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REVIEW ARTICLE

Management of Early Laryngeal Cancer: The Role of Individualized Medicine

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ABSTRACT

Treatment options for early laryngeal cancer include radiation therapy or surgical resection. It is widely agreed upon that early laryngeal cancer should be managed with only one treatment modality. The debate on which treatment modality is best for early laryngeal cancer has essentially been going on for the last 65 years. Many new developments have impacted the treatment decision making process. These developments include the introduction of transoral endoscopic partial laryngeal surgery, such as transoral laser microsurgery (TLM) which is replacing external partial laryngectomy procedures; improvements in external beam radiation therapy (EBRT) delivery techniques and technology which result in enhanced accuracy and decreased extralaryngeal side effects and complications; and the introduction of quality of life measures and understanding their importance, in addition to survival rate, in defining successful outcome or failure. This review article concentrates on some of the important issues facing the patient, his/her family, and the treating physicians in the treatment decision making process.

Keywords: Laryngeal cancer, Laser cordectomy, Partial laryngectomy, Voice handicap index.

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INTRODUCTION

Cancer of the larynx is one of the most common malignancies of the upper aerodigestive tract. There are close to 13, 000 new cases diagnosed in the United States annually.[1,2] The vast majority of these tumors are squamous cell carcinoma.[3]

Over the last 2 decades, cancer statistics and outcome data have revealed worrisome findings. Head and neck surgery and oncology clinicians and researchers are learning that, in contrast to all other human cancer sites, survival rates in laryngeal cancer have been slightly decreasing.[4] Recent epidemiological studies have looked into the possible causes of this trend. One of the major concerns is the possibility that increasing popularity of nonsurgical management options for laryngeal cancer is behind the change in survival rate.[4] Although this may be related mainly to advanced laryngeal cancer, the impact of nonsurgical treatment options in early laryngeal cancer in general and early glottic cancer in particular (especially T2) is considered as possibly having a contribution to the changing statistics. Treatment decision making process in early glottic cancer is the topic of this review.

Although a formal, unanimous definition of the term early laryngeal cancer is lacking, most clinicians define it as tumors staged as T1 or T2 according to the American Joint Committee on Cancer-Cancer Staging Manual.[5,6] This definition is used in this review.

TREATMENT DECISION MAKING IN EARLY LARYNGEAL CANCER

Treatment options for early laryngeal cancer include radiation therapy or surgical (external or endoscopic) resection. It is widely agreed upon that early laryngeal cancer should be managed with only one of these treatment modalities.[6,7-9] The debate on which treatment modality is best for early laryngeal cancer has essentially been going on for the last 65 years. However, many new developments have impacted the treatment decision making process. These developments include the introduction of transoral endoscopic partial laryngeal surgery which is replacing external partial laryngectomy procedures; improvements in radiation therapy delivery techniques which result in enhanced accuracy and decreased extralaryngeal effects and complications; and the introduction of quality of life measures and understanding their importance, in addition to survival rate, in defining successful outcome or failure.

Table 1 summarizes the many important factors that should impact the decision making process. Reviewing each and every one of these factors in detail is beyond the scope of this review. I will attempt to concentrate on the most important issues facing the patient, his/her family, and the treating physicians.

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Second Metachronous Primary Malignancy

It is well-established that patients with head and neck squamous cell carcinoma are at increased risk for developing second metachronous primary malignancy.[10,11] The rate ranges from 17 to 47%, depending on the length of follow-up.[10,11] A significant number of these second malignancies occur in the head and neck region (32.0–59.3%).[10,11] In a large scale study, Gao et al[12] have shown that the head and neck is the region with the highest relative risk for being the site of a second primary malignancy in patients with laryngeal cancer (relative risk for all sites: 1.68; relative risk for head and neck: 4.81). This information is certainly important in designing an individualized treatment protocol, especially in patients who are at higher risk for secondary cancer, e.g., patients who continue to smoke. Additional risk factors for second primary cancer include older age, male gender, and earlier stage at presentation (probably related to longer survival and, therefore, longer time span for developing secondary cancer). However, most importantly, the same large scale laryngeal cancer study showed that radiation therapy given as the treatment modality for the first cancer, is an independent predictor of second primary cancer. These findings should be considered when deciding on treatment for the primary laryngeal cancer. The possible need to 'save the radiation for a rainy day' should be taken into account. Second primary cancer has a significant negative impact on survival and quality of life.[12]

Table 1: Early laryngeal cancer: factors to be considered in management

A.	*Tumor factors*	– Exact site
		– T stage (including subgrouping, e.g., T1a/b, T2a/b)
		– Tumor size
		– Adequacy of laryngeal exposure during endoscopy
		– Neck disease status
		– Likelihood of secondary malignancy
		– Pulmonary status
		– Swallowing status
B.	*Patient factors*	– Age
		– Function
		– Co-morbidities
		– Health literacy
		– Family support
		– Use of voice
		– Voice expectations
		– Exposure to carcinogens, especially tobacco
		– Need for tracheotomy?
		– Potential disfigurement, deformity
		– Length of treatment
		– Geographic availability….commute
		– Cost
C.	*Other factors*	– Treatment resources and availability
		– Expert (RT, conservation surgery) availability

RESOURCES

The availability of knowledge, expertize, and technology in a specific geographic area may affect the treatment decision making process.[13] In fact, it may impact treatment choice in different, occasionally opposing directions. It is a quite unfamiliar and irrelevant issue in developing countries, but may be the reality in third world countries. For example, lack of appropriate radiation therapy technology and expertize may direct patients to this surgical option. Or, unavailability of surgeons with the appropriate expertize in performing conservation laryngeal surgery, and/or unavailability of modern laser technology, may direct patient to nonsurgical management. However, and this is quite unfortunate, we too often witness situations where lack of knowledge about advanced modern treatment options among primary care physicians, general surgeons, or general otolaryngologists, may influence the referral pattern. A classic example that comes to mind is the patient with T1a laryngeal cancer who is being referred for a radiation therapy but never received any information about conservation laryngeal surgical options, preferably from a surgeon who is familiar with these procedures.

COST

Medical practice, including cancer management, in the 21st century must be cost-conscious. Many studies have compared direct costs related to surgical vs nonsurgical management of early glottic cancer.[6,14,15] Mylnarek et al[16] stated 'Surgery and radiotherapy are both very effective… however, surgery tends to be more cost-effective…'; Phillips et al[17] stated '…TLM…most economical…as effective as radiation therapy…cure rates and quality of life.'

Length of Treatment

Studies have shown that longer treatment time adversely impacts outcome. Longer treatment may result from different factors including inherent difference in time requirement for different therapeutic modalities (e.g., radiation *vs* surgery), planned or unplanned interruptions, etc. It should be noted that the negative impact of prolongation of treatment package time is independent of other tumor factors, such as tumor stage and patient factors, such as age or comorbidities. Rosenthal et al[18] found that total treatment package time of less than 100 days is associated with improved tumor control and survival (univariate and multivariate analysis). There are

also many psychosocial issues that may affect treatment package time. They include work, family, and geographic constraints. Therefore, in order to practice appropriate individualized medicine in laryngeal cancer care, the head and neck oncology specialist must consider all of these factors before deciding on a treatment protocol.

Reliability of Follow-up

The ability of the patient to follow closely with the treating physicians both during and after therapy must be considered as it may significantly impact success rate. In developing or third world countries with a limited number of treatment facilities, geographic constraints may limit the reliability of follow up. To a lesser degree, this may affect follow-up in rural areas in more developing countries. In North America, we often realize that family issues, family support, community support, substance abuse, and appropriate educational, psychosocial, and mental abilities, as well as awareness of the diagnosis and the importance of follow up, will also impact the care. Again, as we sit in front of the individual patient, we must consider all of these factors before we proceed with treatment recommendations.

Quality of Life—Non-voice Related[19]

Table 2 summarizes the non-voice related quality of life factors. It is very important to emphasize that quality of life is a very subjective matter and may have different meaning to different patients. That is where the role of individualized medicine is highlighted. Issues, such as length of treatment, cost of treatment, impact on family, impact on work, and appearance, just to name a few, are topics that the practitioner should discuss with the patient and his/her family and allow them to provide significant input to the decision making process. Although immediate complications of both conservation laryngeal surgery and radiation therapy are well-documented, reports on long-term sequelae are very limited.[16] This is mainly relevant to radiation therapy and its relation to edema, laryngeal fibrosis and/or stenosis, hypothyroidism, and carotid stenosis.[16]

Table 2: Non voice-related quality of life considerations

– Length of treatment
– Place of treatment
– Impact on family
– Impact on work
– Cost of treatment
– In-hospital stay
– Need for tracheotomy? PEG?
– Swallowing/airway protection
– Smell
– Taste
– Pain
– Salivary function
– Appearance
– Physical fitness
– Social activity
– Mental well-being
– Emotional well-being

Voice-related Quality of Life

Though not necessarily the most important factor in the therapeutic decision making process, this is probably the most cited and the most discussed quality of life issue in the field of early laryngeal cancer. In general, the following sentence appeared in most articles and textbooks for many decades: 'Voice preservation is thought to be better with radiotherapy than with surgery.' However, today this statement is being challenged.[6,16,19-25]

The belief that voice results are better with radiotherapy is based on studies utilizing therapeutic approaches which are not necessarily updated and modern and, therefore, may not be relevant today. Until the 1990's, most conservation laryngeal surgery was done through an open approach.[8,26] It is widely agreed that voice outcome after external conservation laryngeal surgery is inferior to voice outcome after radiation therapy.[21,26] However, we now learn that it is also inferior to voice results after endoscopic procedures.[21,26] In addition, our techniques and instrumentation continue to evolve and improve. Significant advances in optics as well as newer ablative and extirpative (laser and non-laser) technology result in continuous improvement in voice outcome.

We have also witnessed major advances in surgical voice rehabilitation after endoscopic partial laryngeal surgery during the last 20 years. It is well known that augmentation/rehabilitation surgery after external partial laryngectomy is very challenging. However, we are seeing excellent voice results after augmentation procedures in patients after endoscopic cordectomy.[27-29] Medialization and/or augmentation (external, transcutaneous, or endoscopic) procedures continue to be developed and refined. Also, with the help of our engineering and biochemistry colleagues, the materials that are being used for these procedures provide increasingly consistent and predictable results.

One additional factor that may cause misrepresentation of voice outcome studies is the fact that, for many years, outcome was measured using objective voice analysis. Although objectivity is something that we all strive for in medicine, it may not necessarily translate well to voice outcome. Much like cosmetic surgery, voice is a subjective character of the individual person. Different patients have different voice demands and voice

expectations. Their input and their significant others' input are very important in the pretreatment discussion as well as in the evaluation of posttreatment outcome. We repeatedly state in our tumor board that 'not all patients are teachers and singers.' In fact, studies using patient-oriented and family-oriented instruments, such as the Voice Handicap Index (VHI), have shown that for certain levels of endoscopic partial laryngectomy, there is no difference in voice results when compared to radiation therapy.[20,21,30] It is also important to remember that radiation therapy affects the entire larynx, whereas cordectomy affects only the cancerous region.[9,31] Continuous smoking will also adversely affect voice outcome by adding tissue damage to the postradiation edema and fibrosis.[9]

And last but not least, in order for voice outcome studies to be reliable and effective, so they may be applied during both pretreatment counseling sessions and posttreatment evaluation, they must be stratified by the extent of the resection. Therefore, we strongly recommend that the European Laryngological Society (ELS) classification system[32] for endoscopic partial glottic resection should be used in any voice outcome study whether surgical or nonsurgical.[8]

Considering all the factors and issues discussed above, there is an increasing number of studies showing that voice outcome after surgery is not necessarily inferior to radiation therapy.[20-24] Cohen et al,[20] in a meta-analysis study of 208 patients using VHI, stated that 'We conclude that CO_2 laser excision and EBRT provide comparable levels of voice handicap….' Although good voice outcome is expected after ELS types I-III cordectomy, Vilaseca et al[24] found that, subjectively, '…patients with types III-V cordectomy… dysphonia… rarely an important disability.' Har-El et al[33] studied a group of 24 patients who underwent partial laryngectomy with imbrication laryngoplasty (an external approach procedure). Twenty-three patients (95.8%) were 'satisfied' or 'very happy' with their voice outcome. When evaluated by the surgeons, nine patients (37.5%) had 'good' voice outcome and 15 patients (62.5%) had 'excellent' voice. Based on their experience, the surgeons rated 23 patients (95.8%) as having a better voice than a typical vertical hemilaryngectomy patient, and 15 patients (62.5%) as having the same or better voice outcome when compared to radiation therapy.

Survival Rates and Laryngeal Preservation Rates

Although is it generally believed that surgery and radiation therapy have similar survival outcome[25,26,34,35] a few recent studies challenge this assumption.[9,14] Higgins et al[25] in a meta-analysis study of 7,600 patients stated… 'there is a trend favoring transoral laser surgery for overall survival.' As for preservation of the larynx as a functional organ, Hafidh et al[36] (citing Rothfield et al),[37] discussing radiation therapy for T1 glottic cancer, stated that '…although initial voice quality may be superior, more of these patients require total laryngectomy, thus reducing overall voice preservation.' Schrijvers et al[38] found 'Higher laryngeal preservation rate after CO_2 laser surgery compared with radiotherapy….'

The T2b Subgroup

The American Joint Committee on Cancer's Staging Manual defines T2 of the glottis as a tumor that extend to supraglottis and/or subglottis, or a tumor with impaired vocal fold mobility.[5] Many clinical studies further subdivide this category into T2a stage for a tumor extending to the supraglottis and/or subglottis with normal vocal fold mobility, and T2b stage for impaired vocal fold mobility. Studies, dating back to the 1970's, show a difference in treatment response rate and local control between the two subgroups.[26] McCoul and Har-El[39] performed an extensive meta-analysis to study this issue. With very strict inclusion criteria (clear data on T2a *vs* T2b, radiation therapy, separate 5 years survival data), they found statistically significant difference in survival between T2a and T2b with an odds ratio of 1.63. Their conclusion was that impairment of fold mobility has a negative impact on local control rates regardless and independent of supraglottic or subglottic entension.[39] They recommended considering the inclusion of this subdivision in the formal staging. However, we must realize that appreciation of subtle vocal fold mobility impairment is extremely subjective, and therefore, may not be suitable for defining a clinical stage.

DISCUSSION

There are many factors that should be considered by the clinician, the patient, and the patient's family when deciding on the appropriate treatment protocol for early laryngeal cancer.[31] These factors are divided into two main groups namely, tumor factors and patient factors. In this review, some of these factors were discussed in detail. Not all factors were reviewed and additional considerations should be given to issues, such as age, comorbidity, the status of the cervical lymph nodes, the patient and family's health literacy, continuous carcinogen exposure, and the patient's attitude toward and tolerance of any potential deformity or disfigurement.

CONCLUSION

The days of the single clinician 'playing God' and proceeding to 'decide' on the treatment protocol for a specific

patient are gone. We owe our patients the full picture. Every patient with a known or suspected early laryngeal cancer should benefit from a consultation with a radiation oncologist familiar with treatment to this type of tumor, as well as a surgeon who is familiar with all aspects of conservation laryngeal surgery.[31] We owe it to ourselves as clinicians and researchers but more importantly, we must do it for the benefit of our patients.

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