Title: “Prognostic impact of initial treatment in surgically salvaged recurrences of early glottic cancer.”

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Ethical approval: 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 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Level of Evidence: 2b

Abstract

BACKGROUND: The purpose of this study was to analyse the outcomes of surgically salvaged early glottic cancer (EGC) recurrences after initial radiotherapy (RT) or transoral laser microsurgery (TLM).

METHODS: A matched pair analysis by rTNM considered 27 patients who had TLM as initial treatment and 54 patients who failed after primary RT was performed and post recurrence overall and disease-specific survival were evaluated.

RESULTS: RT-failed group showed worse post-recurrence OS ($p<.001$) and DSS ($p=.005$) compared to TLM-first group despite the same rTNM stage. RT failed patients showed lower larynx-preservation rate (55.5% vs 75.9%, $p=0.076$) and more postoperative complications (fistula $p=.255$, tracheostomy $p=.005$, nasogastric feeding tube $p=.012$) and second local recurrences ($p=.004$).

CONCLUSIONS: Survival, rate of second recurrences, postoperative complications and feasibility of an organ-preserving approach appear to be worse in RT-failed EGC when compared to same recurrent stage TLM-failed cases.

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 T1 and 25% for T2), yet they pose a unique challenge in terms of early diagnosis, accurate restaging and choice of optimal procedure.[5] While 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.[6-8] 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 rTNM stage.

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 ANOVA 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: (a) site of recurrence rigorously the same as that of the original malignancy, and (b) 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, history of myocardial infarction or stroke. Tobacco and alcohol consumption were retrieved from the medical history. Pretreatment and recurrent TNM staging was critically reviewed using the 2009 VII edition, based on the clinical records available.[10] Patients who were treated with curative RT received total laryngeal dose of 65-70 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 two-three months for the second and third year and every six months thereafter until the fifth year. Magnetic resonance imaging and/or CT scans of the head and neck were performed twice a year for the first three 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 tumour. Exclusion criteria were non squamous-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 local, second regional and distant recurrence and larynx-preservation rate. Approval from our institutional review board was obtained for this retrospective analysis.

Standard descriptive statistics were used to summarize data, with respect to demographic and clinical characteristics. Fisher's exact test, Chi-squared test and Student's 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, USA).

Results

Descriptive features of the cohort are presented in Table 1. Those who underwent primary TLM tended to be slightly older and the two groups were similar in terms of smoking and alcohol habits. Considering primary tumour, while there were no differences in terms of TNM stage ($p=0.453$), T1b and T2 lesions tended to be treated more frequently with RT instead of TLM. Table 1 also shows the distribution of matching factors in our cohort. In figure 1, disease-free interval (DFI) from the first diagnosis to the first relapse is shown in the two groups. There is a trend for those who were initially treated by surgery to present earlier with recurrent disease but data are not statistically significant by log-rank test ($p=0.247$).

Considering surgical salvage of recurrences, radiotherapy failures could be less frequently salvaged with an organ-sparing approach (p=0.097) and all resections obtained negative pathological margins. In the group who recurred after primary TLM, ten patients received adjuvant radiotherapy because of adverse features after salvage surgery (advanced stage, extranodal extension or close margin). None of the previously irradiated patients received additional RT boost after surgery. In addition RT-failed patients showed more frequent postoperative complications such as pharyngocutaneous fistula (p=0.255) or a longer mean decannulation time (p=0.005) or nasogastric feeding tube dependence (p=0.012). Considering those patients who have experienced a second local recurrence, 22 (88%) were in the RT-first group while 3 (12%, p=0.004) were in the TLM group. Whereas 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 55.5% for EGC patients who were first cured by RT vs. 75.9% of the TLM-first group (p=0.076). Only four patients had distant metastases, all 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 (25.9% vs. 40.7%, p=0.174). Among the 36 patients who received TL in the RT failed group, 4 (11.1%) developed subsequent regional disease and they were all salvaged with therapeutic neck dissection. All of them had received no neck treatment at time of primary surgery.

Despite the same recurrent stage, the group that had RT as initial treatment for EGC showed significantly lower post recurrence overall survival (log-rank test for PROS,

p<0.001). 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). When multivariate analysis was performed (Table 3), no factor proved to be a statistically significant predictor of death in our population with only cT2 initial stage showing a trend towards lower survival. Lastly, considering the cause of death, figure 4 shows how second local, regional or distant failures or the development of second primary tumours of the upper aerodigestive tract represent the main causes of death with a significant higher proportion in the RT-failed group (p=0.009).

Discussion

There is still controversy as to the best initial management of early glottic cancer. This tumour can be effectively treated by both external RT or TLM.[2] Each strategy has their 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.[2,3] RT, on the other hand, is frequently reported to have better voice outcomes even though some recent studies are in disagreement.[11,12] 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.[13]

In our series, RT-failed patients showed worse outcomes compared to same recurrent stage cancers initially treated by TLM. There is some evidence that initial surgery could yield better disease-specific survival compared with primary RT for T1

lesions[14] but, 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 which have already tried to explore prognosis in case of surgical salvage of EGC failure.[15,16] A study by 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.[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.[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 include recurrent TNM in their analysis.[16]

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

Regarding first recurrence after TLM a recent paper has found that the principal features predicting subsequent relapses are patients' age and pathological status of surgical margins.[19] It is also estimated that two or more recurrences can occur in about 8.9% (11.1% in the present work) of patients even though further studies are

needed to explore this issue and to define risk factors.[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.[3,20]

Considering neck status, RT failed patients had less frequent neck dissection at 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.[1,2] In addition, it has been shown 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.[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.[22] Nevertheless, in the present studies, postoperative complications such as fistula were more frequent in the RT-failed group showing the inherent healing impairment caused by RT.

There can be several reasons why same stage RT-failed EGC patients have a worse prognosis when compared to those initially treated by transoral resection. Patients who relapse after RT have an higher postoperative morbidity thus the risk of salvage surgery must be stressed, especially before suggesting a conservative procedure. Some complications can be life-threatening whereas others like early postoperative pneumonia could represent a negative factor in terms of survival.[23] Another pitfall to consider is the true recurrent stage of the tumours since 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 earlier stage because signs and symptoms often overlap with post-radiation reactions and tumours tend to show a

discohesive and multifocal submucosal spread as shown by pathological analysis.[24] Therefore, we believe that the current diagnostic workup might not be very useful to correctly define recurrent EGC prognosis since it probably underestimates the extent of recurrent cancers, particularly after RT. There are other different published systems to restage recurrent laryngeal cancer: namely CLRSS and CLRSS-2.[25,26] Whereas the rTNM just reconsiders the primary classification, both the other models, developed for all-stage recurrent laryngeal cancer, do not consider the aforementioned clinical and pathological features with the CLRSS-2 mainly stressing recurrent neck disease as a negative prognostic factor.[26] Thus, when considering only EGC relapses where the main issue is the T and not the N,[21,27] all these systems appear to be not well suited in order to predict survival and we are currently working on a newly developed restaging system which is specifically designed for EGC recurrence (unpublished data). Only in the last edition of the TNM a biological parameter has been finally introduced to split oropharyngeal cancer staging in p16+ and p16- lesions.[28] Like human papillomavirus, previous radiation therapy could be possibly taken into account when defining the prognosis of a recurrent EGC.

Another point to highlight is the intrinsic genetic difference between primary and recurrent lesion.[29] While these biological differences are being studied in more and more detail, again we do use the same system to compare different diseases. In addition, it is well known that radiotherapy can profoundly alter the molecular profile of head and neck cancer and, in case of a recurrence, there can be a clonal selection of radioresistant and more aggressive cells.[30] In fact, we have previously documented changes in p53 gene status as well as in several loci among primary and corresponding RT relapsed cancer with prognostic implication.[31] Therefore, if not

curative, radiotherapy could lead to the development of a genetically different and more aggressive disease from the original cancer.[30,31]

There are potential limits of the present study: this is a retrospective review of outcomes at a single institution, the patients were not randomized to either treatment arm and there is a selection bias because we excluded all TLM-failed patients who opted for salvage RT/chemoradiotherapy. Therefore, the results of this study may not be generalizable for all EGC recurrences. However, they highlight the need for both the head and neck surgeon as well as the radiation oncologist to consider oncological and functional outcomes when planning the best initial treatment strategy, as well as when choosing among surgical salvage options for patients with EGC.

Conclusion

In the present study, we have shown that initial treatment for early glottic cancer could affect patients' outcomes. Survival, postoperative complications and risk of having salvage total laryngectomy are different between RT-failed and TLM-failed EGC. This probably underlies a biological difference between the two diseases that the current restaging system do not seem to adequately consider. Future multi-institutional studies are needed to confirm our findings that could possibly change our initial and post-recurrence management philosophy of EGC.

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