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TREATMENT OF STAGE I T1 GLOTTIC CANCER

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Summary of Literature Review

Introduction

Most larynx cancers arise in the glottis, which comprises, for purposes of clinical staging, the superior and inferior surfaces of the true vocal cords (including the anterior and posterior commissures). The glottis occupies a horizontal plane 1 cm in thickness, extending inferiorly from the lateral margin of the ventricle. Stage I T1N0 cancers are limited to the vocal cords and commissures, with normal cord mobility. T1a lesions are limited to a single cord, while disease that involves both cords is stage T1b. A cancer with impairment in cord mobility and/or extension to the supraglottis or subglottis is stage II T2N0 [1]. Three-quarters of patients with larynx cancer in North America present with stage I or II disease [2,3]. Treatment of stage I glottic cancer is highly successful and larynx preservation is usually achieved. Neither total laryngectomy nor chemoradiation are indicated in the initial management of T1 glottic cancer, nor is treatment of the neck. [4].

As single modalities, with intent to preserve the larynx, both radiation and resection afford excellent locoregional control and survival. The small number of treatment failures (through either initial approach), and local variations in treatment preferences on the part of physicians, surgeons, and patients have frustrated efforts to perform randomized trials comparing the modalities. Review of the relevant literature reveals no properly designed and reported randomized trials comparing surgical with radiotherapeutic management of stage I glottic cancer [5]. Thorough recent meta-analyses have been performed [6,7]. No difference in survivorship could be demonstrated, though there was better larynx preservation in patients treated with initial resection. A recent review has considered "levels of evidence" supporting treatment options for glottic cancer [8]. Use of chemotherapy alone to treat stage I glottic cancer should be considered investigational [9].

Radiation Treatment

Surgical treatment of early glottic cancers with total laryngectomy or open partial laryngectomy was historically associated with loss of normal voice or substantial decline in its quality. Radiation treatment has been associated with local control rates from 80%-95% [10-14], and shorter overall treatment times seemed to yield superior results [14,15]. A prospective randomized study comparing 2 Gy fractions with 2.25 Gy fractions (with 60 Gy in 30 fractions vs 56.25 Gy in 25 fractions for lesions involving less than two-thirds of the vocal cord and, for larger lesions, 66 Gy in 33 fractions vs 63 Gy in 28 fractions) showed a significant advantage in local control rate for the shorter treatment time. Five-year local control rate was 77% for the 2 Gy arm and 92% for the 2.25 Gy arm (P=0.004) with no significant difference in survival, acute mucosal reaction, skin reaction, or late effects [16]. Recent results from a single-institution series including some 325 patients with stage I glottic cancer treated with opposed lateral fields demonstrated 10-year local control rates of 93% for T1a and 91% for T1b. Ultimate local control rates (including successful salvage after local recurrence) were 98% and 95% for T1a and T1b lesions, respectively [17].

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Many of the reported radiotherapy outcomes include patients treated predominantly with cobalt-60 units or 2-4 MV x-rays [18-21]. Several authors showed inferior local control with cobalt-60 [15,18], unlike the majority of published results [17,22,23]; some have also reported inferior results with 6 MV photons [24]. The effect of treatment energy is difficult to isolate due to concomitant technologic advances that transpired during the shift from cobalt to linear-accelerator-delivered therapy. Concerns regarding adequate dose delivery with higher-energy 6 MV photons existed previously, but they have largely been assuaged [25,26].

Radiation has typically been delivered with opposing lateral low-energy photon fields with wedges; other approaches described include oblique fields [27], a three-field approach [17,20], a single appositional electron field [18], and a single lateral field [22]. Regardless of the field arrangement chosen, elective treatment of the neck is not warranted [28].

Field size is generally 5 cm x 5 cm. Nonrandomized data concerning field size have been contradictory. Some series suggest inferior local control when larger field sizes are used (although many included patients with T2 disease, perhaps demanding a larger field and expected to manifest inferior control) [22,29]. Others report better local control with a field size >5 cm x 5 cm [11,12,30], or no impact of field size on local control [10,15,18,23], or excellent outcomes with smaller field sizes [25]. In a randomized controlled trial for patients with T1 disease, subjects were treated with either a 5 cm x 5 cm or 6 cm x 6 cm field. Local control was excellent in both arms, with no difference between the smaller and larger field sizes [13].

Shorter overall treatment times have seemed to yield superior results [14,15]. Prolongation of total treatment time has been shown to negatively impact local control [23,31,32]. Conversely, in one series split-course therapy with a planned 3-week break did not negatively impact local control outcomes but did result in worsening toxicities [19].

Intensity-modulated radiation therapy (IMRT) has been considered feasible in order to diminish dose to the carotid arteries [33,34], though its benefit has not been clinically demonstrated. A dosimetric study comparing opposed lateral fields, 3D conformal with either two oblique and one anterior field or a lateral and anterior field, and seven-field IMRT showed similar target volume coverage for all techniques but reduced dose to the carotid arteries with 3D conformal planning and additional reductions with IMRT. This dosimetric sparing of the carotid arteries is balanced by concerns due to increased dose heterogeneity across the larynx as well as an uncertain impact of target motion during treatment delivery [33]. Another dosimetric study compared opposed lateral treatment plans with IMRT plans created using three fields. Again significant reduction in dose to carotid arteries was possible. These investigators also reported successful delivery of treatment using IMRT in an 11-patient pilot series. A prospective series is planned [34].

Photodynamic therapy has demonstrated encouraging results for T1 glottic cancer as initial treatment and in a salvage setting; however, it has not been widely adopted [35].

Surgical Treatment

After Billroth to a great degree initiated modern surgical treatment of larynx cancer with the first reported total laryngectomy and the first vertical hemilaryngectomy [36], procedures to treat glottic cancer with operations increased in popularity, scope, and ambition. Even for T1 glottic cancers, there have been many modifications and extensions of open partial laryngectomy, since the locations of different cancers create varying technical challenges for the surgeon. In practice, tumors of the membranous vocal fold (cord), those with extensions to the anterior commissure, those actually involving the commissure, those involving the arytenoid, and those involving both cords must be managed differently [37].

The nature of the resections, their functional consequences, and their oncologic results depend strongly on the extent of glottic involvement with respect to both surface extent and to depth of invasion. Because surgical treatment should be tailored to a particular tumor, the management is individualized. However, principles include preoperative laryngoscopy (which may include videolaryngostroboscopy), assurance of adequate intraoperative exposure, and resection to clear margins, if feasible. Collaboration with experienced pathologists is of benefit [38]. Transoral excision of T1 glottic cancer lacks the morbidity of open procedures, and it is usually accomplished expeditiously, with hospital stays under 3 days. For T1 lesions the 5-year laryngeal preservation rate (in two series of more than 400 patients each) exceeds 97%, though “salvage” treatment may be required to achieve the reported locoregional control of 96%-99% [38,39].

Most open laryngectomies produce a decline in voice quality. Voice quality depends most strongly on the amount and depth of cord resection, and formal criteria to describe the cordectomy performed have been elaborated [40,41]. For most midcord T1a cancers the overall voice quality after resection or radiation is similar, though the specific voice profiles seem different [42]. A CO_2 laser is typically employed, but other cutting tools may be used. Functional and oncologic results for superficial disease of a single cord are excellent. Surgical tumor control declines for tumors truly involving the anterior commissure, with a substantial increase in recurrence frequency, which even in experienced hands [43,44] may exceed 20%.

Quality of Voice and Life

Voice quality after treatment of glottic cancer with cordectomy and with radiation has been assessed both subjectively and objectively. Because patients with T1 glottic cancer usually have an abnormal voice, it commonly improves after treatment. While patient satisfaction and subjective evaluation of voice quality are often high after either surgery or radiation, more formal studies demonstrate changes associated with tumor size and extent of resection [45-47]. The Voice Handicap Index of pooled results from small series shows no significant difference between patients treated with laser excision and radiation. Maximum phonation time seems to favor patients treated with radiation. With respect to airflow, fundamental frequency, microperturbation in frequency, and microperturbation in amplitude, no significant differences were demonstrated [6,48]. Prospective studies of voice quality are justified [48]. In the treated population smoking seems to affect voice quality [49,50]. There is no significant difference in the University of Washington Quality-of-Life instrument (UW-QOL-R) or the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) for patients with T1 glottic cancer treated with endoscopic resection or radiation [51]. (See Variant 1, Variant 2, Variant 3, and Variant 4.)

Treatment of Recurrence

Surgical salvage of patients with recurrence after definitive radiation should be attempted. Success seems largely related to the extent of tumor at the time of resection. Total laryngectomy is often required, but smaller procedures (ranging from laser excision through supracricoid laryngectomy) may be appropriate and successful [52-55]. Both radiation and resection may be used to salvage patients with recurrence after prior resection [56]. Patients initially treated with radiation have a far higher risk of eventual laryngectomy than those whose cancer was first treated with transoral laser excision [57]. Analysis of patients with less deeply invasive tumors (those with normal or diminished mucosal wave, as opposed to absent wave, on videolaryngostroboscopy) still suggests a higher risk for larynx loss in patients initially addressed with radiation [58]. (See Variant 5.)

Costs of Care

Several analyses of the monetary costs of care for a patient with T1 glottic cancer have been performed. Various degrees of sophistication have been used. A recent evaluation comparing transoral laser excision with radiation for T1 glottic cancer indicates that resection is the less costly approach, principally because the costs to control a recurrence after surgery are less than those needed to salvage a postradiation recurrence [7]. Assumptions surrounding the nature and extent of the treatments for recurrence strongly affect such calculations. “Hidden costs” of care at a major center demonstrated substantial differences in number of treatments, median necessary travel distances, total median travel time, and median number of work hours missed—indicating that other factors besides oncologic control and voice quality warrant consideration in management [51].

Patients living far from a radiation facility and those who face difficulty with transportation or mobility are often far more appropriate candidates for resection than for radiation treatment, since the episode of care is considerably shorter, with equivalent oncologic results. Photodynamic therapy has demonstrated encouraging results for T1 glottic cancer as initial treatment and in a salvage setting; however, it has not been widely adopted.

Summary

- Surgical treatment: The panel recommends transoral endolaryngeal resection for patients with T1a disease visible in its entirety on direct laryngoscopy and an intact mucosal wave. This offers excellent control outcomes and a favorable morbidity profile.
- Radiation treatment: Radiation therapy offers excellent local control and is the preferred first- line therapy in patients with disease not readily amenable to transoral laryngeal resection. Open partial laryngectomy is a viable alternative, although the vocal quality may be better with radiation therapy. Randomized data support the use of 2.25 Gy fractions as opposed to 2.0 Gy.

- Recurrent disease: Most patients with disease recurrence remain candidates for additional definitive treatment, with best therapy at recurrence dependent on the initial treatment strategy. While larynx preservation remains achievable, patients should be counseled regarding the potential requirement for total laryngectomy.
- Costs of care: Thorough costs of care analyses are challenging, due in large part to the difficulty of accurately assessing the hidden costs of initial treatment as well as potential subsequent costs of caring for recurrences. Treatment of choice for many patients will ultimately depend on patient-specific rather than disease-specific factors, including proximity to treatment centers and professional obligations.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Treatment of Stage I T1 Glottic Cancer**

Variant 1: **A 57-year-old man has squamous cancer superficially involving the mid-third of the left true vocal cord. Cord motion is normal, and videostroboscopy shows an intact mucosal wave. The lesion can be readily defined on office examination. He is edentulous, can open his mouth well, and ceased smoking 5 years ago. The cancer can be seen in its entirety with direct laryngoscopy under anesthesia.**

Treatment	Rating	Comments
Total laryngectomy	1	
Open partial laryngectomy	3	
Transoral endolaryngeal resection	9	
External beam radiation in 2 Gy fractions	3	
External beam radiation in 2.25 Gy fractions	7	
Concurrent chemoradiation with cisplatin	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

This is a T1 glottic cancer. All of the methods described should afford excellent control of the cancer, albeit with dramatic differences in subsequent quality of life. Neither total laryngectomy nor concurrent chemoradiation is appropriate for treatment of this lesion. Open partial laryngectomy has more side effects than transoral laryngeal surgery (including a longer hospital stay and need for a temporary tracheotomy). External beam radiation therapy in 2.25 Gy fractions is superior to treatment with 2 Gy fractionations. Both radiation treatment and surgery should confer high quality of life and voice in treating cancers such as this.

Variant 2: **A 57-year-old man has squamous cancer superficially involving the mid-third of the left true vocal cord. Cord motion is normal. He is hoarse, and the mucosal wave is dampened on videostroboscopic examination. The lesion can be defined on office examination. He is edentulous, ceased smoking 5 years ago, and takes no medicines. The cancer cannot be exposed in its entirety with direct laryngoscopy under anesthesia.**

Treatment	Rating	Comments
Total laryngectomy	1	
Open partial laryngectomy	7	
Transoral endolaryngeal resection	4	Transoral endolaryngeal resection should only be performed in this scenario by an experienced surgeon, realizing the potential need to convert to an open procedure.
External beam radiation in 2 Gy fractions	3	
External beam radiation in 2.25 Gy fractions	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Despite the difficulty of exposing this cancer under anesthesia, oncologic control of this tumor should not be more difficult to achieve than in patients whose lesion is more readily defined. Total laryngectomy is not justified. Transoral laryngeal excision should not be performed if the lesion cannot be seen in its entirety during examination under anesthesia. Open partial laryngectomy may be performed with excellent margins, despite inability to expose the tumor fully through line of sight, because angled telescopes may be used to examine the larynx. Quality of voice with open partial laryngectomy is likely to be inferior to that achieved through radiation treatment of this cancer. External beam radiation therapy in 2.25 Gy fractions is superior to treatment with 2 Gy fractions.

Clinical Condition: **Treatment of Stage I T1 Glottic Cancer**

Variant 3: **A 65-year-old man has squamous cancer densely involving the anterior third of both vocal cords. Cord motion is normal, as is videostroboscopy. The lesion can be defined on office examination. Imaging shows no involvement of the thyroid cartilage. He is edentulous, ceased smoking 5 years ago, and takes no medicines. The cancer can be exposed in its entirety with direct laryngoscopy under anesthesia.**

Treatment	Rating	Comments
Total laryngectomy	1	
Open partial laryngectomy	7	
Transoral endolaryngeal resection	5	Transoral endolaryngeal resection should only be performed in this scenario by an experienced surgeon, realizing the potential need to convert to an open procedure.
External beam radiation in 2.25 Gy fractions	9	
Concurrent chemoradiation with cisplatin	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Neither total laryngectomy nor concurrent chemoradiation is justified for this patient with T1b glottic cancer. Transoral laser excision may entail a decline in local control because of the anterior commissure involvement. Open partial laryngectomy (including perhaps a supracricoid partial laryngectomy) should confer adequate tumor control, though voice quality will suffer and morbidity is substantial. External beam radiation should not involve a compromise in tumor control, though voice quality is likely to be inferior to that following treatment of a superficial T1a lesion.

Variant 4: **A 65-year-old man has undergone three prior vocal cord stripping procedures to address carcinoma *in situ* of the left true vocal cord. Cord motion is normal. The lesion cannot be readily defined on office examination, but he brings video documentation of the most recent treatment. He is edentulous, ceased smoking 5 years ago, and takes no medicines. With examination under anesthesia and microdirect laryngoscopy the cord shows evidence of prior manipulation, but no lesion can be seen. Biopsy again shows carcinoma *in situ*.**

Treatment	Rating	Comments
Photodynamic therapy	8	Need for sun exposure is a contraindication to this treatment option. Patients should be carefully staged surgically with particular attention to defining the depth of the lesion.
Open partial laryngectomy	2	
Transoral endolaryngeal resection	4	
External beam radiation therapy	8	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Open partial laryngectomy with cordectomy will entail hospitalization and result in voice decline. It is too morbid an approach for carcinoma *in situ* of the cord. Photodynamic therapy can be accomplished without hospitalization, can be performed repeatedly, and preserves voice quality. It may prove disruptive for individuals with an outdoor occupation or lifestyle and is not available everywhere. Transoral laryngeal surgery should not be undertaken if the site of disease cannot be defined preoperatively. Radiation therapy should confer excellent results in addressing this problem (for control of carcinoma *in situ* and with respect to voice quality).

Clinical Condition: **Treatment of Stage Tis Glottic Cancer**

Variant 5: **A 68-year-old man has recurrent squamous cancer superficially involving the mid-third of the left true vocal cord after radiation 1 year ago. Cord motion is normal. He is hoarse. The lesion can be readily defined on office examination. He is edentulous, can open his mouth well, ceased smoking 5 years ago, and takes no medicines. The cancer can be seen in its entirety with direct laryngoscopy under anesthesia.**

Treatment	Rating	Comments
Systemic chemotherapy	1	
Reirradiation to recurrent tumor volume with limited margin (0.5-2 cm) and concurrent chemotherapy	1	
Reirradiation to recurrent tumor volume and elective coverage of neck levels II and III with concurrent chemotherapy	2	
Total laryngectomy	3	
Open partial laryngectomy	7	
Transoral endolaryngeal resection	8	
Photodynamic therapy	7	Need for sun exposure is a contraindication to this treatment option. Patients should be carefully staged surgically with particular attention to defining the depth of the lesion.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinically, this rT1 glottic cancer is treatable with curative intent. Use of systemic chemotherapy, which is palliative, is not appropriate in this setting. The same applies to reirradiation, which should not be used if resection can be performed with acceptable morbidity and reasonable expectation of tumor control. The true extent of tumor is difficult to define in this setting, since the cancer is often submucosal. It may be far more extensive than examination suggests. Hence, while efforts at larynx preservation are appropriate (and frequently successful with either open or endoscopic techniques), patients should be prepared for total laryngectomy. Technical demands of the procedures exceed those performed in patients who have not received radiation treatment. Photodynamic therapy may cure patients who develop superficial recurrences after radiation fails.