RECURRENT GLOTTIC CANCER

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Panelists: Terry Day, MD, Paul Flint, MD, Marshall Strome, MD

CASE PRESENTATION

A 71-year-old man is referred for evaluation of hoarseness and a right vocal fold lesion. The patient reports that 4 years ago, he was diagnosed with a squamous cell carcinoma (SCC) of his right true vocal fold. He was treated with radiation therapy over 7 weeks to his larynx to a total dose of 70 Gy in 200-cGy fractions. A diagram mapping his original tumor was not available but according to the medical records was a T1aN0M0 lesion of the right true vocal fold. He did well until 9 months ago when he developed persistent, slowly worsening hoarseness. Reevaluation by the referring physician and subsequent biopsy of the anterior right true vocal fold revealed invasive, moderately differentiated SCC, and moderate dysplasia of the anterior left true vocal fold. The patient denied any otalgia, hemoptysis, difficulty breathing, dysphagia, or odynophagia.

His past medical history was significant for hypertension controlled with medication, and coronary artery disease 5 years status post 4 vessel coronary artery bypass grafting (CABG), during which he had a tracheotomy and was ventilator dependent for 2 months postoperatively. He is now able to walk up 2 flights of stairs with no difficulty. He smoked 1 pack of cigarettes a day for 35 years, but quit 15 years previously, and has 1 drink per day. He is retired and does not use his voice professionally.

Physical examination revealed a healthy man who appeared as his stated age of 71. His voice was raspy and high pitched, with no stridor. Indirect mirror exam and flexible fiberoptic examination of his larynx showed normal vocal fold mobility bilaterally, thickening of the free edge of the anterior half of the membranous right true vocal fold up to and including the anterior commissure and 3 to 4 mm of the left true vocal fold. There was no supraglottic or subglottic extension and no obvious subglottic stenosis. Examination of the neck showed no palpable adenopathy, and normal hair-bearing skin except for the skin overlying the thyroid cartilage.
**Question 1: What other additional studies are necessary at this point in the evaluation, and why?**

*Dr. Day:* These cases require a logical approach to diagnosis and treatment accounting for optimal cure while maintaining quality of life. The following diagnostic approach is indicated:

1. Obtain records from prior diagnosis and treatment
   a. Review stage, pathology slides, scans, and clinical exam
   b. Review radiation treatment dose, ports, and techniques
2. Complete comprehensive exam including videolaryngoscopy
   a. Compare pretreatment exam to current exam
   b. Consider modified barium swallow/therapy for conservation laryngectomy procedures
   c. Pulmonary function tests if conservation procedure considered
3. Obtain CT/position emission tomography (CT/PET) scan
   a. Compare findings to pretreatment radiographs
   b. Consider: extent of disease, regional risk, functional goals
4. Educate patient and family on treatment options

This patient would be seen in a multidisciplinary setting including specialists in head and neck surgery, radiation oncology, medical oncology, and speech pathology, a head and neck nurse specialist, and a clinical trials coordinator. Presentation of the case with images/videos would be important for a multidisciplinary tumor board to provide team recommendations. A full physical exam of the head and neck with careful evaluation of the neck and endoscopic evaluation of the entire larynx and pharynx would be performed to look for second primary tumors. Videostroboscopy is necessary to determine the vocal fold function and compare with the laryngeal function prior to radiation therapy and what effect was secondary to tumor versus treatment. If the vocal fold had reduced (rT2) function or fixation (rT3), this would signify the possible need for a more aggressive surgical approach because of muscle, arytenoid, or recurrent laryngeal nerve involvement. The dosage, treatment ports, and technique of radiation therapy vary greatly and, therefore, are important in assessing the adequacy of treatment and assessing options for further therapies. The pretreatment and posttreatment histopathologic slides should be reviewed to confirm the diagnosis and any negative prognostic indicators. It is equally important that the pretreatment videolaryngoscopy, digital images, CT or MRI scan, clinical description, vocal fold function, and videostroboscopic images be reviewed to assess the location and extent of the initial tumor and the function of the larynx. Additionally, updated radiographic imaging is indicated to assess the local extent of tumor and potential for regional metastatic disease. This can be performed equally well with CT or MRI with and without contrast. However, in recurrent disease, our guidelines include the use of CT/PET scan, because of a higher risk of metastatic disease and worse prognosis, which may offer additional information related to the presence of regional and distant metastasis and unilaterality versus bilaterality of disease. It should be kept in mind that functional PET studies provide relative accuracy of nodal positivity to approximately 6 to 8 mm with current technology. The increasing utility of CT perfusion has been utilized in clinical trial settings to assess questionable lesions following chemoradiation that may be nondiagnostic with other technologies. In the case described, a full-body CT/PET with 1.5-mm cuts of contrast and noncontrast CT of the larynx would be obtained to specifically identify the size, extent, and invasion of the primary site. An MRI may provide additional detail, including cartilage involvement, nodal architecture, and subclinical extension. If regional disease were present, the primary site of recurrent would be considered more aggressive than evident from the biopsy material. Obviously, a regional or distant metastatic lesion would also signify more aggressive disease and may alter or obviate the planned type laryngeal intervention.

In cases of recurrent carcinoma following radiation, the clinically evident tumor may be obscured by post-radiation changes, fibrosis, edema, and mucosal damage. These areas may appear to be treatment-related side effects, although at surgical resection has been found to harbor occult microscopic malignancy.

*Dr. Flint:* Additional studies are not required at this time. CT has been shown to be less sensitive than MRI with respect to cartilage invasion. PET/CT may increase sensitivity for detecting lymphatic spread; however, given the recent biopsy, this may result in a false-positive result.
Dr. Strome: A gadolinium MRI was obtained and did not show thyroid cartilage invasion or suspicious adenopathy. A spiral CT would add little, and I would not order such. A PET/CT is not indicated as the likelihood of distant disease is remote. It would be important to review the MRI and pathology.

An MRI with gadolinium was obtained that showed no thyroid cartilage involvement and no metastatic adenopathy. A videostroboscopy demonstrated impairment of the mucosal wave along both membranous vocal folds, but greater on the right side.

**Question 2:** Subsequent direct laryngoscopy confirmed the extent of the lesion as described above and is shown in the Figure. The anterior aspects of both vocal folds are firm, but the posterior half of both vocal folds are soft to palpation. It is staged as rT1bN0M0. What treatment options are available for this patient?

Dr. Flint: Several options are available to this patient and supported by current literature. Endoscopic resection of early glottic lesions post-radiation therapy is becoming more popular with advanced imaging capability. However, given the location of this tumor, I would not recommend endoscopic resection because growing evidence implicates anterior commissure involvement post-radiation as a poor prognostic factor. Margin control intraoperatively is difficult in this region, and the likelihood of anterior extension is high.

Reirradiation is not an option in my experience as laryngeal function is severely compromised; and, alternative therapies such as PDT or pulse dye laser therapy would not adequately address anterior commissure or early cartilage involvement. Open resection may also be considered in this setting, including anterior vertical hemilaryngectomy and supracricoid resection with crico-hyoidopiglottopexy (CHEP). Either procedure is acceptable; however, the CHEP resection that includes the entire anterior commissure and paraglottic space is preferable.

Dr. Strome: Surgery is the only viable alternative. Three procedures are reasonable considerations.

(1) An endoscopic laser resection to which I would add cryoablation.
(2) Fronto-lateral laryngectomy.
(3) Supracricoid laryngectomy with cricohyoid epiglottopexy.

A total laryngectomy would be excessive and should not be performed. I say this recognizing his past history of pulmonary insufficiency. Most important in this regard is that he can climb 2 flights of stairs now and seemingly had no difficulty following his biopsy, which I assume was performed under general anesthesia.

Dr. Day: Regarding the case described that follows biopsy revealing invasive carcinoma on the right and another area of dysplasia of the left vocal fold. This situation can be a result of 2 different presentations of recurrent carcinoma. The first is in a setting of condemned mucosa with field cancerization where adjacent site biopsies would likely identify other areas of carcinoma and the potential for deeply invasive carcinoma also exists adjacent to the area of dysplasia. These cases are difficult to treat and cure and have a high recurrence rate with overall poor prognosis. The second presentation would be that these 2 sites represent a single invasive carcinoma with surrounding contiguous areas of varying degrees of dysplasia and carcinoma in situ but only 1 single recurrent lesion. This situation still requires resection of both the premalignant and malignant areas but clear margins of nondysplastic tissue can be obtained.

Current options for recurrent laryngeal carcinoma depend upon the wide variety of patient-specific issues and comorbidities and treatment options available in the treating institution which
would include chemotherapy with re-irradiation, photodynamic therapy, partial endoscopic laryngectomy, partial open laryngectomy, total laryngectomy, and unilateral or bilateral simultaneous or staged neck dissection with consideration of available clinical trials.

**Question 3: What option would you recommend, and what is your rationale in making this treatment decision?**

**Dr. Strome:** If adequate endoscopic exposure could be obtained, I would perform a laser excision with frozen section control followed immediately by cryoablation. In preparation, the patient would be counseled that his voice quality would be equal to or better than his current voice quality. This is our experience with this combined treatment modality. In experienced hands, involvement of the anterior commissure is not a contraindication to this procedure. The perichondrium can be removed safely. If cartilage were found to be significantly involved, the procedure could be converted to an open option and nothing would have been lost. I would not anticipate the latter, given all the information provided.

Having currently treated 32 glottic carcinomas with this combination, 6 of which involved resection of the anterior commissure, we have had no recurrences to date in lesions crossing the commissure. The obvious advantages to this approach are that a tracheotomy is not necessary and swallowing can be initiated within 48 hours. The hospitalization would be less than 48 hours and thus the cost reduction would be substantive. Bottom line: the overall morbidity would be significantly reduced when compared with the other 2 procedures.

Finally, adding cryosurgery gives an additional margin of safety for tumor control and enhances wound healing and thus voice quality (unpublished data—submitted for presentation).

**Dr. Day:** If the patient had poor pulmonary reserve or preferred the most effective, 1-stage cure, with the most potential for normal swallowing, a total laryngectomy would be offered. If, however, the patient had adequate pulmonary reserve, preferred laryngeal preservation, and was a candidate for extended or multiple procedures, conservation procedures would be offered. In this case, if all tests were negative except for the presence of the visible lesion shown and regional and distant metastatic work-up was negative, this patient would currently (2006) be treated at our institution with endoscopic laser resection of the anterior commissure with partial resection of both true vocal folds, right greater than left, and frozen section and final pathologic analysis would be utilized to confirm margin clearance. If there were extensive positive or questionable margins, full resection would be performed endoscopically to the extent that functional compromise did not occur. If all subsequent margin analysis revealed clear margins with no negative pathologic indicators, the patient would be followed with serial exams and subsequent laryngoscopy with biopsy at 3 months postprocedure. Swallowing function would be assessed postoperatively with a modified barium swallow and preoperative/postoperative swallowing rehabilitation. Due to the difficulty with adequate interpretation of frozen section following radiation therapy, a total laryngectomy would not be performed during this procedure but would be staged if tumor margins were in question following final pathology. If this situation arose in a case where there were positive margins after final pathologic analysis, most patients would be offered open partial or total laryngectomy unless a small area of residual disease could be identified and resected endoscopically. Open hemilaryngectomy, supraglottic laryngectomy, extended supraglottic laryngectomy, or supracricoid laryngectomy is reconstructed in the standard fashion or more frequently with laryngopharyngotracheal reconstruction using free tissue transfer in post-radiation patients who have received over 60 Gy to the larynx. In this particular case, if persistent disease were present following endoscopic resection, a partial laryngectomy with free tissue transfer (radial forearm free flap) reconstruction would be performed unless bilateral arytenoid dysfunction resulted, in which case total laryngectomy would be performed.

**Dr. Flint:** Based on our experience at Johns Hopkins, I would recommend CHEP over a lesser open procedures or endoscopic resection. The risk of cartilage involvement with anterior commissure disease post-radiation warrants aggressive treatment. Furthermore, radiation does not preclude a conservative procedure post-radiation.

**Question 4: Do the neck(s) need to be treated, and if so, what treatment would you recommend?**
Dr. Day: The patient presented has an rT1bN0M0 cancer, and thus, the approach to the primary site may direct the approach to the neck. If an open procedure were performed on the primary site, an ipsilateral neck dissection should be performed, first, since the neck was violated and, second, for consideration of adjuvant therapy since the neck was likely not treated primarily with radiation.

If an endoscopic approach were undertaken for this lesion, we would opt to observe the neck pending final pathologic parameters including margin status, perineural spread, cartilage involvement, and lymphovascular invasion. These situations would direct the surgeon to discuss the increased risk with the patient and consider a staged neck dissection.

Thus, the ipsilateral neck (levels 2, 3, 4) would be addressed if any of the following scenarios existed: (1) evidence of metastatic regional disease on physical exam, MRI, or CT/PET scan, (2) the tumor had extensive involvement beyond the larynx into the supraglottic area, thyroid cartilage, or pharynx, (2) negative pathologic prognostic indicators were identified, including perineural, lymphovascular, or spindle cell differentiation, (3) the patient was not able to comply with frequent follow-up evaluations and endoscopic examinations. The contralateral neck would be addressed with a selective neck dissection (levels 2, 3, 4) if the disease crossed the midline or with invasive carcinoma into the supraglottic larynx.

Dr. Flint: This lesion is currently staged as an rT1b lesion. Treatment of the necks is not indicated unless intraoperative findings or pathology alter the stage of disease. Suspicious nodes should be sent for frozen section analysis. Both anterior hemilaryngectomy and CHEP procedures will provide adequate specimen to determine if tumor has progressed to involve the thyroid cartilage and/or beyond the confines of the larynx. Unfortunately, this is not likely to be evident intraoperatively given the negative imaging study. If it is ultimately determined that cartilage invasion exists, radiation therapy may be considered an option to address the necks, specifically, levels II, III, IV, and VI.

Dr. Strome: The necks do not need to be treated.

DISCUSSION

The management of recurrent, early T-stage SCC of the glottic larynx after radiation therapy remains controversial and is highly individualized. The appropriate diagnostic workup in an ideal clinical situation is well outlined by Dr. Day. The importance of documentation by the initial treating surgeon in carefully mapping the extent of the primary tumor and nodal disease, and videostroboscopy findings in early-stage glottic cancer is very helpful should a recurrence develop. At times, the initial staging evaluation is not available at the time of referral for salvage treatment to a tertiary care center. Restaging is more difficult because of radiation edema or mucosal changes, recent biopsies, and deep submucosal nests of recurrent cancer. Dr. Flint does not recommend additional diagnostic studies to restage the recurrence because of the low incidence of nodal metastasis (<5%), and an imaging study would not change his management of the primary disease. In contrast, Dr. Strome uses MRI data to evaluate cartilage involvement at the anterior commissure and videostroboscopy to evaluate mucosal wave impairment, which may help detect submucosal disease. Neither Dr. Flint nor Dr. Strome recommend PET/CT because of the low risk of distant metastasis, and the increase likelihood of false-positive result in the cervical nodes if recent biopsy had been done.

The recurrent tumor is restaged and rT1bN0M0. The intraoperative photograph shows that the tumor is ill defined, but the mucosa is irregular in the anterior half of the right TVF that is firm to palpation; the anterior commissure is involved but the mucosa is normal near the area of Broyle’s ligament, and 2 to 3 mm of the mucosa of the left anterior TVF is abnormal. All available treatment options are elucidated by the consultants, but the preferred treatment modality is surgical salvage. Dr. Strome makes the observation that even without pulmonary function tests, the patient by clinical history has adequate pulmonary reserve for a conservation laryngeal procedure because of his ability to walk up 2 flights of stairs. Given adequate pulmonary reserve, total laryngectomy should not be performed for salvage unless warranted by unexpected intraoperative clinical findings which are highly unlikely.

The recommended surgical treatment differs with each consultant. Dr. Day recommends endoscopic CO2 laser resection with frozen section control. An open conservation laryngeal procedure or total laryngectomy would be performed only for positive margins that could not be re-resected endoscopically. Dr. Flint recommends CHEP because of the risk of cartilage involvement at the anterior commissure and the ability to clear the paraglottic space. Dr. Strome advocates endoscopic CO2 laser resection with cryoablation because, in his experience, the
combined-modality treatment offers a wider margin with good local control rates, better voice from improved healing, less surgical morbidity, and a shorter hospital stay. He emphasizes that anterior commissure involvement is not a contraindication to endoscopic resection because if the thyroid cartilage were involved the procedure could be converted to an open procedure at that time or a later date.

All of the consultants agree that elective neck dissection is not indicated in this patient because of the low risk of cervical metastatic disease. Staged elective neck dissection (Dr. Day), or postoperative irradiation to the nodal levels at risk (Dr. Flint) are both options if warranted by post-resection histopathologic analysis.

In summary, a myriad of factors must be considered in treatment decision-making that are both patient related and tumor dependent. Patient-related factors include age, medical comorbidities particularly pulmonary disease, voice demands, patient treatment biases, and, if the patient’s anatomy allows, adequate endoscopic visualization. Tumor-dependent factors include extent of local and regional disease both pretreatment and at the time of recurrence, in addition to the degree of tumor differentiation and growth pattern. Distant metastatic disease is unusual in rT1-2N0 disease. Unless the patient indicates otherwise, the treatment goals in order of priority are: to maximize the likelihood of local and regional control; preserve laryngeal voice; maintain airway-protective mechanisms for cough, pulmonary toilet, and Valsalva’s maneuver; and preserve a satisfactory airway without a tracheostoma or indwelling tracheotomy tube. This patient illustrates the controversy and nuances in treatment decision making.