CONTEMPORARY MANAGEMENT OF ADVANCED LARYNGEAL CANCER:
SURGICAL TREATMENT MODALITIES AND POSTOPERATIVE QUALITY OF LIFE

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ABSTRACT
The aim of the present review is to outline the indications for surgical treatment of advanced laryngeal cancer in the contemporary clinical scenario and highlight the implications towards postoperative quality of life.

KEYWORDS: advanced laryngeal cancer, surgical management of T3-T4 laryngeal cancer.

INTRODUCTION
Laryngeal cancer is one of the most common head and neck cancer. Majority of these cancers are squamous cell carcinomas. Major risk factors include smoking and alcohol consumption. Other risk factors may be stated as asbestos exposure, industrial pollution, history of laryngeal cancer in a first-degree relative and inadequate intake of antioxidant micronutrients found in fresh fruits and vegetables. Males are more commonly affected, with most patients aged over 40 years. More recent studies show changing trends, with decreasing number of cases affecting males, while a stable or increasing number of cases involving females. These changes in epidemiology are related to changes in smoking patterns.

ADVANCED LARYNGEAL CANCER
As per UICC/AJCC staging, the term advanced laryngeal cancer denotes stage III or IV cancers. Cancers of the larynx may attain this advanced stage by virtue of advanced T classification (T3 or T4), N classification (N1, N2 or M classification (M1)). For the purpose of simplicity, the following discussion would refer to advanced laryngeal cancer in the sense of T3,4 cancers. The cancers of larynx attain T3 classification if they exhibit vocal cord fixation, invasion of paraglottic space, pre-epiglottic space invasion, extension to postcricoid area or minor thyroid cartilage erosion. T4 classification refers to tumours with cartilage destruction or extralaryngeal invasion.

Accurate staging of laryngeal cancers is associated with the problem of subjectivity, in relation to defining criteria for T1 classification. Thus, vocal cord fixation is an important criterion for classifying a cancer as T3 and when present, is accepted to have a significant adverse impact on probability of control with non-surgical treatment. However, the presence of vocal immobility may be difficult to evaluate in the presence of a bulky tumour precluding adequate visibility. Apart from that, it may be difficult to differentiate between reduced movement (T3a) and vocal fixation (T3b). Other criteria for T3 staging also entail a certain level of subjectivity depending on the type and quality of imaging performed and subsequent radiological interpretation. For instance, minor erosion of inner lamina of thyroid cartilage is difficult to diagnose with a high level of accuracy, yet the positivity of this finding may upstage a small glottic cancer from T1 to T3. On a different note, T3 tumours may include bulky lesions apposed along the entire inner lamina of thyroid cartilage, with many areas suspicious for erosion but without any definite areas of gross cartilage destruction, which would upstage the tumour to T4. In a similar sense, involvement of paraglottic or pre-epiglottic space may include a spectrum of cases. On one end are the cases with very early involvement of these spaces diagnosed on the basis of subtle and possibly subjective radiological appearances, which is easily amenable to transoral laser resection. On the other end are cases of extensive and bulky involvement, which is not amenable to any form of conservation laryngeal surgery and presenting with decreased chances of local control with non-surgical treatment.

Glottic cancers usually reach an advanced stage after involvement of the ventricle, with subsequent invasion of paraglottic space and extension to supraglottis. Vocal cord fixation is the harbinger of an ominous prognosis, which may develop from bulky involvement of vocal cord and paraglottic space, or involvement of the cricoarytenoid joint. The destruction of thyroid cartilage and extralaryngeal extension is a late sign which upstages the tumour to T4 staging. It may be possible that many advanced glottic cancers arise primarily in the
ventricle, which leads to early spread towards paraglottic space and supraglottis.

The so-called transglottic cancers, which involve both supraglottis and subglottis, appear to have a particularly unfavourable biology. On an optimistic note, even the advanced glottic cancers exhibit a relatively low incidence of cervical metastasis (approximately 10%). In sharp contrast, supraglottic cancers may grow to a considerable size before causing symptoms. Due to rich lymphatic drainage, they commonly exhibit nodal metastasis at presentation. As an inference, most supraglottic cancers present at an advanced stage, either due to local symptoms from a large tumour, or with a metastatic neck lump. Supraglottic cancers may rarely present with extension below the level of glottis. Even more problematic is extension to the vallecula and base of tongue, and extralaryngeal extension in the region of thyrohyoid membrane. Nodal metastases are common, even in the presence of a clinically negative neck (30%-40%). The first echelon of lymphatic drainage are lymph nodes at levels II and III, with bilateral metastasis being common.

**TREATMENT**

The treatment options for advanced laryngeal cancer include surgery, radiotherapy, chemoradiation or a combination of these. Surgical management may range from minimally invasive transoral laser or robotic surgical resection, to open partial laryngectomy and total laryngectomy. In the clinical scenario, for many cases of advanced laryngeal cancer, the only feasible option is total laryngectomy. This operation has been the gold standard for treatment of advanced laryngeal cancer.[8]

More recently, there have been changes in the treatment paradigms for advanced laryngeal cancer. The result has been a decrease in the number of T3 laryngeal cancers treated with surgery alone, along with a major increase in the number of T3 cases treated with radiotherapy and chemoradiation. The major drive for these changes has been the publication of two studies – the Veterans Affairs Trial[9] (1991) and the RTOG 91-11 Trial[10] (Forastiere study, 2003). Both of these studies reported high rates of larynx preservation after using chemoradiotherapy protocols to treat advanced laryngeal cancer. However, simultaneous with this shift in treatment paradigm, new concerns have emerged after the more recent publication of Hoffman study,[8] which shows a reduction in survival for larynx cancer, over recent decades. It has been suggested that this may be linked to increasing use of non-surgical management with radiation alone or chemoradiation. The Hoffman study found non-surgical treatment to be associated with higher mortality than surgical treatment of T3N0 glottic cancer.

More recent literature has reopened this debate to discussion once again. Al-Gilani et al[9] (2016) published a retrospective study involving 487 patients of T3 glottic carcinoma, whose data was obtained from SEER registry (Surveillance Epidemiology and End Results) and Medicare databases. All patients with T1 glottic squamous cell carcinoma, who were diagnosed from 1992 to 2010, were included. The objective was to compare 5-year overall survival and functional outcomes for surgical versus non-surgical treatment modalities for T3 glottic cancer. The 5-year overall survival for non-surgical management, surgery alone and surgery plus adjuvant treatment were 36%, 41% and 41% respectively. The authors concluded that overall survival showed a statistically significant and clinically meaningful improvement in patients with T3 glottic squamous cell carcinoma who underwent surgery, compared with a non-surgical treatment.

In a French Randomized Controlled Trial by Richard et al[10] (1998), the study was limited to patients with T3 primary tumours and compared total laryngectomy to induction chemotherapy followed by radiotherapy in responders (or total laryngectomy in non-responders). A total of 68 patients were included in the study, 36 in the induction chemotherapy arm and 32 in the non-chemotherapy arm. The results showed a significantly better survival in the group undergoing immediate surgery. The 2-years survival rates were 69% in induction chemotherapy group and 84% in the non-chemotherapy group.

Megwalu et al[11] (2014) presented a population-based, non-concurrent cohort study of 5394 patients of advanced laryngeal cancer, whose data were extracted from the SEER Database. The objective was to assess the overall survival and disease-specific survival for surgical and non-surgical treatment modalities. The results showed that patients who received surgical therapy had better 2-year and 5-year disease specific survival and overall survival, when compared to patients who received non-surgical therapy.

Timmermans et al[12] (2016) published a 20-year population based study from Netherlands, reporting the treatment and survival for advanced laryngeal cancer. Data was obtained from two combined national cancer registries. A total of 2072 T3 cases and 1722 T4 cases were identified. From 1991 to 2010, T3 disease showed similar survival rates for all primary treatment modalities. For T4 disease, total laryngectomy (+ adjuvant RT) showed the best survival.

Dziegielewski et al[13] (2012) presented a population-based longitudinal cohort study regarding primary total laryngectomy versus organ preservation for T3/T4a laryngeal cancer. A total of 258 patients met the inclusion criteria, whose data was obtained from Alberta Cancer Registry. The objective was to assess the survival outcomes of total laryngectomy (+ RT/CT), radiotherapy (RT) and chemoradiation (CRT) in patients with T3 and T4a laryngeal cancers in Alberta, Canada. The mean follow-up was 3.43 years. The overall survival for T3
cancers at 2 and 5 years for TL (+ RT/CT) was 89% and 70%, for RT was 48% and 18% and for CRT was 66% and 52% respectively. Similarly, the overall survival for T4a cancers at 2 years and 5 years for TL (+ RT/CT) was 60% and 49%, for RT was 12% and 5% and for CRT was 32% and 16% respectively. The authors concluded that TL (+ RT/CT) provided superior survival for T3 and T4a laryngeal cancers versus RT or CRT. Therefore, the current standards of care and clinical guidelines warrant reassessment.

It may be inferred that the major advantages of radiotherapy or chemoradiation for treatment of advanced laryngeal cancer are avoidance of an operation and anatomic preservation of the larynx. On the other hand, disadvantages of non-surgical treatment include a high incidence of severe acute toxicity and a higher rate of long-term laryngeal functional problems, particularly in patients treated with concurrent chemoradiation.

At present, there is no consensus for treatment of T3 laryngeal cancers. Most patients are treated in accordance with institutional protocols and preferences. Some well-defined indications for surgical treatment of T3 laryngeal cancer are:
- Patients who are more prone to aspiration, for any reason. For eg. due to impaired vocal cord mobility.
- Patients older than 70 years in age (where chemotherapy cannot be given).
- Patients in whom tracheostomy has already been done.
- Non-squamous cell malignancies, where surgery is the primary treatment modality.

As far as T4 laryngeal cancers are concerned, the primary treatment is still surgery, which may be followed by postoperative radiotherapy or chemotherapy. This is because there is a clear and evident reduced likelihood of control for patients of T4 cancer presenting with gross cartilage destruction or extralaryngeal extension. Furthermore, among patients who develop local recurrence and require salvage laryngectomy after primary non-surgical management, there is an increased incidence of pharyngocutaneous fistula and major complications in the post-radiotherapy setting.[18]

CONSERVATION LARYNGEAL SURGERY

Conservation surgery (transoral laser or robotic surgery, or open partial laryngectomy) is an excellent option for many patients with early (T1-2N0) laryngeal cancers, offering excellent oncological control and functional outcomes.[19-21] For advanced laryngeal cancers, the role of conservation surgery is limited to selected cases which are either early T stage, but with concurrent cervical metastasis, or select small-volume T3 cases. Cases most suitable for a conservative surgical approach will be those staged T3 based on minor pre-epiglottic or paraglottic space invasion or minor erosion of inner lamina of thyroid cartilage, without full restriction of vocal mobility (indicating absence of arytenoid fixation), in motivated patients with good performance status and pulmonary reserves.

PRIMARY TOTAL LARYNGECTOMY

Total laryngectomy remains the gold standard treatment for locally advanced T4 laryngeal cancers with gross cartilage destruction or extralaryngeal extension. Apart from this, total laryngectomy is the best treatment option for management of locally recurrent laryngeal cancers after primary non-surgical management. The rationale for primary total laryngectomy in cases of advanced T4 laryngeal cancer is the decreased chances of complete response with radiotherapy or chemoradiation,[22] the lack of evidence regarding non-surgical management of such cases, as large volume T4 cases were excluded from many of the organ preservation studies,[23] the reduced success rate of salvage laryngectomy in the setting of extralaryngeal disease; and the increased incidence of major complications after salvage laryngectomy.[18]

Earlier primary total laryngectomy was also recommended for patients with bulky T3 tumours. With the advent of organ preservation protocols, the number of total laryngectomies performed for T3 disease has reduced substantially. However, there is still an important role for primary total laryngectomy in selected patients with T3 primary tumours. An example may be cited of a case of a young patient with a good social support and intelligence, who has a bulky T3 transglottic squamous cell carcinoma with vocal cord fixation, a compromised airway and questionable cartilage destruction on CT scan. The major arguments in favour of consideration of total laryngectomy in such cases include adverse characteristics of primary tumour which may increase the risk of persistence or local recurrence, including large size,[24] vocal cord fixation[25] and transglottic tumour extent; the presence of pre-treatment laryngeal dysfunction which portends a higher risk of permanent laryngeal dysfunction after even successful non-surgical treatment; and good patient performance status, intelligence, motivation and social support, which predicts a better likelihood of good speech and other functional outcomes after total laryngectomy.

Total laryngectomy has been reported to be effective in 67% - 81% of patients with T3 tumours[26-28] and 55% of patients with T4 tumours.[27] Local recurrence may take the form of stomal or peri-stomal recurrence, which is believed to arise from metastatic parastrachal nodes, or pharyngeal / base of tongue / esophageal recurrence, which probably arises due to unrecognized submucosal extension or local lymphovascular invasion.[29] Risk factors for local recurrence include transglottic or subglottic tumour extent,[27] lymph node metastasis,[27,29] poor differentiation,[27] lymphovascular invasion,[29] preoperative tracheostomy,[28,29] and positive resection margins.[29]
Postoperative quality of life
The treatment for laryngeal cancer can have a major impact on physical, social and psychological function of patients, thus altering their quality of life. The major functional impact is due to loss of voice. When total laryngectomy is chosen as a treatment modality, there are three possibilities of vocal rehabilitation – esophageal voice (EV), a tracheoesophageal prosthesis (TEP), and an electronic larynx.

The best method for speech rehabilitation is surgical voice restoration with tracheoesophageal speech after tracheoesophageal prosthesis placement. The advantages of rehabilitation with a TEP are based on good success rates, short learning time, and use of lungs as a source of phonation. This increases the maximum phonatory time of this process and improves vocal intensity, which is stronger compared to other forms of rehabilitation.

Attieh et al[31] (2008) presented a study that assessed the changes in quality of life and degree of voice handicap in patients of total laryngectomy, before and after placement of a TEP. Twelve male patients met the inclusion criteria. Evaluation was done using University of Michigan Head and Neck Quality of Life (HNQOL) questionnaire and the Vocal Disadvantage Index (VDI). In relation to HNQOL evaluation, the “communication”, “emotional” and “total” domains revealed a better quality of life after placement of TEP. The “pain” and “eating” domains did not show significant difference before and after placement of TEP, although the scores of “pain” domain were increased. The subjects reported less vocal disadvantage for each VDI subscale after voice restoration. No significant difference was found for the correlation of time after laryngectomy, which ranged from 1 month to 16 years, with time of questionnaire application after TEP placement.

Hanna et al[32] (2004) published a study on comparison of quality of life for patients following total laryngectomy versus chemoradiation for laryngeal preservation. The study included 42 patients with advanced stage III or IV cancer of the larynx, who were treated with either concurrent chemoradiotherapy or total laryngectomy followed by adjuvant radiotherapy. Patients had to be without evidence of recurrence and to have completed therapy at least 3 months prior to inclusion in the study. The authors concluded that the overall quality of life scores were almost similar for both groups.

CONCLUSION
At present, there is no consensus for treatment of T4 laryngeal cancers. Most patients are treated in accordance with institutional protocols and preferences. As far as T4 laryngeal cancer is concerned, total laryngectomy remains the gold standard for cases presenting with gross cartilage destruction or extralaryngeal extension.

CONFLICT OF INTERESTS
The author declares that there is no conflict of interests that could influence this work.

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