ANTI-TUMOUR TREATMENT

Current opinion in diagnosis and treatment of laryngeal carcinoma

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Summary Laryngeal carcinoma is the 11th commonest form of cancer in men world-wide, with 121,000 new cases in 1985. More than 95% of all laryngeal malignancies are squamous cell carcinomas.

Treatment indications in cancer of the larynx are often controversial, since there are few comparative studies of different available therapeutic approaches. Surgery and radiotherapy are both widely used, and the choice between these two procedures is the most common therapeutic decision which has to be taken. Laryngeal function preservation has gained more and more weight in the last decades and chemotherapy is also a significant component of several curative approaches. In the last decades, several organ-preserving surgical techniques have become available and consequently total laryngectomy results less applied. Regardless of the treatment modality, Tis, T1, T2 laryngeal carcinomas have an 80–90% probability of cure, whereas for more advanced tumours this is approximately 60%.

The most effective approach to laryngeal cancer remains prevention and early diagnosis when this cancer is curable with function preserving treatments.

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KEYWORDS
Laryngeal carcinoma; Diagnosis; Staging; Treatment; Follow up

Anatomy

For clinical and staging purposes, the larynx is currently divided in supraglottic, glottic and subglottic regions. Essential laryngeal anatomy is synthesised by Table 1.

Considering the significant metastatic potential of laryngeal carcinoma to the cervical lymph nodes, concise notes...
of clinical anatomy of cervical lymphatics are mandatory. A widely accepted level-based system can be synthesized as follows:

- **Level I**: submental (IA) and submandibular (IB) lymph nodes;
- **Levels II** (IIA anterior to the vertical plane defined by spinal accessory nerve; IIB posterior to the vertical plane defined by spinal accessory nerve), III and IV: upper, middle, and lower jugular lymph nodes, respectively;
- **Level V**: posterior triangle group is composed predominantly by the lymph nodes located along the lower half of the spinal nerve and the transverse cervical artery;
- **Level VI**: anterior compartment group: pretracheal and paratracheal nodes, precricoid node, and the perihyoidal nodes including the lymph nodes along the recurrent laryngeal nerves.2

### Signs and symptoms

The most important functions of the larynx are to provide airway patency, protect the tracheo-bronchial tree from aspiration, and allow phonation. Tumours that involve the larynx may impair these function in a variable degree depending on location, size and depth of invasion. The presence of hoarseness, sore throat, shortness of breath, dysphagia or “lump in throat” sensation are all symptoms observed in early or moderately advanced stages of laryngeal cancers. Since lymph node metastases are frequently the first clinical sign of laryngeal carcinoma, swelling of cervical soft tissues, in the absence of evident signs of infection, should be carefully evaluated.7

Supraglottic cancers present at later stage of disease typically with sore throat, odynophagia, referred ear pain, change in voice quality, or enlarged neck nodes. Glottic cancers are usually detected because of hoarseness occurrence, airway obstruction occurs later in disease progression. Cancers arising in the subglottic area are rare and present with airway obstruction or vocal fold immobility.

It is recommended that patients with hoarseness persisting longer than 3 weeks or with persisting sore throat, dysphagia, odynophagia lasting for more than 6 weeks are referred from a general practitioner to an otolaryngologist.9

### Histology

More than 95% of all laryngeal malignancies are squamous cell carcinomas.10,11 Less common phenotypic expressions of this malignancy can occur. Verrucous squamous cell carcinoma is a locally aggressive but usually non-metastasizing highly differentiated variant.

Table 2 summarizes the histologic typing of primary laryngeal malignancies.

### Risk factors

Tobacco is the predominant risk factor in laryngeal carcinogenesis. Alcohol is generally regarded as the second major risk factor. In most series, >95% of patients with squamous cell carcinoma of the larynx have a background of tobacco and/or alcohol consumption prior to tumour diagnosis. The appearance of laryngeal cancer has been related to other factors, such as environmental exposure (evidence does not support asbestos exposure itself as increasing the relative risk of laryngeal cancer), gastroesophageal and biliary reflux, viral infection (oncogenic types of human papilloma virus), dietary factors, radiation and individual predisposition. When it rarely occurs in childhood and adolescence, laryngeal carcinoma seems to be a genetic disease associated with specific chromosomal damage.13
Biologic and clinical behaviour

Primary laryngeal squamous cell carcinoma development

Pre-invasive lesions (dysplasia and carcinoma in situ) are characterized by atypical or malignant cytologic features encompassed within the laryngeal squamous epithelium. Dysplasia shows cells which have features of malignancy, but which do not breach the basement membrane to reach into the adjacent lamina propria. In the natural history of laryngeal cancer, both dysplasia and carcinoma in situ of the laryngeal mucosa may subsequently evolve into an invasive neoplasm. It is also a fact that laryngeal cancers may develop directly as invasive neoplasms and do not pass through the stage of carcinoma in situ. Squamous cell carcinoma is by its definition invasive. 14

Cervical lymph nodes metastases

The supraglottic area is richly supplied with lymphatics, and invasive carcinomas of the supraglottic region metastasize in 25–75% of cases when all stages are considered. 15 Bilateral metastases are not unusual 16 being the supraglottis a midline structure.

Although early stage glottic carcinoma (T1–T2) is accepted to have a low incidence of lymph node metastasis (0–10%), the reported incidence with more advanced stage disease (T3–T4), varies between 10% and 35%. 17 The cervical lymph nodes at high risk in advanced (T3 and T4) glottic cancers include levels II–III–IV and VI. 18

Unusual primary subglottic carcinomas spread initially to the paratracheal and recurrent lymph nodes. The jugular chain of lymph nodes should be considered as a secondary site of lymphatic spread for subglottic cancers.

Distant metastases

Distant metastases from laryngeal squamous cell carcinoma are significantly less frequent than metastases from other human malignancies. Considering 1667 primary laryngeal carcinomas, Spector 19 reported an overall incidence of distant metastases of 4.4%. In this series, the incidence of distant metastases in supraglottic carcinomas was 3.6% (19/520 patients). The incidence of distant metastases from supraglottic carcinomas was not related to primary tumour stage but to N stage. The incidence of distant metastases in 1119 glottic carcinoma patients was 4.4% (related to T stage). Primary subglottic SCC had a 14.2% distant metastasis rate (non-TNM stage-related). Incidences of distant metastasis described in autopsy studies were approximately three to four times higher than those reported in clinical studies. 20 Lung metastases are the most commonly found, followed by metastases to bone and liver. Other areas of metastasis from laryngeal carcinoma included skin, brain, kidney, adrenal glands, pleura.

Diagnostic strategy and tools

Clinical assessment

The staging for laryngeal cancers is based on laryngeal sub-sites invasion, vocal cord mobility, and neck involvement. An outpatient setting examination with flexible and rigid laryngoscopes with or without local anaesthesia should assess the lesion extension and vocal cord mobility. The flexible fiberoptic laryngoscope has increased the reliability of endoscopy in patients whose larynx was previously difficult to visualize.

Direct laryngoscopy under general anaesthesia may be useful to allow precise definition of tumour extension, to explore sub-sites as anterior commissure, laryngeal ventricle, subglottis, and pyriform sinus, and to perform lesion biopsies. 7 In cases of advanced laryngeal carcinomas, a fiberoptic evaluation of the esophagus is mandatory to rule out a synchronous malignancy of the upper digestive tract. 21

Considering laryngeal carcinoma metastatic pattern involving neck lymph nodes, neck instrumental investigation is mandatory. The reported false negative rate in assessing

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Histologic typing of primary laryngeal malignancies according to WHO, 1991 75</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelial tumours</strong></td>
<td><strong>Squamous cell carcinoma</strong></td>
</tr>
<tr>
<td>Verrucous squamous cell carcinoma</td>
<td><strong>Soft tissue tumours</strong></td>
</tr>
<tr>
<td>Spindle cell carcinoma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Adenoid squamous cell carcinoma</td>
<td>Malignant fibrous histiocytoma</td>
</tr>
<tr>
<td>Basaloid squamous cell carcinoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Carcinoma in pleomorphic adenoma</td>
<td>Malignant hemangiopericytoma</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>Malignant nerve sheath tumour</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>Alveolar soft part sarcoma</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>Giant cell carcinoma</td>
<td>Ewing sarcoma</td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Carcinoid tumour</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Atypical carcinoid tumour</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>Malignant germ cell tumours</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td><strong>Tumours of bone and cartilage</strong></td>
</tr>
<tr>
<td><strong>Malignant lymphomas</strong></td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td><strong>Miscellaneous tumours</strong></td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Secondary tumours</td>
<td><strong>Unclassified tumours</strong></td>
</tr>
</tbody>
</table>
the presence or absence of cervical lymph node metastasis by palpation is 20–51%.22

Imaging

With the exception of small superficial carcinomas, computerized tomography (CT) and magnetic resonance imaging (MRI) are nowadays useful radiological procedures for staging primary laryngeal carcinoma. Both exams can offer information about primary tumour volume (especially in large lesions), cartilage involvement, invasion of the pre-epiglottic space, and extension beyond the larynx. Regarding cartilage invasion, MRI is a sensitive method to detect cartilage alterations having a high negative predictive value. CT results less sensitive than MRI.23 False positive results seem to be inevitable with both methods because reactive inflammation may lead to overestimation of neo-plastic cartilage invasion.24 Positron emission tomography (PET) is most helpful in differentiating locally recurrent tumour from post-irradiation tissue sequelae after organ preservation approaches.25

Ultrasonography is a sensitive method for detecting neck metastatic involvement. On the other hand, ultrasound does not reliably differentiate large reactive lymph nodes from metastatic ones. Ultrasonography combined with fine needle aspiration cytology is a reasonably accurate technique for the investigation of cervical lymph node metastases from laryngeal carcinoma. Reported figures of the accuracy of fine needle aspiration cytology guided by ultrasonography range between 89% and 97%.26 Substantial literature supports the value of both CT and MRI scans in clinical staging of cervical lymph nodes. An 87–93% accuracy of CT scan in neck staging has been reported.27 MRI evaluation of cervical nodal metastases is less well documented but available data suggest comparable sensitivity and specificity.27

Although in literature it has been suggested that routine work-up to detect distant metastases in patients with head and neck squamous carcinoma is not feasible, standard staging work-up in several institutions include chest X-rays, liver ultrasonography, alkaline phosphatase determination. The guidelines for determining which patients with advanced laryngeal carcinoma should undergo specific imaging evaluation for distant metastasis are still under debate. De Bree et al.28 proposed distant metastases screening for patients with head and neck carcinoma who had three or more neck lymph node metastases, bilateral lymph node metastases, lymph nodes of 6 cm or larger, low jugular lymph node metastasis, locoregional tumour recurrence, or second primary tumours. Interesting techniques for detection of distant metastases (thallium-201 single-photon-emission computed tomography, fluorine-18-fluorodeoxyglucose positron emission tomography [FDG PET], radioimmunoscintigraphy) have been developed but need further evaluation for clinical applicability.

Pathological diagnosis

Biopsy is mandatory to confirm the diagnosis of laryngeal squamous cell carcinoma. Biopsy should be deep and reach necrotic tumour and viable tumour and stroma or muscle to prove the presence of an invasive squamous cell carcinoma.29 Conventional light microscopy following hematoxylin and eosin staining usually allows laryngeal squamous cell carcinoma histological diagnosis. Histopathologically, invasive squamous cell carcinoma is conventionally graded as follows:

- well differentiated (G1);
- moderately differentiated (G2);
- poorly differentiated (G3).

Immunohistochemical reactions and electron microscope analysis are not considered necessary to confirm the diagnosis of squamous cell carcinoma in the majority of the cases. Immunohistochemically, squamous cell carcinoma of the larynx is usually positive for cytokeratins and epithelial membrane antigen. The application of electron microscopy can assist diagnosis of neoplasms considered as undifferentiated at light microscopy evaluation.

Conventional histopathological evaluation after hematoxylin and eosin staining of the neck dissection specimens allows the definitive diagnosis of cervical lymph nodes metastases from laryngeal carcinoma. The histological confirmation of extranodal metastatic spreading is extremely important in adjuvant treatment planning.

Stage information

The staging system estimates the extent of disease before (cTNM) and after treatment (pTNM). Head and neck CT or MRI should be done prior to the therapy to supplement inspection and palpation. The carcinoma presence has to be confirmed histologically, and any other pathological data obtained on biopsy may be included. The sixth edition (2002) of the International Union against Cancer (UICC) TNM classification30 (Tables 3 and 4) is identical to that of the American Joint Cancer Committee (AJCC) (sixth edition, 2002)31 (for AJCC stage groupings see Table 5).

Treatment of laryngeal primary carcinoma

Regardless of the treatment modality, Tis, T1, T2 laryngeal carcinomas have an 80–90% probability of cure, whereas for more advanced tumours this is approximately 60%. Treatment indications in cancer of the larynx are often controversial, since there are few comparative studies of the different available therapeutic approaches.27 Surgery and radiotherapy are both widely used, and the choice between these two procedures is the most common therapeutic decision which has to be taken. Function preservation has gained more and more weight in the last decades and, from this viewpoint, chemotherapy is now also a significant component of several curative approaches.32 In the last decades, several organ-preserving surgical techniques have become available and consequently total laryngectomy results less applied.

Supraglottic cancer

Small superficial cancers without laryngeal fixation or lymph node metastatic involvement (T1N0 and T2N0) are successfully treated by radiation therapy or surgery alone, including laser excision.
<table>
<thead>
<tr>
<th>Regions</th>
<th>T-stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraglottis</td>
<td>T1</td>
<td>Tumour limited to one subsite of supraglottis with normal vocal cord mobility</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>Tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, or medial wall of pyriform sinus) without fixation of the larynx</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>Tumour limited to larynx with vocal cord fixation and/or invades any of the following: post-cricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>Tumour invades through the thyroid cartilage, and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures</td>
</tr>
<tr>
<td>Glottis</td>
<td>T1</td>
<td>Tumour limited to the vocal cord(s), which may involve anterior or posterior commissure, with normal mobility; T1a: tumour limited to one vocal cord, T1b: tumour involves both vocal cords</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>Tumour extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>Tumour limited to the larynx with vocal cord fixation and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>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 the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures</td>
</tr>
<tr>
<td>Subglottis</td>
<td>T1</td>
<td>Tumour limited to the subglottis</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>Tumour extends to vocal cord(s) with normal or impaired mobility</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>Tumour limited to larynx with vocal cord fixation</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>Tumour invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck, including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures</td>
</tr>
</tbody>
</table>

Remarks: TX: primary tumour cannot be assessed; T0: no evidence of primary tumour; Tis: carcinoma in situ.
Current opinion in diagnosis and treatment of laryngeal carcinoma

The major controversies, therefore, surround the selection of treatment for lesions of intermediate size (advanced T2 and T3). For T2 and T3 supraglottic tumours not involving the glottic plane and the arytenoids, a horizontal supraglottic laryngectomy is considered the standard treatment. In supraglottic laryngectomy, the portion of the larynx above the ventricles (the epiglottis, pre-epiglottic space, false vocal cord, the upper segment of thyroid cartilage, and sometimes hyoid bone) are excised. After this procedure that spares the vocal cords, functional results are good. This operation can also be carried out in cases where there is limited extension to the valleculae and the tongue base. The resection may also be extended laterally, to encompass limited tumours of the pyriform sinus, and posteriorly, to include one arytenoid cartilage. Stage for stage, supraglottic laryngectomy tends to result in better local control rates than radiotherapy (RT). In T3 supraglottic cancers that involve the glottis (also with inner cortex thyroid cartilage erosion) or the paraglottic space and when at least one arytenoid cartilage can be preserved and no subglottic involvement is present, a partial supracricoid laryngectomy (SCL) with crico-hyoido-epiglottopy can be considered. With these procedures, the entire thyroid cartilage and both vocal cords are removed, the cricoid, at least one arytenoid with or without the upper half of the epiglottis are preserved. The advantage of this procedure is the preservation of the airway continuity, with the aim of normal oral intake, tracheostomy closure and good oncologic results. Main postoperative complication are humble voice quality and dysphagia. Total laryngectomy, exclusive RT, RT-chemotherapy associations have to be reserved for patients with advanced T3, T4 lesions or with poor general conditions or unable to tolerate potential respiratory complications of partial surgery.

### Table 4 TNM definitions (N-stage)

<table>
<thead>
<tr>
<th>N-stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node &gt;3 cm but ≤6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node &gt;6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

**Remarks:** Midline nodes are considered homolateral nodes.

### Table 5 AJCC Stage groupings

<table>
<thead>
<tr>
<th>Stage group</th>
<th>TNM staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0 M0</td>
</tr>
<tr>
<td>I</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>II</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>T3 N0 M0; T1 N1 M0; T2 N1 M0; T3 N1 M0</td>
</tr>
<tr>
<td>IVa</td>
<td>T4a N0 M0; T4a N1 M0; T1 N2 M0; T2 N2 M0; T3 N2 M0; T4a N2 M0</td>
</tr>
<tr>
<td>IVb</td>
<td>T4b any N M0; any T N3 M0</td>
</tr>
<tr>
<td>IVc</td>
<td>Any T, any N, M1</td>
</tr>
</tbody>
</table>

**Glottic cancer**

Radiotherapy, open surgery and endoscopic surgery with cold steel or laser resection are all accepted modalities of treatment for early stage glottic cancer (Tis/T1/T2, N0). A recent review compared the effectiveness of these commonly used treatments of early glottic cancer and found that there is not enough evidence to show which form of treatment might be better. Endoscopic laser surgery has nowadays gained increasing popularity. The major advantages of the procedure are the preservation of the thyroid cartilage and significant resource savings (one-day case procedure). Indications and results are crucially dependent on the experience of the surgeon. Extension to the anterior commissure may increase the technical difficulty but it is not considered an absolute contraindication. After endoscopic surgery, radiotherapy may be held in reserve for further use.

In the treatment of T1b and T2 glottic cancers recently several authors proposed SCLs with good oncologic and functional results. Laccourreye et al. reported a 98% actuarial 5-year local control estimate for 62 patients with T1b or T2 cancer extending to the anterior commissure. Various vertical partial laryngectomies were also described in the treatment of these cancers. Considering that SCL allows more extensive excision of the paraglottic space, several authors achieved better oncologic results after SCL than after vertical partial laryngectomies in the treatment of glottic T2–T3 tumours. The classical treatment for T3 glottic carcinoma was total laryngectomy and neck dissection often followed by radiotherapy. In patients with T3 glottic cancers without subglottis involvement, when at least one arytenoid cartilage can be preserved, a SCL with crico-hyoido-epiglottopy or crico-hyoido-epiglottoplexy may be suitable. Chevalier et al. reported a 5-year actuarial local control rate of 95.4% in 22 patients with T3 cancer treated with SCL. SCL seems to allow a significant increase in local control rate (85–90%) and ultimate survival when compared with RT alone or other conservative options. Other authors reported good oncologic results with this stage tumours with endoscopic laser resection. Recently promising outcomes were described after combined treatment modalities (RT/chemotherapy) that should be reserved to the cases not suitable for partial laryngectomies.

The treatment of glottic T4a cancers is total laryngectomy with ipsilateral thyroidectomy, ipsilateral comprehensive neck dissection with or without contra-lateral selective neck dissection.
Subglottis cancer

Primary subglottic cancer is uncommon, representing between 1% and 3.6% of all laryngeal cancers. Consequently, there is a dearth of literature reporting treatment outcomes. T1–T2 lesions can be treated successfully by radiation therapy alone with preservation of normal voice. Surgery is reserved for failure of radiation therapy. Laryngectomy plus thyroidectomy and level VI lymph nodes dissection usually followed by postoperative radiation therapy is reserved for advanced T3–T4 subglottic cancers.

Advanced laryngeal cancer: surgical approach

Total laryngectomy is still commonly performed in malignancies extending beyond the larynx or after conservative therapy failures or in patients not otherwise candidates for organ-preserving strategies. Total laryngectomy implies a permanent tracheostoma and voice loss with permanent separation of the upper respiratory and digestive tracts. Speech rehabilitation has become an integral part of these laryngeal cancer treatments. Speech rehabilitation may include electrolaryngeal speech, esophageal speech, or tracheoesophageal puncture (TEP). The electrolarynx is a vibratory sound wave generator that is usually placed directly on the skin of the submandibular area. The result is a monotone, electronic-sounding speech. Some patients are taught to control the release of air through the upper esophageal sphincter producing an esophageal speech. TEP is a surgical shunt between the posterior tracheal wall and the pharynx that may be performed either at the time of laryngectomy or secondarily. This shunt is fitted with a silicon valve that allows the passage of air from the trachea to the pharynx preventing food and liquid penetration into the airway: occluding the stomal opening, air passes into the pharynx with a fluent speech production.

Advanced laryngeal cancer: non-surgical treatments

In 1991 a landmark trial conducted by the Department of Veterans Affairs Laryngeal Cancer Study Group compared chemotherapy (cisplatin plus 5-fluorouracil) followed by radiotherapy vs surgery plus adjuvant radiotherapy. Laryngectomy followed by radiotherapy was performed in patients who did not achieve at least a partial response to the induction therapy or as salvage approach. Sixty-four percent of the patients who had received the non-surgical treatment did not undergo laryngectomy. Two-year survival rate was 68% in both groups. No significant differences in survival rates has been reported after more than a 10-year follow-up period. Less promising results of a French study (2-year survival rates were 69% in the induction chemotherapy group and 84% in the no chemotherapy group) did not lead clinicians to abandon the idea of laryngeal preservation.

Current chemotherapy for head and neck carcinoma is based on 5-fluorouracil and platin (P) combination (PF) in several varieties according to the day/dose of 5-fluorouracil (from 750 to 1200 mg/m²/day for 5 to 5 days; from continuous infusion to other schedules) and P (from 100 to 65 mg/m² day) every 21 days. Such a combination results superior to single agents or other classic combinations. Newer combination regimens are based on P (100 mg/m²) with paclitaxel (135–200 mg/m²) every three weeks, with a Response Rate from 34 to 48%. The median survival after palliative therapy was 6.5–7.5 months. Others have added ifosfamide or docetaxel to PF, gaining a better response rate, with greater toxicity. Thus, at the moment there is not a "reference" regimen besides the older PF and the above quoted chemotherapy types should undergo clinical trials. It is known that chemo-sensitive cancers are more frequently radiosensitive, and radiotherapy results may be previewed on the base of the response rate obtained with chemotherapy.

The currently used chemotherapy is synergistic or at least additive to radiotherapy in terms of anticancer efficacy. However toxicity is enhanced as well, and the local toxicity generally stands as the worst. Platin exerts a peripheral nervous system exquisite toxicity, that is especially manifest in head neck carcinoma field after simultaneous radiotherapy. Swallowing dysfunction after chemo-radiotherapy should be expected. Aspiration pneumonia, prolonged dysphagia and dyspnoea may complicate conservative surgery after full doses of radiation plus minus chemotherapy. A first question might be: is a random phase III study worthwhile of the two less toxic carboplatin or oxaplatin and 5-fluorouracil versus the classic Platin and 5-fluoruracil? Can be currently used a sparing peripheral nervous system toxicity, as pyridoxine or γ lipoic acid. Before instituting chemotherapy, we should be informed of patient’s specific tolerance of 5-fluorouracil and P by means of the normal tissue pharmagenomics. Di-hydropyrimidine deiodrogenase for the 5-fluorouracil, methtentetrahydrofolate-reddutase for toxicity of antifolates (metotrexate, pemetrexed) and 5-fluoruracil, and UDP-glucosil-transferase-A1 for toxicity of the antitopoisomerase irinotecan should be measured in circulating peripheral nucleated cells. Also red blood cell-folate, plasma Vit B12 and omocysteine determination can help as well in knowing some possible metabolic defects, especially in the alcoholists or cirrhotics with laryngeal cancer, that can be pharmacologically corrected. The risk of ischemic stroke in patients radiated to the neck should also be monitored by the study of coagulation, glucose, lipids and urate metabolisms, and by supraortica-arteries echo Doppler.

When chemotherapy is neoadjuvant, or adjuvant after surgery and radiotherapy, could we plan newer chemotherapy regimens based on antitopoisomerases drugs associated with the platin salts? In our experience the Topoisomerases 1, IIα and IIβ rise much and steeply after a DNA-antibiotic damage. In these patients the administration of antitopoisomerases drugs blocks almost completely the topoisomerase rise. The antitopoisomerases drugs could be added to platin after a pharmacological demonstration of utility in the single patient.

Severe late complication following concurrent chemoradiotherapy are common. A recent analyses of the RTSG (Radiation Therapy Oncology Group, Philadelphia) experience concerning 226 evaluable patients allows to consider independent risk factors the following: older age, advanced
T-stage and larynx-hypopharynx primary site. Also, neck dissection after concurrent chemo-radiotherapy plays a risk role. The meta-analysis of radiotherapy in head and neck carcinomas by Bourhis et al\textsuperscript{60} shows that the treatments benefit decreases with increasing age.

The recommendations by Gilbert and Forastiere\textsuperscript{61} about chemotherapy, either neoadjuvant or concomitant or adjuvant for organ preservation, indicate the state of art at the beginning of 2004. That by Lefebvre and Calais\textsuperscript{62} highlights the "état de la question" at the 2005. Both recommendations should be kept in mind.

In laryngeal oncology as in other oncological fields, the place of newer drugs as taxanes has to be explored. According to a French multicenter experience in advanced laryngeal cancer the combination of platin, 5-fluoruracil and Docetaxel (T) (PFT) leads to a significantly superior overall response rate compared to the PF regimen.\textsuperscript{63} Toxicity was reduced because of lesser doses of P and 5-fluoruracil. The postoperative concurrent PF and radiotherapy versus radiotherapy alone has been randomly studied in a phase III trial in Germany, in 440 patients with high risk head and neck carcinoma. The combination that improved both locoregional control and progression free survival (by 10% after 5 years)\textsuperscript{64} had an "acceptable" toxicity.

Increased expression of Epidermal Grow Factor Receptor (EGFR) in head and neck carcinoma has been correlated with poor prognosis. Neoadjuvant Erlotinib (EGFR Tyrosine-Kinase inhibitor) is well tolerated.\textsuperscript{65} This drug will be included in promising controlled trials.

Previously reserved for palliation, chemotherapy is now also a central component of several curative approaches to the management of patients with advanced-stage head and neck cancer.

**Recurrence laryngeal cancer**

Small superficial recurrent cancers without laryngeal fixation or lymph node involvement are successfully treated by radiation therapy or surgery alone, including endoscopic laser excision surgery.\textsuperscript{66} On the other hand more than 80% of the recurrent tumours are staged as rT3 or rT4. Total laryngectomy is considered the treatment of choice in the majority of these cases of laryngeal carcinoma relapse after partial laryngeal surgery or radiotherapy. Selected recurrent laryngeal cancers may be considered for partial laryngectomy also after high-dose radiation therapy failure.\textsuperscript{67,68} The identification of chemotherapy agents active in head and neck cancer first occurred in patients with recurrent disease who were being treated with palliative intent. Historically, the most active single agent is cisplatin, with phase II response rates of up to 30% and median survivals of about 6 months. Methotrexate, carboplatin, fluorouracil, and ifosfamide are also active in this disease, with phase II response rates of less than 30%. Among the newer generation of drugs, the taxanes, docetaxel and paclitaxel, have significant activity in head and neck cancer recurrence.\textsuperscript{62}

**Treatment of cervical lymph node metastases**

Concise notes regarding surgical classification of neck dissection types are synthesized in Table 6.

**Treatment of clinically positive neck**

The comprehensive neck dissection is performed in patients with clinical evidence of lymph nodes metastasis.

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**Table 6 Neck dissections classification\textsuperscript{2}**

<table>
<thead>
<tr>
<th>Neck dissection</th>
<th>Radical neck dissection</th>
<th>Modified radical neck dissection</th>
<th>SND (I–III)</th>
<th>SND (II–V)</th>
<th>SND (II–IV)</th>
<th>SND (VI)</th>
<th>Extended neck dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive neck dissection</td>
<td>Removal of all the lymph node levels I–V and sacrifices the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle</td>
<td>Removal of all the lymph node levels I–V and preservation of one or more non-lymphatic structures. In type I, only the spinal accessory nerve is preserved; in type II, both the spinal accessory nerve and the internal jugular vein are spared; in type III, all the three above mentioned non-lymphatic structures</td>
<td>Removal of levels I, II, III</td>
<td>Removal of the nodes in levels II–V and the suboccipital and retroauricular nodes</td>
<td>Removal of levels II, III and IV</td>
<td>Removal of level VI, surrounding the visceral structures of the anterior compartment of the neck are removed</td>
<td>Additional lymph node groups and/or non-lymphatic structures not encompassed by the radical neck dissection are removed</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Selective neck dissection refers to a cervical lymphadenectomy in which there is a preservation of 1 or more of the lymph node groups that are removed in radical neck dissection.
The overall prevalence of lymph node metastases in laryngeal cancers proportionally increased with T category from 10% in pT1, 29% in pT2, 38% in pT3 to 57% in pT4.69 Cervical node involvement is the most significant prognostic factor in squamous cell carcinoma of the larynx.70 The surgical procedure of choice for N+ necks should be a comprehensive neck dissection.71

**Treatment of clinically negative neck**

The options for N0 neck treatment include neck dissection, irradiation, observation with subsequent salvage neck dissection (the ‘wait and see’ policy). Elective neck dissection refers to the dissection of cervical lymphatics in the absence of clinical evidence of metastatic disease. An elective treatment of the neck is considered as necessary when there is a risk of occult lymph node metastasis higher than 20%.72 Elective neck dissection is a comprehensive term used for different types of neck dissection. The procedure of choice for elective surgery was radical modified neck dissection. Nowadays this operation has been considered an unnecessarily extensive procedure for treatment of the clinically negative neck: the dissection of level I and level V in the absence of clinically evident neck metastases is considered an over-treatment.73 Selective neck dissection [SND (II–IV)] has been indicated for the elective treatment of the clinically negative neck in patients with laryngeal carcinoma. An intraoperative evidence of positive neck node should require a comprehensive neck dissection. Recently, the Brazilian Head and Neck Cancer Study Group74 prospectively compared selective lateral neck dissection vs type III radical modified neck dissection as part of elective treatment for patients with laryngeal carcinoma. After a mean follow-up of 42 months, the authors found no difference in the oncological outcome between patients treated with either modality.

Considering occult neck nodes metastases incidence data, in patients with T1 or T2 glottic carcinoma with normal mobility of the cord or with T1 supraglottic carcinoma there is no indication for elective neck treatment because of the very low metastatic risk. Table 7 summarizes the indications to elective neck dissections according to site and T stage of primary laryngeal lesion. T3–T4 subglottic carcinomas may also involve the thyroid gland: total or sub-total thyroidectomy has to be considered.

Elective neck irradiation, using a dose of 50 Gy, is also indicated in reducing the incidence of recurrence in the clinically negative neck. The choice of elective neck dissection or elective neck irradiation in patients with a clinically negative neck depends on the treatment chosen for the primary cancer.

**Post-operative radiation therapy**

Post-operative radiation with or without chemotherapy is indicated when one or more of this adverse features is found: close/positive surgical margins; pT4 disease; perineural/lymphatic/vascular invasion; multiple positive nodes (three or more metastatic lymph nodes); extracapsular spread or perineural involvement; N3 nodes; subglottic extension of primary carcinoma.

**Follow up controls**

Follow-up controls are scheduled on an individual basis determined by the risk of recurrence, to survey for the development of second primary tumours, to deal with morbidity from treatment (i.e. speech and swallowing problems as well as wound care), to provide social and psychological support, and to deal with co-morbidity not directly related to the cancer itself and to oversee the abstention of these patients from alcohol and smoke or others risk factor.

- Periodic examinations by the head and neck surgeon may be necessary during radiation therapy in patients experiencing difficulty with nutritional intake, airway or pain control.
- After all treatment is completed, a general formula which may be modified according to the individual patient’s characteristics is:
  1. 1st year post treatment: 1–3 months
  2. 2nd year post treatment: 2–4 months
  3. 3rd year post treatment: 3–6 months
  4. 4th and 5th years: 4–6 months
  5. After 5 years: Every 12 months
- Chest X-rays, yearly.
- Liver enzymes in advanced stages, yearly.
- Periodic examinations by the radiation oncologist and, if appropriate, a dentist in patients that received radiation therapy;
- Thyroid function tests should be monitored if the patient received radiation to the lower neck.43

**Conclusions**

Although in the management of laryngeal cancer significant clinical improvements have been allowed by new surgical procedures that have extended the indications to partial laryngectomies and by combination therapies (induction chemotherapy, concurrent administration of chemotheraphy and radiotherapy, and adjuvant chemotherapy administered after the patient has been rendered free of disease), the most effective approach to laryngeal cancer remains

<table>
<thead>
<tr>
<th>Site/T</th>
<th>Ipsilateral neck levels</th>
<th>Contralateral neck levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glottic/T2 with impaired mobility of the vocal cord, T3, T4</td>
<td>II–III–IV</td>
<td>–</td>
</tr>
<tr>
<td>Supraglottic/T2, T3, T4</td>
<td>II–III–IV (strictly lateral lesion)</td>
<td>II–III–IV</td>
</tr>
<tr>
<td>Subglottic/T3–T4</td>
<td>II–IV, VI</td>
<td>VI</td>
</tr>
</tbody>
</table>
prevention and early diagnosis when this cancer is curable with function preserving treatments.

References


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