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European Laryngological Society: ELS recommendations for the follow-up of patients treated for laryngeal cancer

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Abstract It is accepted that the follow-up of patients who had treatment for laryngeal cancer is a fundamental part of their care. The reasons of post-treatment follow-up include evaluation of treatment response, early identification of recurrence, early detection of new primary tumours, monitoring and management of complications, optimisation of rehabilitation, promotion smoking and excessive alcohol cessation, provision of support to patients and their families, patient counselling and education. Controversies exist in how these aims are achieved. Increasing efforts are being made to rationalise the structure and timing of head and neck cancer follow-up clinics. The aim of this document is to analyse the current evidence for the need to follow up patients who have been treated for LC and provide an up to date, evidence-based statement which is meaningful and applicable to all European Health Care Systems. A working group of the Head and Neck Cancer Committee of the ELS was constituted in 2009. A review of the current published literature on the management and follow-up of laryngeal cancer was undertaken and statements are made based on critical appraisal of the literature and best current evidence. Category recommendations were based on the Oxford Centre for Evidence-Based Medicine. *Statements* include: length, frequency, setting, type of health professional, clinical assessment, screening investigations, patient's education, second primary tumours, and mode of treatment considerations including radiotherapy, chemo-radiation therapy, transoral surgery and open surgery. It

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also addresses specific recommendations regarding patients with persistent pain, new imaging techniques, tumour markers and narrow band imaging.

Keywords Laryngeal cancer · Follow-up · Surveillance

Introduction

The incidence of laryngeal cancer (LC) in Europe in 2008 was 3.4 per 100,000 with a mortality of 1.6. The incidence in men is 6.8, with a mortality of 3.4, and the incidence in women is 0.6, with a mortality of 0.2 per 100,000 population [1]. The estimated incidence of LC in Europe ranges from 8.9 in Hungary to 1.6 in Sweden per 100,000, with men more likely to be affected than women (5–7:1). Thus, squamous cell carcinoma of the larynx (SSCL) is the most frequent malignant tumour of the upper aerodigestive tract (UADT) in Europe [2]. The diagnosis of LC in patients younger than 40 years is rare and it most often manifests itself within the age period of 50–70 years [1–4].

LC is a multifocal disease, which is firmly linked to a variety of life-style factors, environmental factors and other host factors. There is general agreement that smoking is the major risk factor for laryngeal cancer. The combined consumption of alcohol and tobacco increases the laryngeal cancer risk in a more than additive way. Chronic alcohol consumption affects carcinogenesis, by malnutrition and depletion of tumour-protective vitamins and minerals [3] There is also an association of lower socioeconomic status, resulting in poor health care, smoking, drinking, and dietary habits as well as exposition to environmental and occupational carcinogenic factors. All these are possible explanations for the increased risk of laryngeal cancer. Gastro-oesophageal reflux has also been identified as a contributing factor [1–5].

The diagnosis of LC is made in patients presenting with local symptoms, such as hoarseness, abnormal and persistent throat discomfort and globus, breathing difficulties and local pain. At examination, any mucosal abnormalities such as red or while patches will necessitate biopsy or excision, to be subjected to histological examination and accurately determine the true nature of the lesion [5]. Lesions which contain or demonstrate keratinising epithelium such as leukoplakia, erythroplakia and mixed leukoerythroplakia are considered pre-malignant. When histopathological evidence of cytologic and architectural atypia is present in the absence of invasion, the lesions are referred to as dysplastic and the presence of laryngeal dysplasia (LD) has been considered to represent an increased risk for malignant transformation over squamous cell lesions that fail to show dysplastic features [5]. LDs have been subdivided according to the degree of architectural and cytological atypia into mild, moderate and severe. Many pathologists merge severe dysplasia and carcinoma in situ into a single category, and others have applied the cervical dysplasia paradigm to that of the larynx using the intraepithelial neoplasia concept (LIN 1, LIN 2 and LIN 3) [6, 7].

The prevalence of carcinomatous transformation of laryngeal hyperplasias has reported a range of 3.8–11.2 %; while in true LD the risk ranges between 10.5 and 32 %. This risk increases with the severity of the LD [6, 7].

It is important to distinguish between pre-invasive lesions (LD and carcinoma in situ) and early invasive cancer, because whilst the former are characterised by atypical or malignant cytological features encompassed within the laryngeal squamous epithelium (without metastatic potential), the latter reaches into the lamina propria (but does not invade muscular or cartilaginous structures), and as a consequence possesses a (small but real) potential for metastasising [7]. The true incidence of pre-malignant laryngeal lesions diagnosed and treated annually is unknown, as such lesions are not registered by cancer registries in any country, whereas invasive SCCL is a registered disease [6, 7].

LC is staged according to the TNM Classification of Malignant Tumours and can be divided into tumours by site and subsites: glottis, supraglottis and subglottis, as well as by stage grouping: early and late [8].

Rationale of follow-up

The natural history of untreated LC is progression from mild dysplasia through to carcinoma in situ, and to invasive cancer with subsequent metastases to involve the cervical lymph nodes and ultimately spreading distally most commonly to lungs, liver and bones ultimately leading to patients' death [7].

It is accepted that the follow-up of patients who had treatment for LC is a fundamental part of their care. The reasons of post-treatment follow-up include:

- Evaluation of treatment response
- Early identification of recurrence
- Early detection of new primary tumours
- Monitoring and management of complications
- Optimisation of rehabilitation
- Promotion smoking and excessive alcohol cessation
- Provision of support to patients and their families
- Patient counselling and education

Controversy exists in how these aims are achieved. Increasing efforts are being made to rationalise the structure and timing of head and neck cancer (HNC) follow-up clinics [9–17].

Clinical and socio-economic implications

The general structure of follow-up clinics is to have initial high-frequency visits, especially in the first 2 years when the risk of loco-regional recurrence is known to be high and then reduce frequency, with follow-up often finishing at 5 years. The structure of these clinics is often arbitrary and reflects national, institutional and clinician-led practices with very little evidence to support any one system [9, 10].

Evidence to support follow-up for early detection of tumour recurrence is lacking. However, there is a belief that follow-up clinics have inherent value and to date all published studies recognise this fact [10].

With the current socio-economic climate and with health care systems reducing costs, there is a real risk that long-term follow-up for patients with benign conditions or even cancer may be affected. Therefore, it may be needed that health care professionals provide risk-assessment strategies to rationalise and reduce potential unnecessary follow-ups [10, 16–18].

To rationalise follow-up, patients could be divided into low, intermediate and high risk of developing recurrence. This is well recognised in thyroid cancer [19, 20] but it is not the case in all other types of head and neck cancer, especially in LC. It is a belief that this categorisation could help to determine which patients should be followed for more than 5 years. It would also help to establish which screening tests might be needed to detect recurrence or second primaries (Table 1).

Aim

The aim of this document is to analyse the current evidence for the need to follow up patients who have been treated for LC and provide an up to date, evidence-based statement which is meaningful and applicable to all European Health Care Systems.

Methods

A working group of the Head and Neck Cancer Committee of the ELS was constituted in 2009. A review of the current published literature on the management and follow-up of laryngeal cancer was undertaken and statements are made based on critical appraisal of the literature and best current evidence. Category recommendations were based on the Oxford Centre for Evidence-Based Medicine using categories A, B, C, and D ("Appendix 1") [21].

Table 1 Proposed follow-up strategy base on risk of developing recurrence

Low risk	Stage I and II	Follow up 5 years
Intermediate risk	Stage III	Follow up 5 years
High risk	Stage IV	Follow up 10 years
With risk with 2nd primary tumours	Life long follow-up	

General considerations

Length

The length of the follow-up is generally 5 years although there are many clinicians who follow-up patients for longer periods or even for the patients life. Follow-up of patients more than 5 years would be justified for the following groups: high-risk patients, specific tumours (e.g. adenoid cystic carcinomas), patients who have undergone complex treatments who require on-going rehabilitation and support, and the detection of new primary tumours as well as patient preference. Fear of recurrence is prevalent in cancer patients and continued attendance at clinic helps to mitigate this [9–18].

- **Statement 1** Patients should be followed up to a minimum of 5 years with a prolonged follow-up for selected patients with high risk of late recurrence—Grade B.

Frequency

At present, there is no evidence that high frequency of follow-up visits per year confers any benefit in terms of reducing morbidity and mortality. However, a majority of clinicians support the follow-up of patients in decreasing frequency. In the first 2 years when the risk of loco-regional recurrence is high, regular high-frequency intervals should be followed by a decrease in frequency after the second year. The follow-up in the first 2 years should be between 4 and 8 weeks and from 3 to 6 months thereafter [9–14]. Longer intervals can be proposed for smaller lesions like glottic T1A with clear margins.

- **Statement 2** When the risk of loco-regional recurrence is high, patients should be followed up at least bimonthly in the first 2 years and quarterly to every 6 months in the subsequent years—Grade C.

Setting

Patients should be seen in dedicated HNC clinics for the duration of the follow-up period [9, 10].

- **Statement 3** Patients should be seen in dedicated multidisciplinary head and neck oncology clinics—Grade C.

Type of health professional

At present, patients tend to be followed up by their treating clinicians and/or a medical member of their teams. Allied Health Professionals (AHP) including speech and language therapists, dieticians and clinical nurse specialists (CNS) may offer specific follow-up in their areas of expertise but this is usually in addition to the clinician's follow-up. The introduction of the CNS and the key worker role in the management of patients with HNC have become vital to open lines of communication between the patient and family, their carers, their general practitioner and the clinical team should any problems arise. In other cancers, such as colo-rectal cancers, CNSs provide screening at initial diagnosis and follow-up. This has proven to be effective and safe. The adoption of this model in LC should also be considered [10, 22, 23].

- **Statement 4** Patients should be followed up within a dedicated multidisciplinary head and neck cancer clinical teams—Grade C.
- **Statement 5** The multidisciplinary head and neck cancer follow-up team should include: clinicians, clinical nurse specialists, speech and language therapists, dieticians, psychologist, social worker and other relevant AHP in the role of key workers—Grade C.

Clinical assessment

Traditionally, clinical assessment has been the most important aspect of the follow-up in patients treated for LC. The clinical evaluation must include inspection of the larynx, and palpation of the neck employing the use of rigid telescope or transnasal video or fibroscopy. By focussing on vocal fold vibrations during phonation, using laryngeal stroboscopy, the laryngologist can contribute considerably to the diagnosis of voice disorders. Use of the laryngostroboscope can thus provide valuable additional information [24]. The diagnostic accuracy of laryngeal imaging in general is some 68 %. Particular diagnoses, however, are more consistently identified; cancer, for example, was much more accurately identified on laryngoscopy (100 %) and stroboscopy (100 %) rather than history and physical examination alone (33 %) [25]. The inspection of the oral cavity, oropharynx and hypopharynx must also be included at each follow-up visit to exclude the possible development of a local second primary tumour (SPTs) [10, 11].

- **Statement 6** Clinical assessment should include adequate clinical examination of the entire mucosal lining of the upper aerodigestive tract and the use of endoscopy—Grade B.

Screening investigations

There is evidence that magnetic resonance (MR) and positron emission tomography with computerized tomography (PET-CT) scanning are superior at detecting recurrence and second primaries. This is especially true in some tumour sites such as the nasopharynx and oropharynx and following treatment with radiation (RT) or chemo-radiation (CRT) therapy [26]. If patients with LC have been treated with CRT or combined modality treatments, the use of PET-CT at 3 months to assess response to treatment should be considered. PET-CT has also the advantage of being a systemic evaluation [27–29].

- **Statement 7** MRI and PET-CT should be employed on completion of treatment after 3 months and subsequently when tumour recurrence is suspected—Grade A.

Patient's education

Patient's education has been identified to be a key factor in the management of LC, and its incorporation into follow-up symptom evaluation is to be recommended. The knowledge of the potential symptoms and signs of recurrence is a key factor in early diagnosis and, therefore, patients should be aware of these so they can seek medical attention as soon as possible [30]. It is also essential that patients can contact their general practitioner or the clinicians or health professionals who are involved in their follow-up so that they can request to be seen as soon as possible if they have any concerns. It is well known that some patients may wait until their assigned follow-up appointment by which time the disease progression has made salvage treatment impossible. Patient's education should also include tobacco smoking and alcohol cessation programmes, which have proven to be of great value for the prevention of the development of second primary tumours [10, 30, 31].

- **Statement 8** Patient's education on possible "red-flag" symptoms or signs suggesting recurrence of disease should be a key element of follow-up and early detection process of recurrence and should include enrolment into a smoking and alcohol cessation programmes—Grade A.

Second primary tumours (SPTs)

Incidence

The diagnosis of an SPT is a frequent event in patients following treatment of LC. The risk of developing SPTs

is constant throughout the follow-up period, with an incidence around 4 % per year [32]. The most frequent SPTs in patients with the index tumour in the larynx are carcinomas of the respiratory tract (larynx–lung) epidemiologically related with tobacco smoking. After a second tumour, the risk for more tumours continues. The chance of developing a third and fourth tumour is significantly higher than the risk for SPT [32–36].

Risk factors for second primary tumours

It seems that the risk of developing an SPT is dependent upon the intensity of smoking and drinking habits prior to the onset of the first neoplasm in head and neck. In the particular case of LC, the risk for developing a second primary cancer increased according to the number of cigarettes smoked per day at diagnosis of the LC. In a case–control study of patients with a head and neck cancer, the odds ratio (OR) of a second neoplasm for patients who continued to smoke was 2.9 (95 % CI OR 1.8–4.1), and for patients who continued to use alcohol it was 5.2 (95 % CI OR 3.3–7.9). According to the attributable risk estimation, persistent tobacco and alcohol consumption would be responsible for one-third of the SPTs in the patients with a head and neck index tumour [35].

Impact on survival and in follow-up

The impact of these SPTs in patients with an index tumour in the larynx is significant. In many cases, SPTs are upper aerodigestive tract (UADT) carcinomas detected too late with poor prognosis, and there is no effective treatment to date to prevent the appearance of a second cancer. As a result, in the long-term, a second neoplasm will be the cause of death in a number of these patients who survive an index LC [33, 34]. Moreover, the impact of SPT on long-term results is particularly important in early stages of LC, when index tumour cure probability is high, so the development of a second tumour will affect final survival more than the index tumour itself. The constant risk of an SPT should be part of rationale of follow-up and, therefore, adequate screening strategies should be used to detect them. Furthermore, the cessation of tobacco and alcohol abuse by patients treated for LC should be a major goal within the follow-up period of these patients to reduce the incidence of SPT, thereby improving long-term survival [32–37].

- **Statement 9** The risk of developing an SPT and its early detection should be part of the follow-up of patients treated with LC and, therefore, appropriate and adequate screening strategies should be employed routinely—Grade B.
- **Statement 10** Patients who develop an SPT and who are successfully treated should be followed up for longer periods than 5 years—Grade B.

Mode of treatment considerations

Follow-up following radiotherapy and chemo-radiation therapy

Patients treated with primary RT alone usually have been diagnosed with an early stage tumour [9]. In these patients, RT is used for the treatment of the primary tumour and the neck except for T1 NO glottic lesions [9]. As a result, there is a need for close follow-up surveillance of the primary site as well as the neck. The surveillance of the primary site is performed by FNPL and or the neck clinical palpation and radiologic evaluation if needed. CT, MR and Ultrasound Scanning USS have poor specificity in differentiating post-radiation oedema from recurrence. For this reason, CT, MR or PET-CT should be obtained 3–6 months after treatment to provide baseline images for later reference [28]. When suspicious lymph nodes are found, fine needle aspiration (FNAC) under USS guidance should be performed [38].

Patients treated with CRT have advanced stage LC. PET-CT has been introduced for the post-treatment surveillance of these patients to assess primary and neck disease response and plan salvage surgery of the neck [28, 29, 38–41]. In a meta-analysis to study the effectiveness of PET-CT in detecting recurrence or relapse after HNC treatment in this setting, it was seen that the pooled sensitivity and specificity were 94 and 82 %, respectively. The positive predictive value was 75 % and the negative predictive value 95 %. The sensitivity was greater for scans performed after 10 weeks of treatment [28]. The combination of PET with CT reduces the false-positive rates by over 50 % compared with CT alone [28, 29, 38–41].

In advanced neck stage disease, the possibility of performing a post-treatment planned neck dissection should be discussed in the event of negative PET-CT and no evidence of any residual lymphadenopathy on CT. Any attempt to resolve the controversy of when and when not to perform planned neck dissection requires a large prospective study [42].

- **Statement 11** Patients treated with radiation therapy (RT) should have CT, MRI or PET-CT at 3–6 months (12–14 weeks) after treatment to provide baseline images for later reference—Grade A.
- **Statement 12** Patients treated with definitive CRT should have PET-CT after 3 months (12 weeks) follow-

ing the completion of therapy to assess the complete response of the neck—Grade A.
- **Statement 13** The post-treatment planned neck dissection in advanced neck stage disease remains controversial and its effectiveness in survival advantage requires a large prospective study—Grade C.

Other than screening for loco-regional recurrence, this group of patients has to be monitored for sequelae related to radiotherapy such as hypothyroidism. This is due to the fact that a part or the whole thyroid gland is often included in the target volume of tissue that is irradiated and most patients with hypothyroidism are asymptomatic. With the incidence of hypothyroidism in these patients reaching 44 %, it seems necessary that they should undergo regular follow-up with thyroid function tests [11, 43, 44].

- **Statement 14** Patients treated with radiation therapy (RT) to the neck should have thyroid function tests every 6–12 months for life—Grade B.

Follow-up following transoral laser surgery (TOLS)

Patients treated using TOLS surgery will in the majority have had early stage LC [9]. As this surgery can be very conservative, this will allow the possibility of the development of tumours at other localisations in the larynx. It is imperative that regular examination of the larynx is performed between 4 and 8 weeks for the first year after surgery in case of extended resections when the risk of loco-regional recurrence is high. Longer intervals can be proposed for smaller lesions like glottic T1A with clear margins. Surveillance of the neck can be performed with clinical examination and CT scanner because such imaging modality remains highly sensitive in these cases [9]. Patients treated with TOLS will benefit from speech therapy after surgery to achieve a better voice quality although the functional outcome is variable [45, 46]

The systematic need of second look microlaryngoscopy (SLM) at 6–12 weeks remains controversial. SLM can be defined as microlaryngoscopic re-evaluation under general anaesthesia of patients previously treated with conservative TOLS or open neck partial laryngectomies (ONPL) [47–49]. It can be dictated by uncertain (close or altered for iatrogenic artifacts) surgical margins, granulomas, web formation or other post-excision abnormal tissue growth at the level of the primary resection site (in spite of appropriate medical and voice therapy), or involvement of certain laryngeal subsites (anterior commissure, ventricle, subglottis) [47–49]. The timing of SLM is still matter of discussion, ranging from 1 to 8 months after primary surgery. The same is true for the need of a third- or further-look microlaryngoscopy. However, both prospective and retrospective series clearly demonstrate a benefit in terms of earlier detection of persistence/recurrence (even in the presence of previous microscopic free surgical margins. This is especially true in the case of anterior commissure involvement, and apparently normal larynx with FNPL [47]. An adjunctive advantage of SLM is the possibility to confirm the benign nature of symptomatic granulomas or webs and to promote their surgical management (improving voice and/or airway patency) [47–49].

- **Statement 15** Routine SLM is still controversial in patients treated with TOLS; however, a second look is mandatory in case of positive margins at histopathological assessment—Grade B.
- **Statement 16** Speech therapy should be encouraged to improve voice quality following TOLS—Grade C.

Follow-up following open neck partial surgery and total laryngectomy or total pharyngolaryngectomy

Open partial surgery

Patients selected for treatment with ONPL have early or intermediate stage tumours with better prognosis [9]. In these patients, a close surveillance of the primary site as well as the neck must be applied. The surveillance of the primary site is performed by FNPL and for the neck, clinical examination with CT scan is advised [9]. If clinical examination is positive, a contrast CT scan should be performed. When suspicious lymph nodes are found either on clinical examination or CT scanning, FNAC under USS guidance should be done. As patients treated with OPNS may benefit from salvage treatment, it is mandatory to detect recurrence at an early stage. Patients with recurrence frequently report their symptoms to clinicians or AHP providing their follow-up surveillance [10, 11]. It is, therefore, recommended to focus on patient education of the signs of recurrence as per recommendation 8 [30, 31].

Total laryngectomy or pharyngo-laryngectomy

Patients treated with TL or TPL have advanced initial stage LC or recurrent LC following previous treatment [9]. The optimal follow-up regime remains a long-standing question [10]. The efficacy of current follow-up regimes to detect LC recurrence varies considerably. The surveillance is performed by clinical examination of remaining UADT structures and of the neck. If clinical examination is positive, a contrast CT with should be performed [10]. As for patients treated with RT or CRT, PET-CT has been introduced for the follow-up of patients treated with TL or TPL [28, 29, 38–41].

- **Statement 17** Patients treated with open surgery should have sequential physical examination including FNLP and CT or PET-CT if indicated—Grade B.

Specific considerations and new technologies in the follow-up

Patients with persistent or recurrent pain without clinical evidence of disease

Pain complaints (either in the form of localised laryngeal or neck pain, or as well as in the referred form, usually otalgia) must be regarded as a serious warning sign of recurrent disease during follow-up of LC patients, even in the absence of an endoscopically visible persistence/recurrence [29, 49, 50]. In a series of head and neck squamous cell carcinomas, persistent neck pain was the first symptom of recurrent disease in 70 % of patients [49]. In another larger group of head and neck cancer patients, post-treatment pain was recently found to be an independent predictor of both recurrence and 5-year survival rate [50]. Pain should always prompt the clinician to initiate a thorough set of investigations, both by imaging and/or endoscopy under general anaesthesia, to reduce possible diagnostic delays. This symptom is usually caused by submucosal growth of disease with extra-laryngeal spread, possibly hidden by oedematous mucosa. Otherwise, it can be associated with chondritis or chondronecrosis as a result of previous treatments. Pain without endoscopic evidence of disease is more frequently encountered after RT or CRT, but it is possible even after TLS and different forms of ONPL [50].

- **Statement 18** Complaints of laryngeal, neck or referred ear pain (otalgia) which is persistent or recurrent following treatment of LC should be always thoroughly investigated and never dismissed—Grade C.

New imaging techniques: diffusion-weighted MR (DWI)

DWI is a relatively novel imaging technique that has been recently applied to HNC with promising results. It is based on the use of strong magnetic field gradients that generate imaging contrast through diffusion motion of water protons inside tissues. Molecular motion can be determined by calculating the apparent diffusion coefficient (ADC) map, which varies according to the specific microstructure or physiopathologic state of a given tissue. ADC is expected to be low in neoplastic tissues and high in the presence of oedema, inflammation, fibrosis or necrosis. Special emphasis has, therefore, been given to the possibility of DWI to specifically distinguish between post-treatment alterations and recurrent/persistent disease, well before clinical appearance of macroscopic disease and/or symptoms. DWI has a very short scanning time and presents no extra cost for patients already undergoing MR evaluation. Moreover, it is less influenced than PET in terms of false-positive results by the time interval after treatment. However, it is less widely used than standard MR, and its accurate interpretation requires specific training and experience. Large series related to its use in follow-up of LC are still lacking, even though promising results have been published in the follow-up of mixed cohorts of head and neck cancer patients after surgery or non-surgical organ preservation protocols. In this latter case, sensitivities in the range of 84–93 % and specificities between 90 and 96 % have been reported [51–53].

- **Statement 19** DWI can be applied during follow-up of selected patients with LC, especially after non-surgical organ preservation strategies—Grade C.

Tumour markers and gene expression profiling

In spite of significant efforts in the last decades from researchers worldwide to find clinically useful tumour markers for HNC, no large, prospective study and/or prospectively planned meta-analysis in this regard has been either performed or is at the horizon. Many adverse factors disfavour such an initiative and, therefore, there is little potential to use prognostic tumour markers on a routine basis. The frequently observed lack of sensitivity and low cost-to-benefit ratio greatly hamper their application in follow-up of LC patients. The same is true for gene expression profiling, which, for both economic and reproducibility issues, is yet to be utilised in every-day clinical practice. Thus, at present, there is no evidence to support the use of routine testing of serum markers or gene profiling in either pre- or post-treatment scenarios of patients affected by LC, outside from well-designed, prospective clinical trials [54, 55].

- **Statement 20** There is no role for tumour markers and gene expression profiling in patients with LC during routine follow-up—Grade C.

Narrow band imaging (NBI)

The ideal clinical investigation tool for patients to be followed after treatment of LC is FNPL with or without topical anaesthesia. Video-recording of serial examinations using high-resolution flexible video endoscopes is of paramount

value for sharing opinions between different examiners, storing images of individual patients, and making comparisons during the entire post-therapeutic period. NBI, possibly associated with high-definition television technology, is an adjunctive imaging tool due to its specific capability to selectively address superficial persistences/recurrences or SPTs by enhancing their pathognomonic neoangiogenetic pattern. It has been reported that its use can detect 18 % more true-positive LC lesions than conventional white light endoscopy. This is true even after RT or CRT, due to the high accuracy (98 %) of NBI in differentiating between neoplastic disease and post-RT inflammatory and/or cicatricial changes [56–58].

- **Statement 21** FNPL, possibly integrated with video-recording, storage of images, and use of NBI, is the most accurate clinical tool for follow-up of LC—Grade C.

Conclusions

It is accepted that the follow-up of patients who had treatment for LC is a fundamental part of their care. The reasons of post-treatment follow-up include: evaluation of treatment response, early identification of recurrence, early detection of new primary tumours, monitoring and management of complications, optimisation of rehabilitation, promote smoking and excessive alcohol cessation and provision of support to patients and their families.

- **Statement 1** Patients should be followed up to a minimum of 5 years with a prolonged follow-up for selected patients with high risk of late recurrence—Grade B.
- **Statement 2** Patients should be followed up at least bimonthly in the first 2 years and quarterly to every 6 months in the subsequent years. Longer intervals can be proposed for smaller lesions like glottic T1A with clear margins—Grade C.
- **Statement 3** Patients should be seen in dedicated multidisciplinary head and neck oncology clinics—Grade C.
- **Statement 4** Patients should be followed up within a dedicated multidisciplinary head and neck cancer clinical teams—Grade C.
- **Statement 5** The multidisciplinary head and neck cancer follow-up team should include: Clinicians, Clinical Nurse Specialists, Speech and Language Therapists, Dieticians, Psychologist, Social Worker and other relevant AHP in the role of key workers—Grade C.
- **Statement 6** Clinical assessment should include adequate clinical examination of the entire mucosal lining of the upper aerodigestive tract and the use of endoscopy—Grade B.
- **Statement 7** If patients have been treated with CRT or combined modality treatments, CT, MRI and PET-CT should be employed on completion of treatment after 3 months and subsequently when tumour recurrence is suspected. The previous imaging modality must be taken in account—Grade A.
- **Statement 8** Patient's education on possible "red-flag" symptoms or signs suggesting recurrence of disease should be a key element of follow-up and early detection process of recurrence and should include enrolment into a smoking and alcohol cessation programmes—Grade A.
- **Statement 9** The risk of developing an SPT and its early detection should be part of the follow-up of patients treated with LC and, therefore, appropriate and adequate screening strategies should be employed routinely—Grade B.
- **Statement 10** Patients who develop an SPT and who are successfully treated should be followed up for longer periods than 5 years—Grade B.
- **Statement 11** Patients treated with radiation therapy (RT) should have CT, MRI or PET-CT at 3–6 months (12–14 weeks) after treatment to provide baseline images for later reference—Grade A.
- **Statement 12** Patients treated with definitive CRT should have PET-CT after 3 months (12 weeks) following the completion of therapy to assess the complete response of the neck—Grade A.
- **Statement 13** The post-treatment planned neck dissection in advanced neck stage disease remains controversial and its effectiveness in survival advantage requires a large prospective study—Grade C.
- **Statement 14** Patients treated with radiation therapy (RT) to the neck should have thyroid function tests every 6–12 months for life—Grade B.
- **Statement 15** Routine SLM is still controversial in patients treated with TLS surgeries; however, a second look is mandatory in case of positive margins at histopathological assessment—Grade B.
- **Statement 16** Speech therapy should be encouraged to improve voice quality following TLS—Grade C.
- **Statement 17** Patients treated with open surgery should have sequential physical examination including FNLP and CT or PET-CT if indicated—Grade B.
- **Statement 18** Complaints of laryngeal, neck or referred ear pain (otalgia) which is persistent or recurrent following treatment of LC should be always thoroughly investigated and never dismissed—Grade C.
- **Statement 19** DWI can be applied during follow-up of selected patients with LC, especially after non-surgical organ preservation strategies—Grade C.
- **Statement 20** There is no role for tumour markers and gene expression profiling in patients with LC during routine follow-up—Grade C.

- **Statement 21** FNPL, possibly integrated with video-recording, storage of images, and use of NBI, is the most accurate clinical tool for follow-up of LC—Grade C.

Appendix 1: Summary of category recommendations based on the Oxford Centre for Evidence-Based Medicine

A. At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to target population.
B. A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results.
C. A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results.
D. Evidence 3 or 4.

Appendix 2: UICC Laryngeal Cancer Current TNM Classification [59]

Supraglottis

T1 Tumour limited to one subsite of supraglottis with normal vocal cord mobility.

T2 Tumour invades mucosa of more than one adjacent subsite of supraglottis of glottis or region outside supraglottis (e.g. Mucosa of base of tongue, vallecula, medial wall of piriform sinus) without fixation of the larynx.

T3 Tumour limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space and/or with minor thyroid cartilage erosion (e.g. inner cortex).

T4a Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus.

T4b Tumour invades prevertebral space, mediastinal structures, or encases carotid artery.

Glottis

T1 Tumour limited to vocal cord (s) (may involve anterior and posterior commissure) with normal mobility.

T1a. Tumour limited to one vocal cord.

T1b. Tumour involves both vocal cords.

T2 T2a. Tumour extends to supraglottis and/or subglottis with normal vocal cord mobility.

T2b. Tumour extends to supraglottis and/or subglottis with impaired vocal cord mobility.

T3 Tumour limited to larynx with vocal cord fixation and/or invades paraglottic space and/or with minor thyroid cartilage erosion (e.g. inner cortex).

T4a Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus.

T4b Tumour invades prevertebral space, mediastinal structures, or encases carotid artery.

Subglottis

T1 Tumour limited to subglottis.

T2 Tumour extends to vocal cord (s) with normal or impaired mobility.

T3 Tumour limited to larynx with vocal cord fixation.

T4a Tumour invades through the cricoid or thyroid cartilage and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus.

T4b Tumour invades prevertebral space, mediastinal structures, or encases carotid artery.

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