Chapter 104: Malignant Neoplasms of the Larynx

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Cancer of the larynx accounts for approximately 1.2% of all new cancer diagnoses and 0.73% of all cancer deaths in the USA according to the National Cancer Institute estimates (Silverberg et al, 1990). These annual cases of laryngeal malignancy represent approximately one fifth of all head and neck cancers.

Laryngeal cancer does, however, have a generally favorable prognosis, with overall 5-year survival rates of 67%. Moreover, it is largely a preventable disease.

Epidemiology

Incidence

Laryngeal cancer is primarily a disease of middle-aged men, and it has a peak incidence ni the seventh decade (Rothman et al, 1980). The ratio of incidence among men compared to women is 4.6:1 (Wynder et al, 1976), although this ratio has diminished from 14.9:1 reported 20 years earlier by Wynder et al (1956). There is no racial predominance, although the incidence among blacks has increased dramatically during this century. Among blacks laryngeal cancer tends to occur in younger patients with poorer outcome (Wasfie and Newman, 1988).

Data from the Third National Cancer Survey have demonstrated a slightly greater prevalence in urban centers (Rothman et al, 1980). Worldwide figures demonstrate a high incidence of laryngeal cancer in men in São Paulo, Brazil, and in Bombay, India.

Risk factors

Environmental risk factors have been associated with cancer of the larynx. Tobacco, especially cigarette, use has been repeatedly implicated in the genesis of laryngeal cancer. Other environmental factors clearly implicated include alcohol, occupational exposure, and radiation. Those implicated but not yet well substantiated include herpes virus infection (Hollinshead et al, 1973) and dietary deficiency (Graham et al, 1981).

Recent studies have identified specific host factors that are linked with laryngeal cancer. The presence of a laryngocele is statistically associated with a higher likelihood of laryngeal cancer (Micheau et al, 1978) but may not be causative (Close et al, 1987). Gastroesophageal reflux has been identified as a probable causative factor, although this is not proved (Ward and Hanson, 1988). Immunosuppression can contribute to carcinogenesis by interfering with normal immune surveillance. Finally, the presence of juvenile papillomas should arouse concern regarding possible malignant transformation. Although irradiation of the lesions may engender early malignant change, carcinoma has been reported to occur 30 years after juvenile papillomatosis in nonirradiated patients (Kashima et al, 1988).

Tobacco

Epidemiologic data have without fail demonstrated the strong correlation between tobacco usage and laryngeal cancer (Burch et al, 1981; Hammond, 1966; Kahn, 1966; Wynder and Stellman, 1977; Wynder et al, 1956). Laryngeal cancer is extremely rare in nonsmokers. Moreover, the risk of laryngeal cancer increases with number of cigarettes smoked per day. Relative risk ratios range from 6.1 to 15.8 compared to nonsmokers. Cigar and pipe smoking have relative risk ratios in the range of 1.6 to 3.9.

Further evidence of the etiologic relationship of smoking with laryngeal cancer lies in the histologic changes of vocal fold epithelium among smokers. Auerbach et al (1970) and Müller and Krohn (1980) have documented that histologic changes in cadaver larynges are related to smoking history. Degenerative changes in the subepithelial mucous glands have been related to tobacco consumption by Neilsen and Bak-Pedersen (1984).

Finally, in an animal model, that of the Syrian hamster, laryngeal cancer has been found to develop after "smoking" (Homberger, 1975). This provides further evidence in establishing the causative role of cigarette smoking in laryngeal cancer.

Alcohol

Wynder et al (1956) demonstrated the importance of alcohol in laryngeal cancer, especially that of the "extrinsic" larynx (hypopharynx). He subsequently (1976) demonstrated the relationship of alcohol to supraglottic carcinoma. Further statistical analysis by others (Flanders and Rothman, 1982) has established both the independent effect of alcohol and the significant synergy of alcohol and tobacco. The combination of these two increases their relative risk by 50% above that predicted by simple addictive effects. It is likely that the carcinogens are found in the nonalcoholic components of such beverages (Rothman et al, 1989). Experimental support for this epidemiologic observation has been documented by the Syrian hamster model (Stevens, 1979).

Occupation

Efforts to identify occupational risk factors are complicated by the overwhelming influence of tobacco and alcohol. Several individual studies in the epidemiologic literature identify workers at risk: nickel workers, mustard gas workers, farmers, woodworkers, and machinists. Other studies have failed to substantiate these findings, however. Asbestos has frequently been suspected as a possible causative agent (Burch et al, 1981) with a risk ratio of approximately 2. The review of evidence by Chan and Gee (1988) does not support an etiologic role for asbestos, however. Further investigation may identify other occupational risk factors; these are also unlikely to be major factors in comparison with tobacco and alcohol.

Radiation

Irradiation, especially in low doses, has long been identified as carcinogenic. Tumors so induced are usually of soft tissue or superficial glandular structures (eg, thyroid, salivary glands). Nevertheless, radiation-induced tumors have been reported in the larynx, including two squamous carcinomas (Sakamoto et al, 1979), one fibrosarcoma (Mahmoud, 1980), and

one acinic cell carcinoma (Reibel et al, 1981).

Carcinogenesis

Saffiotti and Kaufman (1975) reviewed available data on the biochemistry of laryngeal carcinogenesis. Particular attention has been directed to polynuclear hydrocarbons (eg, benzo(a)pyrene) and to N-nitroso compounds. These compounds are found in significant concentrations in the particulate and gaseous components of cigarette smoke. MacDonald and Janson (1981) have found that ethyl nitrite, a carcinogen present in cigarette smoke, is found in greater concentration in the presence of alcohol. Investigations are still under way to identify the principal carcinogens.

Host factors such as the inducibility of arylhydrocarbon-hydroxylase are likely to play a role in carcinogens (Andréasson et al, 1987). This intracellular enzyme metabolizes and activates hydrocarbons, such as those found in tobacco smoke, thereby producing potential carcinogens. The role played by steroidal sex hormones is still unclear (Virolainen et al, 1986).

Although the subcellular events in the initiation and development of laryngeal cancer are still not well understood, the behavior of cells has been well documented. The histologic changes induced by smoking are well characterized (Auerbach et al, 1970). The natural history of these histologic changes has been well described (Ferlito et al, 1981). Keratosis (ie, abnormal mucosal proliferation) proceeds to carcinoma in 3% to 6% of patients (Crissman, 1979; Sllamniku et al, 1989a). The likelihood of malignant transformation is well correlated with the degree of cellular atypia: hyperkeratosis without atypia evolves into invasive carcinoma in only 3% of patients, whereas in hyperkeratosis with severe atypia, this figure rises to 30% (Højslet et al, 1989; Sllamniku et al, 1989a). Carcinoma in situ represents malignant transformation limited to the epithelium. Careful examination shows 36% coexistent microinvasive cancer and in 10% to 15% of patients carcinoma in situ ultimately becomes frankly invasive carcinoma (Crissman et al, 1988; Miller and Fisher, 1971).

Prevention

Cancer of the larynx is largely a preventable disease. The infrequency of laryngeal malignancy in nonsmokers (less than 5% of all larynx cancer) is ample testimony to this fact. Otolaryngologists should encourage educational programs to eradicate cigarette smoking (Wynder and Hoffman, 1979).

The risk of larynx cancer is decreased by cessation of smoking. The risk diminishes dramatically, however, only after 6 years (Wynder et al, 1976) and approaches that of nonsmokers only after 15 years. Nonetheless, no-smoking programs could markedly diminish the incidence of laryngeal cancer.

Finally, "safe" cigarettes may be sought. Cigarette filters diminish the risk of larynx cancer by approximately 50% (Wynder and Stellman, 1979). Low-tar cigarettes may be expected to diminish risk factors further.

Prevention of laryngeal cancer should be a major health concern of otolaryngologists as well as society at large, to effect the best control of this disease.

Diagnosis

Early diagnosis is key to good survival and cure rates. Laryngeal neoplasms often produce early symptoms that may lead to cure with good preservation of function.

Symptoms

The cardinal symptom of laryngeal cancer is voice change, that is, hoarseness. This is usually due to interference of vocal fold mucosal vibration from a glottic tumor that involves the mucosa or thyroarytenoid (vocalis) muscle. Supraglottic lesions generally produce a "muffled" voice.

Airway obstruction may also be a presenting symptom, most commonly in subglottic tumors. This usually represents a mass effect and suggests that the tumor is large. Other symptoms of local inflammation may be present, namely, throat discomfort or fullness. Hemoptysis may be present, though this generally occurs only in large ulcerating tumors.

Symptoms relevant to swallowing may also occur. Odynophagia and otalgia are frequent presenting symptoms of supraglottic lesions. Dysphagia is associated with large tumors and suggests invasion beyond the confines of the larynx.

A neck mass may occur either by direct extension or, more commonly, by nodal metastasis. Finally, weight loss or other constitutional symptoms may occur. The presence of these symptoms is usually indicative of advanced local disease.

Examination

Voice quality is evident during the patient interview. Pitch change or roughness may be heard, suggesting involvement of the true cord. The muffled quality of supraglottic lesions may be detected. Airway obstruction may be noted, especially in subglottic tumors.

Palpation of the neck discloses the presence, location, and fixation of cervical nodes. Fixation of the thyroid cartilage is an ominous sign.

Office examination of the larynx may be performed via indirect mirror examination or fiberoptic examination. The latter allows photographic or videographic documentation of the larynx. The laryngeal examination ought to indicate the appearance of the mucosa, the presence of submucosal lesions, and mobility of the cords, as well as the status of the airway. Stroboscopy and acoustic analysis may provide helpful information in some patients.

Evaluation for metastatic disease should include a complete physical examination, blood count, chest radiograph, and liver enzyme studies.

Radiologic evaluation

To augment the clinical examination, radiologic studies may be undertaken. The simplest of these are soft tissue neck films, principally to examine encroachment of the airway.

Contrast studies may be performed. A barium swallow (Fig. 104-1) is useful in evaluating the laryngeal margins, the vallecula and tongue base, the piriform sinuses, and the postcricoid region. Conventional tomography improves the accuracy of soft tissue films. Evaluation of the endolarynx may be accomplished by a laryngogram (Lehmann and Fletcher, 1964). This study provides detailed information, especially about the laryngeal surface of the epiglottis, the ventricle, and the subglottis, regions that may be difficult to examine satisfactorily (Fig. 104-2). Contrast laryngography has been rendered nearly obsolete by newer imaging techniques.

Recently, computed tomography (CT) and magnetic resonance imaging (MRI) have become widely available. These powerful methods have proved useful in supplementing clinical determination of the size and extent of laryngeal tumors. CT scanning is most helpful in documenting deep invasion (Fig. 104-3) and extension beyond the larynx but is only moderately sensitive in determining early cartilage invasion (Archer and Yeager, 1982; Charlin et al, 1989; Werber and Lucente, 1989). MRI, although more expensive and less widely available, may be superior in demonstrating cartilage invasion (Castelijas et al, 1990; Hoover et al, 1987). Ultrasonography may prove useful, both in evaluating cartilage invasion and in staging neck metastasis. The choice of imaging techniques depends on the expertise and facilities available.

Tissue diagnosis

To distinguish malignancy from the panoply of disorders that may have similar gross appearance (fungal and mycobacterial infections, syphilitic gummas, idiopathic granulomatous disorders, benign neoplasms), a tissue diagnosis must be made. Exfoliative cytologic analysis, which provides correct diagnosis in approximately 90% of cases, may be used (Olofsson, 1982). Fine-needle aspiration of presumed metastasis may also aid in establishing the diagnosis (Feldman et al, 1983).

The accepted standard for diagnosis is histopathologic examination of tissue obtained at laryngoscopy and biopsy. In general this is best performed by direct laryngoscopy with the aid of the operating microscope. Biopsy "mapping" of the observed lesion is helpful in staging and determining therapy. Toluidine blue has been suggested as a useful adjunct to mapping lesions (Strong et al, 1970), although its limitations are numerous (Lundgren et al, 1979). Microlaryngoscopy under general anesthesia provides the ideal setting, allowing a thorough examination of the larynx with the opportunity to obtain a biopsy specimen of the lesion and its margins.

Staging and the Biology of Squamous Cancer

Staging of laryngeal malignancy provides a method of succint description of the lesion. This offers insight into the behavior of the tumor as well as a medium for comparison of treatment outcomes.

The two widely used systems have been those of the American Joint Committee (AJC) and the International Union against Cancer (UICC). In 1987, the UICC and AJC revised their systems, thereby facilitating international data exchange. The unified system, which uses the Tumor-Node-Metastasis (TNM) staging, is presented in Table 104-1. This system of classification is used principally for squamous cell carcinoma. Nonepidermoid malignancy is discussed later in this chapter.

Table 104-1. Tumor-node-metastasis (TNM) staging

T: primary tumor

Tx Cannot be staged
T0 No evidence of tumor
Tis Carcinoma in situ.

Supraglottis

T1 Tumor confined to one subsite of larynx; normal mobility (ie, ventricular bands; arytenoids; epiglottis)
T2 Involving more than one subsite (supraglottis or glottis; normal mobility)
T3 Linked to larynx with fixation or extension to involve postcricoid, medial pyriform, or preepiglottic space
T4 Tumor invasion of cartilage or tissue beyond larynx.

Glottis

T1 Tumor limited to vocal cords, normal mobility
T1a one cord
T1b both cords
T2 Extension to supraglottis and/or subglottis; may be impaired cord mobility
T3 Limited to larynx with cord fixation
T4 Extension beyond larynx or into cartilage.

Subglottis

T1 Tumor limited to subglottis
T2 Extension to vocal cord; mobility may be impaired
T3 Limited to larynx with cord fixation
T4 Extension beyond larynx or into cartilage.

N: regional nodes

Nx	Cannot be assessed
N0	No regional metastasis
N1	Single positive ipsilateral node, less than 3 cm
N2	Nodes less than 6 cm
N2a	Single ipsilateral node 3-6 cm
N2b	Many ipsilateral nodes less than 6 cm
N2c	Bilateral and contralateral node less than 6 cm
N3	Node(s) greater than 6 cm.

M: distant metastasis

Mx	Cannot be assessed
M0	No distant metastasis
M1	Distant metastasis.

Stage grouping

0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1-3	N1	M0
IV	T4 or N2-3 or M1.		

T: the anatomy of the primary tumor

The anatomy of the larynx has been carefully delineated. First, the boundaries may be identified: superiorly, the tip and lateral borders of the epiglottis; anteriorly, the anterior lingual surface of the epiglottis, thyroid membrane, thyroid cartilage, cricothyroid membrane, and cricoid cartilage; posterolaterally, the aryepiglottic folds, arytenoids, interarytenoid space, and mucosa overlying the cricoid; and inferiorly, the lower border of the cricoid cartilage. The vallecula is part of the superior hypopharynx; the piriform sinus and postcricoid region are part of the inferior hypopharynx.

The larynx is divided into three parts: supraglottis, glottis, and subglottis (Fig. 104-4). Most cancers occur in the glottis; the supraglottis is next most frequent; subglottic tumors are rare. The supraglottic/glottic boundary occurs at the level of the apex of the ventricle. The junction of the glottis and subglottis occurs 1 cm below the free edge of the vocal fold. Norris et al (1970) and Tucker (1974) have discussed the partitions and boundaries of the larynx, especially in relation to its submucosal compartments.

Transglottic carcinoma is a term coined by McGavran et al (1961) to describe tumors that cross the laryngeal ventricle, thus involving at least two of the three described portions of the larynx. Although not included in the AJC or UICC definitions, this concept has been stressed by several authors, including Mendonca and Bryce (1973), Kirchner et al (1974), and Tucker (1974).

Anatomic basis of classification

The subdivision of laryngeal (squamous cell) malignancy into anatomic types has extensive investigative justification. In 1981, Hajek recognized that laryngeal swelling followed specific anatomic "rules". His investigations were extended by Pressman and his colleagues in two studies published in 1956 using dye injections in living and cadaver larynges. Welsh et al (1989) have recently duplicated and amplified these earlier studies, correlating their findings with whole organ sections. They determined that the mucosa was continuous throughout. The submucosa, however, is compartmentalized. First, the right and left hemilarynx are distinct throughout from epiglottis to cricoid. Second, several regions were specifically identified (Fig. 104-5):

1. An epiglottic region corresponding to the cartilage.

2. A marginal epiglottic region lateral to the cartilaginous epiglottis.

3. A posterolateral supraglottic region, which does not transgress the ventricle.

4. A ventricular region, which includes the inferior surface of the vestibular band, superior surface of the vocal fold, and apex between.

5. A sacciform region (possibly part of the ventricle).

6. A bursa on the margin of the true cord (Reinke's space).

7. A subglottic region from the free margin of the cord to the cricoid below.

The laryngeal compartments so described have been demonstrated embryologically by Tucker and Smith (1962). These studies provides the ontogenetic basis for the distinction among the compartments. Hast (1974) has also related laryngeal embryology to the subdivision of the larynx. The right and left hemilarynges arise independently. The supraglottic larynx arises from the buccopharyngeal anlage, arches III and IV; the subglottic portion is derived from the pulmonary anlage, arch VI. The vascular, lymphatic, and neuroanatomic subdivisions follow these boundaries (Pearson, 1975).

Critical to the understanding of the laryngeal compartments are the connective tissue boundaries, which act as barriers. The cartilaginous epiglottis serves as the anterior limit of the epiglottic submucosal compartment. The quadrangular membrane separates the supraglottis from the lateral paraglottic space; the ventricle and sacculus form a niche in the paraglottic space. The conus elasticus serves as the inferior/lateral border of the glottic and subglottic spaces, again separating these from the paraglottic space. The significance of these boundaries lies in the observation that cancer tends first to follow the planes of least resistance, that is, within compartments (Kirchner and Carter, 1987; Pressman et al, 1960). Invasion across boundaries generally is associated with a worse prognosis.

The ligamentous and cartilaginous structures of the larynx are of great importance. These connective tissue structures display great resistance to invasion by carcinoma. Once they are invaded, however, the survival rates diminish dramatically.

The thyrohyoid membrane forms the anterior margin of the preepiglottic space. Once the latter space is involved, the tumor may spread through the membrane into the soft tissues of the neck or into the deep muscle of the tongue base.

The thyroid cartilage surrounds only a small portion of the endolarynx; the piriform region and paraglottic space about the cartilage on most of its surface. Once tumor has invaded the paraglottic space (ie, the intrinsic muscle of the vocal fold), it may invade the cartilage, particularly in regions of ossification.

Of particular importance is the anterior commissure tendon (Fig. 104-6). The tendon comprises the confluence of the paired vocal ligaments as they insert into the midline posterior surface of the thyroid cartilage (Broyles, 1943). Parallel to the tendon are numerous vessels and lymphatics (Pearson, 1975; Sessions et al, 1975b). The collagen bundles may serve as a preformed pathway for extension of tumor (Harrison, 1984; Yeager and Archer, 1982). The region of the tendon also represents a distinct margin between the supraglottis and glottis. The vestibular bands loosely converge around the thyroepiglottic ligaments but are distinct from each other and from the vocal ligaments (Bagatella and Bignardi, 1983; Tucker et al, 1973). Thus, the anterior commissure region provides a limiting structure of lateral supraglottic lesions but is a potential pathway for spread of large glottic and midline supraglottic lesions.

The cricothyroid membrane represents a vulnerable point below the shield of the thyroid cartilage. The mucosa of the larynx is in direct contact with the cricothyroid membrane. Subglottic tumors may grow through this membrane into the soft tissues of the neck (van Nostrand and Brodarec, 1982).

Inferiorly and posteriorly, the cricoid serves as a barrier to tumor. That laryngeal tumors should reach the cricoid without also reaching the cricothyroid membrane is unlikely. Posterior submucosal spread along the cricoid, however, can reach the arytenoid and interarytenoid regions. Vocal cord immobility may then ensue. Alternatively, involvement of the hypopharyngeal piriform sinus or postcricoid mucosa may also occur (Lam, 1983; van Nostrand and Brodarec, 1982).

Cartilage invasion usually occurs in ossified portions of the cartilage (Kirchner, 1969, 1984a; Pittam and Carter, 1982) and rarely in the hyaline regions. The invasion of ossified portions may relate to the vascularity associated with ossification. The explanation for the resilience of cartilage is still unknown (Blitzer, 1979), although Folkman (1976) has found that cartilage may produce a substance that inhibits tumor angiogenesis factor. In 1988 Repássy et al reported the finding of activated connected tissue, especially histiocytes, adjacent to cancer. The stimulus for this increased production of fibrils remains unclear.

Knowledge of the laryngeal compartments and their boundaries provides insight into the pathways of growth and invasion of laryngeal cancer. The histologic study of excised larynges has provided this information (Kirchner, 1989; Tucker, 1961). Retrospective analysis of patient material thus may provide clues to the behavior of new laryngeal malignancies.

Staging of supraglottic primary tumors

Supraglottic primary tumors account for 24% to 42% of all laryngeal primary tumors. The description of laryngeal compartments aids in understanding the spread of supraglottic cancer. The supraglottis may be subdivided into (1) three marginal regions, namely, the anterior marginal region or suprahyoid epiglottis, and two lateral marginal regions (ie, along the aryepiglottic folds); (2) the midline infrahyoid epiglottis; and (3) the lateral infrahyoid areas of the vestibular bands.

Marginal supraglottic carcinoma should be regarded as distinct by virtue of its propensity to "spill over" into the vallecula, arytenoids, and piriform sinuses (Fig. 104-7). As such it behaves more like an hypopharyngeal lesion and is not "compartmentalized" as readily as other laryngeal sites. These tend to be asymptomatic for longer intervals and present with more advanced disease. Laccourreye et al (1983) found that approximately 57% of their patients had T3 or T4 primary lesions.

The prognosis of the more inferiorly located supraglottic primary tumors is better than that of those on the margin (Bocca, 1975). The pattern of spread of supraglottic cancer is notable for its restriction to the supraglottic region for long intervals. Supraglottic cancer does not invade the vocal cords unless it is, in fact, transglottic, as described later (Kirchner and Som, 1971a). Its growth anterioinferiorly is limited by the anterior commissure tendon so that only massive tumors actually invade the anterior glottic and subglottic regions. Moreover, supraglottic cancer rarely invades the thyroid cartilage (unless it has first become transglottic by invading the paraglottic space).

The most important route of spread of supraglottic cancer is anteriorly into the preepiglottic space. This occurs by means of fenestrae in the elastic cartilage of the epiglottis through which cancer may spread. The preepiglottic space is often clinically silent. Thus, underestimation of tumor may occur; T3 supraglottic cancer may appear to be T2. Gregor (1990) has reported that preepiglottic space invasion frequently augurs involvement of the strap muscles or tongue base and that it may merit reclassification from T3 to T4. Radiologic investigation, especially with computed tomography, may greatly improve diagnosis of spread to this space or beyond and improve staging accuracy (Sagel et al, 1981; Sulfaro et al, 1989).

The pathways of spread of supraglottic cancer are depicted in Figure 104-8. Spread occurs (1) outside the endolarynx along mucosal pathways, especially in lesions arising on the margins; (2) into the preepiglottic space; and (3) across the anterior commissure tendon or through the paraglottic space to become transglottic. The last occurs, in general, only with large, ulcerative lesions.

Staging of glottic primary tumors

Glottic carcinomas constitute the majority of laryngeal malignancies, accounting for 55% to 75% of primary sites. Since tumors arising from the vocal cord should interfere with movement of the mucosa, these patients tend to have early symptoms. Indeed most glottic carcinomas are small: 55% to 65% are T1; 12% to 22% T2; 15% to 19% T3; and only 4% or less T4 (Daly and Strong, 1975; DeSanto et ak, 1977a; Kirchner and Owen, 1977).

Spread of glottic cancer first follows Reinke's space along the length of the vocal ligament. Since the anterior commissure is composed of the conjoined vocal ligaments and the mucosa of the anterior commissure is continuous, it is evident that bilateral lesions (so-called horseshoe lesions) can occur.

Involvement of the vestibular structures or subglottis characterizes T2 lesions (Fig. 104-9). The preservation of normal cord mobility suggests invasion limited to submucosal compartments. Deeper invasion, thereby entering the intrinsic laryngeal muscle or paraglottic space in the region of the ventricle, results in impaired mobility. This clinical observation is very important. Indeed, several authors have distinguished T2a and T2b tumors with normal and impaired mobility, respectively (Harwood and deBoer, 1980; Kaplan et al, 1984; Olofsson et al, 1973; van den Bogaert et al, 1983). Although this is not included in current staging systems, survival statistics are worse with impaired mobility. That this should be true follows from the assumption that impaired mobility suggests deep invasion. As well, invasion of the paraglottic or subglottic space may also be associated with clinically undetected invasion of the laryngeal cartilage.

Fixation of the cord defines T3 glottic lesions. The principal mechanism of vocal cord fixation has been identified by Kirchner and Som (1971b) and Kirchner (1977) as replacement of the thyroarytenoid muscle (Fig. 104-10). Extensive tumor involving the entire superior surface of the cord or the subglottic "shoulder" can also cause fixation though such extension occurs infrequently without actual invasion of the muscle. Moreover many lesions with vocal cord fixation also demonstrate invasion of the thyroid cartilage (Kirchner, 1969) Olofsson et al (1973) also cited cricoarytenoid invasion as a cause of cord fixation. Because cord fixation generally implies deep invasion, it has a worse prognosis and requires more extensive treatment.

Invasion of the laryngeal cartilage or invasion beyond the larynx constitutes a T4 cancer. Kirchner (1977) found 5 of 52 glottic lesions with cartilage invasion, associated in 4 with with extensive (more than 1 cm) infraglottic extension. Van Nostrand and Brodarec (1982) similarly found that extension beyond the larynx occurred in association with subglottic extension and egress through the cricothyroid membrane. The other route of framework invasion is via the ventricle. These last lesions are, by definition, transglottic.

In summary, the staging of glottic cancer relies principally on the careful observation of cord mobility and extent in the subglottis or ventricle. CT scanning may improve the ability to document the full extent of glottic cancers.

Staging of subglottic primary tumors

Primary subglottic tumors are rare, constituting 1% to 5% of laryngeal primary sites (Harrison, 1971; Kirchner and Owen, 1977; Sessions et al, 1975a; Shaha and Shah, 1982; Warde et al, 1987). Most subglottic tumors present with large primary tumors since they are clinically silent until they produce voice change (usually with cord fixation) or airway obstruction. Combining the small series cited leads to the documentatin of 14% T1, 18% T2, 23% T3, and 45% T4 subglottic lesions.

The pathway of invasion of subglottic cancer is first into the thyroarytenoid muscle to produce cord fixation. Tumor usually invades the cricothyroid membrane or, more inferiorly, invades along the trachea. Fifty percent (four of eight) of the subglottic lesions of Kirchner (1977) demonstrated cartilage invasion. Lam (1983) described three of seven subglottic tumors with framework invasion. Subglottic tumors also demonstrate a high incidence of thyroid gland invasion (Gilbert et al, 1986).

Although subglottic tumors are rare, subglottic extension of glottic or supraglottic (in the latter case, therefore, transglottic) tumors is not uncommon. The significance of the inferior margin of the thyroid cartilage, generally 10 mm below the anterior and midcord and 3 to 4 mm posteriorly, cannot be overemphasized. The mucosa below this line directly abuts the cricothyroid membrane or cricoid space and provides a direct passage for extralaryngeal invasion.

Staging of transglottic tumors

Transglottic tumors are not included in the UICC or AJC classification. They deserve attention because of the high incidence of framework invasion and extralaryngeal spread associated with these lesions. Since, by definition, thransglottic lesions cross the ventricle, they already involve the paraglottic space and are in close proximity to the thyroid ala laterally and to the hypopharynx medially. Kirchner et al (1974) demonstrated cartilage invasion in 32 of 42 (76%) transglottic cancers. They noted invasion usually in the thyroid ala; invasion of the cricoid occurred with extensive subglottic invasion (Fig. 104-11). Cartilage invasion occurred only in tumors larger than 2 cm. Pittam and Carter (1982) conifirmed the latter finding. As well, they documented framework invasion in 80% (21 of 26) of transglottic cancers. Lam (1983) identified invasion in 91% of his 22 specimens. Eighteen of the 20 involved the thyroid cartilage, thyrohyoid membrane, and/or cricothyroid membrane. Moreover, 15 of the 20 spread posteriorly to involve the thyroid ala, piriform sinus, or postcricoid region. Thus, the propensity of these lesions for extralaryngeal spread is amply demonstrated.

The most significant clinical feature of transglotic cancer is the difficulty of establishing that a lesion is truly transglottic. Direct laryngoscopy frequently cannot establish framework invasion or extent of submucosal invasion. Pittam and Carter (1982) found radiologic techniques (laryngography and CT) also inadequate. Archer and Yeager (1982) have documented similar limitations of CT.

Thus, transglottic invasion of cancer must always be suspected, especially in extensive tumors arising from the glottis. They require aggressive treatment and have a strong propensity for recurrence.

It is important to stress that staging of primary disease is based on clinical evidence. It is, therefore, not surprising that understaging does occur. Since we often lack the ability to perceive deep invasion on clinical grounds, lesions are often understaged when compared with histopathologic documentation (Norris et al, 1970; Pillsbury and Kirchner, 1979). The current T classification is designed to reflect invasion, however. T1 and T2 lesions are confined to their respective mucosal and submucosal regions. T3 lesions demonstrate evidence of invasion of deeper spaces: into the preepiglottic space (ie, through or around the epiglottis)

or into the paraglottic space, as demonstrated by involvement of piriform mucosa or by vocal cord fixation caused by muscle infiltration. T4 lesions demonstrate obvious extralaryngeal spread or invasion of cartilage. Errors in clinical staging occur most frequently in T2 and T3 lesions in which deep invasion is not clinically apparent.

N: pathways of nodal metastasis

The lymphatic anatomy and patterns of nodal metastasis reflect the location and extent of invasion of the primary tumor. The supraglottic region is well endowed with lymphatics, whereas the glottis demonstrates a paucity of lymphatics. The subglottis behaves more like the trachea, with which it shares its embryogenesis.

The likelihood of nodal metastasis depends on many factors. The site of tumor involvement and the relative extent of lymphatic drainage are the most significant factors. McGavran et al demonstrated in 1961 that perineural infiltration and poor differentiation also were associated with nodal metastasis.

Node metastasis from supraglottic tumors

The lymphatics of the supraglottic larynx are numerous. They exit from the larynx via the thyrohyoid membrane and drain to the upper and midjugular chain. Since many supraglottic tumors are at or near the midline, tumors may metastasize bilaterally.

The frequency of nodal metastases has been variously reported to be 12% to 54% as indicated by clinical examination, with most series reporting 25% to 35% (Bocca, 1975; DeSanto et al, 1977b; Johns et al, 1982; Kirchner and Som, 1971a; Lindberg, 1972; Ogura et al, 1971; Shah and Tollefsen, 1974). As might be anticipated, larger primary lesions have a higher rate of metastasis, although T1 lesions still had 39% nodal metastasis in Lindberg's series (1972) and 40% in Shah and Tollefson's (1974). Moreover, many patients have demonstrated bilateral nodal metastasis: 7% in the Mayo Clinic series (De Santo et al, 1977b) and 10% in that of Johns et al (1982).

In addition to clinically suspicious nodes, several series have documented a significant incidence of "occult" nodes: 16% in the series of Ogura et al (1971) and 11% in Bocca's (1975). Neck metastasis in untreated necks has been reported to be 25% by DeSanto et al (1977b).

Tumors arising from the marginal supraglottis have a higher incidence of node metastasis (perhaps a result of later stage disease). Anterior lesions demonstrated a 60% rate of bilateral node metastasis; the lateral marginal region demonstrated a 62% to 65% incidence of ipsilateral metastasis (Laccourreye et al, 1983; Lefebvre et al, 1987). Shah and Tollefson (1974) noted a doubling of nodal metastasis with lesions at and over the margin. Kirchner and Som (1971a) have indicated the greater propensity of posterior supraglottic lesions to be metastatic. This reflects, perhaps, the likelihood of hypopharyngeal involvement.

In summary, supraglottic lesions are frequently metastatic to the neck even in early stages. This is particularly true of posterior marginal lesions. Anterior lesions especially may produce bilateral metastasis. It is not surprising that recurrence in the neck is frequently cited

as the cause of failure in treatment of supraglottic cancer.

Node metastasis from glottic tumors

In sharp contrast to neck metastasis in supraglottic cancer is the infrequency of metastasis in glottic cancer. The vocal cords have sparse lymphatics, especially in the anterior portion (Werner et al, 1990). The overall incidence of node metastasis is less than 10%; Ogura et al (1975) reported 8% metastases (36 in 463) of glottic primary tumors. The vast majority of node metastases occurred in T3 (24 of 113) or T4 (3 of 14) lesions. Kirchner and Owen (1977) reported 1% metastases (3/209).

The incidence of posttreatment failure caused by neck metastasis is also low: 5% to 8%, according to the authors cited. Thus, the clinical impression of rare metastasis is borne out.

Node metastasis from subglottic tumors

The lymphatic vessels of the subglottic larynx drain to the cricothyroid region, over which lies the prelaryngeal (Delphian) node. Metastasis to the Delphian node portends a poor outcome (Olsen et al, 1987). Of great importance also is the propensity of node metastasis to occur along the clinically silent paratracheal chains (Fig. 104-12). Harrison (1971) noted that this plays a part in the high recurrence rate of subglottic tumors. Most studies have documented palpable lymph nodes in 18% to 20% of the small series accumulated (McGavran et al, 1961; Sessions et al, 1975a; Shaha and Shah, 1982).

Node metastasis from transglottic tumors

Since transglottic tumors must be supraglottic and glottic (and often subglottic as well), they should demonstrate a high rate of neck metastasis. Moreover, the high likelihood of framework invasion or extralaryngeal spread should increase the incidence of metastasis. Clinical experience has confirmed this hypothesis: McGavran et al (1961) found that 52% (13 of 25) of transglottic tumors had cervical metastasis (15 of 50). This was more likely to occur in large tumors or those that were poorly differentiated. Mittal et al (1984) documented a 26% rate of metastasis (40 of 152); the rate increased with T stages (to 40% in T4). Furthermore, they demonstrated a 19% neck recurrence rate in untreated necks. Thus, transglottic carcinoma carries a high risk of nodal metastasis.

Staging of neck disease

Table 104-1 lists the staging of nodal disease. The 1987 revisions resulted in uniform AJC and UICC standards. Of note is that contralateral or bilateral neck disease now falls into the N2 (N2c) category. The most significant factor remains the presence of absence of node disease.

Node histology

Gilmore et al (1975) demonstrated that histologic analysis of lymph nodes does not aid in prediction of successful host-tumor interaction. Stell (1988) has also stressed that node histologic characteristics are far less important than presence or absence of metastasis. Extracapsular spread, however, does lead to a higher likelihood of recurrence (Snyderman et al, 1988).

M: distant metastasis

Distant metastasis from laryngeal cancer is distinctly uncommon. Abramson et al (1975) cited a clinical estimate of 1.3% to 4.1%. Autopsy studies have demonstrated a metastasis rate of up to 88% with a compiled incidence of 26.5% in advanced laryngeal malignancy. Papac (1984) noted a high incidence of distant metastases in advanced laryngeal cancer (58.6%).

Kotwall et al (1987) found a 44% incidence of distant metastasis at autopsy; most of these (89%) also had residual or recurrent locoregional disease.

The most common site for metastasis is the lung, followed by mediastinal nodes. Less frequent are osseous, hepatic, and other distal sites.

The evaluation of patients with laryngeal malignancy ought to include a physical examination, chest roentgenogram, and routine blood chemical analyses. Whether chest tomography would improve the yield of information is controversial. Available data suggest that a vigorous search for distant metastasis is appropriate only in advanced disease.

Clinicians should also be cognizant of the possibility of new (second) primary tumors of the upper aerodigestive tract. This is particularly true of subsequent pulmonary neoplasms.

Treatment of Invasive Squamous Cell Carcinoma

Since the first laryngectomy for cancer by Theodore Billroth in 1873 and the discovery of x-rays by Roentgen in 1895, the modalities of laryngectomy and irradiation have served as the mainstay of treatment of laryngeal cancer. Vast experience has been accumulated for both methods, and current treatment protocols are largely based on empirical results. Knowledge of the biologic behavior of epidermoid malignancy aids in determining optimal treatment, providing a sound basis for empirical results.

Many factors must be considered in the determination of optimal treatment for a particular patient. These include:

1. Age and sex.

2. General health.

3. Personal preferences and social circumstances of the patient and family.

4. Treatment facilities available, including the experience of surgeon and radiotherapist.

5. Location and stage of tumor.

The first two categories relate primarily to the relative risk of surgery. Certainly significant comorbid illness or extreme age would argue against major surgery. Clinical pulmonary dysfunction is of special importance in consideration of conservation surgery. The capacity of a patient and family to adapt to loss or change of voice must also be considered (Berkowitx and Lucente, 1985; McNeil et al, 1981). Finally, the experience of surgeon and radiotherapist may play a role in the determination of therapy.

Of paramount importance is accurate clinical staging, since determination of therapeutic options is most dependent on the tumor size and location. For example, the presence of deep invasion as evidenced by fixation or framework invasion (T3 or T4) diminishes the effectiveness of radiation therapy. Appropriate radiologic studies should be undertaken to provide the most accurate staging.

Irradiation therapy has proved valuable for treatment of laryngeal squamous cancer in many patients. The effectiveness of irradiation has been correlated with smaller tumor volume (Gilbert et al, 1987). Radionecrosis is a potential complication, however. Radiotherapy also does not permit histopathologic "control" of margins. Moreover, the posttreatment follow-up evaluation of irradiated patients is more difficult, for nests of tumor may remain clinically and even histologically unrecognized for long intervals. Thus, irradiation therapy possesses limitations that must be borne in mind.

Surgery also has limitations. The requirement of a general anesthetic has been noted. Perioperative complications may also ensue: mortality in 1% to 2% of patients and other significant morbidity in 6% to 8% (Arriaga et al, 1990; Sarkar et al, 1990). Wound complications, including fistula formation, can lead to prolonged hospitalization and necessitate further surgery. As well, most conservation surgical techniques lead to a significant change in voice that occurs more frequently than it does after irradiation therapy. Moreover, aspiration is a frequent reslt of conservation surgery, requiring completion laryngectomy in some patients.

Surgery and irradiation techniques are discussed in greater detail elsewhere in Chapter 113 through 116. It is important, however, to recognize the general limitations of these two modalities and to offer a rationale for selection of treatment based on tumor pathophysiology. Some authors (Dimery et al, 1989) have described neoadjuvant chemotherapy plus irradiation for tumors that would otherwise require total laryngectomy. These results are still preliminary; such treatment is best carried out under the auspices of a formal investigational protocol.

Thus, choice of therapy is contigent on many factors. Specific treatment modalities and results are discussed with reference to TNM staging. Presence of metastatic disease dramatically alters management as well.

Supraglottic tumors

The major considerations in supraglottic cancer include (1) location, (2) status of the preepiglottic space, and (3) treatment of the neck. As noted, marginal lesions carry a worse prognosis because of their tendency to escape the confines of the larynx. As well, node metastases are more frequent. The significance of the preepiglottic space lies in the high incidence of understaging (29%) produced by unrecognized involvement (Pillsbury and Kirchner, 1979). The high incidence of palpable and occult metastasis argues for treatment of the neck.

Surgical treatment consists of conservation surgical procedures, especially supraglottic laryngectomy, and total laryngectomy. Marginal lesions may be excised occasionally by ultraconservative techniques (eg, epiglottectomy) for very limited suprahyoid lesions (Laccourreye et al, 1983). For supraglottic lesions limited to the supraglottis and preepiglottic space horizontal supraglottic laryngectomy is oncologically as sound as total laryngectomy (Fig. 104-13). Indeed, part of the tongue may be excised in an extended supraglottic laryngectomy for some T4 lesions (Bocca et al, 1987). Obviously, extensive supraglottic lesions with subglottic extension (ie, transglottic) usually require total laryngectomy, although near-total laryngectomy may be appropriate for some patients. Extensive posterior or lateral extralaryngeal spread requires laryngopharyngectomy, since these lesions behave as hypopharyngeal cancer does.

A traditional supraglottic laryngectomy can be performed only when the arytenoids and glottis are not involved. Since the glottis remains intact, voice is preserved. Aspiration is, however, a frequent result. Thus, pulmonary reserve must be adequate. If not, total laryngectomy is the necessary surgical treatment.

Cervical metastatic disease may be treated by radical or functional neck dissection. Elective (ie, for N0) neck dissection has been advocated by most authors (Bocca, 1975; Bryce, 1979; DeSanto et al, 1977b; Laccourreye et al, 1983), but its rationale has been challenged by others (Nadol, 1981; Shah and Tollefsen, 1974). The significant incidence of bilateral nodes argues for treatment of both sides of the neck, especially in the midline lesions.

Irradiation is effective for early lesions. The major limitations are spread beyond the larynx to the preepiglottic space or to the hypopharynx, neither of which does as well with irradiation therapy.

Survival statistics bear out the preceding observations. Early lesions (T1 and T2) do reasonably well with surgery or irradiation. For surgical treatment of T1 and T2 lesions most authors have demonstrated cure rates of approximately 70%. Vermund (1970) found that 73% (42 of 58) combined T1 and T2; Kirchner and Som (1971a) cited 68% for both supraglottic and total laryngectomy; Bocca (1975) 90% (105 of 132); Coates et al (1976) 68%; Bryce (1979) 70%; and DeSanto (1985) reported 85% survival in T1 and 82% in T2 tumors treated surgically. Moreover, most treatment failures occurred in the neck. This perhaps accounts for the improved statistics of Bocca, who routinely performed bilateral functional neck dissection. Coates et al (1976) and Bryce (1979) similarly demonstrated excellent control of primary tumors; most recurrences arose in the neck. Thus, surgical treatment is highly effective and

preserves the voice, but prophylactic treatment of the neck would seem to be indicated, especially in marginal lesions and those staged T2.

The cure rates of irradiation therapy for T1 and T2 lesions are similar to those of surgery. Vermund found that radiation was curative in 73% of patients (53 of 73) in his 1970 review. Wang (1983) noted cure of 75% of T1 and 50% of T2 lesions after irradiation. Surgical salvage improved these rates in 82% and 58%, respectively, and 67% overall. Bryce (1979)_ cited a 62% cure rate of irradiation with surgical salvage. Weems et al (1987) reported local control of 92% of T1 and 81% of T2 lesions. Surgical salvage improved these survival rates in 100% (13/13) and 89%. These rates were virtually identical to control rates of surgery alone. Most recurrences after irradiation alone occur at the primary site or in N2 or N3 necks. Surgical salvage is usually effective in this circumstance but frequently requires total laryngectomy, thereby resulting in loss of voice.

The treatment results of T3 and T4 tumors demonstrate better cure after surgery as compared with irradiation. Vermund (1970) found surgical cure in 59% (41 of 69) T3N0 and T4N0 tumors as compared with 25% (9 of 36) by irradiation. Kirchner and Owen (1977) showed that surgery cured 38% (6 of 16) T3 and T4 tumors, whereas irradiation cured only 5% (1 of 19); combined treatment was more effective in their series. In 1985 DeSanto reported 60% survival of T3-4 supraglottic cancer patients treated primarily with surgery. Weems et al (1987) found that irradiation produced a 48% control rate (versus 92% in surgery and postoperative radiotherapy); surgical salvage improved control to 66%. The regimen of radical irradiation with surgical salvage may be offered to appropriate patients, provided they can be followed closely and are willing to accept the possibility of increased surgical morbidity. Most irradiation failures occurred at the primary site, consistent with the previously described limitation of radiation. Bocca (1975) advocated supraglottic laryngectomy for many T3 tumors, especially those with preepiglottic space invasion and, to a more limited degree, base of tongue invasion. When tumor escapes inferiorly to the subglottis or to the hypopharynx, total laryngectomy must be performed.

Marginal supraglottic tumors carry a worse prognosis than the more common ventricular and infrahyoid epiglottic lesions. Laccourreye et al (1983) demonstrated better cure after surgery than after irradiation for these lesions.

In summary, early lesions may be reasonably well treated either by conservation surgery or by irradiation therapy. The potential for preepiglottic involvement argues in favor of surgery, but selected patients may undergo radical irradiation (including hyperfractionation) or combined chemotherapy-radiotherapy protocols with surgical salvage in reserve. Surgery or combined therapy appears to be the choice for more advanced lesions. With any treatment of the primary tumor, the high incidence of palpable and occult cervical metastasis argues for treatment of the neck.

Glottic tumors

The most important factor in glottic lesions is cord mobility. Other important factors are the presence of tumor at the anterior commissure or on the arytenoid. As with supraglottic primary tumors, understaging is frequent (29% according to Pillsbury and Kirchner, 1979) and usually occurs because of subglottic or paraglottic extension, often with associated cartilage

invasion.

Surgical treatment includes a number of options. Surgical therapy may include laser excision (Shapshay et al, 1990; Strong, 1975) for lesions on the cord. This should be performed with frozen section control to assure complete tumor excision. Transoral excision has been advocated by DeSanto (1982) for appropriate tumors; this permits treatment over a very short interval with good voice preservation. Larger lesions including some T3 lesions may be treated by laryngofissure and cordectomy or vertical hemilaryngectomy (Ogura and Whawley, 1980). These provide the opportunity for histopathologic "control" with preservation of glottic voice, albeit hoarse. Larger lesions may require total laryngectomy, although near-total laryngectomy may be suitable in selected patients.

Irradiation therapy is highly effective for cord lesions with limited invasion. Voice preservation has been reported to be superior with irradiation therapy and complications rare (Karim et al, 1983). For some patients with larger (ie, T3) tumors, irradiation may be voice-sparing. Moreover, surgical salvage may still be performed. The major limitation is the difficulty of treating deep invasion, which is often difficult to determine clinically. Follow-up evaluation is more difficult because of potential submucosal tumor. The approximately 6- to 7-week course of therapy may prove an inconvenience especially for patients who live far from the treatment center or those who may not be compliant with the rigorous treatment schedule.

Carcinoma in situ or intraepithelial carcinoma represents malignancy still limited to the mucosa by its basement membrane. It cannot be metastatic but, if untreated, has a significant likelihood (16%, Miller and Fisher, 1971) of subsequent invasion. Moreover, patients who have in situ carcinomas usually have regional premalignant changes (dysplasia), which may subsequently evolve into in situ or invasive carcinoma.

Both surgery and radiotherapy have proved to be effective treatments. Surgical treatment can usually be accomplished by mucosal stripping, either by conventional means or with the CO_2 laser (Vaughan, 1978). As such, voice preservation is good. More extensive disease may require cordectomy, either transorally or by laryngofissure (DeSanto et al, 1977a). When cordectomy is required, hoarseness ensues. This is especially true with bilateral disease when aspiration also becomes a risk. The other limitations of surgery are the requirement of rigorous follow-up observation, the risk of anterior web formation, and the need for good exposure of the larynx. Irradiation therapy allows treatment of the entire larynx, theoretically reducing the risk of subsequent malignant evolution of premalignant lesions. Voice preservation is excellent: 76% of patients not a normal voice (Pêne and Fletcher, 1976). The major limitations are the potential for radiation-induced malignancy and the difficulty of examination caused by laryngeal edema.

The results of surgical treatment have been excellent. DeSanto et al (1977a) reported 98% survival after surgical treatment. Miller and Fisher (1971) noted 25% initial failure after stripping alone, half of whom subsequently developed invasive carcinoma. Irradiation therapy in their study was effective initially in only 50%; in most of the initial failures invasion subsequently develioped. Pêne and Fletcher (1976) found that irradiation was curative in 87% of the small lesions and 74% of extensive lesions, all of which could be salvaged by subsequent surgery. Harwood et al (1980) found that none of their 47 patients had recurrence

in 5 years.

Thus, treatment results are excellent with any therapy. Ferlito et al (1981) polled 52 international laryngologists; one third used surgery to the exclusion of irradiation, one third used irradiation alone, one third used either modality. Most authors in the literature (Crissman et al, 1988; Espirity and Mathog, 1980; Ogura and Thawley, 1980; Wang, 1983) have suggested an individualized approach, advocating endoscopic removal for patients who are easily treated by this method and irradiation for uncooperative patients or those who have bilateral lesions. In either case, long-term close follow-up observation is mandatory for the significant possibility of recurrence or second malignancy.

T1 lesions do very well with surgery or irradiation with 5-year cure rates in the range of 80% to 95% with both forms of treatment. Irradiation therapy has produced 5-year relative cure rates of 80% (Skolnik et al, 1975); 86% (Vermund, 1970); 89% (Kaplan et al, 1984); 90% (Kirchner and Owen, 1977); 92% (Harwood et al, 1980); 95% (Wang, 1983); 96% (Menednhall et al, 1988); and 94% (Kelly et al, 1989). These rates generally include surgical salvage for irradiation failures, which accounted for approximately 5% to 10% of these cures. Failures occur more frequently in lesions that are on the posterior portion of the cord (Miller, 1975; Wang, 1983). Anterior commissure tumor cure rates are slightly lower after irradiation but not significantly different from surgical results by hemilaryngectomy or anterior commissure techniques (Sessions et al, 1975). Surgery for all T1 lesions has resulted in 5-year cure rates of 85% to 93% (85%, Vermund, 1970; 86%, Skolnik et al, 1975; 87%, Ogura et al, 1975; 92%, Kirchner and Owen, 1977; 93%, Neel et al, 1980; 93%, Daniilidis et al, 1990). The vast majority of these were treated by conservation techniques, with fair voice preservation. Posterior membranous cord lesions may be removed by conservation techniques, but involvement of the arytenoid indicates a worse prognosis and total laryngectomy may be necessary. Clinical experience with endoscopic CO_2 laser extirpation has shown excellent control rates: 96% (Ossoff et al, 1985); 95% (Hirano and Hirade, 1988); and 90% (Shapshay et al, 1990). These authors note that laser excision is most effective in small midcord lesions; it should be noted that such lesions do well with all forms of therapy and that voice results are good in most patients.

Cord mobility is important in determining outcome in T2 lesions. Although overall cure rates are generally 70% to 80%, distinguishing normal and impaired mobility is of considerable diagnostic value, especially in relation to irradiation therapy. This follows from the knowledge that impaired mobility implies deeper invasion and, thus, a poorer response to irradiation. Wang (1983) found cure rates of 92% when cord mobility was normal and 78% with impaired mobility. Harwood et al (1980) found similar results, 87% and 75%, as did van den Bogaert et al (1983), 85% and 72%; Kaplan et al (1984), 92% and 50%; Kelly et al (1989), 87% and 50%, respectively, Thus T2 lesions with normal cord mobility may be regarded like T1 tumors while those with impaired mobility behave more like T3 lesions. Surgical treatment has produced cure rate of 69% to 88%: 69% (Vermund, 1970), 72% (Skolnik et al, 1975), 75% (Ogura et al, 1975), 86% (Leroux-Robert, 1975), and 88% (Kirchner and Owen, 1977). Kaplan et al (1984) found little difference between cure rates of normal and impaired mobility after surgical treatment: 88% and 83%. Conservation surgery has traditionally been limited to those patients with subglottic extension less than 1 cm anteriorly and 3 to 4 mm posteriorly. Below this area lies the cricoid, which should not be partially resected; thus, total laryngectomy must be performed. Cure rates are equivalent for

conservation techniques and total laryngectomy.

Fixation of the vocal cord defines T3 lesions and, therefore, deep invasion. As a consequence, irradiation therapy is less effective. Cure rates have generally been in the range of 30% to 60%; 30% (Kaplan et al, 1984); 55% (Harwood et al, 1980; Vermund, 1970); and 57% (Wang, 1983). The use of twice-daily radiotherapy (hyperfractionation) has been reported by Parsons et al (1989) to produce 67% local control and 81% survival in a small group of patients with T3 glottic lesions. Interestingly, Harwood et al noted better survival rates among women than among men. These statistics include surgical salvage, which acounts for a substantial number. Salvage by total laryngectomy results in cure of two thirds of the patients in whom surgery is feasible (Poncet, 1975) but may be attended by considerable morbidity (DeSanto, 1984). Surgical treatment has been curative in 49% to 87% of patients: 49% (Skolnik et al, 1975); 56% (Leroux-Robert, 1975); 69% (Vermund, 1970); 73% (Ogura et al, 1975); 78% (Kaplan et al, 1984); 87% (Kirchner and Owen, 1977); and 76% (DeSanto, 1984). Hemilaryngectomy or extended laryngectomy may be used in selected patients, as Biller and Lawson (1986) have shown, producing 73% 2-year local control. Cervical metastasis is infrequent even in T3 glottic carcinoma. Thus, elective neck dissection would not appear to be indicated unless transglottic invasion is suspected. Treatment of palpable adenopathy obviously requires neck dissection or irradiation therapy.

Extralaryngeal spread of tumor defines T4 lesions. Irradiation therapy is generally reserved for palliative treatment, although cure rates of 14%, 20%, and 17% have been recorded (Kaplan et al, 1984; Meredith et al, 1987; Vermund, 1970). Surgical treatment has resulted in cure of 35% to 57%: 35% (Vermund, 1970), 54% (Jesse, 1975), 56% (Kaplan et al, 1984), and 57% (Ogura et al, 1975). Good surgical margins (greater than 2 mm pathologically normal) and appropriate management of the neck are critical for the best results. Combined therapy has been recommended by most authors for T4 lesions (Sisson and Hendrickson, 1976).

In summary, treatment of glottic lesions is most dependent on cord mobility. Early lesions (ie, T1 and T2 lesions with normal mobility) may be treated well by either modality, the choice depending on the particular patient and social circumstances. Bilateral cord lesions and better preservation of voice quality generally argue for irradiation; posterior cord lesions generally do less well with both techniques. More advanced lesions may be best treated by surgery, although circumstances may predicate combined therapy or irradiation therapy with surgical salvage, especially in women with T3 lesions who do reasonably well. Finally, far advanced disease may require either aggressive combined therapy or nonsurgical palliation.

Subglottic tumors

Subglottic tumors are rare. Moreover, they tend to present as advanced lesions, frequently with cervical adenopathy. Because of the proximity of subglottic lesions to the cricothyroid space and the cricoid cartilage, surgical treatment usually requires total laryngectomy, although hemilaryngectomy may occasionally be feasible (Sessions et al, 1975a). Surgery generally includes the soft tissues that may become involved, that is, the thyroid lobe and strap muscles. Curative irradiation may also be used, though the significant likelihood of cartilage invasion renders this more likely to fail. On the other hand, radiation portals usually include the superior mediastinm, a region less well treated by surgery (Wang,

1983).

Vermund in 1970 collated the results of 20 previous authors. He demonstrated cure (5-year survival) of 36% (46 of 122) of patients treated by irradiation and 42% (23 of 58) treated by surgery. Harrison (1971) and Kirchner and Owen (1977) have noted surgical cure rates of approximately 40%. Combined therapy as recommended by Shaha and Shah (1982) resulted in 70% cure of their 14 patients. Warde et al (1987) used irradiation therapy alone and found it highly effective for the 12 T1-3 lesions they treated. They achieved only 36% local control in the 11 patients with T4 tumors, however. Postoperative irradiation is likely to result in fewer complications than preoperative irradiation (Thawley, 1981) and probably represents the best sequence of treatment. This produces adequate surgical removal of tumor from cartilage and extralaryngeal soft tissue with the benefit of treatment of the paratracheal nodes by irradiation.

Stomal recurrence is not uncommon after treatment of subglottic primary lesions and glottic lesions with significant subglottic spread. This is especially true in patient who have required emergency preoperative tracheostomy for airway management (Keim et al, 1965). Postoperative irradiation may eradicate submucosal and lymphatic spread, which is a major contributor to this complication. Breneman et al (1988) reported that a 5-day course of preoperative irradiation is also effective. Alternatively, emergency laser debulking and biopsy may obviate the need for emergency tracheotomy.

In summary, subglottic primary tumors may be treated by irradiation alone or conservation surgical techniques for very limited tumors. Combination therapy is the most logical treatment for the more common advanced lesions since it treats the full extent of local disease, including extralaryngeal soft tissue and the paratracheal nodes.

Transglottic tumors

Transglottic cancer must involve at least the supraglottis and glottis. These tumors are usually advanced and have a high incidence of neck metastasis and extralaryngeal spread. As a consequence, treatment must generally be radical. Moreover, there is a high incidence of understaging. Pillsbury and Kirchner (1979) found that half of the 42 patients who had transglottic lesions were clinically understaged. This results from undetectable cartilage invasion or from the appearance of cord mobility in anterior transglottic lesions in which the more mobile posterior cord may demonstrate some movement (Kirchner et al, 1974). Nevertheless, some lesions may be superficial (Bryce, 1979), and conservation techniques may occasionally be used (Biller and Lawson, 1986).

Kirchner and Owen (1977) reported surgical care by total laryngectomy in 44% of all lesions, the vast majority of which were Y3. Mittal et al (1984) have described their experience with 152 transglottic lesions. Most of these lesions were T3 or T4, although 31% were T2. Tumors suitable for conservation surgery were mot common in T2 lesions (43% of the T2 lesions); 92% of these patients received irradiation therapy in addition. Most patients (64%) were treated by total laryngectomy and irradiation; 70% also underwent neck dissection. Finally, a small number were treated with irradiation alone. The cure rate with combined therapy was 55% (adjusted 5-year survival). Survival was better with small lesions (60%), especially those amenable to conservation techniques (67%). Irradiation therapy alone

resulted in only 8% 5-year survival. These data provide excellent guidelines. Transglottic lesions should be treated aggressively with combined therapy. Occasionally conservation techniques may be used, but patients must be chosen with care.

Advanced cancer and palliation

Extensive laryngeal cancer can usually be treated with reasonable expectation of cure in up to 50% of patients. The presence of distant metastasis, however, alters treatment plans. Generally, these patients may be offered chemotherapy or radiotherapy or, on some occasions, surgical removal of solitary metastases. As well, patients who have failed standard surgical and radiotherapeutic management may be improved or, occasionally, cured by chemotherapy. This has been reported by Ervin et al (1984) in stomal recurrence, extensive neck disease, and skin infiltration.

End stage or inoperable laryngeal disease may be amenable only to palliation. The goals of palliative treatment are to alleviate pain, allow for adequate airway and nutrition, and provide emotional and social support. The choice of modality - pharmacologic, radiologic, chemotherapeutic, surgical, or combination - depends primarily on the multipe patient factors described earlier (Evans, 1976).

Unusual Laryngeal Malignancies

Squamous cell carcinoma is by far the most common histopathologic diagnosis in laryngeal malignancy, accounting for 90% to 95% of all cases (Ferlito, 1976). Other malignancies do occur, althoug infrequently (Table 104-2). These may derive from all cell types present in the larynx: epithelium, melanocytes, neuroendocrine cells, mucous glands, supporting mesenchymal structures, and the lymphoreticular system. The behavior and treatment of these lesions are largely determined by cell type and tumor location.

Table 104-2. Frequency of laryngeal malignancy histologic types

Invasive squamous cell carcinoma	92.5%
Squamous cell variants	3.5
Squamous cell in situ	1.8
Verrucous squamous cell carcinoma	1.7
Lymphoepithelioma	-
Melanoma	-
Carcinosarcoma and other variants	0.8
Carcinoma of glandular origin	1.0
Well-differentiated neuroendocrine carcinoma	-
Moderately differentiated neuroendocrine carcinoma	0.03
Poorely differentiated neuroendocrine carcinoma	0.05
Adenocarcinoma	0.35
Clear cell/giant cell variants	-
Adenoid cystic	0.23
Mucoepidermoid	0.27
Adenosquamous	0.07
Acinic cell	-

Sarcomas of structural origin	0.3
Fibrosarcoma	0.10
Chondrosarcoma	0.10
Osteosarcoma	-
Synovial sarcoma	-
Rhabdomyosarcoma	0.03
Leiomyosarcoma	-
Liposarcoma	-
Vasculogenic sarcoma	-
Neurogenic sarcoma	-
Tumors of lymphocytic origin	0.6
Lymphoma	0.3
Plasmacytoma	-
Mycosis fungoides	-
Fibrous histiocytomas	0.2
Metastases to the larynx	-
Undifferentiated/unclassified	2.1

- Limited to isolated case reports of small number.&

Verrucous squamous cell carcinoma

Verrucous carcinoma accounts for 1% to 4% of the malignancies identified by various authors (see Table 104-2). Most verrucous lesions arise on the glottis or supraglottis (Fisher, 1975) and are found in cigarette-smoking men above 50 years of age (Batsakis et al, 1982).

The ontogeny of verrucous lesions lies in proliferation of suprabasal cells so that the basement membrane is apparently uninvaded. Thus, these lesions rarely produce deep invasion or metastasis but do spread along mucous membranes, "pushing" the basement membranes forward, and produce a warty exophytic mass, which may interfere with phonation and respiratory function. The gross appearance of a warty lesion arising from the glottis is virtually pathognomonic (Fig. 104-14). Pathologic evaluation necessitates a full-thickness biopsy so that the basement membrane may be identified and verrucous carcinoma distinguished frmo invasive squamous cell carcinoma. The histopathologic characteristics have been thoroughly discussed by Batsakis et al (1982), Ferlito (1985), Lundgren et al (1986), and Sllamniku et al (1989b).

Treatment of verrucous lesions is the subject of controversy. Surgical eradication by conservation techniques is often feasible, although total laryngectomy has been required in 6% to 30% of cases (Ryan et al, 1977; Biller et al, 1971; Ferlito and Recher, 1980). The collated recurrence rate after surgery was 6.8% (7 of 103); death occurred in 3.9% (4 of 103), according to Batsakis et al (1982). Thus, surgery is highly effective therapy, although rougly one quarter of patients require total laryngectomy.

Irradiation therapy has been challenged as ineffective and dangerous. Ferlito and Recher (1980) cited the experience of 13 authors: of 90 patients treated by irradiation, 64 had recurrence or persistence of the lesion. Moreover, many authors noted that verrucous lesions behaved in a far more malignant manner after irradiation, with an increased incidence of

cervical metastasis and anaplastic transformation. Nevertheless, some authors have reported good results with irradiation therapy (Lundgren et al, 1986; Schwade et al, 1976). The weight of evidence supports the contention that irradiation therapy is far less effective than surgery and incurs the risk of anaplastic transformation, although the latter may be overstated (Batsakis et al, 1982).

Other epithelial tumors

Lymphoepithelioma

Lymphoepithelioma is a rare tumor. Ferlito (1976) found only 1 among the 2052 malignancies seen at Padua. He cites two previous reports and only three more have been reported since (Stanley et al, 1985). These tumors arise at the laryngeal "tonsil" in the ventricle, where clusters of lymphocytes may be found. Accordingly, these tumors should act as transglottic tumors do. Four of the six lymphoepitheliomas described have shown rapid progression and wide dissemination. The fifth was cured by total laryngectomy with neck dissection and the sixth cured by irradiation therapy.

Melanoma

Malignant melanoma of the larynx has also been identified, although it is extremely rare. To date, 31 cases have been recorded (Hussain and Whitehead, 1989). Most patients have been elderly men and have exhibited hoarseness. Melanoma of the larynx usually arises in the supraglottic larynx and is usually pigmented (15 of 20) and polypoid. In spite of laryngectomy and/or irradiation, most patients (9 of 17) died of their disease and 4 of the remaining 8 had evidence of disease at the time of follow-up observation. The remaining 3 had follow-up study at 5, 17, 21, and 28 months. Since melanoma has a well-known tendency to recur late, these early follow-up results should not yet be regarded as cures. Thus, melanoma of the larynx, like other mucosal melanomas, has a bleak prognosis.

Pseudosarcomatous carcinoma

Pseudosarcomatous carcinoma (Fig. 104-15) is a puzzling and controversial malignancy that appears to result from simultaneous squamous cell epithelial malignancy and sarcomatous degeneration. Most authors (Batsakis et al, 1982; Ferlito, 1987; Hyams, 1975; Miller, 1975; Recher, 1985) have concurred that this tumor is principally an epidermoid malignancy with a pseudosarcomatous stroma or with an epithelial sarcoma. The existence of true biphasic epithelial and mesenchymal tumors was noted by Batsakis et al (1982) and Srinivasan and Talvalker (1979), but these are probably exceedingly rare. Notwithstanding, these tumors carry a poor prognosis. Irradiation therapy is generally of no avail. Surgical resection has accounted for some long-term survivors, especially in polypoid glottic tumors. These tumors have an aggressive histopathologic appearance; their behavior mirrors that appearance. Treatment should be appropriately radical.

Other squamous cell variants have been recognized, including those with papillary, basaloid, and adenoid features (Luna et al, 1990). The implications of these distinctions are still being investigated.

Adenocarcinoma

Adenocarcinoma arises from glandular structures of the larynx. The two major types are those that arise from neuroendocrine Kulchitsky cells, formerly called carcinoid and small cell (oat cell) carcinomas, and those that arise from minor salivary glands, namely adenocarcinmoa and adenoid cystic, acinic cell, mucoepidermoid, adenosquamous, and anaplastic (giant cell) carcinoma. Altogether these account for less than 1% of all laryngeal malignancies (Ferlito, 1976; Spiro et al, 1976).

Neuroendocrine tumors

The nomenclature of neuroendocrine (NEC) tumors, formerly carcinoid, atypical carcinoid, and small cell cancer, is not universally adopted as yet. They are thought to arise from Kulchitsky cells and their relation to the disseminated amine precursor, uptake, and decarboxylation (APUD) system is unclear. Well-differentiated NEC (carcinoid tumors) represents low-grade malignancy that has not been shown to be metastatic. Poorly differentiated NEC (small cell or oat cell cancer) represents a more aggressive lesion (Paladugu et al, 1982). The moderately differentiated NEC (atypical carcinoid) is characterized by malignant potential of intermediate magnitude. The histopathologic description of these tumors has been amplified by Ferlito and Friedmann (1989) and Wenig and Gnepp (1989). All are characterized by the electron microscopic finding of neurosecretory granules.

Well-differentiated neuroendocrine carcinoma is quite rare. Ferlito and Friedman (1989) could document only eight cases, noting that most of the "carcinoid tumors" in the literature would be reclassified instead as moderately differentiated NEC, that is, atypical carcinoids. Immunocytologic studies demonstrate 5-hydroxyindoleacetic acid (5-HIAA) in the plentiful secretory granules; hormonal secretion (carcinoid syndrome) is rare, however. The clinical course is generally benign and the recommended therapy is surgical excision.

Moderately differentiated tumors have been documented in 69 patients in the review of Ferlito and Friedman (1989) and in 54 patients reported by Wenig and Gnepp (1989), probably with some overlap. This tumor behaves more aggressively than its well-differentiated counterpart. Metastasis was found in 70% at the time of diagnosis, principally to the cervical nodes. Surgical excision, often with neck dissection, is the recommended treatment. Disease-free survival after surgical treatment was reported in 33% and 52% of patients (Ferlito and Friedmann, 1989; and Wenig and Gnepp, 1989, respectively).

Poorly differentiated neuroendocrine carcinoma portends a bleak prognosis. Since the first report of oat cell cancer of the larynx by Olofsson and van Nostrand in 1972, numerous reports have appeared, totaling approximately 120 patients. Baugh et al (1986) noted that metastasis is frequent (67%) and that the result of treatment is poor. Long-term survival has been reported in only 20% to 25% of patients (Baugh et al, 1986; Ferlito, 1986; Wenig and Gnepp, 1989). Consonant with the treatment protocols for small cell cancer of other sites, the best results are obtained by combination therapy (irradiation and chemotherapy, plus surgery in selected patients), especially in the few patients who have localized disease.

Salivary gland tumors

Malignancy arising from the minor salivary glands accounts for 100 (1.0%) of the 13.142 laryngeal cancers collated by Batsakis et al (1980) with the addition of the patients reported by Cohen et al in 1985. Since these malignancies arise from minor salivary glands, they usually are found in the subglottis or supraglottis, especially the aryepiglottic fold. Moreover, their clinical behavior is similar to that of cancers of other minor salivary glands.

Of the 100 mucous gland malignancies encountered in the five large studies collated by Batsakis et al (1980) and Cohen et al (1985), 47 were classified as adenocarcinoma and its variants. Adenocarcinomas are usually large, bulky lesions and usually arise from the supraglottis, although they may be transglottic at the time of presentation. Most patients are men above the age of 60 (Fechner, 1975). Nearly all of the patients have cervical metastasis at the time of presentation and most of the remainder subsequently develop adenopathy. Although the presence of adenocarcinoma in situ has been documented (Ferlito, 1976), most tumors are locally advanced. The outlook is dismal. In general, these tumors are considered to be radioresistant. Spiro et al (1976) described the outcome of 12 patients treated for adenocarcinoma. They noted only one survivor. The recommended treatment is aggressive surgical management. As well, one other patient treated by conservation surgery has been reported alive and well after 2.5 years (Bloom et al, 1987).

Giant cell and clear cell carcinoma are variants of adenocarcinoma, which are exceedingly rare. Ferlito (1976) described the only patients with giant cell adenocarcinoma. Clear cell carcinoma has been reported in five patients. All were supraglottic; four of these demonstrated cervical metastasis on presentation, all of whom died. Pesavento et al (1980) suggested that this tumor is a variant of adenocarcinoma similar to clear cell carcinoma of the lung. Seo et al (1980) hypothesized that this form is related to mucoepidermoid carcinoma, as documented histopathologically. Both clear cell and giant cell tumors are very rare and the prognosis is dismal. Three cases of carcinoma ex pleomorphic adenoma of the larynx have been described (Milford et al, 1989). Surprisingly, results of surgical treatment have been excellent.

Adenoid cystic carcinoma was found in 29 of the 100 mucous gland carcinomas. Batsakis et al (1980) noted that two thirds of these tumors were subglottic. There is a slight female predominance. The clinical behavior mimics adenoid cystic cancers elsewhere with early perineural spread (Tewfik et al, 1983) and long-term persistance of tumor (Sessions et al, 1975). Cervical metastasis is rare, occurring in 10% to 15% of cases (Tewfik et al, 1983). Most authors have recommended wide local excision (total laryngectomy) with neck dissection for palpable nodes followed by irradiation therapy. The treatment results have been disappointing, in part because of the tendency of this malignancy to persist or recur many years after treatment.

Mucoepidermoid tumors follow a clinical course determined principally by the grade of the tumor. They are identified by the presence of mucous, squamous, and intermediate cell elements. Histologic grade depends on the morphologic characteristics and predominance of the cell types (Ferlito, 1976). Most tumors are supraglottic and have occurred predominantly in men to daye (Cumberworth et al, 1989). Low-grade mucoepidermoid tumors respond well to therapy; most patients are cured. On the other hand, high-grade lesions have an ominous

prognosis. Treatment is usually effected by total laryngectomy; irradiation may be used adjunctively for high-grade lesions. Damiani et al (1981) reported that all of their patients who had low-grade malignancy were free of disease at 1 to 15 years. Of the three patients with high-grade malignancy, one was cured, one died of metastatic disease, and the third died of the disease. Thus, prognosis is closely linked to histopathologic features.

Adenosquamous tumors are similar to and occasionally indistinguishable from high-grade mucoepidermoid lesions (Damiani et al, 1981). They appear to be made up of adenocarcinomatous and epidermoid elements; indeed, some pathologists regard these tumors as variants of squamous cancer (Batsakis and Huser, 1990). Because of their aggressive nature, treatment should probably include irradiation and surgery. Damiani et al (1981) reoprted their experience with nine patients who had adenosquamous carcinoma. Three of the five patients who were disease-free at follow-up observation had been treated by surgery, one by irradiation, and one by combined treatment. Thus, adenosquamous lesions should be treated aggressively, similarly to squamous cell lesions of comparable size and located.

Acinic cell carcinoma is exceedingly rare: five cases have been reported to date. These tumors evidently arise frmo the serous cells of the duct acini and should be treated by wide-field excision with irradiation in reserve (Reibel et al, 1981), by analogy with the treatment of other acinic cell lesions.

Mucous gland cancers of the larynx are rare but highly lethal. Only tumors classified as low-grade mucoepidermoid carry a good prognosis. Treatment should generally include wide-field surgery; irradiation is useful in most lesions.

Tumors arising from structural elements of the larynx

Malignancy may arise from any structural element of the larynx. These tumors are quite rare, and for the most part, prognosis depends on the type and grade of the tumor. Collecting the incidence information from Yugoslavia (Krajina, 1975), Padua (Ferlito, 1976), Mayo Clinic (Gorenstein et al, 1980), Turkey (Hacihanefiogly and Öztürk, 1983), Thomas Jefferson University Hospital (Gadomski et al, 1986), and Royal Marsden Hospital, London (Hamlyn et al, 1986), supporting tissue sarcomas accounted for 57 of 18.241 malignancies (0.3%). The most common sarcoma type is chondrosarcoma, followed by fibrosarcoma. Osteosarcoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, and angiosarcoma have all been reported, as have synovial sarcomas, a malignant mesenchynoma, Kaposi's sarcoma, and malignant neurogenic tumors. Experience with most of these lesions is limited to isolated case reports, and treatment is based primarily on experience with sarcomas in other sites.

Fibrosarcomas (Fig. 104-16) evidently arise from the fibroblasts of the laryngeal support structure (Gorenstein et al, 1980). Ferlito (1990) has noted, however, that cure should be taken in this histopathologic diagnosis and that immunocytologic studies are imperative. These tumors arise most frequently from the anterior vocal cords and anterior commissure region and grow as polypoid masses (Batsakis et al, 1982). Well differentiated lesions tend to grow slowly but have a high rate of local recurrence (40%); poorly differentiated lesions tend to metastasize early. Accordingly, 5-year survival rates of 50% and 5% have been reported for well- and poorly differentiated lesions (Gorenstein et al, 1980). Wide-field excision is recommended as primary therapy; the role of irradiation therapy is as yet poorly

defined.

Chondrosarcomas (Fig. 104-17) originate most frequently from the cricoid cartilage (75%); thyroid cartilage is occasionally involved and the arytenoids only rarely (Batsakis, 1979; Nicolai et al, 1990). Since they usually arise subglottically, they usually manifest airway obstruction (Gorenstein, 1980). The pathologic criteria have been described by Hyams and Rabuzzi (1970). Most chondrosarcomas are well differentiated and behave more like benign neoplasms. Poorly differentiated lesions are rare but may produce early distant metastasis and tend to recur quickly if inadequately excised. Dedifferentiated chondrosarcomas have also been diagnosed (Nicolai et al, 1990). Their anaplastic appearance is in accord with their aggressive malignant behavior. Treatment is based on adequate but conservative surgical resection. Since most tumors arise from the cricoid, total laryngectomy is often required. Irradiation therapy is of little value.

Osteosarcoma has been described in 10 patients (Pinsolle et al, 1990; van Laer et al, 1989) and by Gorenstein et al (1980). These tumors are highly malignant; in spite of wide-field resection, 8 of 10 patients died of pulmonary metastases within 2 years. The other 2 were alive and had demonstrated recurrence. Management should consist of wide-field resection and, perhaps, chemotherapy or irradiation. Chemotherapy in particular has proved beneficial in osteosarcoma of other sites.

Synovial sarcoma of the larynx has been identified in five patients (Ferlito et al, 1983; Pruszczynski et al, 1989). Surgical extirpation was curative in three of the four patients for whom follow-up observation was available. Kawashima et al (1990) reported the only case of malignant mesenchymoma. This tumor must have at least two distinct sarcomatous elements of soft tissue origin in addition to a base of fibrosarcoma.

Liposarcoma of the larynx is also exceedingly rare. A total of 20 cases can be collated (Gertner et al, 1988; Narula and Jefferis, 1985; Wenig et al, 1990). Most occur in men and typically arise in the supraglottic larynx. Batsakis et al (1980) noted that prognosis of all head and neck liposarcomas depends on histopathologic subtype: well-differentiated tumors have a 53% recurrence rate, followed by myoid, pleomorphic, and round cell lesions, which have a 85% recurrence rate. Wenig et al (1990) recommended adequate surgical excision for these tumors, with irradiation therapy decided on an individual basis.

Rhabdomyosarcoma is the most common soft tissue sarcoma of the head and neck, especially in children (Batsakis et al, 1980). Laryngeal rhabdomyosarcoma has been reported in a newborn (Abramowsky and Wilt, 1983) and in adults. The most common cell subtype is embryonal, although pleomorphic, alveolar, and botryoid rhabdomyosarcoma have also been reported (Diehn et al, 1984; Dodd-o et al, 1987). Treatment has usually included surgical resection. Because these tumors are radiosensitive and susceptible to chemotherapy, individualized combined therapy may be pursued. Results of treatment show that 58% (14 of 24) of patients became disease-free; the best results are those after adequate surgery (4 of 7) and combined modality protocols (5 of 9).

Leiomyosarcoma arises from smooth muscle. Friedmann (1975) has included these tumors in his review of laryngeal sarcomas and was able to find three documented tumors. Treatment is primarily surgical.

Sarcoma may rise from vascular tissue. Angiosarcoma of the larynx has been reported in 20 patients (McRae et al, 1990). It bears a poor prognosis; surgery and adjunctive radiotherapy are recommended. Hemangiopericytomas differ from angiosarcomas in that they arise perivascularly rather than intravascularly. Ten cases have been reported to date (Bradley et al, 1989). Surgery is the recommended treatment; results have been acceptable, although follow-up observation is inadequate in most reports. Kaposi's sarcoma of the larynx has also been described (Coyas et al, 1983). This last lesion was treated by irradiation alone, in keeping with the efficacy of this treatment in other sites.

Neurogenic malignancy may be theoretically divided into neurofibrosarcoma and malignant schwannoma. Stanley et al (1987) reported one case of neurofibrosarcoma. This patient died with extensive regional and distant metastasis. The single case of malignant schwannoma was reported by DeLozier in 1982. Surgical treatment, perhaps followed by irradiation, is the recommended therapy.

Malignant paragangliomas of the larynx have been alluded to but Batsakis (1979) did not find any case that was adequately documented as malignant. Marks and Brookes (1983) have subsequently demonstrated one case and discussed the controvery about malignancy.

Tumors arising from lymphoreticular tissue

Malignancies may arise from the lymphoreticular tissue of the larynx. These include non-Hodgkin's lymphoma, mycosis fungoides, plasmacytomas, and malignant histocytomas. Treatment of these malignancies is based on the treatment regimens for other sites.

Non-Hodgkin's lymphoma occurs in extranodal sites in 25% of cases. Lymphoma limited to the larynx has been documented in 83 cases, as reported by Diebold et al (1990). Local irradiation is the main treatment modality, although partial or total laryngectomy has occasionally been required. All patients have achieved excellent local control by these means.

Mycosis fungoides is a T-cell neoplasm that usually presents with cutaneous lesions. Mucosal involvement generally occurs in its terminal phase. Ferlito and Rechner (1986) described a total of three patients in whom mycosis fungoides was demonstrated in the laryngeal mucosa. Local control was achieved with irradiation in one patient, but she developed widespread cutaneous mycosis fungoides, which led to her death.

Plasmacytoma is a B-cell lymphocyte malignancy whose usual expression is multiple myeloma. Extramedullary plasmacytoma usually occurs (90%) in the head and neck, including the larynx. Gormley et al (1985) related that about 300 cases of laryngeal plasmacytoma had been reported. These tumors occur most frequently in the epiglotis and other supraglottic sites. Localized lesions are best treated by local excision followed by irradiation therapy. Widespread disease, including myeloma, is best treated by irradiation and chemotherapy.

Malignant fibrous histiocytoma is a tumor that arises from tissue histocytes of the larynx. Sixteen such malignancies have been described (Ferlito et al, 1983); an additional 8 isolated case reports have also discussed this unusual tumor. These tend to occur in elderly men. It was noted to be an aggressive tumor with potential for different morphologic patterns. Nervetheless, long-term control has been achieved in 22 of 23 patients for whom follow-up

information is available, usually after wide-field surgical excision. This appears to be the treatment of choice, with irradiation and chemotherapy held in reserve.

Metastases to the larynx

Metastatic disease to the larynx is rarely diagnosed during life. Ferlito et al (1988) were able to identify 120 cases of metastasis to the larynx. Most primary tumors were melanomas or renal carcinomas; both spread frequently by hematogenous routes. Tumors of the breast, lung, prostate, gut, and reproductive organs have also been reported. The prognosis in these patients is usually dismal, in that laryngeal metastases rarely occur without widespread disease elsewhere.