Outcome of Salvage Total Laryngectomy Following Organ Preservation Therapy

The Radiation Therapy Oncology Group Trial 91-11

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Objective: To evaluate the incidence of morbidity, mortality, and disease control for patients requiring salvage total laryngectomy (TL) following organ preservation therapy.

Design: Patients entered into a 3-arm randomized prospective multi-institutional trial for laryngeal preservation who required TL following initial treatment.

Setting: The Radiation Therapy Oncology Group 91-11 trial for laryngeal preservation.

Patients: From 1992 to 2000, 517 evaluable patients were randomized to receive chemotherapy followed by radiation therapy (arm 1), concomitant chemotherapy and radiation therapy (arm 2), or radiation therapy alone (arm 3).

Results: Overall, TL was required in 129 patients. The incidence was 28%, 16%, and 31% in arms 1, 2, and 3, respectively (P=.002). Of these, 7 patients (5%) required TL for aspiration or necrosis. Following TL, the incidence of major and minor complications ranged from 52% to 59% and did not differ significantly among the 3 arms. Pharyngocutaneous fistula was lowest in arm 3 (15%) and highest in arm 2 (30%) (P>.05). There was 1 perioperative death. Local-regional control following salvage TL was 74% for arms 1 and 2 and 90% for arm 3. At 24 months, the overall survival was 69% (arm 1), 71% (arm 2), and 76% (arm 3) (P>.73).

Conclusions: Laryngectomy following organ preservation treatment is associated with acceptable morbidity. Perioperative mortality is low but up to one third of patients will develop a pharyngocutaneous fistula. Local-regional control is excellent for this group of patients. Survival following salvage TL was not influenced by the initial organ preservation treatment.


Prior to 1990, most patients with advanced laryngeal cancer underwent total laryngectomy (TL) for management of their tumor. In the early 1990s, Wolf et al1 reported the outcome of the Veterans Affairs (VA) Cooperative Study, a randomized prospective organ preservation trial, for patients with advanced laryngeal cancer. Total laryngectomy was compared with induction chemotherapy and radiation therapy (RT). The patients in the experimental arm received 2 cycles of cisplatin and fluorouracil. Major responders received a third cycle of chemotherapy and then definitive RT. Nonresponders underwent TL. Approximately two thirds of the patients in the organ preservation group retained their larynxes, and their survival was equivalent to patients treated by initial TL. However, the local failure rate was higher in the experimental group compared with those receiving standard therapy (TL), and the distant failure rate was higher for those not receiving chemotherapy.

Although the VA trial provided a basis for the routine use of neoadjuvant chemotherapy in hopes of preserving the larynx, it did not address the rationale for its use. Some believed that chemotherapy was acting as a selector for inherently radiosensitive tumors that did not require surgery to be cured. Others thought chemotherapy was providing additional cell kill that, when added to the effects of RT, rendered surgery unnecessary. Still, others thought both effects were operative.

In 1991, the Radiation Therapy Oncology Group (RTOG) initiated a 3-arm randomized prospective study (RTOG 91-11) to test these theories and to try to improve outcome. In addition to a neoadjuvant chemotherapy arm, a concomitant RT and chemotherapy arm was included in hopes of decreasing the high local failure rate associated with the neoadjuvant therapy in the VA study. Radiation therapy...
alone was included to ascertain if neoadjuvant chemotherapy added substantially to modern RT. The neoadjuvant chemotherapy organ preservation arm, modeled from the VA trial with minor modifications, served as the control arm for RTOG 91-11.

The preliminary analysis of this trial, which was presented at the American Society of Clinical Oncologists in 2001, found that the highest rate of organ preservation was in patients treated with concomitant RT and chemotherapy; however, no significant difference in survival was obtained among the 3 arms. Although the goal of nonsurgical management was preservation of speech and swallowing, treatment failed in many patients, who then required salvage TL. The morbidity of TL for patients refractory to nonsurgical treatment is not well defined in the literature. Furthermore, the impact of the type of initial cancer treatment on morbidity and survival of patients requiring salvage TL is unclear. We undertook this analysis of patients entered into RTOG 91-11 to determine their surgical morbidity and survival as a function of their initial treatment.

### METHODS

Between August 1992 and May 2000, 547 patients with biopsy-proven stage III and IV squamous cell carcinoma of the larynx were randomized to 1 of 3 treatment arms. Of the 547 patients randomized, 30 were excluded from the analysis owing to ineligibility (22 patients) or delinquent data (8 patients). The stratification variables were shown in Figure 1. Patients in arm 1 received 2 cycles of cisplatin, 100 mg/m² for 20 to 30 minutes, followed by fluorouracil, 1 g/m² every 24 hours by continuous infusion for 120 hours. The patients received 2 cycles of chemotherapy 3 weeks apart, and the responders received a third cycle. Nonresponders underwent salvage TL and postoperative RT as indicated. Patients in arm 2 received concomitant chemotherapy consisting of the identical dose of cisplatin as in arm 1 on days 1, 22, and 43 of RT. Patients in arm 3 were treated with conventionally fractionated RT. Radiation therapy consisted of 7000 rad (70 Gy), total dose in 200 rad (2.0 Gy) fractions delivered over 7 weeks. Patients with lymph nodes greater than 3 cm in diameter underwent posttreatment neck dissection 6 to 8 weeks following the completion of RT. The indications for laryngectomy were disease progression in arm 1 after 2 cycles of chemotherapy, biopsy-proven disease at the primary site at least 8 weeks after RT, and laryngeal dysfunction with aspiration or laryngeal necrosis. The institutional review board of all participating institutions approved the study, and informed consent was obtained from each patient prior to randomization.

Overall survival and disease-free survival rates were estimated using the Kaplan–Meier method. Overall survival and disease-free survival times were measured from randomization rather than from the time from surgery because salvage TL was performed at different time points. Statistical testing was done by both the log-rank and Wilcoxon tests. Multivariate analysis was performed using the Cox proportional hazards model. Categorical variables were examined by χ² analysis.

### RESULTS

Of the 517 evaluable patients, 173 were in arm 1 and 172 were in arms 2 and 3 each. Overall, 129 (25%) patients required a laryngectomy. The pretreatment demographics and disease stage for the patients who required laryngectomy are listed in Table 1. Laryngectomy alone was performed in 58 patients, whereas 71 patients had a concomitant neck dissection. The mean and median follow-up duration for the salvage TL patients in each treatment arm are provided in Table 2.

Salvage laryngectomy was performed on 48 (28%) patients in arm 1, 27 (16%) patients in arm 2, and 54 (31%) patients in arm 3 (P = .002). The indications for laryngectomy (Table 3) were lack of response to treatment and progression or recurrence, which occurred in 95% of patients. Disease progression with chemo-
therapy occurred in 5 patients in arm 1. Two patients refused additional treatment (1 patient each in arms 1 and 2). Seven patients (5%) required a laryngectomy for necrosis or dysfunction, and 1 patient had a laryngectomy prior to protocol treatment. These 8 cases were included in the assessment of complications but were not included in the subsequent analysis by protocol treatment of survival following salvage TL for recurrent or persistent cancer.

Surgical complications following salvage TL were defined as systemic or wound related and classified as major or minor. Major complications significantly prolonged hospitalization or were considered life threatening. Minor complications were self-limited, managed with local wound care, and did not significantly prolong hospitalization.

The overall incidence of major and minor complications was 58%, 59%, and 52% for arms 1, 2, and 3, respectively. Systemic complications included perioperative death (myocardial infarction), nonfatal cardiovascular events in 7 patients, and 1 cerebrovascular accident. There were no significant differences in the frequency of systemic complications among the 3 treatment arms. Wound complications included cellulitis, skin dehiscence, flap failure, pharyngocutaneous fistula, and hemorrhage. Pharyngocutaneous fistula occurred in 12 (25%) of 48, 8 (30%) of 27, 8 (15%) of 54 patients in arms 1, 2, and 3, respectively (P > .05). A summary of the surgical complications is listed in Table 4. The incidence of complications across the 3 arms was independent of the time from the end of treatment to laryngectomy (P = .86, Wilcoxon test) (Figure 2).

Following salvage TL, 56% in arm 1, 72% in arm 2, and 69% in arm 3 remained free of disease. Local-regional control was obtained in 74% of patients in arms 1 and 2, while 90% of patients in arm 3 remained disease free in the head and neck following salvage TL. Distant failure with above clavicle control occurred in 18%, 8%, and 20% in arms 1, 2, and 3, respectively (Table 5). Using a time-dependent Cox model, patients undergoing salvage TL had significantly worse survival than patients who did not undergo salvage TL (P < .001; hazard ratio, 1.90 [95% confidence interval, 1.38-2.62]). Figure 3 shows a landmark analysis of overall survival of patients surviving at least 1 year, comparing patients who underwent salvage TL with those who did not. The overall survival at 24 months for the salvage TL patients was 69% for arm 1, 71% for arm 2, and 76% for arm 3 (Figure 4). Overall and disease-free survival of the 121 patients who underwent salvage TL (by assigned treatment arm) can be seen in Figure 4 and Figure 5, respectively. It is important to note that the comparisons by assigned treatment limited only to patients needing salvage TL for disease are biased because whether a patient would require salvage TL was unknown at the time of randomization. These comparisons are not invalid, but they may not reflect the overall treatment results among the entire group of randomized patients.

**COMMENT**

Organ preservation treatment is now considered an option for appropriate patients with advanced laryngeal cancer. Wolff et al demonstrated a 68% 2-year survival for patients treated with induction chemotherapy and RT. Importantly, there was no statistically significant difference in survival between patients treated with initial laryngectomy vs induction chemotherapy and RT. The investigators found a higher local recurrence rate among patients receiving RT and chemotherapy; however, these patients also had a significantly decreased incidence of distant metastases.

Contemporary nonsurgical approaches to improve cancer control have explored treatment intensification. Recent therapeutic approaches include altered fractionated RT, concomitant intravenous chemotherapy and RT and supraosseous intra-arterial chemotherapy and RT. While treatment intensification may increase local-regional control, initial treatment still fails in many patients, who then require salvage TL. Following nonsurgical organ preservation treatment, the factors that affect disease control, survival, perioperative morbidity, and

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### Table 2. Follow-up Time of Patients Undergoing Salvage Laryngectomy

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT + induction chemotherapy</td>
<td>35.4</td>
<td>39.3</td>
<td>8.0-93.7</td>
</tr>
<tr>
<td>RT + concomitant chemotherapy</td>
<td>39.0</td>
<td>41.3</td>
<td>11.4-98.1</td>
</tr>
<tr>
<td>RT alone</td>
<td>36.5</td>
<td>40.4</td>
<td>5.2-94.6</td>
</tr>
<tr>
<td>Alive Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT + induction chemotherapy</td>
<td>47.1</td>
<td>51.0</td>
<td>22.9-93.7</td>
</tr>
<tr>
<td>RT + concomitant chemotherapy</td>
<td>48.1</td>
<td>47.3</td>
<td>17.2-77.1</td>
</tr>
<tr>
<td>RT alone</td>
<td>48.1</td>
<td>50.6</td>
<td>5.2-94.6</td>
</tr>
</tbody>
</table>

Abbreviation: RT, radiation therapy.

### Table 3. Surgical Cases*

<table>
<thead>
<tr>
<th>Reasons for Laryngectomy</th>
<th>RT + Induction Chemotherapy (n = 48)</th>
<th>RT + Concomitant Chemotherapy (n = 27)</th>
<th>RT Alone (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence/progression</td>
<td>30 (63)</td>
<td>20 (74)</td>
<td>36 (67)</td>
</tr>
<tr>
<td>Inadequate response to chemotherapy</td>
<td>5 (10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Residual disease after radiation therapy (RT)</td>
<td>9 (19)</td>
<td>4 (15)</td>
<td>15 (28)</td>
</tr>
<tr>
<td>Patient refusal of additional treatment after starting</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Necrosis</td>
<td>2 (4)</td>
<td>1 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Laryngeal dysfunction</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Prior to protocol treatment</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients.

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Mortality for patients who require salvage TL are not well defined.

More aggressive therapy produces deleterious effects on normal tissues. These include impaired vascularity and increased fibrosis that diminish tissue oxygenation and alter wound healing. Salvage TL after conventional RT is associated with an increased risk of wound and systemic complications. In Goodwin's comprehensive review of complications following salvage TL for upper aerodigestive tract cancer, the major complication rate reported was 27% and ranged from 5% to 48%.

Johansen et al reported a fistula rate of 80% in 21 patients undergoing salvage TL following 6800 to 7200 rad (68-72 Gy). Sassler et al reviewed the incidence of postoperative complications in patients requiring salvage TL following chemotherapy with or without RT. Of 18 patients requiring salvage TL, 11 (61%) developed major wound complications and 50% had pharyngocutaneous fistulas. Metson et al noted a significantly higher incidence of minor postoperative complications following twice-a-day RT as opposed to conventional fractionation. The authors concluded that the increased rate of non–life-threatening complications was justified for increased tumor control obtained with altered fraction radiation schedules.

In the present study, the incidence of pharyngocutaneous fistula ranged from 15% to 30% and is equivalent to or lower than rates reported by others. The reason for the lower rate of fistulas is unclear but may be related to the experience surgeons have gained over time in dealing with radiated tissues. Similar to Lavertu et al, we found that the rate of wound complications did not increase directly with the duration from the end of treatment to salvage TL. Because fibrosis and diminished tissue vascularity are expected to increase over time, the lack of a correlation was interesting. The reasons are multifactorial and may include improved nutrition through the use of gastrostomy tubes and increased awareness by surgeons of the need for careful soft tissue technique and meticulous pharyngeal closure in irradiated patients.

Whether the addition of chemotherapy to RT over RT alone increases the risk of postoperative complications in the setting of salvage TL is uncertain. Newman et al reported a pharyngocutaneous fistula rate of 11.5% in a group of 28 patients treated with induction chemotherapy and RT. The major complication rate of patients enrolled into this randomized trial was similar for patients receiving RT alone or more intensive therapy with either sequential or concomitant chemotherapy.

Surgical mortality in the present study was equivalent or lower than that reported in other series. In Goodwin’s comprehensive meta-analysis of 7 published series on salvage TL comprising 718 patients, the perioperative mortality rate averaged 5.2% (range, 0%-18%). Death following salvage TL may be secondary to wound or systemic complications. Wound-related mortality is most frequently due to sepsis or carotid rupture secondary to pharyngocutaneous fistula. Systemic complications contributing to perioperative mortality are frequently cardiovascular or cerebrovascular events. One could postulate that the low perioperative mortality rate for the
salvage TL patients in RTOG 91-11 was due to exclusion of those who were deemed poor candidates for chemotherapy.

Disease control and survival after salvage TL is a function of the primary tumor site, stage of the recurrent or persistent disease, emergence of second primary tumors, time to recurrence, and intercurrent disease. Historically, patients with early-stage laryngeal cancer who require salvage TL experience a better local-regional control and survival than those with more advanced disease. The local-regional control rate following salvage TL for RTOG 91-11 was excellent. Overall, 82% of patients requiring salvage TL remained disease free in the head and neck region.

The survival rates following salvage TL are higher than those for patients with primary tumors at other sites in the head and neck.14 In a meta-analysis, the overall survival at 2 years for 203 patients requiring salvage TL was 76%. The survival rate for patients in the present study was similar; the 24-month survival of 72% for patients

Table 5. Site of Failure After Laryngectomy of Patients Undergoing Salvage Laryngectomy*

<table>
<thead>
<tr>
<th>Site</th>
<th>RT + Induction Chemotherapy</th>
<th>RT + Concomitant Chemotherapy</th>
<th>RT Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Laryngectomy Only (n = 20)</td>
<td>Laryngectomy and Neck Dissection (n = 25)</td>
<td>Laryngectomy Only (n = 9)</td>
</tr>
<tr>
<td>No failure</td>
<td>12</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Primary only</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nodes only</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Primary and nodes</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Distant mets only</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Primary and mets</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nodes and mets</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Primary, nodes, and mets</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Second primary only</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Distant mets and second primary</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: Mets, metastasis; RT, radiation therapy.
*Data are given as number of patients.

Figure 3. Overall survival of all patients surviving at least 1 year, comparing patients who underwent salvage total laryngectomy with those who did not. (Patients requiring laryngectomy for reasons other than cancer recurrence are included in the no laryngectomy group.)

Figure 4. Comparison of survival among patients undergoing salvage total laryngectomy as a function of initial treatment. There was no statistically significant difference among the 3 treatment arms.
Organ preservation for advanced laryngeal cancer is now considered a viable alternative to TL. Although salvage TL is necessary in approximately one third of patients treated by induction chemotherapy and RT or RT alone, fewer patients require salvage TL when the initial treatment is concomitant chemotherapy and RT. Furthermore, only 5% of patients will require laryngectomy for treatment-related toxic effects such as radiation necrosis or aspiration. The most common complication following salvage TL is pharyngocutaneous fistula. The incidence of fistula is independent of the time interval between initial treatment and salvage TL or the type of initial treatment. Most fistulas resolve with local wound care and are not associated with excess perioperative mortality. Local-regional control is excellent following salvage TL. Following nonsurgical therapy for laryngeal cancer, survival for patients who require salvage TL is lower than for patients who remain continuously disease-free at the primary site.

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REFERENCES