# Laryngeal Tumors

# 22

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## Content



Laryngeal tumors are extremely rare in children and adolescent, thus extensive experience with laryngeal neoplasms under the age of 18 years is very limited, even in major head and neck cancer centers. Dyspnoea, dysphonia, hoarseness, and dysphagia are symptoms which shall lead to a suspicion of laryngeal mass: in these cases flexible fiberoptic laryngoscopic examination is mandatory. Any suspicious case must be scheduled for a direct microlaryngoscopy and biopsy under general anesthesia, which allows for both establishing the local relationships and taking a sample for microscopic examination (Kato et al. 1991; Sessions et al. 1993; Strong and Jako 1972). Diagnosis is frequently delayed, due to the rarity of this disease, but early detection of any malignancy located in this critical region is of greatest value, so any persistent change in a child's voice or hoarseness is an indication for prompt and adequate diagnostic work-up in order to treat the disease with a conservative approach, avoiding mutilative surgery.

The clinical extension of the neoplasm must be precisely assessed. Computed tomography and MRI are useful for local–regional assessment. Distant metastasis must be searched mainly in the lungs, bones, and liver and, in case of rhabdomyosarcoma, also in bone marrow (Pransky and Kang 2003).

Among benign neoplasms, the most common is *subglottic hemangioma*: it behaves like other hemangioma of the head and neck (see salivary gland tumors chapter for further details) with the possible additional complication of airway obstruction and/or dysphagia in the proliferative phase of a wide lesion. Subglottic hemangioma occurs in a 2:1 female to male ratio and prefers the left posterior-lateral subglottic mucosa. Diagnosis is made at a mean age of 3.6 months (Bitar et al. 2005).

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Infants with subglottic hemangioma and cutaneous facial hemangiomas in a "beard" distribution should be evaluated for PHACE syndrome (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Coarctation of the aorta and cardiac defects, and Eye abnormalities) (Smith et al. 2004).

The optimal treatment of subglottic hemangioma is still not defined: a wait-and-see policy, based on spontaneous regression of the lesion, is indicated in asymptomatic cases without respiratory distress, while transoral laser resection is the most common approach for small and circumscribed lesions, with a success rate of 88.9% using a mean of two sessions. Intralesional corticosteroids injection has been used with a success rate of 86.4%, using a mean of three injections; unfortunately, it requires general anesthesia and postoperative intubation (Bitar et al. 2005).

Tracheotomy is advised to secure airway in case of extensive hemangioma. Open-neck surgical excision was performed in the past, but is reserved to cases resistant to all conservative treatments today.

Systemic treatment includes corticosteroids, alpha-interferon and, since 2008, propranolol, which is taught to displace other drugs in the medical cure of pediatric hemangiomas.

Other benign submucosal lesions include the *nerve sheath tumors*: 10% of them are diagnosed in patients under the age of 21 years, and 25–40% of such lesions occur in the head and neck region. They derive from the Schwann cell of peripheral nerves and include neurilemmoma, which is a solitary encapsulated tumor that very rarely shows malignant change, and neurofibroma, a non-encapsulated neoplasm that can be found in multiple locations (when associated with von Recklinghausen's disease) and can undergo malignant degeneration in 10% of cases, usually into malignant peripheral nerve sheet tumor (MPNST), rarely into liposarcomas (Pulli and Coniglio 1997; Golledge et al. 1995).

The vast majority of laryngeal nerve sheath tumors are supraglottic, with the aryepiglottic fold and false vocal cord being the most common sites. They are not radio-sensitive, and thus transoral laser excision is the treatment of choice (Pulli and Coniglio 1997).

*Granular cell tumors* are uncommon neoplasms that appear most frequently in the tongue; in pediatric population laryngeal involvement is very rare and usually subglottical. These tumors are usually benign, with slow growth; the treatment is based on a surgical approach, usually complete removal with carbon dioxide laser (Holland et al. 1998).

**Table 22.1** Summary of two reviews of malignant tumors of the larynx in children by Gindhart and Ferlito. (Ferlito et al. 1999; Ginhart et al. 1980)

| Histotype | Gindhart et al. (1980) No. of patients (%) | Ferlito et al. (1999) No. of patients (%) |
|---|---|---|
| Rhabdomyosarcoma | | 20 (42.5) |
| Squamous cell carcinoma | 53 (98.2) | 13 (27.6) |
| Synovial sarcoma | | 3 (6.4) |
| Malignant fibrous histiocytoma | | 2 (4.3) |
| Non-Hodgkin's lymphoma | | 2 (4.3) |
| Chondrosarcoma | | 1 |
| Ewing sarcoma | | 1 |
| Fibrosarcoma | | 1 |
| Malignant schwannoma | | 1 |
| Mixed sarcoma | | 1 |
| Mucoepidermoid carcinoma | | 1 |
| Adenocarcinoma | 1 | |
| Primitive neuroectodermal tumor | | 1 |
| Total | 54 (100) | 47 (100) |

*Inflammatory myofibroblastic tumor* is an uncommon neoplasm that is usually located in the lung in pediatric population; it rarely occurs in the larynx and in this site it does not appear so aggressive as in other locations. This tumor is usually indolent, does not metastasize and can rarely recur locally. The mainstay of treatment is wide local excision (Rodrigues et al. 2005).

*Hamarthoma* of the larynx is very rare; Rinaldo and colleagues reviewed 11 cases from the literature and 5 of them occurred in children. Treatment consists of local excision; recurrences are usually seen associated with incomplete removal (Rinaldo et al. 1998).

Malignant tumors of the larynx are rare in children. Two of the most extensive and recent reviews are reported by Gindhart and Ferlito in Table 22.1 (Ferlito et al. 1999; Ginhart et al. 1980).

*Rhabdomyosarcoma* is the most common sarcoma arising in the larynx and the average age of the patients at the diagnosis is 9 years and 2 months (Ferlito et al. 1999). Sarcomas have well-established strategies of treatment (see chapter 44).

The local treatment in case of laryngeal location, however, remains challenging. Radical resections are clearly mutilating, conservative surgery may not be

complete and radiotherapy is followed by well-known postirradiation complications. A limited series of laryngeal rhabdomyosarcomas from Institut Gustave Roussy, published in 1991, underlines the rarity of this location (5 cases among 126 patients with rhabdomyosarcoma treated in that center from 1955 to 1981) and a very good survival, achieved with chemotherapy and radiotherapy, avoiding mutilative surgery (no laryngectomies in this series). Authors also emphasize on long-term important sequelae associated with radiotherapy, such as arrest in growth of irradiated structures, huskiness, subclinical thyroid insufficiency, abnormalities in offspring, carotid stenosis, and an increased risk of radiation-induced malignancy (Ferlito et al. 1999; Kato et al. 1991; Nikaghlagh et al. 2007).

Other malignant mesenchymal tumors located in the larynx are also reported, but taking into account the variety of the histological subtypes, the incidence of each is negligible.

*Squamous cell carcinoma (SCC)* is the second most frequent pediatric malignancy of the larynx. However, some authors consider this tumor more frequent than rhabdomyosarcoma (Ferlito et al. 1999; Ginhart et al. 1980; Pransky and Kang 2003; Smith 2008). Etiology is controversial and it is not related to the well-recognized risk factors for laryngeal cancer in adults: pediatric SCC of the larynx seems to be a genetic disease in which there is an interaction between environmental, genetic, and immunological factors, such as:

- Malignant spontaneous degeneration of juvenile papilloma of the larynx (Figs. 22.1 and 22.2)
- Previous radiation therapy for a benign condition, such as adenoid hypertrophy
- Asbestos exposure
- Second-hand smoke
- Presence of chromosomal translocation (15;19)
- Infection with Human Papilloma Virus (Chow et al. 2007; Ferlito et al. 1999; Joos et al. 2009)

Recent studies have suggested that the prognosis of laryngeal SCC may be affected by the presence of chromosomal translocation (15;19) or human papilloma virus (HPV) DNA.

Several authors evaluated the role of chromosomal translocation (15;19) in young patients with carcinoma of the upper aerodigestive tract and found that the balanced chromosomal translocation t(15;19), resulting in the *BRD4-NUT* fusion oncogene, is part of a distinct clinicopathological entity characterized by young age, female predilection, midline epithelial carcinoma of the neck or upper thorax (as far as we concern, larynx),

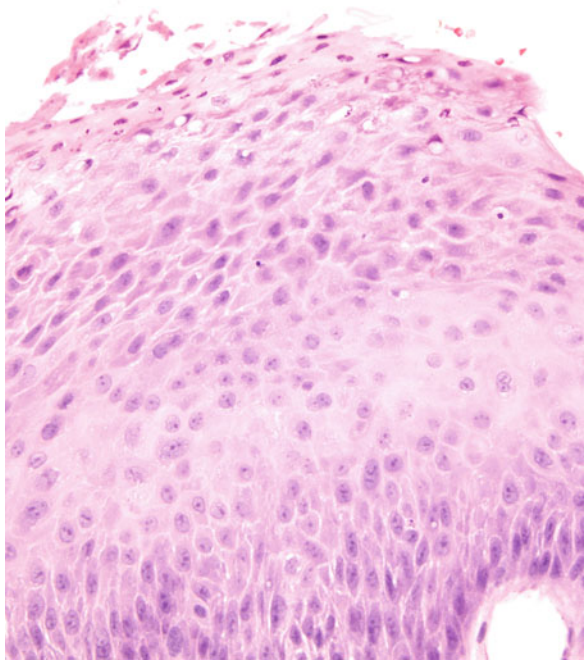

**Fig. 22.1** Laryngeal papillomatosis

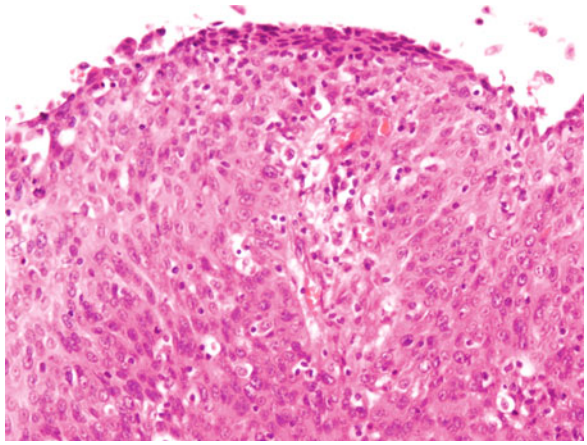

**Fig. 22.2** Laryngeal papillomatosis in transformation to carcinoma

and a very poor prognosis, despite aggressive multimodal treatment (Vargas et al. 2001; Rahbar et al. 2003; French et al. 2004).

Most studies show a HPV positivity rate in head–neck SCC close to 35%; with regard to SCC of the larynx, the frequency of HPV positivity varies from 13% to 50% and the most frequently isolated subtype is HPV-16 (Chow et al. 2007; Joos et al. 2009). In the literature there are sporadic cases of SCC of the larynx in children that are positive for HPV DNA, but the real

**Table 22.2** Management of laryngeal squamous cell carcinoma in children and adolescents

| | |
|---|---|
| | Anamnesis: prolonged and worsening symptoms, diagnosis is frequently delayed, due to the rarity of this disease. The average age is 12 and 9 years for SCC and sarcomas, respectively |
| Physical examination | Signs and symptoms: persistent dysphonia or hoarseness, eventually associated with dyspnea and dysphagia; rarely cervical painless lymphadenopathy. Flexible fiberoptic laryngoscopic examination is mandatory. Any suspicious case must be scheduled for a direct microlaryngoscopy and biopsy. Vocal folds are the most common site of involvement by SCC (Squamous Cell Carcinoma) in adolescent |
| | Anamnesis: prolonged and worsening symptoms, diagnosis is frequently delayed, due to the rarity of this disease. The average age is 12 and 9 years for SCC and sarcomas, respectively |
| Laboratory assessment | There are no specific alterations |
| Radiological assessment | |
| – First assessment | MRI or CT of the neck |
| – Pretreatment assessment | Metastatic work-up includes CT/PET |
| – FU | MRI or CT, CT/PET periodically |
| Pathological assessment | Biopsy during direct microlaryngoscopy under general anesthesia, consider tracheotomy in advanced/stenosing neoplasm, before any other treatment |
| Staging system (carcinomas of the larynx) | TNM UICC AJCC (seventh ed.) |
| | The larynx is divided into three sites (supraglottis, glottis, and subglottis) and several subsites |
| | Supraglottis (suprahyoid epiglottis, aryepiglottic fold, arytenoid, infrahyoid epiglottis, and ventricular bands or false cords) |
| | Tis: carcinoma in situ |
| | T1: tumor limited to one subsite of supraglottis with normal vocal cord mobility |
| | T2: tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., base of tongue, vallecula, and medial wall of piriform sinus) without fixation of the larynx |
| | T3: tumor limited to larynx with vocal cord fixation, and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage |
| | T4a: tumor 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 tongue, strap muscles, thyroid, and esophagus |
| | T4b: tumor invades prevertebral space, encases carotid artery or mediastinal structures |
| | Glottis (vocal cords, anterior commissure, and posterior commissure) |
| | Tis: carcinoma in situ |
| | T1: tumor limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility |
| | T1a tumor limited to one vocal cord |
| | T1b tumor involves both vocal cords |
| | T2: tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility |
| | T3: tumor limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or inner cortex of the thyroid cartilage |
| | T4a: tumor invades through the outer cortex of the thyroid cartilage, and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscles of tongue, strap muscles, thyroid, and esophagus |
| | T4b: tumor invades prevertebral space and encases carotid artery or mediastinal structures |
| | Subglottis |
| | Tis: carcinoma in situ |
| | T1: tumor limited to subglottis |
| | T2: tumor extends to vocal cord(s) with normal or impaired mobility |
| | T3: tumor limited to larynx with vocal cord fixation |
| | T4a: tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the |
| | larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscles of tongue, strap muscles, thyroid, and esophagus |
| | T4b: tumor invades prevertebral space, encases carotid artery or mediastinal structures |
| | Nx: regional lymph node metastasis cannot be assessed |

**Table 22.2** (continued)

| | |
|---|---|
| | Anamnesis: prolonged and worsening symptoms, diagnosis is frequently delayed, due to the rarity of this disease. The average age is 12 and 9 years for SCC and sarcomas, respectively |
| | N0: no regional lymph node metastasis<br>N1: metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension<br>N2: metastasis as described below:<br>–N2a metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension<br>–N2b metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension<br>–N2c metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension<br>N3: metastasis in lymph node more than 6 cm in greatest dimension<br>M0: no distant metastasis<br>M1: distant metastasis |
| Stage grouping | Stage 0: Tis N0 M0<br>Stage I: T1 N0 M0<br>Stage II: T2 N0 M0<br>Stage III: T1,T2 N1 M0; T3 N0,N1 M0<br>Stage IVA: T4a,T4b N0,N1 M0; T1,T2,T3, N2 M0<br>Stage IVB: T4b any N M0; Any T, N3 M0<br>Stage VIC: any T, Any N M1 |
| General treatment guidelines | –Need for multidisciplinary approach<br>–Need for referral to prime oncology center with expert physicians professionally dedicated to the management of this cancer in adults (or strict collaboration with them) because pediatric treatment protocols have not been well established due to the scarcity of cases; are based upon stage of the tumor |
| – Surgery | Conservative technique (open-neck or laser transoral surgery) are recommended when feasible; total laryngectomy is reserved in case of relapse |
| – Radiotherapy | Radical in early-stage disease and in sarcomas, after neoadjuvant chemotherapy; adjuvant with or without chemotherapy in high-risk patients after surgery; concomitant with chemotherapy in organ-preservation techniques. Consider long-term complications (arrest in growth of irradiated structures and radiation-induced malignancy) |
| – Chemotherapy | Neoadjuvant in advanced stages; concomitant with radiotherapy in organ-preservation strategies or in postoperative treatment of high-risk patients |

pathogenetic role of HPV infection is still under debate. However, it seems that this virus has not any implication in the genesis of laryngeal cancer, in contrast with oropharynx (Joos et al. 2009; Simon et al. 1994)

In children, the average age for SCC of the larynx is 12 years, and 60% of cases affect boys, compared to adults, in whom there is a greater male predominance (Ferlito et al. 1999; Joos et al. 2009). Vocal folds are the most common site of origin followed by supraglottic and subglottic locations (Joos et al. 2009).

SCC of the children has been reported to mirror that of adults, in regard to the pattern of local spread and is usually well differentiated and keratinizing (Joos et al. 2009). This characteristic potentially offers good chance for survival, and reasonable efforts to spare good laryngeal function must be undertaken. On the other hand, some reports emphasize a poorer outcome between 15 and 19 years of age (60.1% 5-year survival) than in those aged over 20 (87.7% 5-year survival) (Rutt et al. 2010). Radiotherapy and surgery are the treatment of choice and, depending on tumor extension, may be used alone or in combination (Kato et al. 1991; Pransky and Kang 2003; Preuss et al. 2009; Sessions et al. 1993; Strong and Jako 1972). Small lesions may be managed successfully with laser surgery, and by using this method only very limited sequelae were seen (Ambrosch 2007; Pransky and Kang 2003; Strong and Jako 1972; McWother and Hoffman 2005). Chemotherapy potentially applies to advanced stage laryngeal cancers and shall probably be based on the experience gained in adults (Holsinger et al. 2009; Strong and Jako 1972).

In summary, the management of children with laryngeal carcinoma (Table 22.2) remains a challenge: early diagnosis of children presenting with symptoms

suggestive of laryngeal pathology is essential in order to secure definitive local therapy and minimize long-term complications.

A malignant hemopathy such as *non-Hodgkin's lymphoma* or, rarely, an *extramedullary plasmacytoma* could affect the larynx. In these cases, histologic examination of the biopsy specimen is fundamental to address cures that are based on chemotherapy and radiotherapy (Ferlito et al. 1999; Rutherford et al. 2009).

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