

Chapter 2

Laser Interventions for Early Cancer in the Upper Aerodigestive Tract

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Introduction

The glottis is a unique subsite of the aerodigestive tract where cancer often presents early. A small lesion of the vocal fold often causes a marked change in an individual's voice, leading to the discovery of early glottic cancer. Further, the glottis is a unique subsite of head and neck cancer as its lymphatic drainage is sparse. This combination of factors causes a large number of glottic cancers to present early without spread to adjacent lymph nodes.

Due to this unique presentation of early glottic cancer, diverse treatment methods have been developed. Historically treatments have been in the form of open transcervical surgery, endoscopic transoral surgery using cold steel instrumentation, and external beam radiation therapy. However, the introduction of lasers to the management of early glottic cancer has revolutionized management of this disease. Lasers offer unique benefits in terms of accurate ability to cut and simultaneously coagulate tissue.

The challenge in surgically treating laryngeal cancer is that there is little space to work and stray damage can result in loss of function. Lasers have been used to increase accuracy of surgery in a confined space. Other advantages of lasers include decreased postoperative edema and the ability to seal small blood vessels and lymphatics thereby minimizing potential metastatic spread [1].

The laser has revolutionized the way in which early glottic carcinoma is treated. Prior to the widespread use of the laser, patients with early glottic carcinoma would require open transcervical surgery with laryngofissure and cordectomy, or endoscopic

cold steel-assisted resection, which was fraught with decreased visibility due to the propensity of the tissue to bleed. In the mid-twentieth century, radiation therapy became an option for treating patients with laryngeal cancer, but this has been associated with higher cost, as well as acute and late side effects of radiation [2]. Additionally, patients that live far away from a city that has radiation therapy centers can ill afford to make the daily travel to the center over the required 7 weeks. As the laser became more available and affordable, patients now have another excellent option for treatment for their laryngeal cancer. Understanding the role of lasers and the challenges in the use of lasers may help engineers to design improved lasers that could increase efficacy of treatment, decrease complications of treatment, decrease costs, and increase availability of technology.

Definition of Early Laryngeal Cancer

Laryngeal cancer is prevalent worldwide, and in the United States is expected to affect over 12,000 new persons in 2014, while 3600 people with laryngeal cancer are expected to die in 2014 [3]. An estimated 3400 new cases of hypopharyngeal cancer will develop in 2014. Of laryngeal cancer, 60 % will affect the glottis, 35 % will affect the supraglottis, and the remaining 5 % will affect the subglottis.

The most common type of malignancy that presents in the larynx is squamous cell carcinoma, and the discussion of this chapter will focus on management of this disease. Tables 1 and 2 show the American Joint Committee on Cancer staging of supraglottic and glottic cancer, recently updated in 2010 [4]. T1a lesions may involve the superficial lamina propria layer, vocal ligament, or vocalis muscle of one vocal fold. Both surgical and radiation treatment create defects or scarring that adversely affect normal laryngeal function, namely, voice and swallow. As the depth of invasion increases, surgical resection creates glottic incompetence with resulting dysphonia [5].

The unique challenge with management of glottic malignancies is maintenance of vocal fold microstructure. Hirano's seminal description of the cover-body model of phonation led to further understanding about relation of depth of invasion and vocal outcomes [6, 7]. The goal for treatment is the removal of all cancerous tissue with a small margin of normal tissue, while preserving maximal normal tissue to optimize vocal function. The laser, with its ability to remove submillimeter segments of tissue, allows the surgeon the precision to balance the complete removal of cancerous tissue while avoiding removing excess noncancerous tissue that could adversely affect the functions of the larynx.

Table 1
Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
<i>Supraglottis</i>	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
<i>Glottis</i>	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Nodal and distant metastatic staging have been omitted as early laryngeal cancer features neither nodal nor distant metastasis

As long as the contralateral vocal fold is without significant disease, then vocal function will be largely preserved if glottic closure is complete [8]. For this reason, T1b lesions and lesions of the anterior commissure create defects in the contralateral vocal fold that result in significantly decreased vocal function. T2 lesions

Table 2
Anatomic stage/prognostic groups

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

likewise require deeper resections thereby causing larger glottic gaps. The surgeon must counsel the patient regarding these effects as goals for treatment are discussed.

Mechanisms of Lasers Used in Laryngeal Cancer

Two lasers have been described to commonly manage laryngeal cancer: carbon dioxide (CO₂) and potassium titanyl phosphate (KTP). The first description of the carbon dioxide laser in laryngeal surgery was in 1972 when Jako and Strong treated benign and premalignant laryngeal lesions [9]. In 1975, Strong described the use of the CO₂ laser for excising carcinoma [10]. To date the carbon dioxide laser is the most commonly used laser for excision of glottic cancer. The carbon dioxide laser, with its 10,600 nm wavelength, is preferentially absorbed by water. Traditionally carbon dioxide laser beam is delivered into the larynx during direct microlaryngoscopy using a micromanipulator to target the tissues of interest. The laser spot size can be focused to 250 µm with recent technological advances [11], and a very precise cut may be made with this laser while decreasing thermal injury to surrounding tissue. This precision is critical in the larynx where

Table 3
Summary of lasers used to treat laryngeal cancer

Laser	Wavelength	Chromophore	Delivery
KTP	532 nm	Oxyhemoglobin	0.4 and 0.6 mm fiber optic
CO ₂	10,600 nm	Water	(1) 1.2 mm hollow core with dielectric mirror (photonic band-gap fiber) (2) Line-of-site/micromanipulator

preservation of tissues leads to dramatic improvement in voice after surgery.

Recently, a hollow fiber has been developed that delivers the energy from the carbon dioxide laser. (currently manufactured by OmniGuide and Clinicon). The fiber consists of a hollow-core tube surrounded by a dielectric mirror, which allows the use of CO₂ either within a flexible endoscope or delivered through a handpiece. The fiber-based delivery permitted improved angulations for tangential surfaces that were difficult for line-of-site lasers [12].

The 532 nm KTP laser is the other laser commonly used to treat early glottic cancer. This differs from the carbon dioxide laser in that its energy is transmitted through a glass fiber. Additionally, the energy from this laser is preferentially absorbed by oxyhemoglobin. This also preferentially targets hypervascular lesions [13], which includes cancerous lesions [14]. It also may result in improved hemostasis over CO₂ laser due to preferential absorption and destruction of the target lesion's supporting microvasculature. Unlike the CO₂ laser, the KTP laser has only recently seen use for treating glottic cancer. Initially it was used in the larynx for benign disease [13, 15, 16]. In 2008, Zeitel and colleagues described the use of the potassium titanyl phosphate laser (KTP) to treat carcinoma [14]. Table 3 summarizes key KTP laser characteristics compared to other lasers used in excising laryngeal carcinoma.

Surgical Technique

Before undergoing surgery, patients must be counseled with a thorough discussion of surgery and its alternatives. The surgeon must be able to counsel patients regarding the cure rates, the treatment effects on voice and swallow, and treatment complications. Patients must also have the cardiopulmonary reserve to handle the risks of general anesthesia. Finally, the surgeon must be able to

adequately expose the larynx with the laryngoscope and be prepared to perform an open resection if the larynx cannot be exposed endoscopically. Mandibular anatomic problems, such as retrognathia, enlarged tori, trismus, or problems with neck extension may prevent placement of the laryngoscope, thus requiring patients to undergo transcervical surgery or radiation instead.

Intraoperatively, the surgeon must take precautions to avoid potential fire. Flammable gases and potential fuel sources such as the endotracheal tube are within the line of site of the laser. First, the door to the room is closed and signage to alert potential incomers of laser use is placed on the door. Personnel in the room are distributed with appropriate laser-safe eyewear. Each laser has specific protective eyewear that filters the corresponding wavelength of light, and therefore eyewear for different lasers should not be used. A laser-resistant endotracheal tube is used in the patient. Because the tip of the endotracheal tube is susceptible to laser fire, it should be covered with saline-soaked cottonoid pledgets. Suction is used to evacuate laser plume, which allows improved visualization and decreases toxic and carcinogenic fumes that may inadvertently be inhaled by operating room personnel. The anesthesiologist must reduce use of flammable gases and decrease the percentage of supplementary oxygen below 30 %. Finally, the patient's face is covered in saline-soaked towels, and OR staff should always be at the ready to immediately douse any flames that start.

Endoscopic Laser Resection of Early Glottic Carcinoma

The patient is placed under general anesthesia and is intubated with a laser-safe endotracheal tube. A tooth guard is used to protect the upper dentition, and a laryngoscope placed through the oral cavity and positioned to fully expose the endolarynx and the lesion. The largest laryngoscope that fits within the patient's oral cavity and oropharynx should be used in order to permit wide binocular visualization. Univalve or bivalve laryngoscopes may be used. Regardless of the choice, the anterior commissure must be exposed; laryngoscopes such as the Storz Triangle laryngoscope or the Endocraft Zeitels Universal Modular Glottiscope permit excellent anterior commissure exposure. The laryngoscope is placed on fulcrum or gallows suspension to allow bimanual technique. The binocular microscope is used for magnification and allowing depth perception. Laser safety precautions are followed as previously discussed. In many cases, the vestibular fold may be resected to optimize exposure for surgery as well as for future cancer surveillance [17]. Saline with epinephrine is injected into the superficial lamina propria to provide vasoconstriction, hydrodissection, and to establish depth of tumor invasion; it also acts as a heat sink to decrease thermal damage to noncancerous tissue [18]. Laser-assisted resection of the cancer may then be performed by one of several techniques. Three methods will be described.

The extent of resection has been classified by the European Laryngological Society [19]. Such a classification has been developed

Table 4
Endoscopic cordectomy: classification by European laryngological society

Subepithelial cordectomy	Type I
Subligamental cordectomy	Type II
Transmuscular cordectomy	Type III
Total or complete cordectomy	Type IV
Extended cordectomy encompassing	
Contralateral fold	Type IVa
Arytenoids	Type IVb
Ventricular fold	Type IVc
Subglottis	Type IVd

in order to help better relate extent of resection to outcomes. Table 4 shows ELS type for depth of excision. The type of resection is determined postoperatively rather than as preoperative plan. The first three types describe successive layers. Type I is performed during an excisional subepithelial resection, whose biopsy reveals carcinoma in situ and thus deeper resection is not needed. Types III and IV include cordectomies for carcinomas that invade the superficial lamina propria and the vocalis ligament, respectively; these may be T1 or T2 carcinomas, but spare the contralateral vocal fold.

***Partial Cordectomy:
En Bloc Resection***

The CO₂ laser has been traditionally used for performing a laser-assisted endoscopic partial cordectomy technique as described by Strong [10], Eckel and Thumfart [20], and Ossoff et al. [5]. Once laryngeal exposure is achieved, the lesion is grasped by the surgeon with forceps in one hand while the other hand operates the micro-manipulator. Retraction forces are placed on the lesion while the laser is fired around the margins of the lesion. The margin is initially outlined superficially and is continued into deeper planes layer by layer. The lesion is excised en bloc down to the vocalis muscle or deeper if the lesion is larger. Once the lesion is excised, small specimens are removed from the periphery and deep layers to be sent for frozen section. Any positive margins may thus be treated by additional laser resection. During the procedure, any excessive hemorrhage may be treated by a defocused beam. Rarely does laryngeal edema from surgery result in airway obstruction, and therefore the patient in most cases can be extubated immediately after surgery.

***Partial Cordectomy-
Piecemeal Resection***

Although oncologically successful, en bloc resection may increase the risk of excising excessively large margins, thereby resulting in worse vocal outcomes. Steiner described a piecemeal resection method that excised the lesion in successive fashion, allowing the

surgeon to preserve as much normal tissue as possible [21, 22]. The tumor is bisected, which allows accurate assessment of depth of tumor. The technique demands maintaining correct orientation of the specimen as well as having excellent surgical pathology that can accurately assess frozen sections. Performed correctly, the surgeon is able to avoid excising excessive noncancerous tissue, while preserving adequate margins.

Photoangiolytic Laser Corpectomy

The photoangiolytic lasers such as KTP and PDL have recently begun to be used to treat carcinomas. This technique was initially described by Zeitels et al. in 2008 [14]. His group used the KTP and PDL to treat 13 T1 and 9 T2 lesions and at the time of the report, none of the patients had recurrence of cancer. Rather than excising the lesion en bloc, the surgeon ablates the lesion with a 3 mm peripheral margin layer by layer until normal tissue is reached. This technique takes advantage of the increased density of vascularity of cancerous lesions, as the energy from the photoangiolytic lasers is preferentially absorbed by blood vessels. Success of this operation is predicated on the surgeon's ability to recognize the interface between cancerous and normal tissue, which can be challenging. Depth and width of treatment are thus determined by the exact interface with normal tissue, which is progressively seen as each layer is ablated. This results in avoidance of removing excessive normal tissue and thus optimizes vocal function. Intraoperative frozen histopathologic sections are obtained at the periphery as well at the deep margins to confirm complete treatment.

Importance of Intraoperative Frozen Sections

Frozen sections are essential for determining extent of resection, while preserving noncancerous tissue. In the past, there has been concern that the thermal effect of the laser on tissue decreases the reliability of frozen section. However, Remacle et al. retrospectively reviewed multiple patients undergoing endoscopic CO2 laser corpectomies for T1 through T3 glottic cancers [23]. This group found that frozen sections were concordant with permanent sections in nearly 95 % of cases.

Endoscopic Laser Resection of Supraglottic Carcinoma

Early supraglottic carcinoma may also be resected with endoscopic approach and laser. Laser resection for supraglottic cancer was first reported by Vaughan in 1978 [24]. Zeitels et al. reported on a series of 45 patients who had T1 to T3 lesions of the supraglottic larynx or posterior pharyngeal wall without any neck disease [25]. T1 and smaller T2 tumors were easily resected with negative intraoperative margins and did not undergo radiotherapy, and only one patient had developed a neck recurrence, subsequently undergoing neck dissection and postoperative radiation. The 23 patients with larger tumors all received postoperative radiation, and despite this, four patients had recurrence, eventually requiring total laryngectomy, and a total of four patients died from their disease. This study

as well as early works by Rudert [26], Eckel [27], Steiner [28], and Davis [29] has established endoscopic laser resection for supraglottic carcinoma as a viable option for selected patients. Because of the propensity of epiglottic lesions to spread to the preepiglottic space, especially with infrahyoid epiglottic lesions, this space must be resected as well. In fact, Zeitels' group did not perform endoscopic resection at all if this space was involved [25].

Complications of Endoscopic Laser Surgery

Complications directly related to use of the laser are rare, but potentially devastating. Healy et al. described nine complications in 4416 CO₂ laser cases of the aerodigestive tract for a rate of 0.2 % [30]. Six of these complications were fires, and of these four were fires from ignition of the endotracheal tubes that were not laser protected. Two complications were due to excessive bleeding from bronchial tumors. One complication resulted in a facial burn from an overheated rigid bronchoscope resting on a patient's cheek. Other potential complications related to endoscopic resection are granuloma from exposed cartilage or char left after the operation. Chondritis may also develop from exposed cartilage and may be prevented by perioperative antibiotics and steroids. Hemorrhage should be controlled by a return to the operating room and defocused beam or electrocautery to site of bleeding.

Outcomes of Endoscopic Laser Surgery

Voice Quality with Endoscopic Laser Surgery versus Radiation Therapy

Early studies contrasting radiation versus surgery for early glottic carcinoma found that although disease control was similar, voice quality was significantly worse for surgical resection [31–33]. A meta-analysis by Higgins et al. of 7600 patients with early glottic cancer showed a trend for better voice quality with radiation over endoscopic laser surgery. In contrast, some recent studies suggest that voice outcomes after endoscopic laser surgery for glottic carcinoma are no worse than radiation therapy [34, 35]. One study found that voice was better with endoscopic laser surgery, but patients undergoing surgery were selected due to a more superficial involvement of the tumor, and therefore only required either ELS type I or type II cordectomy [36]. Indeed, while ELS type I and II resections showed better voice compared to radiation, ELS type III and type IV, sub-ligamentous and submuscular resections, had significantly worse voices compared to radiation [32]. This suggests that depth of invasion and deeper resection worsens voice quality. Additionally significant worsening was noted when the anterior commissure was involved [34, 37].

***Oncologic Efficacy
of Endoscopic Laser
Surgery***

Surgeons must guide patients deciding between radiation and surgery for early glottic carcinoma as both modalities have been shown to be essentially equivalent in terms of disease control [2, 38–41]. The most important factors to consider in determining modality of treatment are efficacy of removing disease, maintenance of voice and quality of life, and costs of care. Disease control as well as overall survival is established to be high for early glottic carcinoma. Lucioni and colleagues found that overall survival was 90 %, and when excluding mortality not related to laryngeal carcinoma, disease-free survival was 98.8 % [42]. Indeed most studies performed to date support that endoscopic laser resection of early glottic carcinoma is equivalent and in some cases superior to radiation therapy regarding control of disease. Remmelts et al. found that 5-year laryngeal preservation for T1 glottic cancers treated with laser was 93 %, which was statistically significantly better than those treated by radiation therapy versus 83 % for radiation therapy [37]. Additionally Krengli et al. found that local control over 60 months was 95.6 % with endoscopic laser surgery while 91.2 % for radiation therapy [32]. The meta-analysis by Higgins et al. examined local control and laryngectomy-free survival in 7600 patients with T1 or T2 glottic cancer and found that there was no difference between endoscopic laser surgery and radiation therapy, although there was a trend toward better survival in endoscopic laser surgery [43].

***Costs of Endoscopic
Laser Resection
Compared to Radiation
Therapy***

Several studies in Europe and North America suggest that endoscopic laser resection is less costly than radiotherapy for Tis and T1 cancers. Goor et al. reviewed 89 patients with T1a glottic carcinoma over 2 years. 35 were treated with 6000 cGy whereas 54 were treated with endoscopic laser resection. Radiotherapy cost 8322 euros per case versus 4434 euros per case for surgery. Furthermore, disease control and voice quality were not found to be different [40]. Similarly Higgins performed a meta-analysis comparing radiotherapy versus endoscopic laser resection for T1 glottic cancers [2]. Average costs of radiotherapy were found to be \$4829 whereas endoscopic laser resection cost \$2407.

***Endoscopic KTP Laser
Surgery Efficacy***

Although not used as extensively as CO2 laser, the KTP laser is showing some promise as an excellent tool for treating early glottic carcinoma. Murono et al. performed KTP endoscopic KTP laser surgery for T1a glottic carcinoma in 24 patients. Tumor was excised with KTP laser, followed by circumferential ablation surrounding the surgical margin, and found local control in 22 of the 24 patients (91.7 %). This is comparable to the local control rate noted in the literature [44]. Additionally voice results were found to be excellent as patients had significant improvement from pre- to postoperative voice after KTP laser surgery in T1 and T2 glottic carcinomas [45].

Summary

Laser laryngeal surgery is a powerful tool for management of early glottic cancer. Laser surgery may offer patients improved cancer-free and voice outcomes as well as cost much less to perform.

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