Introduction

Laryngeal cancer has been a field of head and neck cancer with evolving treatment. While initially treated with open surgery, the evolution of radiation oncology has placed radiation therapy at the forefront of treatment for laryngeal cancer. While dealing with more advanced cases, articles such as the VA trial for laryngeal cancer endorsed radiation therapy as equally effective as cancer with regards to tumor control but also provided functional preservation. While these remain the standard, the treatment of early glottic cancer deserves special attention. Although patients with supraglottic cancer present with advanced stages, patients with glottic cancer present early due to early changes in voice, stridor, or persistent globus sensation. As these patients continue to present early, the advances in transoral laser surgery bring the spotlight back on surgical treatment. For the purposes of this talk, we will consider early glottic cancers as T1 and T2 lesions. Further, due to the overwhelming frequency of squamous cell carcinomas, the articles quoted and discussed below concentrate on squamous cell carcinoma (SCCa) when stating cancer. Areas of comparison between the two include tumor control, voice outcomes, and cost analysis.

Brief Review of Anatomy and Staging of Glottic Cancer

A brief word on anatomy is needed when discussing glottic cancers. Unlike any other site in the larynx, the true vocal folds are unique in their structure. With 5 unique layers – epithelium, superficial lamina propria, intermediate lamina propria, deep lamina propria, and muscle – lesions can be judged not only by their size but their depth of involvement. It is for this reason that videostroboscopy is paramount as this procedure allows one to see if the lesion has penetrated to a sufficient depth to cause decreased wave. Understanding the depth of lesions leads to better treatment planning.
Prior to starting our discussion, it is important to review the staging of glottic cancer. The AJCC\textsuperscript{1} staging for glottic cancer has remained unchanged over several editions. Lesions, which do not invade the basement membrane, are classified as Tis (in situ). T1 lesions are those which are localized to the vocal folds only but do not affect vocal mobility. T1 can be broken into T1a if involving only one vocal fold and T1b if involving both vocal folds. T2 lesions extend to supraglottis or subglottis or cause impaired vocal fold mobility. T3 lesions either demonstrate vocal fold fixation and/or invade the inner cortex of the thyroid lamina and/or invade paraglottic space. T4 lesions invade through the thyroid cartilage and/or invades beyond the larynx. These are split into T4a and T4b – the b designation is given if the carotid artery is encased, mediastinal involvement is noted, or invasion to prevertebral fascia.
Tumor Control

In 2004, Mendenhall et al.² delved into the very question of assessing which modality was better. They began by discussing tumor control. They performed a meta-analysis to compare trans-oral laser resection, open partial laryngectomy, and radiotherapy. For trans-oral laser resection, the control rate for 80-90% for T1 lesions and 70-85% for T2 lesions. For radiation therapy, the control rate for T1 lesions was 85-94% while the control rate for T2 lesions was 70-80%.

They evaluated factors which led to poor outcome and found three main items. First, lesions which involved the anterior commissure were difficult to adequately resect via transoral resection. Complications of open partial laryngectomy had unfavorable complications, including subglottic stenosis, bleeding, infection, and aspiration pneumonia, which occurred at an unacceptably high frequency (6-8%). Finally, a significant number of T2 lesions tend to be unfavorable for transoral resection either due to size or location. Therefore, the overall recommendation was to treat all T1 and T2 lesions with radiation therapy. However, patients with T1a lesions could be given the option of transoral laser resection.

Moving forward a few years, Agrawal and Ha³ revisited the topic. They first noted that there has been significant strides forward in transoral microsurgical techniques in the late 90s and 2000s. This movement led to a drastic decrease in open procedures. Further, these surgical advances as well as those in radiation therapy led to improved local control rates in both modalities. Also, laryngeal preservation following radiation therapy failures also had taken steps forward.
Their review of literature showed that final local control including salvage therapy for early glottic lesions had reached 97-98% while that of radiation therapy was 90-96%. Laryngeal preservation was achieved in 90-99% of transoral laser resection cases while only 83-95% in radiation therapy cases. Finally, the 5 year disease specific survival rates were roughly similar – 90-98% for surgery and 95-98% for radiation therapy.

Radiation therapy took a significant step forward with better determining amount per single dose and total dose. While variable initially, the standard became 65 Gy. Initially, the amount of radiation per day was dosed low – about 1 Gy per day – but has since been raised to at least 2 Gy – if not 2.25 Gy – to achieve better results. Research also determined that radiation treatment lasting less than 40 days had significantly better local control than those lasting longer (95-100% vs 79-84%). Finally, in the cases of recurrence, these were diagnosed earlier and treated with trans-oral laser resection more frequently than before.

Agrawal and Ha concluded that local control including laryngeal preservation rates were roughly similar between both laser resection and radiation therapy. The prior concern voiced by Mendenhall regarding anterior commissure challenges had now been contradicted by work by Dr. Steiner. Finally, radiation therapy had showed significant improvement in results. Therefore, their recommendation was that laser resection and radiation therapy may be equally effective. Thus, care for each patient should be individualized. It is with decision in mind that we now proceed to discuss voice quality.

**Voice Quality**

With tumor control rates being roughly similar, the evaluation of voice quality has been intensely studied. The effects of radiation on the vocal folds has been well studied and include changed mucosal wave, stiff mucosal wave dynamics, hyperventricular fold activity, chronic inflammation, fold tissue inelasticity, and glottal incompetence. In a review of 12 articles from 1985 to 2003 that compared voice outcomes for early glottic lesions treated with surgery versus radiation therapy, 5 deemed a significant improvement in voice outcomes for radiation, 5 found the results to be equivocal, and 2 did not compare to sufficient depth. However, each of these articles used different methods to compare and evaluate their patients. To that end, we will analyze a few of these in depth.

In 1994, McGuirt et al reviewed 24 patients – 11 undergoing surgery and 13 receiving radiation therapy. All patients were diagnosed with T1a glottic SCCa. All patients were male to allow easier voice comparisons. All evaluations were performed 6 months post-treatment, and no recurrences were noted. With all surgical cases, as much as possible of the vocalis muscle and thyroarytenoid muscle was preserved. In the authors opinion, in all cases, less than half the cordal muscle mass was resected. They reviewed maximum phonation time, intensity, fundamental frequency, perturbation scores, and voicing percentage. Their results demonstrated improved perturbation scores and overall voicing with laser resection; however, radiation demonstrated improved fundamental frequency and intensity. Therefore, their recommendation was treatment of early glottic carcinomas with laser as it is more expeditious and cost-effective.

In 2004, Krengli et al studied 57 patients – 30 receiving surgical cordectomy and 27 receiving radiation therapy. In both groups, the gender ratio and age were similar. All patients underwent definitive evaluation of their voice at 2 years after completion of therapy. They showed that nearly 25% of patients in the XRT arm demonstrated severe glottic inadequacy. This was contrasted with nearly 65% of patients in
the surgical arm showing insufficient ventricular compensation or arytenoid hyperadduction. They demonstrated that patients whose surgery did not include resection of vocalis muscle did better than those whose did. Finally, they reviewed dysphonia scores and found that severe dysphonia was noted in 25% of patients receiving XRT versus 70% of patients undergoing surgery. Thus, their recommendation was that all patients with early glottic cancer should receive radiation therapy.

In 2004, Peeters et al\(^6\) published on their research – specifically analyzing T1a lesions only. 102 patients were included with 56 placed in the surgical arm and 46 in the radiation therapy arm. All patients underwent a pre-operative videostroboscopy to evaluate for mucosal wave. If present, patients were selected to undergo surgical treatment. If no wave was noted, patients were diverted to the radiation therapy arm. The voice handicap index was used to assess these patients. 60% of patients in the surgical arm had normal scores while only 42% of patients in the XRT arm had normal scores. They noted greater problems with intelligibility in patients with XRT than Surgery (60% vs 39%). Further, they noted that vocal deterioration by nighttime was greater in patients treated with XRT than surgery (70% vs 49%). They concluded that all T1a glottic cancer patients should undergo routine videostroboscopy. Also, T1a glottic cancer treated with radiation may lead to more voice-related problems. Therefore, their recommendation was that superficial tumors – especially if a wave is present – should be treated with surgery.

While these three articles presented a few perspectives, a more exhaustive meta-analysis was performed by Cohen et al\(^7\) in 2006. They performed a meta-analysis which included 6 studies for a total of 208 patients treated surgically and 91 treated with external beam radiation therapy. All patients had T1 glottic SCC and completed pre-/post-treatment VHI questionnaires. Of the 6 studies, all showed an average VHI of 25 or better. Of these articles, Peretti et al\(^8\) was unique in that they also compared their VHI findings to those of non-neoplastic lesions. They noted that, while VHI in glottic SCC patients were 11.5, the VHI of patients with non-neoplastic lesions – cysts, polyps, nodules – were between 30 and 50. The meta-analysis concluded that the average VHI of patients undergoing trans-oral laser resection was 12.9. The average VHI for patients undergoing radiation therapy was 18.5. They concluded that the differences between the two treatments’ VHI outcomes was because of possible understaging of tumors in radiation group, decreased vibration in radiation group in the unaffected contralateral vocal fold, altered microcirculation of vocal folds, and loss of salivary glands in the larynx.

**Cost Analysis**

While several articles have been written in the past regarding cost-analysis, one recent article laid out the individual costs clearly and succinctly. Higgins\(^9\) compared the cost of laser treatment of early glottic carcinomas with radiation therapy. The laser treatment cost was averaged to $1836 per case, and this cost included operating room cost, professional fees (surgeon, anesthesia, and pathology), CO2 laser cost, and the operating room microscope. Similarly, radiation treatment of these lesions was estimated at $2454 per case which included radiation center staffing and material costs, LINAC annual cost, and professional fees (radiation oncologists and nurses). Further analysis included finding the cost for surgical treatment of initial therapy failures. The cost of a partial laryngectomy with local flap was $7675.82 while a total Laryngectomy was estimated at a cost of $8062.80. Finally, a partial Laryngectomy with free flap was the most costly procedure at $13201.89. As a way of acknowledging the necessary post-operative care, these figures included 10 day hospital stay and home health nursing visits for 4 weeks.
Using rates of local control as well as percentage treatment failure, the article summarizes the full impact of treatment cost by calculating both the best case scenario as well as scenarios factoring in surgical intervention for recurrences. For the best case scenario where the patient is cured by primary treatment with no long-term sequelae, the cost of CO₂ laser for therapy was $1836.86 while that for radiation therapy was $2386.95. This was only a slight margin of $550. In the scenario of accounting for accurate local control rates including surgical therapy for primary treatment failures, CO₂ laser therapy when chosen for initial treatment led to a total cost of $2407.32 while patients treated with radiation as primary therapy led to a total cost of $4828.79. These figures show a significant difference as radiation costs approximately double what CO₂ laser therapy costs.

**Surgical Intervention**

Finally, we will discuss briefly the various types of cordectomies as decided by the European Laryngeal Society\(^\text{10}\). The figures below show the range from type I through type V. Type I is subepithelial resection while Type II is subligamentous resection. Type III resections involve removal of some portion of the vocalis muscle with or without some removal of the ventricular fold. Type IV are complete cordectomies with removal of all layers. Type Va resections include the contralateral cord while Type Vb include the ipsilateral arytenoid. Type Vc include the false vocal fold while type Vd include the subglottis.

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**Fig. 1a, b** Subepithelial cordectomy (type I)
Fig. 2a, b Subligamental cordectomy (type II)

Fig. 3a, b Transmuscular cordectomy (type III). In order to expose the entire vocal fold, partial resection of the ventricular fold may be necessary (hatched area)
**Fig. 4a, b** Total or complete cordectomy (type IV). The ipsilateral ventricular fold can be removed partially or totally to ensure complete resection of the vocal fold (hatched area)

**Fig. 5** Extended cordectomy encompassing the contralateral vocal fold (type Va). The extent of the resected contralateral vocal fold depends on the extent of the tumor
Fig. 6 Extended cordectomy encompassing the arytenoid (type Vb)

Fig. 7 Extended cordectomy encompassing the ventricular fold (type Vc). The inferior resection of the vocal fold is maximum
While classic thinking suggests that less resection can lead to better voice outcomes, one recent paper suggests that this may not be true. A key surgical principle of glottic lesion management is to preserve as much of the ligament and epithelium as possible. Hillel et al\textsuperscript{11} reviewed 17 patients with T1 or T2 glottic SCC who were treated with either subligamentous resection (13/17) or subepithelial resection (4/17). They noted that patients with subligamentous resection showed excellent glottic closure in comparison to the subepithelial resection group. Further, the mucosal wave in patients with subligamentous resection was only mildly decreased while those with subepithelial resection was moderately decreased. While only a small cohort of patients, this study calls into question a classic teaching of—less resection leads to better outcome. The authors felt that loss of the superficial lamina propria leaves the vocal ligament exposed which is poorly pliable. However, removal of the ligament allows the exposed vocalis muscle to undergo hypertrophy and hyperplasia. This growth leads to sooner post-operative glottic closure and provides a fair wave.

**DISCUSSION: Dr. Michael Underbrink on Management of Early Glottic Cancers**

That was a very nice talk Dr. Ventkatesan, and I’ll add a few comments. Those are all very good considerations that we all go through. One is voice quality, local control, and the cost analysis and you know when we talk to patients at this point in time for select lesions I always tell them that in addition to the savings in radiation which is a good consideration for should they have another primary somewhere there is the drying of the larynx, the loss of salivation.

I also tell them, the younger the patient, since the control rates are so good with these early glottis lesions that they’re going to have drying of the larynx and loss of salivation that they’re going have to deal with. And as time goes on I don’t know if it’s a logistical possible study fifteen years down the road sometimes these patients have a difficult time with their larynxes that they wouldn’t have otherwise. The longer you wait after even a subligamental resection the better the voice gets over time. Sometimes it will take over a year to get a ligamentous wave back once you’ve disrupted that process, but usually they do quite well compared to the radiation arm and we can see that based on the studies that it’s pretty equivocal, so given the treatment options I always think that it’s based on the selection of the tumor. I wouldn’t necessarily say that losing the mucosal wave is any contraindication to the surgical resection but sometimes, depending on the patient’s age that’s what I make my decision.
With a younger patient, probably I’m going to offer them surgery because they’re going to have later effects down the road. If they have lack of mucosal wave or stiffening before the surgery and they’re older then I’ll say that they’re probably not going to have the same problems later on down the road. But we’ve come a long way with transoral laser I think another important consideration is margins and sending margins to the pathologist.

The nice thing about these tumors is that we’re going to be monitoring them postoperatively on a monthly basis and so as most transoral laser surgeons do if there happens to be a pop down the road you can always re-excite margins so that’s nice. I think the radiation therapy person would probably say well that’s ok, if we radiate you we can always save your surgical treatment for later.

**Bibliography**

1. AJCC Cancer Staging Manual 2002