

Solid Tumour Section

Review

Head and neck: Laryngeal tumors: an overview

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Identity

Note

More than 95% of laryngeal tumours are squamous cell carcinomas (SCC). Most commonly, they arise from the glottic region of the larynx, namely the true vocal cords, so they usually present with changes in voice quality (i.e. hoarseness). The vast majority of patients have a history of smoking, while alcohol consumption is considered a significant co-factor.

Classification

Note

Light microscopy and occasionally immunohistochemistry are the main procedures of histological diagnosis and classification in laryngeal tumours. A histopathological classification of squamous cell carcinoma can be performed based on Broder's method. The use of microarray generated data is likely to radically improve disease sub-classification. True benign tumours constitute 5% or less of all laryngeal tumours. The most common benign tumour of the larynx is papilloma (85%). Other types include: chondroma, haemangioma, lymphangioma, schwannoma, neurofibroma, adenoma, granular cell myoblastoma, leiomyoma, rhabdomyoma, fibroma, lipoma and paraganglioma.

Classification

Laryngeal cancer mainly consists of conventional squamous cell carcinomas. Other laryngeal malignancies include:

- Carcinoma in situ
- Verrucous, spindle cell and basaloid SCC
- Undifferentiated carcinoma
- Adenocarcinoma
- Miscellaneous carcinomas (adenoid cystic, neuroendocrine carcinomas, etc)
- Sarcomas.

Squamous cell carcinoma is further divided according to tumour location into four subtypes:

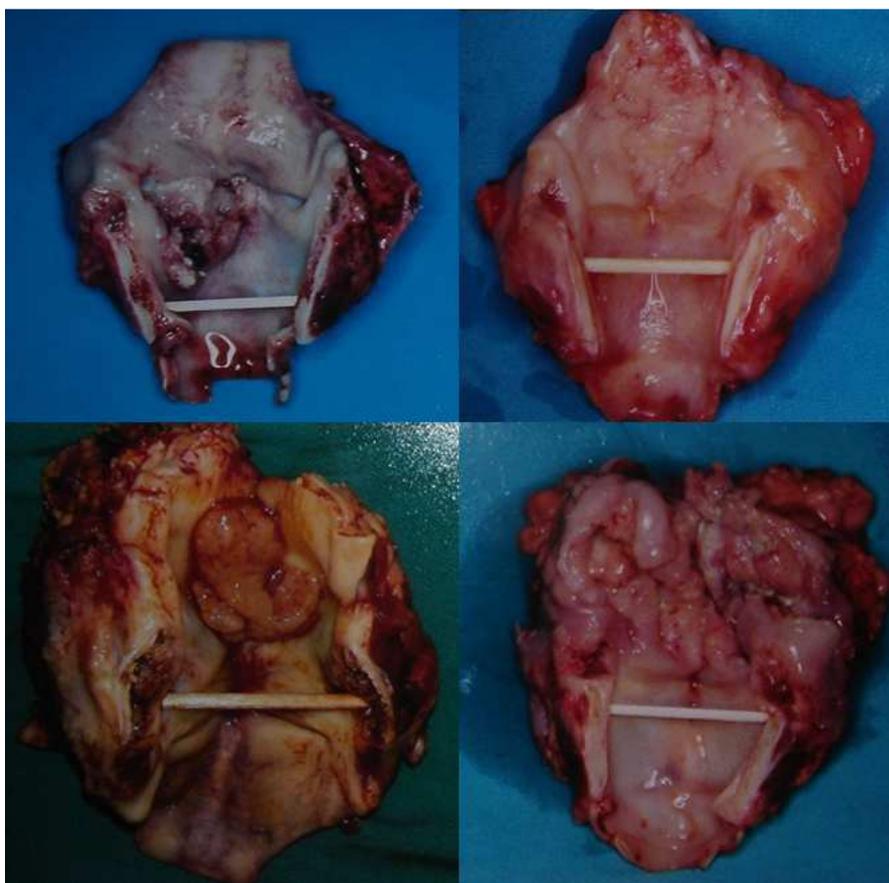
Glottic carcinoma: involves the true vocal folds.

Supraglottic carcinoma: confined to the supraglottic area (free border of the laryngeal epiglottis, false vocal folds and laryngeal ventricles).

Subglottic carcinoma: extend or arise more than 10mm below the free margin of the true vocal fold up to the inferior border of the cricoid cartilage.

Transglottic carcinoma: cross the ventricle from the supraglottic area to involve the true and false vocal folds or involve the glottis and extend subglottically more than 10mm or both.

Glottic carcinomas represent the majority of laryngeal cancers (50%-60%), followed by the supraglottic carcinomas (30%-40%), while the subglottic carcinomas are uncommon (5% or less).



Morphological appearance of laryngeal cancers after laryngectomy.

Clinics and pathology

Etiology

The exact cause of laryngeal cancer is still unknown. However, several interrelated co-factors (mainly tobacco smoking and alcohol consumption), are clearly associated with an increased incidence in laryngeal cancer. Both of them increase the risk of cancer in a dose-dependent way. It appears that nicotine is not responsible for cancer itself, but polycyclic aromatic hydrocarbons and nitrosamines are carcinogenic. Poor diet and oral hygiene, vitamins deficiency, cirrhosis and depressed immune system often found in alcoholics may also contribute to cancerous process. Infections from herpes simplex and HPV, gastroesophageal reflux disease, anatomical malformations, Plummer-Vinson syndrome, steam and heat inhalation, thermal burns and exposure to ionizing radiation, asbestos, nickel, textile fibers and various chemicals, like formaldehyde, vinyl chloride and benzopyrenes, have also been considered as aetiological factors. Many ongoing studies are awaited to identify genetic factors and oncogenes that may have an aetiological interest.

Epidemiology

The incidence of laryngeal carcinoma is relatively low in comparison to that of carcinomas of all organs.

Laryngeal cancer comprises 2 to 5% of all malignant diseases diagnosed annually worldwide. The incidence is comparable to that of cancer of mouth and thyroid, but only one tenth as high as that of lung cancer. There are areas where the incidence is higher (greater than 10 per 10,000) including Spain, Italy, France, Brazil, India and the Afro-caribbean populations in parts of the USA. Low incidence areas (less than 2 per 100,000) include Japan, Norway and Sweden. Worldwide, the peak incidence of laryngeal cancer is highest in men aged between 55 to 65 years. The male-to-female ratio varies from 5 to 20:1, however the last decades there is a decrease in this ratio, because of an increase of laryngeal cancer in women. There is a notable social class difference, in that laryngeal cancer is twice as common in men with low socioeconomic status. It is also more common in people residing in cities than in rural areas. Most studies show that inhabitants of the most industrialized cities have an incidence of laryngeal cancer 2 to 3 times higher than that of rural inhabitants. These racial, social and urban variations may be reflect different lifestyle and habits and also confirm the already recognized harmful effects of tobacco and alcohol. Survival, in terms of the relative 5-year survival rate, for laryngeal cancer has been increasing the last four decades. However, long-term (10-year) relative survival rates have remained at about 50% for quite some time.

Clinics

The natural history and clinical picture of laryngeal cancer is dictated by its site of origin and its tendency to disseminate to the regional lymphatics. Progressive continuous hoarseness is the cardinal symptom of laryngeal carcinoma, especially the glottic one. Dyspnoea and stridor, pain, dysphagia, cough, swelling in the neck, haemoptysis, halitosis, reflective otalgia, tenderness of the larynx and weight loss can also occur during the course of disease. Neck metastases are more common in supraglottic cancers due to rich lymphatic network leading to early dissemination of primary tumour to the regional lymph nodes. On the contrary, glottic tumours because of the poor lymphatic network of the true vocal cords rarely present with regional neck metastases at the time of diagnosis. Staging of primary laryngeal tumours is dependent on the surface extent of the lesion to various sites within the same region of the larynx or from one region to the other or its extension beyond the larynx to adjacent organs as well as on the vocal cords mobility. Fixation of the vocal cords referred as T3 lesion independently of the initial tumour location and signifies a deeply invasive lesion. About 70% of the patients with supraglottic tumours at the time of diagnosis presented with advanced disease stage (III-IV). On the contrary, 75% of the glottic tumours presented with localized disease at initial stages (I-II). Distant metastasis is uncommon to be the first symptom of laryngeal cancer, however it can be found in about 5% at the time of initial presentation with appropriate investigation and lung comprises the most commonly involved site. At the time of diagnosis a second primary tumour can be found within the respiratory tract in 5% to 10% of the cases. Half of them are located in the lungs and have to be differentiated from distant metastases. In this setting it is important to perform a panendoscopy and appropriate radiological evaluation to exclude such pathology.

Pathology

Pathological diagnosis for laryngeal cancer is achieved after biopsy which is obtained at direct laryngoscopy under general anaesthesia.

The vast majority of all laryngeal malignancies (95%) are conventional squamous cell carcinomas (SCC) and they vary according to their degree of differentiation to well, moderate and poor carcinomas. Glottic cancers are generally well differentiated and have a less aggressive behaviour in comparison with carcinomas at the other sites of the larynx. SCC often arises in a background of mucosal squamous dysplasia or carcinoma in situ and typically presents islands, tongues and clusters of atypical cells invading the laryngeal stroma. Features of squamous differentiation also comprise individual cell keratinisation, intercellular bridges and keratin pearls. Recognition of the less common variants like verrucous, spindle cell

and basaloid SCC is significant because their biological course often is different from that of conventional SCC.

- **Verrucous SCC:** comprises approximately 1% to 4% of laryngeal malignancies. It presents as a locally invasive fungating mass and characteristically does not metastasize to regional lymph nodes. Histologically, it appears broad pegs of highly differentiated squamous cells invading the laryngeal stroma in a pushing pattern and mitoses rarely found mainly at the tumour base. Surgical excision is the cornerstone of therapy since radiotherapy associated with poor results and the possibility of anaplastic transformation of the tumour.

- **Spindle SCC:** presents usually as a polypoid or less as an endophytic mass. Comprised of a pleomorphic spindle cell component related with typical in situ or invasive SCC, which sometimes cannot be identified, especially in the presence of extensive ulceration. Spindle cell SCC has been reported to be more aggressive than conventional one. Surgery is the treatment of choice, while radiotherapy is ineffective.

- **Basaloid SCC:** usually presented at an advanced stage with neck metastases. Microscopically, the tumour is characterized by nests and lobules of small basaloid cells with a high nuclear-to-cytoplasmic ratio and areas demonstrating abrupt squamous differentiation, foci of carcinoma in situ or invasive SCC. Comedonecrosis and stromal hyalinosis are also common findings. Surgery of the primary tumour and neck and radiation therapy is the usual therapeutic approach.

Except of conventional methods, various ancillary techniques provide information about a tumour that cannot be obtained by routine histopathologic examination. These methods have been applied to LSCC in order to evaluate a range of potential prognostic indicators, including DNA ploidy, proliferative activity, and oncogene amplification.

- **DNA ploidy:** refers to the nuclear DNA content and is determined by either DNA flow cytometry or image analysis.

- **Proliferative activity:** may reflect the biologic potential and therapeutic responsiveness of a tumour. It can be measured by mitotic index, flow cytometry, image analysis, and immunohistochemical demonstration of proliferation markers, such as proliferating cell nuclear antigen (PCNA), or Ki67.

- **Oncogenes:** Proto-oncogenes are genes that normally promote cell growth. Alteration of either the structure or regulator of a proto-oncogene converts it to an oncogene. The protein encoded by the oncogene (i.e. oncoprotein), is abnormal either in quantity or structure (i.e. ras proto-oncogene encodes p21 ras oncoprotein, c-erb B/ERBB2 encodes epidermal growth factor receptor-EGFR, etc)

Nowadays, cDNA microarrays, is a useful method from which large amounts of genetic information can be obtained, in order to establish a molecular classification in LSCC, based on patterns of global gene expression.

Treatment

Over 95% of patients with LSCC are treatable. Causes of untreatability include the presence of distant metastases, very advanced locally and regionally tumours, poor general health, and patient's refusal.

The standard options for treatment of LSCC are surgery, radiotherapy, chemotherapy or a combination of them. Radiotherapy is used in more than 70% of patients, surgery in about 55% and chemotherapy in about 10%. The management of laryngeal cancer varies in different parts of the world. However, it is widely accepted that early-stage LSCC can be adequately treated with single-modality therapy, either surgery or radiotherapy, with a 5-year local control of 85-95%. For more advanced disease (stages III and IV), a multimodality treatment based upon a combination of surgery and irradiation is the most common approach.

Recently, new therapies based on a molecular basis of LSCC are in use or under development. The use of cellular tumour markers as therapeutic targets is being studied in order to block specific pathways involved in the cancerous process and tumour aggressiveness or invasiveness, restoring effective oncosuppression. Considering this, EGFR pathway is a good target for therapeutic interventions in LSCC. Several approaches can interfere with EGFR function and may be useful for anticancer treatment such as, the use of monoclonal antibodies (MAb) against the extracellular ligand binding domain, ligand-toxin conjugates that kill target cells following endocytosis, tyrosine kinase inhibitors that inhibit ligand-induced EGFR activation, and antisense oligonucleotides against EGFR mRNA. Furthermore, transient overexpression of the wild-type p53 gene could provide a potential molecular treatment strategy in LSCC. In head and neck cancer, the most used gene-delivery tool has been the recombinant adenovirus Ad-p53. A gene therapy approach using wild-type human p53 has already been demonstrated to induce apoptosis and radio-, chemosensitisation in cell lines. Thus, the use of p53 gene therapy in combination with radio- or chemotherapy could be considered a rational possibility. Another potential application is the treatment of dysplastic lesions, as p53 mutations seem to occur early in laryngeal carcinogenesis. However, the main problem of all these approaches, remains the absence of a really efficient, long-term gene-delivery system.

Prognosis

Once the diagnosis of laryngeal cancer has been documented the disease is staged according to the TNM classification system (stages I-IV) using the UICC/AJCC criteria. This system takes into account tumour size and location (T), lymph node involvement (N) and presence of distant metastasis (M). In general, the higher the stage (both overall and within each category) the poorer the prognosis.

Small glottic cancers have better prognosis than supraglottic ones. The overall 5-year survival following treatment is 80% for glottic and 50% for supraglottic tumours, mainly because the latter present an increased incidence of nodal metastases. Nearly two-thirds of patients with supraglottic cancers have neck metastases at the time of initial treatment. Survival decreases by more than one third when clinically positive lymph nodes are present. Five-year disease free survival of patients with supraglottic cancer is 80% for stages I-II, 70% for stage III and 40% for stage IV. Patients with glottic cancers have a better long-term prognosis. Five-year disease free for stages I-II is 85%-90%, for stage III is 75% and for stage IV is 45%-50%. However, in cases with an extremely advanced local and regional disease the overall 5-year survival is less than 5%.

Cytogenetics

Note

Various chromosomal alterations have been observed in laryngeal SCC, such as 9p21 loss which contains the p16 gene, 11q13 which contains the CCND1 locus, 17p13 where the p53 gene is located, 3p with at least three putative tumour suppressor loci, 13q21, 6p and 8. Some of these alterations have been demonstrated to precede the development of cancer by several years, while others may be also detected as late late-occurring cytogenetic events. A few of them could be proposed targets for preventive strategies. Among the most frequent and relevant cellular changes in laryngeal carcinogenesis are those involving p53, cyclin D1 (CCND1), p16 and EGFR.

The nuclear phosphoprotein p53 is involved in gene transcription, DNA synthesis and repair, cell cycle coordination and apoptosis. Disruption, or perturbation of p53 function have been detected not only in the laryngeal but almost in all head and neck cancers. p53 point mutations or deletions (also by LOH at 17p13) are frequent and p53 inactivation occurs in the transition from the preinvasive to the invasive state.

Cyclin D1 is involved in cell cycle progression and interacts with cyclin-dependent kinases.

When Cyclin D1 gene (CCND1) amplification is observed in precancerous and cancerous lesions, cyclin D1 is always overexpressed. In turn, cyclin D1 overexpression does not determine, but always anticipates gene amplification, which probably represents a more stable, non-reversible, alteration in tumour cells.

Early in the cancerous process altered p53 gene function and CCND1 gene overexpression increase genetic instability and promote further genetic and chromosomal alterations, such as CCND1 amplification which is considered as the ultimate transforming event by the selection of a malignant subclone from a genetically altered field.

Genes involved and proteins

Note

Environmental or genetic factors may be responsible for individual susceptibility to LSCC. A genetic predisposition for the development of LSCC is highly probable. Genetic polymorphisms of carcinogen-metabolizing enzymes have been found in tobacco smoke and there is evidence that they are associated with the risk of cancer development of the aerodigestive tract. Polymorphisms of genes encoding for arylamine N-acetyltransferases, human OGG1 DNA repair enzyme, CYP1A1, XRCC and glutathione S-transferases have been evaluated in relation to the risk LSCC development, however with controversial results.

Identification of tumour suppressor genes and proto-oncogenes may be critical for an understanding of the biological initiation and progression of laryngeal cancer. Knowledge about the time course of a single molecular alteration may be helpful in its clinical use for molecular epidemiology, diagnostics or characterisation of laryngeal cancer.

The perfect marker for molecular characterisation of LSCC should have the following properties: 1. not be constantly present in malignant cells, 2. associated with precise biological features and predictable clinical behaviour and, 3. easily detected by a standard, simple and reliable method on a small tissue sample. Unfortunately, no such marker yet exists.

Alterations of p53 protein expression and mutations of the p53 gene have been proposed as independent predictors of recurrence in LSCC, however with controversial prognostic value.

p53 protein overexpression has been detected in a high percentage of LSCC correlating well with p53 gene mutation.

p53 gene mutation has been suggested more reliably than p53 protein overexpression for characterisation, predicting also the response to radiotherapy in LSCC patients. This observation is in accordance with the biological role of p53, which mediates apoptosis associated with DNA damage.

Alterations in p53 status have been evaluated in healthy mucosa, precancerous lesions and tumour cells in order to predict the development of LSCC and secondary primary tumours. Mutations of p53 have also been evaluated to detect whether multiple primary tumours have a mono- or polyclonal origin, without however, definitive conclusions.

In LSCC, degradation mediated by other cellular proteins, such as MDM2 or by human papillomavirus (HPV) E6 oncoprotein may represent alternative pathways leading to loss of p53 function.

A p53 gene therapy approach has already been shown to induce apoptosis, radio- and chemosensitisation in cell lines and this, in combination with radiotherapy or chemotherapy, is a rational possibility. Another

potential application considered the treatment of dysplastic lesions, as p53 mutations seem to occur early in laryngeal carcinogenesis.

EGFR is frequently and early overexpressed in LSCC, mainly by post-translational mechanisms. EGFR expression retains a strong predictive value independently of treatment (surgery, chemotherapy and radiation) and adversely influences overall relapse-free and metastasis-free survival in LSCC. At present, EGFR is the most reliable biological marker for molecular characterisation, aggressiveness and invasiveness of LSCC.

Telomerase activity often is present at high levels in most laryngeal cancer cells. It can at least partly depend on h-TERT gene (coding for catalytic subunit of telomerase) overexpression. It can be used for molecular epidemiology, diagnostics and targeting.

An early CCND1 overexpression is often detectable without evidence of gene amplification; it can be used for molecular epidemiology but it seems to retain a lower prognostic value, if compared with CCND1 amplification. The latter is a marker of aggressiveness and has an impact on relapse-free and overall survival in LSCC.

An overexpression of metalloproteases, hyaluronidases and cathepsin D is often detectable in tumour cells. These molecules are responsible for degradation of extracellular matrix and thus play an important role in tumour growth, invasion and metastasis, as well as in tumour-induced angiogenesis. In addition, overexpression of CD44 hyaluronan receptor in a less glycanated form is observed.

Among the extracellular matrix components, the proteoglycan versican appears to be overexpressed becoming the macromolecule characteristic of the tumour state and being another marker of aggressiveness. Similarly, hyaluronan is found in increased amounts and of rather smaller molecular size. Alterations, also, in the sulphation pattern of chondroitin/dermatan sulphate are observed, indicating different expression of sulphotransferases.

Human papillomavirus (HPV) may affect epithelia with mucosal or epidermal tropism according to genotype. It has been reported that oncosuppressors such as p53 and pRb/RB1 are inhibited and degraded by HPV oncoproteins, while overexpression of oncogenes such as EGFR and cyclins A and B is induced.

Type II oestrogen binding sites (EBS), normally found in laryngeal mucosa, have been reported that may partly mediate tumour growth inhibition by tamoxifen and quercetin and could be possible targets for chemoprevention and therapy.

S100A2 has recently been described as an actual oncosuppressor with a prognostic significance stronger than simple histopathological grading. Its underexpression in cancer cells is inversely proportional to tumour differentiation.

Methyl-hydroxyphenyllactate esterase (MEPHLase)

low activity in LSCC is associated with poor differentiation and shorter overall survival and metastasis-free survival.

Type 2 cyclo-oxygenase activity seems to promote tumour neoangiogenesis. However, evidence exists that low COX2 expression indicates poor differentiation and higher aggressiveness and invasiveness.

Galectin-3 participates in a variety of cell processes and mediating cell-to-cell interactions. Its expression seems positively associated with tumour keratinisation and histological grade and a significant correlation was described between galectin-3 tumour positivity and longer metastasis-free and overall survival in LSCC patients.

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