PATHWAYS OF INVASION IN LARYNGEAL CANCER: THE CONCEPT BEHIND THE STRATEGY OF SURGICAL MANAGEMENT

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ABSTRACT
Understanding the behaviour of laryngeal cancer is essential to define rational treatment strategy. Cancer of the larynx follows well-defined pathways of invasion, acquaintance of which is pertinent to the understanding of surgical treatment strategies. All surgical techniques, whether total or partial laryngectomy, are based on the knowledge of intrinsic barriers to spread of cancer.

KEYWORDS: Laryngeal cancer, pathways of invasion, invasion of laryngeal framework, barriers to spread of laryngeal cancer, surgical management of laryngeal cancer.

INTRODUCTION
Understanding the behaviour of laryngeal cancer is essential to define rational treatment strategy. Numerous efforts have been made to understand regional variation in tumour behaviour. One of the earliest approach was to explain the embryologic basis for patterns of spread in cancer of the larynx. It was observed from fetal studies that the supraglottis develops primarily from the third and fourth pharyngeal arches (the buccopharyngeal anlage), while the glottis and subglottis from the fifth and sixth arches (the tracheopulmonary anlage), which fused in development at the laryngeal ventricle. The lymphatic system, which may develop from a condensation of mesenchymal clefts or a secondary outgrowth of the venous system, grows separately with each anlage. This fact underlies the mysterious differences in metastatic pattern of supraglottic and glottic carcinomas, thus laying foundation pillars for the practice and philosophy of supraglottic laryngectomy. On the other hand, the formation of glottis takes place through the fusion of two lateral and one anterior midline cell masses which migrate and fuse. This may explain the limitation of spread within the glottis. There appear to be embryologically distinct portions of the larynx which fuse in the development. Tumours appear to respect these boundaries of embryological fusion lines, exhibiting no spread from one embryological zone to the other. [1,2]

Another enigma related to pathways of invasion in laryngeal cancer is the framework of laryngeal cartilages and membranes which may inhibit the growth of tumours. The laryngeal cartilage does act as a barrier to tumour invasion, but may occasionally be invaded. Kirchner[3] found that the cartilage was invaded in one half of pyriform sinus carcinomas and 15 of 19 transglottic carcinomas. The invasion of cartilage was found to be in areas of ossification in most of these cases. Micheau et al[4] reported that in 94% of the cases, cartilage invasion was related to areas of bony metaplasia with partial or total ossification. In the supraglottis however, the epiglottic cartilage appears to offer little resistance to tumour invasion. Micheau observed that tumour may spread through the cribriform areas in the cartilage, disinsert or actually destroy the cartilage.

The various membranes of the larynx also seem to offer some resistance to tumour spread. Micheau et al[4] did not find any spread of supraglottic tumours above the thyroepiglottic ligament, although the tumour frequently destroyed the thyroepiglottic ligament, penetrating the pre-epiglottic space. In the glottis, small tumours were often well contained, yet 78% of the large tumours exhibited destruction of the conus elasticus.

Successful resection of laryngeal cancer by partial or total laryngectomy depends primarily on precise knowledge of the tumour’s location before the first incision is made into the soft tissue or into the laryngeal framework. Although the computerized tomography (CT) scan can provide information on the deep invasion of laryngeal soft tissues in many cases, the technique is not entirely reliable for identifying invasion of the thyroid and cricoid cartilages because of the many unpredictable variations in ossification patterns within the laryngeal framework.[5]
Though there are many modifications and extensions of the two basic types of partial laryngectomy (vertical and horizontal), they all share two common principles of resection of the tumour – (1) incision of the laryngeal soft tissues, (2) incision through the framework of thyroid and cricoid cartilages. It is for this reason, that the surgeon must know answers to two important questions. Firstly, how likely cancer is to have spread under an intact mucosal surface. Secondly, to what extent the laryngeal framework is invaded by cancer.

It is pertinent to organize further discussion in relation to specific anatomical areas of the larynx, so as to develop an understanding of the treatment modalities as pertains to different primary tumour sites.

**GLOTTIC CANCER**

The T1 and T2 lesions of the true cord present no real problem in treatment. Most advanced laryngeal cancers may be treated by total laryngectomy. Small lesions associated with a fixed vocal cord, i.e., those that do not extend below the level of inferior edge of thyroid ala or 1 cm below the level of glottis, can occasionally be removed by hemilaryngectomy. In such cases, the most frequent site of local recurrence is subglottic, along the inferior margin of resection. An ominous sign is the bulge sometimes seen on tomography in the subglottic area. This usually represents spread of cancer under the conus elasticus, with cancer tending to escape the larynx through the cricothyroid membrane. It is this type of lesion that has produced most of the recurrences after hemilaryngectomy.

Invasion of the thyroid ala nearly always begins in the ossified portion, i.e., its lower edge. It is only in the later stages of invasion that the unossified parts of the laryngeal framework are attacked and destroyed. For this reason, CT scans should be examined with particular care along the upper edge of the cricoid. Areas of questionable invasion more cephalad in the laryngeal framework probably represent random variations in the ossification pattern, if the lower edge of the thyroid cartilage is intact.

**ANTERIOR COMMISSURE**

The dense homogenous connective tissue at the level of upper surface of vocal cords at their anterior attachment to thyroid cartilage acts as a barrier to the deep invasion of cancer at this point. Cancer that remains confined to the level of the glottis at the anterior commissure does not invade the laryngeal framework. This group includes mainly T1b glottic lesions.

On the other hand, the most destructive type of lesion at the anterior commissure is the one that shows grossly identifiable tumour extending upwards onto the base of epiglottis. These lesions are usually ulcerative and exhibit tendency to invade the laryngeal framework.

**SUPRAGLOTTIC CANCER**

Two initial remarks are necessary to introduce the discussion of supraglottic laryngectomy for cancer. The first concerns the embryology of the larynx. The supraglottic or vestibular portion of the larynx, which includes the epiglottis and the ventricular bands (Fig. 1) develops from the buccopharyngeal anlage, whereas the glottic and subglottic portions develop from the tracheobronchial anlage. This is enough to understand why the larynx virtually consists of two hemilarynges, each of them with its own different derivation and with its largely independent lymphatic circulation. This means that each of these hemilarynges may become invaded by cancer independent of one another, and that the extension of cancer is limited within the boundaries of embryological demarcation.

As a consequence, supraglottic cancer shows no tendency to become a glottis cancer and glottic cancer never shows a tendency to invade the supraglottic stage. Exception to this rule may be rarely observed. As a matter of fact, cancer invading both areas at one time is most often regarded as transglottic or primary plurifocal in origin.

The second remark concerns the direct observation which Bocca made (and which was repeatedly made afterwards) from 160 larynges totally removed for supraglottic malignancies. Even in the most advanced stages of evolution, primary vestibular growths never invaded the floor of the ventricle or the vocal cords. Extension always took place in an upward direction, towards the free margin of the epiglottis or the aryepiglottic folds; much more frequently it took place towards the pre-epiglottic space. In all cases, the embryological barrier running horizontally through the ventricles firmly withstood the neoplastic invasion (Fig. 2). Since that time, supraglottic cancer was defined as an ascending cancer.

It is worth noting that recurrences in operated cases most often observed in the base of tongue, or lateral pharyngeal walls, only on the side where surgical excision had been more generous, thus demonstrating further that a wide margin of healthy tissue is no valid obstacle to the spread of the tumour, in the absence of preformed barriers. It cannot be overemphasized that the discussion of the validity of supraglottic laryngectomy in vestibular cancer is always concerned with the lower limit and never with the upper limit. That was the reason why opponents of this technique are prone to admit that supraglottic laryngectomy may be used for high-situated or marginal growths which may also spread to the lingual aspect of the epiglottis. It can be pointed out that even though total sacrifice of the larynx is unjustified in these cases, the indication for supraglottic surgery is much poorer. Sometimes, indeed, there seems to be no indication at all. Here, the pathological, prognostic and therapeutic problem is altogether different and much closer to the problem of pharyngeal and hypopharyngeal...
growths. These tumours do not spread within the vestibule, but outside of it, to the base of the tongue and lateral pharyngeal and hypopharyngeal walls. In spite of extensive surgery, they escape all valid criterion for radical surgery as was proven by former investigations. In the series of Bocca et al. in several cases of vestibular cancer operated by supraglottic laryngectomy, they observed lingual or pharyngeal recurrences, while a supra commissural recurrence occurred only once. Incidentally, this was a case of a circumscribed lesion of the laryngeal aspect of epiglottis reaching one-half inch above the level of the anterior commissure, where the surgical excision did not follow exactly the anatomical limits of the vestibule.

As a consequence, Bocca et al. state that the main indication to perform supraglottic laryngectomy concerns primary vestibular growths lying in the lower portion of the laryngeal aspect of epiglottis and in ventricular bands. The higher they extend towards the margin and the aryepiglottic folds, the poorer is the indication. Both arytenoids must be mobile. Vestibular cancer is not observed to spread posteriorly. Bocca et al. found no recurrence in the arytenoid region, even when the growth extended posteriorly very near to arytenoid cartilage. However, in rare instances, the sacrifice of one of the arytenoids may be indicated.

Special mention needs to be made of the problem of pre-epiglottic space. The pre-epiglottic space in supraglottic cancer has been the object of repeated investigations. The following observations were made in the various studies.

(a) The spread of the tumour takes place by direct tissue infiltration or by lymph vessel embolization. Although many vascular hiatuses are found at the base of the epiglottis through which small ducts connect the lymphatic net of the pre-epiglottic space with the lymph vessels of the anterior commissural region, generally the tumour invades the pre-epiglottic space by direct extension, surrounding or less frequently perforating the lowest part of the epiglottic cartilage.

(b) It is difficult to ascertain whether the histology of the tumour may affect the frequency of invasion of the pre-epiglottic space because squamous cell carcinomas are found in 83% of Bocca’s cases. However, in undifferentiated carcinoma, infiltration of the pre-epiglottic space was observed in 100% of cases.

(c) On the whole, serial sections of pre-epiglottic space revealed a tumour involvement in 55% of Bocca’s cases. This percentage may be considered remarkably high when one considers the fact that most of the tumours in Bocca’s series had a limited extension. It must be emphasized that supraglottic surgery should always include radical excision of the pre-epiglottic space.

A large lesion limited to the ventricular band is often overtreated at surgery, mainly because the lower edge is difficult to identify, creating the impression that the growth has crossed the ventricle and become transglottic. This is particularly true when the true cord cannot be seen by direct or indirect laryngoscopy. In such instances, the preoperative examination fails to expose the true vocal cord so that the lesion may be incorrectly treated by total laryngectomy, when all that is required is a horizontal supraglottic laryngectomy.

**Histologic studies of supraglottic cancer by Kirchner** indicate the following

(a) As long as inspection reveals that the ventricular recess is free of gross tumour, the microscopic margin of resection is secure when horizontal supraglottic laryngectomy is performed.

(b) Supraglottic cancer does not invade the thyroid cartilage in most of instances. Thus, the conventional cut made in the thyroid ala is oncologically sound. Resection of the hyoid bone is rarely necessary even with pre-epiglottic space invasion. The preservation of hyoid provides a secure means of anchoring the laryngeal remnant to the base of tongue and facilitates post-operative deglutition. In most horizontal supraglottic laryngectomies, the pre-epiglottic tissue can safely be separated from the hyoid bone as the tumour is being removed.

Invasion of the thyroid ala was not observed in any of the 63 cases of supraglottic cancers reported by Kirchner.

**TRANSGLOTTIC CANCER**

Two hidden pitfalls await the surgeon who attempts to resect a T3 transglottic cancer by partial laryngectomy. Firstly, the cancer would have extended through the thyroid and cricoid cartilages in over 75% of lesions whose surface presentation measures 3 cm or more. Secondly the cancer may infiltrate the ossified portion of the thyroid cartilage beyond the limit of visible tumour. In some cases, the laryngeal framework is invaded under intact mucosa and un-involved soft tissues on the side of the larynx opposite the visible lesion. This type of infiltration within the cancellous substance of the ossified thyroid ala and cricoid ring supports the concept advanced by Yeager and Archer that it is the perichondrium rather than cartilage or bone that acts as the primary barrier. Once the cancer infiltrates the ossified portions of the laryngeal framework, it continues to advance under an intact perichondrium.

The most important question that arises is whether there is any method of anticipating this type of infiltration preoperatively, either by surface presentation, degree of cellular differentiation on biopsy, anatomic location or by CT scan. Computerized tomographic scanning might reveal infiltration in case of large tumours but it is with the smaller lesions for which partial laryngectomy is being considered that the surgeon needs this type of
information before operating. Since ossification patterns are not completely symmetrical on the two sides of the larynx, CT scanning would not be completely reliable in detecting small areas of infiltration between the inner and outer layers of perichondrium.

Surface appearance of the lesion does not seem to be a reliable index. Exophytic and ulcerative lesions show equal predominance. The anatomic location of the lesion is probably the best indicator of extensive invasion within the framework. In the series reported by Kirchner, most of the lesions crossed the anterior commissure in a vertical direction, so that cancer was grossly detectable above and below the level of glottis in the anterior larynx. The other specimens showed significant (more than 1 cm) subglottic tumour identifiable preoperatively by inspection or radiography.

**PYRIFORM SINUS**

Partial laryngectomy should not be attempted for cancer involving the apex of the pyriform sinus. Invasion of the posterior and inferior edges of the thyroid cartilage and upper edge of cricoid occurs in over half of such cases, thus precluding a safe cut into the thyroid ala.

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**Fig. 1.**—The two portions of the larynx, of different embryologic derivation, are separated by the horizontal line. The upper one is the vestibular or supraglottic portion of the larynx. The oblique line divides the inferior from the superior part of the vestibule which includes the free portion of the epiglottis and the aryepiglottic folds. Cancers arising in this part (C) must be considered clinically as marginal cancers, and generally beyond the limits of supraglottic surgery.

**Fig. 2.**—Arrows and figures show modalities of invasion of supraglottic cancer and their respective frequency. Extension upwards is most dangerous, but only present for tumors originating in, or spreading to, B. It represents the most frequent cause of local recurrence in the pharynx or tongue, both in total and in supraglottic laryngectomy.
CONFLICT OF INTERESTS

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