Laryngeal Carcinoma

15

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Introduction

Laryngeal squamous cell carcinoma comprises 1–2% of malignancies but is slowly decreasing in incidence with cessation of tobacco use. Tobacco and alcohol use are synergistic risk factors; these cancers occur most frequently in patients between 50 and 60 years of age and in males at least twice as often than in females. Persistent hoarseness is an early finding in glottic cancers but a late finding in supraglottic and subglottic forms; occasionally with dysphagia, dyspnea, stridor or cervical lymphadenopathy. Investigation is by fibre-optic endoscopy passed through an anesthetized nose or indirectly visualized using a laryngeal mirror held against the soft palate. Biopsies can be readily obtained under general anaesthesia using a laryngoscope and operating microscope. Endoscopy of the upper aerodigestive tract is performed for malignant disease for staging purposes, to identify occult second primary neoplasms, and assess surgical resectability. CT and MRI scans are used to stage the tumour and cervical lymph node enlargement can be followed by ultrasound guided fine needle aspiration cytology (FNAC) to establish if there are metastases. Tumour stage and fitness of the patient determine the appropriate choice of treatment i.e. radiotherapy, laser resection, local excision, laryngectomy, or neck dissection. Laryngectomy may also accompany a pharyngectomy for cancer of the hypopharynx.

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Gross Description

Specimen

- Biopsy/transoral laser resection/hemi-/partial or total laryngectomy/neck dissection. Local anatomy usually permits orientation in larger resections but orientation of smaller specimens by the surgeon is crucial in identifying resection margins when assessing clearance.
- Size (mm) of largest, if fragments
- Anatomical sites and tissues represented
- Length of larynx (from base of cricoid to tip of epiglottis)
- Other tissues, e.g., lobe of thyroid; levels of neck dissection, tracheostomy skin.

Tumour

Site

Supraglottis: from the tip of the epiglottis, both surfaces of the epiglottis, laryngeal aspect of aryepiglottic folds, arytenoid region, false vocal cords and ventricles.

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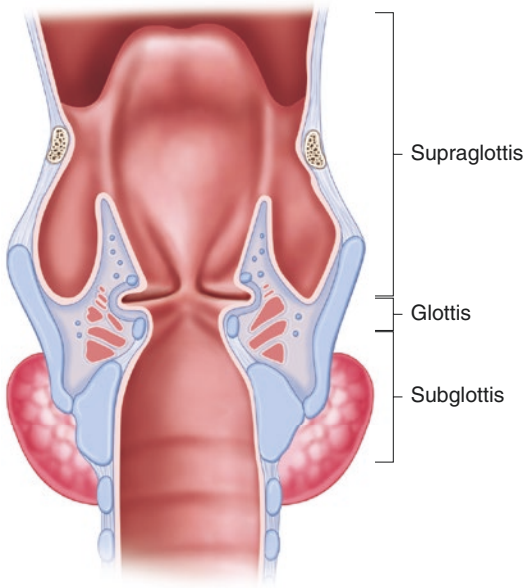

Fig. 15.1 Larynx. Reproduced, with permission, from *TNM Atlas: Illustrated guide to the TNM/pTNM classification of malignant tumours, 5th ed.*, © 2005, Springer-Verlag

Glottis: both true vocal cords including anterior and posterior commissures.

Subglottis: from the lower border of the true cords to the first tracheal cartilage (Fig. 15.1).

Glottis and supraglottic commonest sites but marked geographic variations: continental Europe: 60% supraglottic, 25% glottic;

British Isles, North America and Scandinavia: 60% glottic, 25% supraglottic.

Subglottis the least common site (10%).

Transglottic tumours span all three regions of the larynx (5%).

Size

- Length × width × depth (mm) or maximum dimension (mm).
- Tumour size is the main contributor to pathological stage as it is an indicator of disease extent. The maximum depth of invasion is subordinate to the nature of the tissue planes involved. Invasion of or through thyroid or cricoid cartilages or the elastotic membranes that join them is an important staging criterion.

Appearance

- Polypoid/warty/plaque-like/ulcerated/fungating

Histological Type

Squamous Cell Carcinoma

- *90% of cases.*
- Keratinising/non-keratinising.
- Prognosis is *better* (verrucous/papillary), *usual* (spindle cell/adenoid squamous) or *worse* (basaloid/adenosquamous)

Variants:

- *Verrucous:* broad based exophytic and "church-spire" hyperkeratosis with a pushing deep margin of cytologically bland bulbous processes arising in the glottis. Locally invasive, rarely metastatic; 70% 5 year survival. If contains a focus of conventional squamous cell carcinoma, manage as conventional SCC.
- *Papillary:* >70% papillary or exophytic fronds, covered by malignant type epithelium with focal invasion at the base. Better prognosis (70% 5 year survival).
- *Spindle cell:* polypoid, conventional squamous cell element may be present; immunohistochemical staining for cytokeratin not always positive. Distinguish from sarcoma and bizarre post-irradiation granulation tissue.
- *Basaloid:* poor prognosis, nests of basaloid cells with peripheral palisading and central comedonecrosis. Presents with more extensive disease but is more radiosensitive than other squamous cell carcinoma subtypes.
- *Adenoid squamous:* usual prognosis, acantholytic (pseudoglandular) pattern.
- *Adenosquamous:* poor prognosis, mixed differentiation squamous cell carcinoma and adenocarcinoma (either obvious glands or solid with mucin positive cells).
- *Lymphoepithelial carcinoma:* very rare, absence of squamous cell or glandular differ-

entiation; not usually associated with EBV, propensity for cervical lymph node and distant metastases.

Neuroendocrine Carcinomas

- Usually supraglottic larynx; middle aged and older men in particular.
- Distinctive morphological patterns with positive staining for CD56 and at least one of chromogranin/synaptophysin; TTF1 variable. Ki-67 index is not used in grading.
- Well differentiated: previously known as *carcinoid tumour*. Low mitotic count (<2/10 hpfs).
- Moderately differentiated: previously known as *atypical carcinoid tumour* with characteristic spread to locoregional lymph nodes.
- Poorly differentiated: *small cell/large cell carcinoma* 60-90% of which present with distant metastases. High Ki-67 index and mitotic count.

Moderately differentiated and poorly differentiated large cell neuroendocrine carcinomas are commoner in the larynx than well differentiated neuroendocrine carcinomas and they present with advanced disease and have *high recurrence and mortality (50-70%)*.

Adenocarcinoma

- *Salivary type:* most types of salivary gland tumour but adenoid cystic carcinoma is the commonest form.
- *Adenocarcinoma of no special type*
- *Amphicrine carcinoma* with both neuroendocrine and exocrine differentiation patterns

Metastatic Carcinoma

- *Direct spread:* oropharynx/hypopharynx; thyroid.
- *Distant spread:* breast, bronchus, kidney, thyroid, prostate, GI tract, malignant melanoma. Usually associated with disseminated disease.

Differentiation

Well/moderate/poor

- For conventional squamous cell carcinoma based on cellular atypia, keratinisation and intercellular bridges.
- Usually moderately differentiated.
- Most *salivary gland tumours* are *graded according to type*

Extent of Local Tumour Spread

Growth pattern of invasive front

- Degree of keratinisation, nuclear pleomorphism, pattern of growth and peritumour inflammatory response: the higher the "invasive front grading" score, the poorer the outcome

Perineural spread: when beyond the invasive front of the tumour, a predictor of *local recurrence, nodal metastasis* and *poorer survival.*

Glottic and subglottic tumour is best demonstrated by horizontal slices to demonstrate its anatomical relationships, tumour in the supraglottis is better seen with radially orientated slices in the vertical plane.

The TNM8 classification applies only to carcinomas.

Supraglottis

pT1	One subsite, no fixation of larynx (i.e., normal vocal cord mobility)
pT2	Mucosa of more than one adjacent subsite of supraglottis or glottis or adjacent region outside the supraglottis (e.g., medial wall of pyriform fossa); without fixation
pT3	Tumour limited to larynx with vocal cord fixation and/or invasion of post cricoid area, pre-epiglottic tissues, paraglottic space, and/or erosion of inner cortex of thyroid cartilage
pT4a	Through thyroid cartilage and/or into tissues beyond larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, styloglossus), strap muscles, thyroid, oesophagus
pT4b	Invades prevertebral space, mediastinal structures, encases carotid artery

Glottis

pT1	Limited to vocal cord(s), normal cord mobility (a) One cord only (b) Both cords
pT2	Into supraglottis and/or subglottis and/or with impaired cord mobility
pT3	Limited to larynx with vocal cord fixation and/or invasion into paraglottic space and/or erosion of inner cortex of thyroid cartilage
pT4a	Through thyroid cartilage and/or into tissues beyond larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, styloglossus), strap muscles, thyroid, oesophagus
pT4b	Invades prevertebral space, mediastinal structures, encases carotid artery

Subglottis

pT1	Limited to subglottis
pT2	Extends to vocal cord(s) with normal/impaired mobility.
pT3	Limited to larynx with vocal cord fixation
pT4a	Through thyroid cartilage and/or into tissues beyond larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, styloglossus), strap muscles, thyroid, oesophagus
pT4b	Invades prevertebral space, mediastinal structures, encases carotid artery (Fig. 15.2)

Lymphovascular Invasion

Present/absent.

Vascular invasion is associated with a high probability for cervical lymph node and/or distant metastasis, peristomal recurrence and poor survival.

Perineural invasion indicates *more aggressive disease* with likelihood of local recurrence, cervical nodal metastasis and the need for adjuvant therapy.

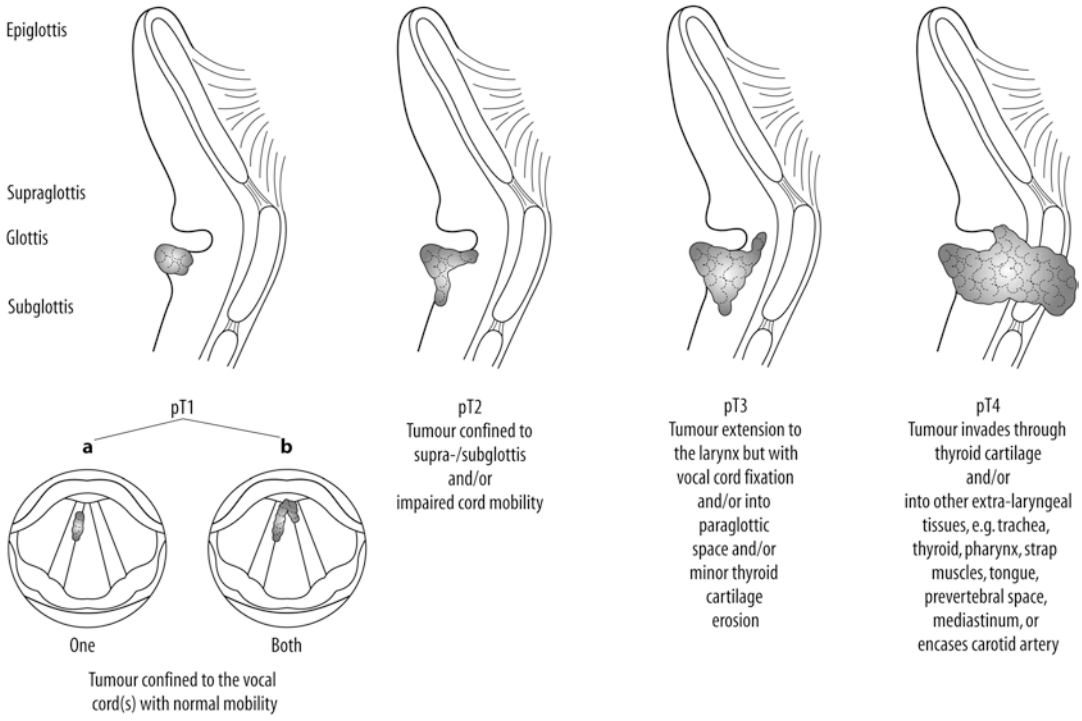

Fig. 15.2 Laryngeal carcinoma: glottis. Reproduced, with permission, from *Histopathology Reporting: Guidelines for Surgical Reporting*, *2nd ed.,* © 2006, Springer

Lymph Nodes

The *incidence of lymph node metastases at presentation* varies according to the site of the primary tumour from glottic (<10%) to supra-/subglottic (30–50%). Well differentiated carcinomas are less likely to metastasise than poorly differentiated cancers.

Size/number involved/size of metastatic deposit/extranodal extension (extracapsular spread).

Regional nodes: cervical.

Level I:	Submental, submandibular (rarely if ever involved)
Level II:	Upper jugular
Level III:	Middle jugular
Level IV:	Lower jugular
Level V:	Posterior triangle

Radical and modified radical neck dissections are not performed as Level I nodes are rarely involved. Selective neck dissection specimens represent harvesting of specific groups of nodes, such as Levels II-IV or II-V. There is no agreed minimum number of lymph nodes that must be recovered but it is questionable whether a specimen that generates fewer than 8 nodes for examination can be classed as a "neck dissection".

pN0	No regional lymph node metastasis
pN1	Metastasis in a single ipsilateral node ≤3 cm without extranodal extension
pN2	Metastasis in:
	a. Ipsilateral single node ≤3 cm with extranodal extension OR > 3 cm to 6 cm without extranodal extension
	b. Ipsilateral multiple nodes ≤6 cm without extranodal extension
	c. Bilateral, contralateral nodes ≤6 cm without extranodal extension
pN3	a. Metastasis in a lymph node >6 cm without extranodal extension
	b. Metastasis in a lymph node >3 cm with extranodal extension OR multiple ipsilateral or any contralateral or bilateral node(s) with extranodal extension.

Extranodal extension (previously known as *extracapsular extension*) increases the risk of local recurrence and distant spread. Metastasis is usually to *ipsilateral lymph nodes* but bilateral or contralateral lymph node involvement is common, especially in supraglottic, subglottic and transglottic tumours.

Excision Margins

Distances (mm) to the tracheal limit, aryepiglottic fold and pre-laryngeal anterior fascia of infiltrating carcinoma and any mucosal dysplasia. Tumour or mucosal dysplasia at or near (<5 mm) a margin indicates a *greater likelihood of local recurrence* and requires consideration of adjuvant therapy. Intraoperative frozen section assessment of surgical margins usually not required.

Other Pathology

Laryngeal precursor lesions: twice as often in males as females, usually 50–60 years of age; rarely in those who have never smoked; high-risk HPV occasionally implicated (<10%). Present with hoarseness or chronic cough; lesions may appear white, red or both, small or large, localized or diffuse on laryngoscopy; other sites in upper aerodigestive tract also at risk; Candida may be present. Several different grading systems but all agree the greater the degree of disturbance of epithelial maturation, the greater the likelihood of invasive tumour (at presentation and with the passage of time). Proportions of patients with precursor lesions developing infiltrative squamous cell carcinoma: 1–2% if no dysplasia, 10–12% with low-grade lesions, 40% with high grade lesions); average time to SCC 4–5 years.

Radionecrosis: post-radiotherapy laryngeal dysfunction due to confluent necrosis which may lead to local airway compromise and aspiration ("crippled larynx"). Mucosal ulceration with exposure and infection of cartilages; necessitates laryngectomy.

Concurrent carcinoma bronchus/oral cavity/pharynx/oesophagus: 10–15% of cases. Can become apparent on CT staging scan of

the primary laryngeal cancer or on upper aerodigestive tract endoscopy; usually requires biopsy.

Verrucous squamous cell carcinoma: must be distinguished from benign squamous epithelial papilloma and hyperplasia by its pushing deep margin but not always seen in small biopsies. It can also co-exist with squamous cell carcinoma of usual type. Beware the large and/or recurrent "squamous papilloma" in a smoker. Also granular cell tumour with overlying pseudoepitheliomatous hyperplasia—the granular cells (Schwann cell origin) are S100 protein positive.

Juvenile laryngeal papillomatosis: multiple HPV related squamous cell papillomas of the upper respiratory tract and a rare cause of squamous cell carcinoma, usually in association with smoking or radiotherapy. These papillomata often require *repeated endoscopic laser or microdebrider debulking* to avoid airway obstruction. A minority persist and can spread to trachea and bronchi.

Prognosis

Prognosis relates to tumour site, stage and certain histological factors: grade/invasive front, vascular invasion and, where relevant, *resection margins.* Early (pT1, pT2) glottic and supraglottic carcinomas may be treated by voice sparing *local excision, laser* or *radiotherapy. Partial laryngectomy* (supraglottic or vertical hemilaryngectomy) is a rare procedure but may be carried out for small volume T2 cancers. Total laryngectomy is the operation of choice in cases of radiotherapy failure, bulky T3 and T4 lesions, subglottic tumours, and in post-radiation "crippled larynx".

Site-related 5 year survival:

Glottic	80%
Supraglottic	65%
Transglottic	50%
Subglottic	40%

Stage-related 5 year survival:

Glottic	I	90%
	II	85%
	III	60%
	IV	<5%

Other Malignancy

Malignant Lymphoma/Leukaemia

- Primary MALToma or more commonly secondary to lymph node/systemic disease.
- Sinonasal (angiocentric) T/NK cell lymphoma.

Plasmacytoma/Myeloma

- Initially localised but generally becomes part of disseminated myeloma. Look for κ, λ light chain restriction and evidence of systemic disease (elevated ESR, immune paresis and monoclonal gammopathy, Bence-Jones proteinuria, radiological lytic bone lesions).

Sarcoma

- Particularly low-grade chondrosarcoma (mostly the cricoid or thyroid cartilages), inflammatory myofibroblastic tumour (especially ALK1-negative ones) and rhabdomyosarcoma (embryonal—childhood; alveolar—young adults).
- NB: A malignant-looking spindle cell lesion in the larynx of a smoker is most likely to be a spindle cell carcinoma.

Malignant Melanoma

- Primary (rare) or secondary (most likely): S100, HMB-45, Melan-A positive.

- *Aggressive (20% 5 year survival)* usually present with bulky local disease and involved nodes; TNM8 designates as moderately advanced (pT3: mucosal) or very advanced (pT4: beyond mucosa) disease.

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