Definitive radiotherapy plays a role in the treatment of patients with glottic SCC.

Definitive Radiotherapy for Squamous Cell Carcinoma of the Glottic Larynx

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Background: Depending on the extent of disease, squamous cell carcinoma (SCC) of the glottis is managed with surgery, radiotherapy (RT), or a combination of these modalities. Patients with advanced disease may receive concomitant chemotherapy in conjunction with definitive or postoperative RT.

Methods: The treatment policies of the University of Florida and patient outcomes are reviewed.

Results: The likelihood of cure after RT for carcinoma in situ (Tis) to T2 glottic SCC varies from 70% to 94% depending on tumor stage. Consideration should be given to adding weekly cisplatin for patients with T2b SCC because of the high local recurrence rate after RT alone. The probability of cure is about 65% to 80% for select low-volume (≤ 3.5 cc) T3 to T4 glottic SCC after RT. These patients should be considered for concomitant weekly cisplatin. Higher-volume tumors, particularly those with airway compromise, should be treated with laryngectomy and postoperative RT.

Conclusion: Definitive RT is an excellent treatment for select patients with laryngeal cancer.

Introduction

Depending on the extent of disease, squamous cell carcinoma (SCC) of the glottis is managed with surgery, radiotherapy (RT), or a combination of the 2 modalities. Patients with advanced disease may receive concomitant chemotherapy in conjunction with definitive or postoperative RT. Herein we review the role of definitive RT in the treatment of patients with SCC of the glottis.

Unless otherwise specified, outcomes data are from the University of Florida. Patients were staged according to the prior edition of the American Joint Committee on Cancer (AJCC) staging system.1 Previously, vocal cord fixation was required to upstage a patient to T3; however, the AJCC staging system was subsequently modified (7th edition) so that paraglottic space invasion without vocal cord fixation upstages T2 to T3.2 Dagan et al3 subsequently demonstrated that paraglottic space invasion did not adversely impact outcomes for patients with T2 SCC of the glottis treated with definitive RT.

Carcinoma In Situ

Cases of carcinoma in situ (Tis) are managed with vocal cord stripping. If the lesion recurs and remains in situ, then the procedure may be repeated. However, after multiple vocal cord stripplings, voice quality may dete-
riorate so that definitive RT becomes an alternative option for patients with recurrent Tis after prior surgery.

Patients are treated with parallel-opposed 4 to 6 MV photon fields limited to the glottis. For lesions limited to the true vocal cords, the top of the field is the midthyroid notch, the bottom is the inferior aspect of the cricoid cartilage, the posterior aspect is 1 cm behind the thyroid ala, and the anterior border is 1 to 1.5 cm anterior to the skin. If the lesion extends off of the true vocal cords, then the fields are accordingly enlarged. Depending on the extent of the lesion, the fields are weighted 1:1 or, if the lesion involves mostly 1 vocal cord, then 3:2 to the side of the tumor. A third anterior field may be used to give 5% to 10% of the dose to reduce the dose laterally (Fig 1). The dose-fractionation schedule employed is the same as that used for patients with T1 invasive SCC: 63 Gy at 2.25 Gy per once-daily fraction, and 5 fractions per week for 5.5 weeks.

Sengupta et al\(^1\) reported on 37 study patients with Tis of the glottic larynx treated with definitive RT between 1967 and 2005. The median dose given was 60 Gy (range, 56.25–66.50) at 2.25 Gy per fraction, and the mean follow-up time was 9.5 years.\(^4\) The 5-year local control rate was 91%, the local control rate with larynx preservation was 91%, the ultimate local control rate was 91%, and the cause-specific survival rate was 100%.\(^4\) No patient experienced a severe late complication.\(^4\)

**T1 to T2 Disease**

All patients with invasive SCC of the glottis undergo pretreatment computed tomography as part of their diagnostic evaluation. Although the yield is low, select patients with anterior commissure invasion will have anterior extension along the Broyles ligament to the thyroid cartilage. It is also an excellent way to detect the presence and extent of subglottic invasion.

Patients with T1 to T2 SCC may be treated with surgery or RT.\(^5\) We typically offer transoral CO\(_2\) laser excision to those with well-defined T1 SCC limited to the midthird of 1 vocal cord and then treat the remainder with RT. Open partial laryngectomy is reserved for patients with local recurrence following RT.

The risk of subclinical disease in the regional nodes is low so that RT fields are limited to the larynx. The dose-fractionation schedules are 63 Gy in 28 fractions for T1 to T2a disease (normal vocal cord mobility) and 65.25 Gy in 29 fractions for T2b disease (decreased vocal cord mobility but not fixed). Patients with T2 disease — particularly T2b — may be considered for treatment with hyperfractionated RT to 74.4 Gy at 1.2 Gy twice a day.\(^6\) It is also reasonable to consider the addition of concomitant weekly cisplatin 30 mg/m\(^2\) for those with unfavorable T2 lesions.\(^7\) Fig 1 illustrates the treatment field and dosimetry of a patient with T1N0 SCC confined to the anterior two-thirds of the vocal cord. Fig 2 shows the typical appearance of T1a SCC in the vocal cord before and after RT.

Chera et al\(^6\) reported on 585 study patients with T1N0 to T2N0 SCC of the glottis treated with definitive RT between the years 1964 and 2006. This is a relatively unselected series of patients because the policy during that time period was to treat nearly all patients with T1 to T2 cancer with RT alone. T1 disease was stratified as T1a (limited to 1 vocal cord with or without invasion of the anterior commissure) or T1b (involvement of both true vocal cords), and T2 disease was stratified as T2a (supraglottic extension, subglottic extension, or both with normal vocal cord mobility) or T2b disease (vocal cord mobility diminished but not fixed).\(^6\) Paraglottic space invasion did not upstage a lesion to T3 in the absence of vocal cord fixation.\(^6\) No pa-
A patient received adjuvant chemotherapy or elective nodal irradiation.\textsuperscript{6}

The distribution according to tumor stage appears in the Table.\textsuperscript{6} The anterior commissure was invaded in 369 study patients (63%). A total of 81 (14%) were treated twice daily at 1.2 to 1.25 Gy per fraction; the remainder was treated once daily. The median follow-up period was 12.3 years. Parameters included in the multivariate analysis of local control were tumor stage (T1a vs T1b vs T2a vs T2b), anterior commissure invasion, histological differentiation (well, moderate, or not otherwise specified vs poor), total dose ($\leq 63$ vs $> 63$ Gy), fractionation ($\geq 2.25$ daily vs $\geq 1.2$ Gy twice daily vs $< 2.25$ Gy once daily), overall treatment time (continuous variable), and beam energy ($^{60}$Co vs other).\textsuperscript{6}

The 5-year local and ultimate local control rates, which included successful salvage after local failure, appear in the Table.\textsuperscript{6} The 5-year rates of ultimate local control rates, which included successful salvage after local failure, appear in the Table.\textsuperscript{6} The 5-year rates of ultimate local control with larynx preservation were 95% for T1a, 94% for T1b, 81% for T2a, and 74% for T2b. Multivariate analysis revealed that the rate of local control was adversely impacted by tumor stages of T2a and T2b ($P = .0001$), overall treatment time of more than 41 days ($P = .0016$), poorly differentiated histology ($P = .0126$), and once-daily fractionation ($P = .0494$).\textsuperscript{6}

The 5-year overall rates of neck control and neck control with continuous local control of the primary site, respectively, were 98% and 100% for T1a, 99% and 100% for T1b, 96% and 98% for T2a, and 88% and 94% for T2b.\textsuperscript{6} The 5-year rates of neck control with continuous local control were 75% for T1a, 80% for T1b, 87% for T2a, and 75% for T2b.\textsuperscript{6} Thus, the risk of isolated nodal failure ranges from 0% to 6% depending on tumor stage; however, the risk of nodal failure increases to 13% to 25% if the tumor recurs at the primary site. Therefore, we suggest that salvage surgery should include elective neck dissection.

The 5-year distant metastasis-free rates were 99% for T1a, 99% for T1b, 99% for T2a, and 94% for T2b.\textsuperscript{6} The 5-year cause-specific and overall survival rates, respectively, were 97% and 82% for T1a, 99% and 83% for T1b, 94% and 76% for T2a, and 90% and 78% for T2b.\textsuperscript{6}

Ten study patients (1.7%) experienced severe, acute, late, or postoperative complications. One study patient with T2N0 SCC who was treated twice daily was hospitalized for dehydration. Two others underwent salvage laryngectomy for suspected local recurrence and had no tumor in either specimen. Three study patients with T2N0 SCC required permanent tracheostomy for laryngeal edema. One study patient who underwent salvage total laryngectomy for local recurrence had a pharyngocutaneous fistula. Two received permanent percutaneous gastrostomy tubes. One patient died due to radiation-induced carotid artery angiosarcoma.

### T3 to T4 Disease

Patients with fixed-cord T3 and T4 SCC may be treated with definitive RT, surgery, or a combination of the 2 modalities.\textsuperscript{8} The probability of local control with a functional larynx varies with the volume of the primary tumor. Local control rates were 93% for T3a and 77% for T4a.\textsuperscript{8} Thus, the risk of isolated nodal failure ranges from 0% to 6% depending on tumor stage; however, the risk of nodal failure increases to 13% to 25% if the tumor recurs at the primary site. Therefore, we suggest that salvage surgery should include elective neck dissection.

### Table

Actuarial Local Control Rates by Tumor Stage for Squamous Cell Carcinoma of the Glottic Larynx

<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>No. of Patients</th>
<th>5-y Local Control Rate, %</th>
<th>5-y Ultimate Local Control Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>37</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>T1a</td>
<td>253</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>T1b</td>
<td>72</td>
<td>93</td>
<td>97</td>
</tr>
<tr>
<td>T2a</td>
<td>165</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>T2b</td>
<td>95</td>
<td>70</td>
<td>93</td>
</tr>
<tr>
<td>T3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>87</td>
<td>63</td>
<td>89&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>T4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22</td>
<td>81</td>
<td>86&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Selected low-volume T3 to T4 disease. <sup>b</sup>Crude ultimate local control rates. Data from reference 6.
ry tumor calculated on a pretreatment scan. The primary tumoral volume may vary based on the observer and whether contrast-enhanced diagnostic computed tomography is employed vs planning computed tomography; the former is preferred.

Tumors with a primary tumor volume of 3.5 to 4 cm³ or smaller have a high probability of local control with a functional larynx, and patients with such tumors are good candidates for definitive RT. Those with larger tumors have a high likelihood of local failure after definitive RT and, if controlled, a higher risk of a poorly functioning larynx and may require permanent placement of a percutaneous endoscopic gastrostomy tube, tracheostomy, or both. In addition, the risk of a major complication after salvage laryngectomy is approximately 30% to 35%. These patients’ cancer is best managed with total laryngectomy and neck dissection, typically followed by postoperative RT. Patients who require tracheostomy prior to treatment are likely to have high-volume tumors that should be surgically managed.

Patients with T4 disease who are suitable for definitive RT are highly selected and have tumors less than 3.5 to 4.0 cm³ in size. Their disease is often staged as T4a based on limited exolaryngeal spread through the thyrohyoid membrane, and they commonly have a more favorable prognosis than fixed-cord T3 SCC. The more common, high-volume T4 SCC with cartilage destruction has a poor prognosis after definitive RT and is best treated with total laryngectomy, neck dissection, and postoperative RT.

Patients treated with definitive RT are irradiated with an altered fractionation schedule, preferably 74.4 Gy in 62 twice-daily fractions in 31 treatment days for 6.5 weeks. If this is not feasible for logistical reasons, then the Danish Head and Neck Cancer Group schedule can be employed, which consists of 70 Gy in 35 fractions for 30 treatment days with 2 fractions per day, 1 day per week, during weeks 2 through 6. The simultaneous integrated boost technique is employed if this schedule is chosen. The high-risk planning target volume receives 70 Gy at 2 Gy per fraction, the intermediate-risk planning target volume receives 63 Gy at 1.8 Gy per fraction, and the low-risk planning target volume receives 56 Gy at 1.6 Gy per fraction. Patients receive concomitant cisplatin 30 mg/m² per week.

Hinerman et al reported on 109 previously untreated patients with fixed-cord T3 (n = 87) and T4 (n = 22) SCC of the glottic larynx treated between the years 1966 and 2002. The stage distribution was T3N0 in 68 patients (62%), T3N1 in 14 patients (13%), T3N2b in 5 patients (5%), T4N0 in 17 patients (16%), T4N1 in 4 patients (4%), and T4N2b in 1 patient. Five patients received induction chemotherapy with cisplatin and fluorouracil, 4 patients received concomitant cisplatin alone or combined with fluorouracil, 1 patient received concomitant carboplatin and taxol, and 3 patients underwent planned neck dissection. The median follow-up period was 5.7 years for all patients and 10.6 years for living patients.

The 5-year local control rates appear in the Table. The crude local control and ultimate local control rates for T3 disease were 67% (n = 58/87) and 89% (n = 77/87); for T4 disease, they were 82% (n = 18/22) and 86% (n = 19/22); and the overall rates were 70% (n = 76/109) and 88% (n = 96/109). Multivariate analysis of local control revealed cord fixation (P = .5706), once- vs twice-daily fractionation (P = .4936), extent into soft tissue (P = .9324), subglottic extension of at least 1.0 cm (P = .2106), dose of no more than 70 vs more than 70 Gy (P = .4655), histological differentiation (P = .8181), and tumor stage (P = .1484). Although all of the T3-stage cancers had cord fixation, some of the T4-stage lesions had at least partially mobile vocal cords. The 5-year outcomes by AJCC stage for stage III vs IVa, respectively, were 62% and 78% for locoregional control (P = .1010), 97% and 100% for distant metastasis-free survival (P = .4323), 83% and 87% for cause-specific survival (P = .5075), and 52% and 67% for overall survival (P = .5259). Severe complications were observed in 13 patients (12%) and included cartilage necrosis (n = 1; fatal case), permanent gastrostomy (n = 2), dysphagia/stricture (n = 1), edema requiring tracheostomy (n = 2), and fatal aspiration (n = 1).

Pameijer et al reported on 42 study patients with fixed-cord T3 SCC of the glottis who were treated with definitive RT between the years 1980 and 1993, correlating local control rates with primary tumor volume and presence of cartilage sclerosis. All patients were followed for at least 2 years. Patients were stratified into low risk (volume < 3.5 cm³ and no cartilage sclerosis [n = 13] or volume < 3.5 cm³ and 1 cartilage sclerosis [n = 8]), moderate risk (volume < 3.5 cm³ and 2 cartilage sclerosis [n = 5] or volume > 3.5 cm³ and no cartilage sclerosis [n = 3] or volume > 3.5 cm³ and single cartilage sclerosis [n = 6]), and high risk (volume > 3.5 cm³ and ≥ 2 cartilage sclerosis [n = 7]). Rates of local control after RT were 90% (19 of 21) for the low-risk group, 43% (6 of 14) for the moderate-risk group, and 14% (1 of 7) for the high-risk group.

Conclusions
Radiotherapy can produce a high rate of local control for patients with squamous cell carcinoma of the glottic larynx. It also can be used to help maintain a functional larynx in patients with carcinoma in situ, T2 disease, and low-volume T3 to T4 disease.

References