Transoral Carbon Dioxide Laser Supraglottic Laryngectomy and Irradiation in Stage I, II, and III Squamous Cell Carcinoma of the Supraglottic Larynx

Report of Southwest Oncology Group Phase 2 Trial S9709

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Objective: To evaluate feasibility, functional outcome, and disease control of endoscopic surgery and irradiation in patients with squamous cell carcinoma of the supraglottic larynx.

Design: Prospective, single-arm, phase 2 multi-institutional trial.

Setting: Southwest Oncology Group trial S9709.

Patients: Thirty-four patients diagnosed as having stage I, stage II, or selected stage III (T1-2N1M0) supraglottic laryngeal carcinoma enrolled from September 15, 1997, to December 1, 2001.

Interventions: Transoral supraglottic laryngectomy by carbon dioxide laser followed by planned postoperative radiotherapy.

Main Outcome Measures: Three-year progression-free survival, proportion of patients requiring tracheotomy as a result of surgery, and time to adequate oral intake.

Results: All 34 patients underwent surgery without major protocol deviation. Thirty-two patients (94%) completed planned postoperative radiotherapy without major deviation. At the time of analysis, only 1 patient (3%) had documented local disease recurrence at the primary disease site and required salvage total laryngectomy, and 2 patients (6%) had documented regional recurrence and required salvage neck dissection. Estimated 3-year progression-free survival and overall survival were 79% and 88%, respectively. No subjects required tracheotomy as a direct consequence of endoscopic resection. Patients who required tracheotomy before endoscopic resection due to either obstructive tumor bulk or unfavorable anatomy that precluded safe intubation (4 patients [12%]) were all decannulated in the early postoperative period (<1 week). Of the 34 patients, 24 (71%) recovered adequate oral intake (no longer requiring supplemental intravenous fluids or tube feeding) in the early postoperative period (before hospital discharge) (median time, 2 days; range, 1-7 days), with an additional 7 patients (21%) achieving delayed recovery (2.7-9.8 months). Three patients (9%) remained dependent on a feeding tube at last documented follow-up.

Conclusions: Transoral endoscopic carbon dioxide laser excision of supraglottic tumors combined with postoperative radiotherapy appears feasible in a multi-institutional setting, with reasonable disease control. Although timing was variable, most patients recovered adequate swallowing in the early postoperative period.

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The use of radiotherapy in the primary treatment of supraglottic cancers has been advocated as a reasonable alternative to open supraglottic laryngectomy in that organ function, particularly as it relates to speech and deglution, is often preserved. There is evidence, however, that primary radiotherapy alone is also associated with reduced rates of local disease control compared with surgery, particularly in bulkier tumors or when compared with combination therapy involving both surgery and irradiation.1-7

With wide acceptance of microlaryngeal surgery techniques often in conjunction with use of the carbon dioxide (CO2) laser to effectively treat many early glottic malignant neoplasms, extrapolation of such less invasive surgical techniques to other regions, including the supraglottic larynx, has been described.9-11 Although initially used in the management of bulkiy obstructing supraglottic tumors to stabilize compromised laryngeal airways,9 subsequent single-institution studies have since reported the use of transoral CO2 laser microlaryngeal resection techniques in the management of early supraglottic tumors, often noting rapid recovery of swallowing function and absence of the need for adjunctive tracheostomy.10,11

Early experiences describing encouraging oncologic and functional results with this technique in combination with irradiation10,11 prompted the development and initiation of the current phase 2 surgical trial within the Southwest Oncology Group (SWOG). The objectives of the current study were 3-fold: (1) to assess the feasibility of treating stage I and II and selected stage III squamous cell carcinoma of the supraglottic larynx with endoscopic surgery and irradiation in a multi-institutional setting with several participating surgeons, (2) to estimate 3-year progression-free survival and describe the location of disease progression, and (3) to assess 2 aspects of return of function in patients treated with this technique: the length of time patients require feeding tubes and the proportion of patients requiring tracheostomy as a result of surgery.

METHODS

SUBJECT POPULATION AND ELIGIBILITY

Patients must have had newly diagnosed, previously untreated, histologically proved squamous cell carcinoma of the supraglottic larynx that was stage I, II, or selected stage III (T1-2N1M0). The vocal cords must have been free of disease. Patients found to have microscopic escape into the preepiglottic space were allowed to participate in the study. Patients must have had a SWOG performance status of 0 or 1 and adequate bone marrow reserve, and have undergone the prestudy evaluations listed in the protocol, including biopsy of the primary tumor and disease assessments by staging endoscopy and computed tomography and/or magnetic resonance imaging.

STUDY INTERVENTIONS

Surgery at Primary Site
(Endoscopic Laser Resection)

All surgical investigators were provided with both written and videotaped instructions before enrollment of study subjects. The recommended surgical technique was as follows.

After endotracheal intubation with a laser-protected tube, the epiglottis was visualized with an adjustable bivalved laryngoscope. Initial transverse epiglottectomy of the suprazyoid portion of the epiglottis was then performed, providing additional inferior exposure. The tumor was completely removed as additional tumor exposure and required limits of resection became defined during the procedure. The following regions were excised as necessitated by location of tumor involvement: infrahyoid epiglottis (anterior limit, preepiglottic space and/or thyroid perichondrium; inferior limit, anterior commissure), aryepiglottic folds (posterolateral limit, main body of arytenoid cartilage), and unilateral or bilateral false vocal cords (inferior limit, true vocal cords; inferolateral limit, deep paraglottic space). Patients in whom microscopic tumor escape was noted histologically within the preepiglottic space (hence, pathologic T3 disease) were permitted to remain in the study and their results were considered evaluable provided that tumor removal could be adequately encompassed with the resection procedure. Adequacy of resection and final tumor margin status were determined by frozen section and subsequent permanent analysis of microsurgical biopsy specimens taken from the surgical bed after tumor removal. If positive margins were identified at the foregoing limits of resection (ie, gross preepiglottic space disease, anterior commissure/true vocal cord involvement), conversion to open procedure (open supraglottic, supracricoid, or total laryngectomy) was specified.

Endoscopic procedures performed by investigators were videotaped and subjected to surgical discipline review along with accompanying operative and pathology records. Additional central pathologic review was required of submitted representative histopathologic specimens obtained during previous biopsy and surgery. Documentation pertaining to overall surgical adequacy, need for tracheostomy, and duration of feeding tube use in the postoperative period was required for all treated subjects.

Surgery on Regional Lymphatics

For subjects with N0 neck status (clinical and radiographic), no neck surgery was performed, and prophylactic radiotherapy was administered as described in the following section. For subjects with N1 disease status, optional ipsilateral neck dissection (to include at least levels 2, 3, and 4) was permitted at the surgeon's discretion. In all subjects, radiotherapy to the neck was used adjunctively or definitively as described in the next section.

Radiotherapy

Radiotherapy was specified to be conducted at a SWOG-approved facility with general treatment guidelines as follows. External beam postoperative radiotherapy was initiated approximately 14 days after endoscopic surgery. Adjunctive treatment to the primary site (larynx) was specified to a total dose of 60 Gy in cases of clear margins according to the results of final pathologic analysis (based on the foregoing intraoperative microsurgical margin biopsy specimens), to 66 Gy in the event of in situ margins, and to 70 Gy to the primary site in the event of positive final margins. The total radiotherapy dose to the neck in subjects with N0 status was specified as 30 Gy (bilateral). In cases of N1 status with a node less than 2 cm without extracapsular spread, boost radiation was given to positive node-bearing regions to a total dose of 66 Gy. In the event of nodes larger than 2 cm or extracapsular spread, the total dose was 70 Gy. Relevant toxic effects were recorded (with grading performed according to the National Cancer Institute's com-
mon toxicity criteria), and radiotherapy records were subjected to appropriate discipline review.

**Posttreatment Surveillance**

After completion of study treatment, specified follow-up was undertaken to include evaluation for disease status (history and physical examination) every 3 months for the first 18 months, every 6 months until 3 years after initial registration, and annually thereafter. Radiographic imaging including either computed tomographic scanning or magnetic resonance imaging of the neck and posteroanterior and lateral chest radiographs were specified to be obtained at 6, 12, and 24 months after completion of treatment, and then annually thereafter.

**STATISTICAL ANALYSIS**

The primary goal of the study was to estimate the 3-year progression-free survival probability in patients with stage I and II and selected stage III squamous cell carcinoma of the supraglottic larynx treated with transoral CO₂ laser surgery and irradiation. Assuming complete follow-up, 30 patients would be sufficient to estimate the 3-year progression-free survival probability to within 14% (95% confidence interval).

Secondary endpoints included assessing 2 functional measures in patients treated with this technique: the time patients would be sufficient to estimate the percentage of patients who did not require feeding tubes at 2 weeks, the proportion of patients requiring tracheostomy as a result of CO₂ laser surgery. Fifty patients would also be sufficient to estimate the percentage of patients who did not require feeding tubes at 2 weeks, the proportion of patients requiring tracheostomy as a result of surgery, and adverse event rates to within 14%. Any adverse event occurring with at least 5% probability had a 95% chance of being observed at least once.

The 3-year progression-free survival and overall survival probabilities were estimated by the method of Kaplan and Meier.13

**RESULTS**

**STUDY ACCRUAL AND ELIGIBILITY**

From September 15, 1997, to December 1, 2001, a total of 42 patients were registered for the study from 9 participating institutions. The study was closed on December 1, 2001, because of diminished ongoing accrual. Seven registered patients were subsequently deemed ineligible and their data were not evaluable: 5 with locally advanced disease (T3-4) not amenable to laser endoscopic resection according to prestudy evaluations and 2 in whom pretreatment biopsy specimens were negative for squamous cell carcinoma. In addition, 1 eligible patient died before receiving study-related intervention, and this patient's data were also deemed not evaluable. The remaining 34 patients constituted the group with evaluable data. Their demographic characteristics are listed in Table 1. Of the 34 patients, 7 (21%) had clinically staged T1 tumors and 27 (79%) had clinically staged T2 tumors. Ten patients (29%) had N1 (stage III) disease before treatment.

**COMPLETION OF STUDY INTERVENTIONS**

Of the 34 patients in the group with evaluable data, 32 completed all treatment as planned, including endoscopic resection and postoperative radiotherapy. Review of available documentation, including intraoperative videotapes, operative records, and pathology reports, showed no major surgical deviations. After receiving 7 fractions of radiotherapy, 1 patient decided to complete radiotherapy off protocol at a non-SWOG facility for unknown reasons not related to adverse events. Another patient died during radiotherapy secondary to acute myocardial infarction deemed not related to the study treatment (see the next section). Seven of 10 patients (70%) with clinically staged N1 disease underwent selective or modified radical neck dissection at the time of endoscopic resection.

**ADVERSE EVENTS**

The 34 patients in the group with evaluable data were assessed for adverse events. Of these, 8 patients experienced grade 4 adverse events, including 6 cases of significant postoperative dysphagia requiring prolonged feeding tube use (&gt;6 months), and 1 case each of cardiac ischemia/myocardial infarction and radiation-related severe dysphagia. One patient died during radiotherapy; postmortem examination disclosed the cause of death to be acute myocardial infarction without evidence of airway obstruction or tumor recurrence, and the death was deemed not related to study treatment. Adverse events related to study treatment are summarized in Table 2.

**DISEASE PROGRESSION AND SURVIVAL**

The 3-year progression-free survival estimate was 79% (95% confidence interval, 66%-93%) (Figure 1). By 3

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
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<td>Age, y</td>
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<td>Race</td>
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</tr>
<tr>
<td>1</td>
<td>7 (21)</td>
</tr>
<tr>
<td>2</td>
<td>27 (79)</td>
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</table>

*a* Indicates Southwest Oncology Performance Status, for which 0 indicates fully active and 1, mild restriction.
years of follow-up, 7 events had been observed: 1 patient (3%) developed local recurrence at the primary site (at 7 months) and subsequently underwent salvage total laryngectomy; 2 patients (6%) (both clinically staged N0 before treatment) developed regional nodal recurrence (both at 11 months) and underwent salvage neck dissection; and 4 patients (12%) had died before disease progression was observed. Median follow-up for patients alive and free of disease progression was 69 months (range, 30-104 months). In addition, 3 patients developed second primary tumors (1 of the hypopharynx and 2 of the lung). The 3-year overall survival estimate was 88% (95% confidence interval, 77%-99%) (Figure 2).

FUNCTIONAL MEASURES

Need for Tracheostomy

Four patients (12%) underwent tracheostomy during the initial surgical procedure (Table 3). Review of their surgical records showed that, in all 4 patients, tracheostomy was performed before actual endoscopic surgical resection as a consequence of either obstructing tumors or unfavorable anatomy, and not by carbon dioxide laser surgery.
Open supraglottic laryngectomy typically achieves high rates of local disease control for many T1 and T2 supraglottic cancers and affords the potential for retaining speech and swallowing, often without the need for permanent tracheostomy. In most published series, the long-term local failure rate after supraglottic laryngectomy for T1 and T2 supraglottic tumors is low, ranging from 0% to 15%. However, the inherent potential for postoperative dysphagia and aspiration associated with this procedure necessitates thoughtful patient selection, particularly with regard to preexisting medical comorbidities, to accomplish consistent functional results. Historically, patients with significant pulmonary conditions were likely offered either primary irradiation or total laryngectomy.

In addition, patients who subsequently undergo open supraglottic laryngectomy often experience a protracted treatment course involving increased risks related to surgical morbidity, significant length of inpatient hospitalization, and necessary placement of tracheostomy and feeding tubes in the perioperative period. These devices, particularly feeding tubes, are often required for several weeks thereafter and, in patients who subsequently undergo adjuvant radiotherapy, recovery of adequate swallowing function is commonly delayed for several additional weeks or months. Some patients never fully regain the ability to eat.

Primary radiotherapy remains an important oncologic option in the management of early-stage supraglottic carcinoma, with acceptable rates of local tumor control for T1 and T2 tumors in several published series, and is typically characterized by preserved swallowing function. Concern regarding morbidity associated with open conservation laryngeal surgery or the prospect of total laryngectomy has also supported the use of primary radiotherapy in the treatment of these tumors. However, data suggest that local oncologic outcome with primary radiotherapy alone in treating early and intermediate-stage supraglottic cancers, particularly bulkier tumors, is poorer than that with surgery alone or surgery and irradiation combined.

Early reported experience with endoscopic resection of supraglottic tumors described its application primarily as an adjunct to radiotherapy, particularly where substantial tumor bulk threatened airway compromise. The observation that swallowing function was typically retained without the need for tracheostomy in most of these patients suggested that the endoscopic approach might be advantageous rather than associated with severe functional decline. Because results with this type of approach were derived primarily from single-institution experiences, the current phase 2 study sought to explore the feasibility of such an approach within an expanded multi-institutional setting.

Initial enthusiasm for this study was evidenced by its activation and enrollment of subjects from several participating institutions. Individual discipline review of available study documentation, including intraoperative videotapes, operative records, pathology reports, and radiotherapy records for patients in the group with evaluable data, suggest that the treatment approach used in this study was highly feasible from a procedural perspective. No major surgical deviations were observed in the 34 subjects, and all treatment components (surgery and radiotherapy) were completed without major deviation in 32 of 34 subjects (94%).

Despite the technical feasibility of the described treatment protocol, the protocol was closed because of diminishing subject accrual, and the study investigators were asked about the reasons for this. The primary reasons cited by enrolling surgeons included overly rigid study criteria, such as those mandating repeat procedures (such as separate staging endoscopy/biopsy apart from surgical resection), as well as exclusion of subjects presenting with greater than N1 neck disease whose primary tumors could otherwise have been encompassed via transoral endoscopic resection. Furthermore, several investigators were unwilling to enroll otherwise eligible subjects because of the compulsory use of postoperative radiotherapy; they cited increasing comfort in treating similar patients with endoscopic resection alone outside the context of the current protocol. These reasons notwithstanding, the high rate of completion of the required protocol among enrolled subjects across a multi-institutional setting supports the feasibility of such treatment for early supraglottic cancers.

Local disease control observed in this study, which combined endoscopic resection and radiotherapy, was excellent in that only 1 documented case of local disease recurrence at the primary site (3%) was observed. Although it was not possible to ascertain the relative oncologic contributions of endoscopic resection vs radiotherapy in achieving this outcome, the high local and regional disease control observed in the current study with continued initial local control at last documented follow-up compares favorably both with previous reported experience with similar combined treatment and with that achieved via pri-
mary radiotherapy alone for similarly staged tumors.\textsuperscript{1,2,4} Although not studied herein, it is conceivable that results from histopathologic analysis obtained as a consequence of surgical resection could justify further reduction or elimination of planned postoperative radiotherapy. Additional studies, however, are needed to investigate whether similar disease control can be sustained with modification of any planned adjuvant therapy based on pathologic findings obtained from surgery.

The results of the current study support previous reported experience indicating that most patients undergoing endoscopic management of early supraglottic malignant neoplasms do not need tracheostomy.\textsuperscript{5,11,14} Although 4 patients in the current study required initial tracheostomy, in all cases this was done before endoscopic resection because of tumor bulk or anatomic considerations that precluded safe endotracheal intubation, rather than as a consequence of the endoscopic resection procedure itself. In fact, in all cases in which initial tracheostomy was needed, decannulation was achieved within the early postoperative period (before hospital discharge), further supporting the contention that endoscopic resection was likely instrumental in achieving a stable postoperative airway in these patients rather than the compromised airway that typically exists after open conservation laryngeal procedures.

Although swallowing function was not directly measured, the duration of treatment with supplemental intravenous fluids or a feeding tube provided useful insight into the effect of endoscopic supraglottic laryngectomy on swallowing. Similar to previous reported experience,\textsuperscript{4,9,10} most patients rapidly recovered the ability to swallow after endoscopic supraglottic laryngectomy. It is encouraging that most patients were capable of sustaining adequate oral nutrition in the very early postoperative period (24 of 34 subjects; 71%), at a median of the second postoperative day. This contrasts sharply with the postoperative course after open procedures for supraglottic cancer, such as standard horizontal laryngectomy, where swallowing recovery is characteristically more prolonged.\textsuperscript{15}

Although the results of the current study as well as previous published reports\textsuperscript{5-11,14} clearly suggest that swallowing recovery is typically more rapid in patients undergoing endoscopic resection than in those undergoing traditional open procedures, it cannot be so stated definitively given the nonrandomized nature of the current study and the fact that the 2 procedures were not directly compared. In fact, swallowing was negatively affected in a subset of patients undergoing endoscopic resection, as evidenced by delayed (\textgeq2 weeks after surgery) or inadequate recovery in 10 of 34 subjects (29%). However, in 7 of these subjects, adequate recovery of oral intake occurred in delayed fashion after completion of radiotherapy, which suggests a negative effect of radiotherapy on swallowing as well. Typically, 3 to 6 weeks is required for healing before patients begin a course of radiotherapy after standard open supraglottic laryngectomy. As specified per protocol, most patients from this cohort began radiotherapy within 2 weeks of surgery. It is conceivable that a subset of patients may not have adequate healing of the open wound at the tongue base and supraglottic larynx at 2 weeks, and initiation of radiotherapy with this unhealed wound may explain the prolonged dysphagia observed in some of these patients. Several studies have also suggested a similar detrimental effect of postoperative radiotherapy on functional recovery in patients having undergone partial laryngectomy.\textsuperscript{15-17} Given the somewhat small total number of patients in this study in whom swallowing recovery was delayed or prolonged, however, it was not possible to isolate additional factors that could have predicted this outcome.

CONCLUSIONS

The current cooperative group study indicates that transoral endoscopic CO\textsubscript{2} laser excision of early to intermediate-stage supraglottic tumors (clinically T1-2N0-1M0) combined with postoperative radiotherapy appears to be feasible in a multi-institutional setting. Local and regional disease control appears to be reasonable with this type of combined treatment approach. Adjunctive tracheostomy was not required as a direct consequence of endoscopic supraglottic resection. Although timing was somewhat variable, most patients rapidly recovered adequate swallowing in the early postoperative period after endoscopic supraglottic laryngectomy.

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Author Contributions: Drs Agrawal, Moon, Valentino, and Truelson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Agrawal, Moon, Davis, Sakr, Giri, Valentino, LeBlanc, Truelson, Yoo, Ensley, and Schuller. Acquisition of data: Agrawal, Moon, Davis, Giri, Valentino, Truelson, Ensley, and Schuller. Analysis and interpretation of data: Agrawal, Moon, Giri, LeBlanc, and Truelson. Drafting of the manuscript: Agrawal, Moon, Sakr, Yoo, and Ensley. Critical revision of the manuscript for important intellectual content: Agrawal, Moon, Davis, Giri, Valentino, Truelson, and Schuller. Statistical analysis: Moon, LeBlanc, and Truelson. Obtained funding: Davis and Ensley. Administrative, technical, and material support: Agrawal, Sakr, Valentino, Yoo, and Ensley. Study supervision: Agrawal, Davis, Giri, Valentino, Ensley, and Schuller. Financial Disclosure: None reported.
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REFERENCES