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INTRODUCTION

Early-stage squamous cell carcinoma of the glottis (EGC) portends an excellent prognosis in terms of overall survival (OS) and local control rates.1,2 Transoral laser microsurgery (TLM) and radiotherapy (RT) are considered equally effective as a single-stage treatment with comparable recurrence rates, OS, and laryngeal functional outcomes.3,4 Recurrences are considered to be infrequent (around 5%–13% for tumor T1 and 25% for T2), yet they pose a unique challenge in terms of early diagnosis, accurate restaging, and choice of optimal salvage procedure.3 Whereas total laryngectomy (TL) remains the mainstay in managing recurrent disease, it has been shown that a carefully selected subgroup can be effectively salvaged with laryngeal conservative surgery.5–8 Nevertheless, it is not clear whether and how the choice of primary treatment could affect survival and organ-preservation rates. We wanted to analyze the outcomes of a cohort of surgically salvaged EGC who recurred after RT compared with those who relapsed after initial TLM according to recurrent tumor-node-metastasis (rTNM) stage.

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MATERIALS AND METHODS

From a database of 228 patients who underwent salvage surgery between January 2002 and June 2017 for early laryngeal cancer recurrence at the Department of Otorhinolaryngology of the University of Florence, we identified 27 patients who received TLM as the primary treatment modality. To avoid bias, we have conducted a matched pair analysis (1:2 ratio) by rT, rN, and rTNM stage, extracting a control group of 54 patients who failed after elective radiotherapy for EGC using a computerized search system.9 Groups were compared using the chi-squared test and analysis of variance to determine if matching had been successful. All primary and recurrent tumors were biopsy-proven squamous cell carcinomas. Mean follow-up time from the recurrence for all patients was 46.57 months (minimum 4, maximum 99). The criteria for distinguishing recurrence from second primary cancer or persistent disease were: 1) site of recurrence rigorously the same as that of the original malignancy, and 2) time of relapse not exceeding 3 years from initial therapy but after 6 months from its completion. Comorbidities were defined as the presence of diabetes mellitus and history of myocardial infarction or stroke. Tobacco and alcohol consumption were retrieved from the medical history. Pretreatment and recurrent TNM staging were critically reviewed using the 2009 VII edition based on the clinical records available.10 Patients who were treated by curative RT received total laryngeal dose of 65 to 70 Gy (mean, 66 Gy) fractionated over a period of 6 to 7 weeks. All TLM were performed by the same surgeon (O.G.). Follow-up consisted of clinical examinations scheduled every month for the first year, every 2 to 3 months for the second and third year, and every 6 months thereafter until the fifth year. Magnetic resonance imaging and/or computed tomography (CT) scans of the head and neck were performed twice a year for the first 3 years, and then annually. When recurrence was suspected, a panendoscopy with multiple biopsy was undertaken, along with a CT scan of the chest in order to exclude distant metastases or second primary tumor. Exclusion criteria were nonsquamous cell...
histology at primary or recurrent treatment and the presence of other cancers outside the head and neck region.

Our primary endpoints were post-recurrence overall survival (PROS, defined as time elapsed from the recurrence to death by any cause or they are censored) and post-recurrence disease-specific survival (PRDSS, defined as time elapsed from the recurrence to death by disease). Secondary endpoints include second locoregional and distant recurrence and larynx-preservation rate. Approval from our institutional review board was obtained for this retrospective analysis.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Standard descriptive statistics were used to summarize data, with respect to demographic and clinical characteristics. Fisher exact test, chi-squared test, and Student t test were used when appropriate to compare variables; Kaplan–Meier analysis with log-rank test was used to compare survival. Multivariate analysis by Cox proportional hazard model was used to identify factors associated with worse prognosis. A two-sided P value <0.05 was considered statistically significant. All calculations were made with SPSS for Windows (v.21, SPSS Inc., Armonk, NY).

RESULTS

Descriptive features of the cohort are presented in Table I. Those who underwent primary TLM were slightly older, and the two groups were similar in terms of smoking and alcohol habits. With regard to primary tumor, although there were no differences in terms of TNM stage (P = 0.453), T1b was in particular treated more frequently with RT instead of TLM. Table I also shows the distribution of matching factors in our cohort.

In Figure 1, disease-free interval from the first diagnosis to the first relapse is shown in the two groups, and the groups were comparable (P = 0.247).

When surgical salvage procedures are considered (Table II), RT-failed patients tended to more frequently undergo TL compared to other group; however, the difference was not significant (P = 0.097), and all resections obtained negative pathological margins. In the group that recurred after primary TLM, 10 patients received adjuvant radiotherapy because of adverse features after salvage surgery (advanced stage, extranodal extension, or close margin), whereas none of the previously irradiated patients received additional RT boost after surgery. In Table II, it is also shown that RT-failed patients showed more frequent postoperative complications such as a significantly longer mean decannulation time (P = 0.005) or nasogastric feeding tube dependence (P = 0.012). On the other hand, difference in pharyngocutaneous fistula rate was not significant (P = 0.255). Considering those patients who have experienced a second locoregional recurrence, 26 (48%) were in the RT-first group, whereas only three (12%, P = 0.004) (Table II) were in the TLM group.
Although most of such patients were not deemed fit for curative intent and received palliative care, five RT-failed patients who had partial salvage surgery received TL, and three of them were alive at the end of follow-up. Thus, global larynx-preservation rate resulted in 24% for EGC patients who were first cured by RT versus 44.4% of the TLM-first group, but this was not significant (P = 0.061). During follow-up, only four patients had distant metastases, and all were in the RT-first group.

In terms of neck management, RT failed patients had less frequent neck dissection at time of first surgical salvage, as per our Institution’s policy, although this difference was not relevant (25.9% vs. 40.7%, P = 0.174). In addition, among the 36 patients who received TL in the RT-failed group, four (11.1%) developed subsequent regional disease. Of those, all were salvaged with therapeutic neck dissection and all had received no neck treatment at time of surgery.

When analyzing survival outcomes, strikingly we noticed that despite the same recurrent stage, the group that had RT as initial treatment for EGC showed a significantly lower PROS (log-rank test, P < 0.001) (Fig. 2). Even when accounting for disease-specific survival in the time following the first recurrence, log-rank for PRDSS remains statistically against those initially treated by RT (P = 0.005) (Fig. 3). When multivariate analysis was performed, however, no factor proved to be a statistically significant predictor of death in our population (Table III).

In our series, RT-failed patients showed worse survival outcomes compared to same recurrent stage cancers

### DISCUSSION

There is still controversy as to the best initial management of early glottic cancer. This tumor can be effectively treated by both external RT or TLM. Each strategy has its own advantages and disadvantages that must be shared and discussed with patients: for instance, TLM offers shorter treatment duration, less morbidity, and a lower cost. Radiotherapy, on the other hand, is frequently reported to have better voice outcomes even though some recent studies are in disagreement. A recent study has actually identified shorter treatment time and more options in case of a recurrence as the main factors that explain why patients tend to prefer TLM as initial strategy when both are feasible.

In our series, RT-failed patients showed worse survival outcomes compared to same recurrent stage cancers
initially treated by TLM. Although there is some evidence that initial surgery could yield better DSS compared with primary RT for T1 lesions,\textsuperscript{14} to the best of our knowledge this is the first study exploring the impact of initial treatment on EGC failures' outcomes.

There are other studies that have already tried to explore prognosis in case of surgical salvage of EGC failure.\textsuperscript{15,16} A study from the Memorial Sloan Kettering has investigated survival rates and complications of salvage surgery showing that OS and DSS are significantly better in those who receive partial laryngectomy.\textsuperscript{15} However, they considered only RT-failed patients, and their larynx-preservation rate was comparable to ours. A more recent retrospective and multi-institutional series has considered both RT- and surgery-failed EGC patients who have received total or supracricoid laryngectomy.\textsuperscript{16} The authors found no difference in OS according to initial treatment, but their cohort included early- and advanced-stage laryngeal cancer and they did not consider recurrent TNM in their analysis.\textsuperscript{16}

A recent meta-analysis has identified male gender and low hemoglobin level as strong risk factors for failure after initial RT for EGC, whereas anterior commissure involvement, tumor volume, and histological grade are viewed as potential ones.\textsuperscript{17} Once relapsed, we have found that RT-first patients have a small chance to undergo conservative surgery, which in accordance with the most recent literature showing a reduced laryngeal preservation rate for such patients.\textsuperscript{3} On the other hand, there is increasing evidence that a careful and correct restaging allows for planning a salvage partial laryngectomy without compromising oncological results.\textsuperscript{6,18}

With regard to the first recurrence after TLM, a recent article has found that the principal features predicting subsequent relapses are patients' age and pathological status of surgical margins.\textsuperscript{19} It is also estimated that two or more recurrences can occur in about 8.9% (11.1% in the present work) of patients, although further studies are needed to explore this issue and define risk factors.\textsuperscript{3} In this work, the RT-first group showed more second locoregional recurrences compared with surgical failures, but there are conflicting results among published series on this topic.\textsuperscript{3,20}

Considering neck status, RT-failed patients had less frequent neck dissection at the time of surgical salvage, and it is known from the literature that these patients tend to have lower occult neck metastases rates compared to surgical series.\textsuperscript{1,2} In addition, it has been shown that no survival advantage is obtained when neck treatment is performed at salvage total laryngectomy for RT-failed recurrent EGC cases without clinical or radiological suspicion of node involvement.\textsuperscript{21} Furthermore, it is feared that performing an elective neck dissection in such rcN0 patients could possibly worsen the healing of tissues already affected by actinic effects.\textsuperscript{22}

An intriguing result of the present study is the significant advantage in terms of survival for the group initially treated by TLM. There can be several reasons to explain these figures. Patients who relapse after RT notoriously have an higher postoperative morbidity; thus, the risk of salvage surgery must be stressed, especially before suggesting a conservative procedure.\textsuperscript{23} Some complications can be life-threatening, whereas others such as early postoperative pneumonia could represent a negative factor in terms of oncologic outcomes.\textsuperscript{23} Another pitfall to consider is the true recurrent stage of the tumors because we have conducted our analysis by rcTNM, which is the only information available for head and neck surgeons when choosing the best surgical salvage. It is well known that post-RT relapses are notably difficult to diagnose at

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**TABLE III.**
Multivariable Analysis of Predictors of Post-Recurrence Overall Survival for Matched Cohorts.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.024 (0.985–1.065)</td>
<td>0.229</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.913 (0.267–3.117)</td>
<td>0.913</td>
</tr>
<tr>
<td>Smoke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.257 (0.568–2.782)</td>
<td>0.572</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.049 (0.442–2.492)</td>
<td>0.913</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.387 (0.680–2.830)</td>
<td>0.368</td>
</tr>
<tr>
<td>Primary T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>1.644 (0.593–4.563)</td>
<td>0.340</td>
</tr>
<tr>
<td>T2</td>
<td>2.174 (0.671–7.044)</td>
<td>0.195</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; T = tumor.

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Fig. 4. Cause of death in the two groups. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
CONCLUSION

In the present study, we have shown that initial treatment strategy for early glottic carcinoma could affect patients’ outcomes. Radiotherapy-failed EGC showed a significantly worse OS, DSS, a higher complication rate and a higher risk of developing second locoregional recurrences compared to same rTNM patients who had initially been treated by TLM. This probably underlies a biological difference between the two diseases that the current restaging system does not seem to adequately consider. Future multi-institutional studies are needed to confirm our findings, which could possibly change the initial and post-recurrence management philosophy of EGC.

BIBLIOGRAPHY


