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INVITED REVIEW

Treatment of Laryngeal Cancer

WM Mendenhall, RJ Amdur

Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, Florida, USA

ABSTRACT

Surgery and radiation therapy are the main treatment modalities for laryngeal cancer, although patients with unfavourable disease may require a combination of radiotherapy and chemotherapy. Computed tomography or magnetic resonance imaging is required to stage the cancer and decide on the treatment modality.

In order to compare treatment modalities, it is necessary to evaluate treatment end-points and data should be analysed using a clinical staging system rather than a pathological system. Follow-up should be of sufficient duration to ensure accurate data analysis. This review will discuss the treatment protocols for laryngeal carcinoma and study requirements for comparison of treatment.

Key Words: *Cancer, Chemotherapy, Larynx, Radiotherapy, Surgery*

The two major modalities for treating laryngeal cancer are surgery and radiation therapy, with the selection of treatment depending on the location of the tumour and the stage of the disease. Computed tomography (CT) and/or magnetic resonance imaging (MRI) of the neck and larynx are routinely used to evaluate patients with laryngeal cancers. Findings from these tests and from physical examination are used to determine the clinical stage of disease.

The two major staging systems are the American Joint Committee on Cancer (AJCC) system[1] and the International Union Against Cancer (UICC) staging.[2] Both systems have recently been modified and are essentially the same. A specific change that occurred in the most recent versions of the staging systems is that, for patients with supraglottic cancer, involvement of the medial wall of the pyriform sinus no longer up-grades the lesion to T3. These cancers remain in the T2 category unless there are other reasons for the T3 classification, such as vocal cord fixation or involvement of the pre-epiglottic space. This shift of patients with favourable T3 supraglottic lesions to the T2 category will probably result in an artificial decrease in the likelihood of local control following treatment for patients with both T2 and T3 tumours.

Another change in the most recent versions of the AJCC and UICC staging systems is that stage IV disease is now stratified into favourable and less favourable subsets of patients. However, within these stage IV subsets, as within stage III, heterogeneity exists so that some patients with stage III and IV disease have relatively favourable lesions suitable for larynx preservation, whereas others have high volume disease and are better treated with ablative surgery.

In order to compare treatment modalities, it is necessary to evaluate the end results of treatment. Data should be analysed using a clinical staging system rather than a pathological staging system as has been used by some authors, particularly proponents of transoral laser excision. This is because pathological staging tends to use a higher stage for patients compared with clinical staging so it is not possible to compare end results for those treated with nonsurgical modalities. Useful parameters for evaluation of outcome studies include local control, local control with larynx preservation, ultimate local control (including successful salvage therapy following local recurrence), neck control, ultimate neck control, local regional control, ultimate local regional control, survival, cause-specific survival (censoring patients who die of other unrelated causes),

Correspondence: *Dr. WM Mendenhall, Department of Radiation Oncology, University of Florida College of Medicine, PO Box 100385, Gainesville, FL 32610-0385 (Street address: 2000 SW Archer Road). Telephone: (352) 265 0287; Fax: (352) 265 0759; E-mail: mendewil@shands.ufl.edu*

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and complications. Although there is little data pertaining to quality of life, this is also an important end-point. Data should be analysed using the product limit method. The number of patients lost to follow-up should be stated; patients should be followed up to within 1 year of data analyses or death. Most of the data management decisions are based on levels 2 to 4 evidence and grade B recommendations.

Patients with early lesions (Tis, T1, and T2) should be treated with a single modality. Options include transoral laser excision, open partial laryngectomy and radiation therapy. Our inclination is to use radiation therapy for most of these patients because of the very high cure rates afforded by irradiation, excellent voice quality, and because a significant portion of these patients are not medically suitable for partial laryngectomy. Larynx preservation should be one of the treatment goals for these individuals in all but the most extraordinary cases, where a total laryngectomy might be necessary as the first step in treatment.

Patients with more advanced disease often require combined modality therapy. CT or MRI may be used to measure the volume of the primary tumour to select favourable low-volume lesions that are likely to be cured by radiation alone.[3,4] Patients with moderately advanced T3 tumours selected for treatment with radiation therapy alone are better treated with altered fractionation schedules, such as a concomitant boost or hyperfractionation protocol, rather than once-daily radiation therapy.[5,6] Doses in the range of 60 Gy at 1.8 to 2.0 Gy per fraction, using once-daily fractionation, are too low and will yield suboptimal results compared with more aggressive fractionation schedules.

Patients with high volume, unfavourable T3 and T4 tumours are not likely to be cured with radiation therapy alone and are better treated either with a total laryngectomy or with a combination of radiation therapy and adjuvant chemotherapy. Several randomised trials indicate that induction chemotherapy may be used to select patients who are more likely to be cured with radiation therapy if they have had a partial or complete response to induction chemotherapy.[7,8] However, there is no convincing data that induction chemotherapy will improve the likelihood of long-term local regional control or survival.[9] Additionally, it is unclear whether induction chemotherapy will be useful for an additional subset of patients who are likely to be cured with radiation therapy after the most favourable patients have already been triaged to radiation therapy based on CT and/or MRI determination of primary tumour volume. In contrast, data from several randomised trials and recent multivariate analyses indicate that concomitant chemotherapy and irradiation is more effective than induction chemotherapy and irradiation, and may improve both local regional control and survival.[9-13]

Two studies have shown hyperfractionated irradiation and concomitant chemotherapy to yield superior results compared with hyperfractionated radiotherapy alone.[10,13] It is unclear how best to combine concomitant chemotherapy and irradiation. At one end of the spectrum are schedules that employ suboptimal radiation therapy, given in a split-course manner over an extended period of time (9 or 10 weeks), combined with very aggressive chemotherapy. At the other end of the spectrum are aggressive altered fractionation schedules combined with less aggressive, but tolerable, chemotherapy.

In between these two extremes, are optimal once-daily fractionation schedules such as 70 Gy in 35 fractions, combined with moderately aggressive chemotherapy. Another option that has been used successfully in a small number of institutions, and which we have recently initiated at the University of Florida, is radiation therapy combined with targeted intra-arterial chemotherapy using cisplatin.[14]

Our current philosophy is to use either the intra-arterial cisplatin and once-daily irradiation (RadPlat), or twice-daily irradiation with weekly cisplatin (30 mg/m^2/week) for patients who are not optimal candidates for the targeted intra-arterial cisplatin.[14] A caveat to aggressive larynx preservation schedules for patients with advanced disease (based on extensive cartilage destruction and/or extension into the soft tissues of the neck) is that a subset of patients may be cured, but have a larynx and/or pharynx that does not function. These patients may have a permanent tracheostomy tube due to laryngeal oedema, or a permanent gastrostomy due to impaired swallowing and may be better treated with a total laryngectomy. Data precisely defining this subset of patients is lacking. A soon-to-be-completed Radiation Therapy Oncology Group protocol (91-11) compares once-daily radiation to induction chemotherapy plus irradiation, or combined once-daily radiation and concomitant chemotherapy for patients with advanced laryngeal cancer. This will hopefully provide some additional data pertaining to the optimal timing of adjuvant chemotherapy.

Patients with clinically positive neck nodes that are low volume (N1 or early N2b) and within the high-dose radiation therapy fields, and which have also completely regressed by the end of treatment can be managed by radiation therapy alone with a high likelihood of neck control.[15-17] Patients with more advanced neck disease and those who have an incomplete response at the end of radiation therapy are best treated with a post-radiation therapy neck dissection.[15]

Patient follow-up is scheduled as follows:
- every 4 to 6 weeks for the first year
- every 2 months for the second year
- every 3 months for the third year
- every 6 months for the fourth and fifth years
- and annually thereafter.

Follow-up CT may be useful in detecting some patients with local recurrences following irradiation earlier than would be detected by clinical examination, thus improving the likelihood of successful salvage surgery, sometimes via a partial laryngectomy.[18]

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