosis of superficial lesions.

Several stains are available:

- methylene blue and indigo carmine are particularly used in screening for intestinal metaplasia and high-grade dysplasia in Barrett's esophagus;
- Lugol's 2% iodine (which has replaced toluidine blue) isolates abnormal yellowish-white islands within otherwise uniformly green-brown stained esophageal mucosa, enabling targeted biopsy [37]; it shows high sensitivity (96%) but poor specificity (63%), and fails to stain the glandular mucosa, erosion and inflammation or leukokeratosis.

In 2006, Dubuc et al. [36] reported a French prospective multicenter study of the contribution of routine screening for neoplastic and preneoplastic esophageal lesions in patients considered at risk of esophageal squamous cell carcinoma but asymptomatic at the time of endoscopy. Esophageal fiberoptic endoscopy was usually performed under local anesthesia with premedication, first under white light and then polarized light, 2 to 5 minutes after vaporization with 10–20 mL Lugol 2%. Between September 2000 and June 2003, 1095 patients were included, 393 of whom had been previously treated for head and neck cancer or bronchial squamous cell carcinoma. Incidence of esophageal cancer was 5.4%.

In 2013, Su et al. [38] reported a retrospective study of 3053 patients followed for head and neck cancer. Those who had undergone routine screening for esophageal cancer showed significantly higher incidence than those diagnosed only in case of positive symptomatology without routine screening: 4.5% vs. 3%; $P = 0.4$. Moreover, in patients diagnosed on routine endoscopy, early-stages were significantly more frequent: 41% vs. 20%; $P = 0.2$.

Finally, recent use of narrow-band imaging (NBI) suggests that it enhances sensitivity in esophageal fiberoptic endoscopy.

In 2009, Kuraoka et al. [39] compared Lugol versus NBI in the detection of malignant esophageal lesions in 49 patients at risk of esophageal cancer: chronic alcohol abuse, history of head and neck cancer. NBI was performed ahead of Lugol 1.5% vaporization. Results showed:

- 118 suspect mucosal lesions, including 5 with an aspect of squamous cell carcinoma;
- that carcinoma was systematically positive on NBI and iodine-negative on Lugol staining;
- not all iodine-negative lesions on Lugol staining were carcinomas.

Sensitivity was 100% for both NBI and Lugol, but specificity was 59% for NBI and 4.4% for Lugol.

In 2010, Lee et al. [40] assessed the contribution of NBI in esophageal fiberoptic endoscopy in 69 patients treated for head and neck squamous cell carcinoma. White light examination was performed ahead of NBI. Twenty-one esophageal neoplasias were diagnosed (30.4%), including 57.1% multiple lesions and 47.6% early grade. NBI was more effective than white light in detection: 35 lesions diagnosed in 21 patients (including 13 dysplastic lesions) on NBI versus 22 in 18 patients (including 3 dysplastic lesions) under white light. Sensitivity was 62.7% and 100% for white light and NBI, respectively.

*1.2.4. Synthesis*

Improved patient survival is directly related to the stage of progression of the metachronous esophageal tumor.

The only examination able to improve survival is endoscopy with staining, which detects early-stage lesions. Novel techniques such as NBI are not presently feasible for routine application and are available only for controlled prospective studies.

There are no reports in the literature of survival gain with routine esophageal cancer screening by fiberoptic endoscopy with Lugol staining in head and neck cancer. It is a heavy examination and prognosis is poor in esophageal cancer; endoscopy cannot therefore be considered standard but only as an optional examination.

Large-scale prospective randomized studies will be needed to assess its contribution, and should be encouraged.

When head and neck endoscopy is performed under general anesthesia, esophageal examination can be associated (expert opinion).

**Guidelines for bronchial and esophageal metachronous tumor screening**

- There are no validated biological markers for bronchopulmonary and esophageal cancer screening (grade A).
- The patient should be informed of the risk of pulmonary and esophageal second cancer and of the alarm symptoms (expert opinion).
- Low-dose thoracic CT without contrast enhancement is recommended in patients who have not quit smoking for at least 15 years (grade A). This examination also detects thoracic metastases. If cervical CT is required, the two may be associated, but with contrast medium injection (expert opinion).
- Routine esophageal fiberoptic endoscopic screening is only optional, at a two-yearly rhythm. It should use Lugol staining (expert opinion).

## 2. Head and neck cancer and metastasis

### 2.1. Incidence

Mean incidence of metastasis during head and neck cancer follow-up is 11.8% (range, 3–20.5%), close to the 11% reported by Merino in the largest clinical series to date (5019 patients) [29,41–45].

### 2.2. Location and disease type

The most frequently involved organs are, in decreasing order, the lungs, the bone skeleton and the liver [41–44]. In 80% of cases, there is a single metastatic site: the lung [44]. Isolated bone or liver involvement is exceptional: the lungs are associated in 97% of cases [42,43].

### 2.3. Time to onset

Ninety-five percent of metastases are diagnosed within 2 years of primary diagnosis. Except in a few reports, onset after 3 years is exceptional [29,41,42,46]. Median time to onset in the first location is 10 months [46].

### 2.4. Factors for onset of metastasis

In 50% of cases, metastases are associated with persistent locoregional progression [41,42]. The roles of location, size and histologic differentiation in onset of metastasis remain controversial, but there is near unanimity as to a significant relation between lymph node status and incidence of metastasis [41–44,46–48].

Metastasis risk increases in case of [43,48]:

- 3 cervical nodes (N2b or c);
- bilateral metastatic nodes (N2c);
- node(s) $\geq$ 6 cm (N3);
- node(s) low in the neck;
- $\geq$ 1 capsule rupture and/or lymphatic and perineural emboli on histology;
- and according to histologic type: basaloid squamous cell carcinoma (BSCC) is associated with elevated rates of metastasis, which is the prime cause of mortality in this histologic type, implicated in 45–65% of deaths; the largest clinical case-control series of BSCC to date was that of Soriano, with 62 patients [49].

### 2.5. Complementary examinations contributive to diagnosis

Lung X-ray is the most frequently prescribed examination for lung metastasis screening. Sensitivity ranges between 20% and 50% and specificity between 90% and 98% [42,43]. False negatives are common as metastatic pulmonary lesions are usually peripheral, where lung X-ray is least effective. Thoracic CT is sensitive, but with poor specificity of around 30% [46,47,50]: CT detects numerous nodules, but these are not always malignant; they may, for example correspond to infection sites, especially in case of swallowing disorder. PET-CT can determine whether a nodule is "metabolically active", which, in context, may contribute to diagnosis of metastasis. [45]. However, PET-CT fails to distinguish between metastasis and infection site, both giving rise to hyperfixation. It is, even so, a very effective means of screening for secondary locations, wherever they may be situated, with 91% sensitivity and 93% specificity [45].

Isolated nodules of < 1 cm diameter found on CT may be monitored on CT (at 3 months); in case of progression or > 1 cm nodule, PET-CT, fine-needle aspiration under CT or surgical exploration may be considered.

Bone metastasis screening is indicated only in case of pain or hypercalcemia. The basic examinations are plain X-ray and CT, or MRI. Bone scintigraphy should be prescribed in case of isolated hypercalcemia. Risk of neural compression in the spine should lead urgently to specialist (orthopedic or neurosurgical) opinion with a view to decompression.

In liver metastasis screening, examinations are needed only in case of clinical signs: hepatalgia, hepatomegaly. Ultrasound is the first-line examination, supplemented if need be by CT.

Biological liver analyses (SGOT, SGPT, alkaline phosphatase, Gamma GT, LDH, bilirubin) and alkaline phosphatase assay to screen respectively for liver and bone metastasis, are non-contributive, have poor sensitivity and no specificity [42,43].

Lung metastasis does not systematically require screening for bone and/or liver metastasis, which should rather be guided by clinical findings.

### 2.6. Synthesis

Only a single lung metastasis can in some cases be associated with long survival, justifying curative treatment.

Onset of multiple metastases following head and neck cancer is of poor prognosis, as there is presently no curative attitude. The interest of screening is therefore questionable. Ferlito et al., in contrast, consider metastasis screening to be mandatory in head and neck cancer, for two reasons: firstly, the patient and family need to be informed regarding progression; secondly, screening helps anticipate:

- the medical complications some metastases induce (compression, fracture in case of bone metastasis);
- the familial and social consequences of approaching death, the aim being not curative treatment but a better physical, moral and social comfort toward the end of life.

A third objective may be included: to limit investigation in the follow-up of the primary cancer, both for the patient's comfort and for economic reasons.

**Guideline**

For metastasis screening:

- there are no indications for biological analyses to screen for metastasis (grade A);
- screening for lung, bone and liver metastasis should be guided by clinical findings (expert opinion);
- in case of late metastasis (> 3 years) without local recurrence, a second primary cancer should be looked for (Expert opinion).

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