Treatment of advanced squamous cell carcinoma of the external auditory canal: Critical analysis of persistent failures in diagnosis and surgery with a competing-risk model

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Abstract

Background: A series of temporal bone squamous cell carcinomas (TBSCCs) was analyzed with the aim of (i) better understanding the causes for the persistent high failure rate in advanced SCCs and (ii) discussing a possible way out from this stalemate in treatment.

Methods: Forty-five TBSCCs consecutively treated surgically were reviewed.

Results: The 5-year cumulative incidence for postoperative local recurrence was 41.8%. At multivariable analysis, pT3-4 stages were associated with eight-fold relative incidence of developing local recurrence during follow-up (sHR = 9.06, 95% confidence interval [CI] = 1.18–69.46, p = 0.034) and cause-specific death (sHR = 7.95, 95%CI = 1.01–62.27, p = 0.048).

Conclusions: The poor outcome in advanced TBSCC occurred because of local recurrence due to defective resection. The fundamental pitfall of surgery on advanced TBSCC appeared to be the insufficient knowledge of microscopic tumor growth in the different sites and subsites of the temporal bone. The serial histopathological study of the en bloc surgical specimen and autopsy temporal bones seems to represent a way to enhance our understanding of these tumors.

KEYWORDS

advanced squamous cell carcinoma of external ear, external ear tumors, failures in temporal bone tumors, surgery in temporal bone carcinoma, temporal bone carcinoma

1 | INTRODUCTION

Squamous cell carcinomas (SCCs) of the external auditory canal are classified as advanced tumors (T3-T4) when they grow beyond the canal walls.1–3 SCC erosion of the osseous canal, tumor growth in the temporal bone and close sites are categories of both TNM Pittsburgh1,2 and AJCC3 classification systems. The Pittsburgh classification refers to full thickness erosion of the osseous canal and tumor growth into specific sites of the temporal bone and adjacent soft tissues.

The AJCC uses generic criteria of tumor size and cortical or gross bone erosion and skull base invasion. The prognosis of advanced SCCs is poor despite aggressive
therapy combining surgery, radiotherapy, and chemotherapy. Growth beyond the external auditory canal walls as well as the dismal surgical outcome raised several problems which prompted this study. Our series of external auditory canal SCCs was critically analyzed with the aim of (i) better understanding the causes for the persistent high failure rate in advanced SCCs and (ii) discussing a possible way out from this stalemate in treatment.

2 | MATERIALS AND METHODS

2.1 | Patients

The medical charts of patients undergoing primary surgery for malignancies involving the temporal bone in the years between 1980 and 2015 were considered. The study was conducted in accordance with the principles of the Helsinki Declaration. All data were examined in agreement with Italian privacy and sensitive data laws and the in-house rules of the Otolaryngology Section at Padova University (Italy). Before undergoing surgery, all patients operated on between 2005 and 2015 preoperatively signed a consent form for disclosure of privacy in managing personal data for scientific purposes. In particular, they consented “to the use of their clinical data for scientific research purposes in the medical, biomedical, and epidemiological fields, also in order to be recalled in the future for follow-up needs.” Alive patients treated before 2005 were retrieved and signed a retrospective detailed informed consent. The medical charts of all patients from our group undergoing primary surgery for malignancies involving the temporal bone were considered. Non-SCC, tumors of the auricle or parotid extending to the EAC were excluded. This study retrospectively included 45 consecutive patients surgically treated for primary temporal bone SCC (TBSCC), according to the principles of en bloc resection.²

Preoperatively, the patients underwent microotoscopy with biopsy, temporal bone computerized tomography (CT) and/or contrast-enhanced magnetic resonance imaging (ceMRI), neck ultrasonography (with or without fine needle aspiration cytology), chest X-ray, and liver ultrasonography, as previously reported.⁵ ⁶ Positron emission tomography (PET) was used in selected cases. Tumors were classified according to the revised Pittsburgh classification system.²

The senior surgeon of our surgical team operated on all the cases. Parotidectomy and neck dissection were variably performed according to the following criteria. Superficial parotidectomy was performed as a prophylactic measure in all locally advanced cases (T3-T4) and in most T2 cases. Total parotidectomy was performed when intraparotid nodes were involved or direct tumor infiltration through the anterior wall of the external auditory canal was diagnosed. The cN0 cases were treated by elective selective neck dissection, the cN+ cases by type III modified radical neck dissection. Parotidectomy and/or neck dissection were not performed in a few elderly patients where adjuvant RT was planned or if already performed in cases of recurrences. Adjuvant RT was indicated in cases of advanced tumors, positive or close (<5 mm) margins, neck nodes metastases, extracapsular spread, and in all those cases where aggressive pathological features were evidenced at pathology, as reported in our previous paper.⁷

Patients were followed up clinically every 3 months in the first year, then every 6 months up until the fifth year, and then annually. ceMRI or contrast-enhanced CT (ceCT), if MRI was unavailable, was performed every 6 months in the first year and annually thereafter. Neck ultrasonography and chest X-rays were also performed at least annually.

2.2 | Statistical analysis

Continuous variables have been reported as median and range, categorical variables as numbers and percentages. The Fisher's exact test or the chi-square test were applied for comparison, as appropriate. Survival analysis considered local recurrence-free survival (expressed as the time between the end of primary treatment and TBSCC recurrence) and disease-specific survival (expressed as the time between the end of primary treatment and death due to TBSCC recurrence) as main outcome measures. For event-free patients, data were censored at date of last follow-up control. Given the long follow-up period and high mortality rate due to causes other than the TBSCC, a competing risk analysis was performed, estimating the probability of local disease recurrence or disease-specific death in the presence of a competing event, which was death from other causes. The cumulative incidence (CI) functions for the given outcomes were calculated at 5 years and stratified according to relevant patient and tumor variables. Gray's test was applied for CI comparison. Subsequently, the regression model for subdistribution hazard according to Fine and Gray was adopted to estimate the effect of the variables on the CI functions, resulting in the subdistribution hazard rates (sHR) determination. Multivariable analysis was conducted for covariates with an inclusion value of p < 0.05 at univariate analysis, after checking for multi-collinearity. All tests were two-sided. The best model was selected according to a stepwise selection based on the Akaike information criterion. p-values <0.05 determined statistical significance. EZR, a modified version of R Commander,⁸ was used for all analyses.
FIGURE 1  Cumulative incidence functions for (A) local disease recurrence (event 1) and (B) disease-specific survival (event 1) after temporal bone squamous cell carcinoma surgery. Competing event 2 = death from other causes.

TABLE 1  Cumulative incidence functions for local disease recurrence and disease-specific mortality stratified by relevant covariates

| Variable | Local disease recurrence | Disease-specific mortality |
|----------|--------------------------|----------------------------|
|          | 5-year, % (95% CI)       | Comparison of CI p-value*  | 5-year, % (95% CI)       | Comparison of CI p-value*  |
| Overall  | 41.8 (27.1–55.9)         | NA                         | 37.2 (23.1–51.3)         | NA                         |
| Sex      |                          |                            |                            |                            |
| Male     | 40.0 (19.3–60.0)         | 0.900                      | 30.0 (12.3–50.1)          | 0.569                      |
| Female   | 43.5 (23.3–62.1)         |                            | 43.5 (23.3–62.1)          |                            |
| Age      |                          |                            |                            |                            |
| ≤60 years| 45.8 (25.6–64.0)         | 0.628                      | 37.5 (19.0–56.0)          | 0.785                      |
| >60 years| 36.8 (16.5–57.5)         |                            | 36.8 (16.5–57.5)          |                            |
| cT stage |                          |                            |                            |                            |
| cT 1–2   | 11.2 (19.0–29.8)         | 0.001                      | 11.1 (1.9–29.8)           | 0.0023                     |
| cT 3–4   | 64.0 (42.2–79.4)         |                            | 56.0 (34.8–72.7)          |                            |
| pT stage |                          |                            |                            |                            |
| pT 1–2   | 7.1 (0.5–27.5)           | 0.0024                     | 7.1 (5.0–27.5)            | 0.0041                     |
| pT 3–4   | 58.6 (38.8–74.0)         |                            | 51.7 (32.5–67.9)          |                            |
| N stage  |                          |                            |                            |                            |
| N0 (c/pN0)| 37.1 (21.6–52.7)       | 0.152                      | 31.4 (17.1–46.8)          | 0.131                      |
| pN+      | 62.5 (22.9–86.1)         |                            | 62.5 (22.9–86.1)          |                            |
| Grading  |                          |                            |                            |                            |
| G1       | 25.0 (10.2–43.1)         | 0.02                       | 16.6 (5.2–33.7)           | 0.0078                     |
| G2-3     | 63.2 (37.9–80.4)         |                            | 63.1 (37.9–80.4)          |                            |

Note: Death from other causes is the competing event. *p < 0.05 with statistical significance are evidenced in italics.

Abbreviations: 95% CI, 95% confidence interval; CI, cumulative incidence.

*Gray's test for comparison of cumulative incidence functions.
3 | RESULTS

3.1 | Demographics and surgical results

The 45 patients (25 females [55.6%] and 20 males [44.4%]) had a median age at diagnosis of 60 years (range 37–82). According to the revised Pittsburgh classification system, 8 cases were cT1 (17.8%), 10 cT2 (22.2%), 14 cT3 (31.1%), and 13 cT4 (28.9%); five patients resulted cN+ (11.1%). Thirty-one patients (68.9%) underwent en bloc lateral temporal bone resection (LTBR), and 14 (31.1%) en bloc subtotal temporal bone resection (STBR), of whom 2 were submitted to incomplete resection partly with a piecemeal technique for palliative intent, and were excluded from the analysis. Parotidectomy was performed in 43 cases (95.6%) and neck dissection in 38 (84.4%). At diagnosis, the facial nerve function was clinically impaired in 8 cases (17.8%); 21 patients underwent facial nerve sacrifice during surgery because of clinical involvement, or as part of an en bloc subtotal temporal bone resection on tumor-free margins. Parotidectomy was performed in 43 cases (95.6%) and neck dissection in 38 (84.4%). At diagnosis, the facial nerve function was clinically impaired in 8 cases (17.8%); 21 patients underwent facial nerve sacrifice during surgery because of clinical involvement, or as part of an en bloc subtotal temporal bone resection on tumor-free margins. Pathological analysis revealed 7 pT1 cases (15.5%), 7 pT2 (15.5%), 8 pT3 (17.8%), and 23 pT4 (51.2%) at pT classification. Overall, 12 patients (26.7%) were reclassified after pathological analysis to higher revised Pittsburgh classification, namely 1 cT1 (8.3%), 3 cT2 (25%), and 8 cT3 cases (66.7%). Among those who underwent neck dissection, 29 patients were pN0 (76.3%), 5 pN1 (13.2%), 3 pN2a (7.9%), and 1 pN2b (2.6%). The pathological grading of most of the patients was G1 (25 cases, 55.6%); on the other hand, 15 cases were G2 (33.3%), and 5 G3 (11.1%). Postoperative radiotherapy was administered in 26 patients (57.8), but none received preoperative or postoperative chemotherapy.

3.2 | Survival analysis

The analysis of survival was conducted on 43 patients, the two palliative cases being excluded. The median overall post treatment follow-up was 58 months (range 1–232), and 118 months for the censored cases (range 58–232). At last follow-up, 13 patients (30.2%) were alive without evidence of disease, 17 patients (39.6%) had died of the disease, and 13 (30.2%) had died of tumor-unrelated causes. Locoregional recurrence rate was 41.8% (18/43 cases): in particular, among these patients, 16 had developed a local recurrence (37.2%), while 2 (4.4%) only a nodal recurrence. Given that the absolute percentage of deaths from other causes was over 10%, a competing risk analysis was adopted. The 5-year CI for postoperative local recurrence was 41.8% (95% CI = 27.1–55.9), as depicted in
Figure 1A. The 5-year CI stratified according to the considered variables is summarized in Table 1. Clinical and pathological T stages, clinical nodal stage, and tumor grading showed a significant association with a higher local recurrence incidence. Regression analysis results for local recurrence are shown in Table 2. At multivariable analysis, pT3-4 stage were associated with a ninefold relative incidence of developing local recurrence during follow-up (sHR = 9.06, 95% CI = 1.18–69.46, p = 0.034).

The 5-year CI for disease-specific mortality was 37.2% (95% CI = 23.1–51.3) (Figure 1B). Table 1 shows the 5-year CI stratified according to the relevant variables. As observed for recurrence-free survival, clinical and pathological T stages, clinical nodal stage and tumor grading had a significant impact on disease-specific mortality. Regression analysis results for disease-specific mortality are summarized in Table 3. At multivariate analysis, pT3-4 stage was associated with an almost eightfold relative incidence of cause-specific mortality (sHR = 7.95, 95% CI = 1.01–62.27, p = 0.048).

### TABLE 4 The Padova Scoring System for temporal bone squamous cell carcinoma

| Variables                          | Variable class | Score |
|-----------------------------------|----------------|-------|
| Revised Pittsburgh staging system: T category | 1              | 1     |
|                                   | 2              | 2     |
|                                   | 3              | 3     |
|                                   | 4              | 4     |
| Dural involvement if T4 category  | Non-involved   | +0    |
|                                   | Involved       | +1    |
| Tumor spread if T4 category       | Anterior       | +0    |
|                                   | Non-anterior   | +1    |
| Histological grade (G)            | 1              | +0    |
|                                   | 2              | +1    |
|                                   | 3              | +2    |

Note: Non-anterior tumor spread to subsites other than peri-auricular soft tissues or parotid space (medially, inferiorly, posteriorly into the temporal bone and skull base). A total score <5 identified tumors with a better prognosis, while scores of ≥5 identified cases with a worse prognosis (see Zanoletti et al.51).

Figure 1A. The 5-year CI stratified according to the considered variables is summarized in Table 1. Clinical and pathological T stages, clinical nodal stage, and tumor grading showed a significant association with a higher local recurrence incidence. Regression analysis results for local recurrence are shown in Table 2. At multivariable analysis, pT3-4 stage were associated with a ninefold relative incidence of developing local recurrence during follow-up (sHR = 9.06, 95% CI = 1.18–69.46, p = 0.034).

The 5-year CI for disease-specific mortality was 37.2% (95% CI = 23.1–51.3) (Figure 1B). Table 1 shows the 5-year CI stratified according to the relevant variables. As observed for recurrence-free survival, clinical and pathological T stages, clinical nodal stage and tumor grading had a significant impact on disease-specific mortality. Regression analysis results for disease-specific mortality are summarized in Table 3. At multivariate analysis, pT3-4 stage was associated with an almost eightfold relative incidence of cause-specific mortality (sHR = 7.95, 95% CI = 1.01–62.27, p = 0.048).

### DISCUSSION

The alarming aspect of our experience in this specific field was the high local recurrence rate, which was by far the main cause of failure. The 5-year CI for postoperative local recurrence and for disease-specific mortality were
classification was thus based on a setting where several data on microscopic tumor diffusion could have been missed, including tumor margins. In fact, DOD occurred in 25% of free margins cases and NED was found in 25% of margins positive cases, thus supporting the hypothesis that findings on margins could have been missed. Since the Arriaga et al. investigation, the lack of serial studies on full specimens has been a persistent pitfall that has prevented further progress in the evaluation of resection appropriateness at pathology.

The current debate on TBSCC prognostic factors local failure and outcome of advanced tumor continued with the original bias of defective data provided by imaging and histopathology. The understanding of local failure due to an undetected tumor emerged as the main unsolved problem. Although already recognized by Arriaga et al., histopathological evaluations and images of the full temporal bone were not reported in clinical studies, but only in the pathology atlas of the ear until recent papers. Ungar et al. described the carcinoma growth from mastoid and tympanum to the apex along the peri-labyrinthine cells, as well as the areas of resistance to growth, and offered a fundamental contribution to surgery. On the other hand, the correlation between tumor extent at histopathology and radiological evidence could not be investigated, due to the lack of appropriate imaging, as pointed out by the authors.

The current staging systems for TBSCC, as well as the recently proposed systems are based on various tumor features, of which its “extent” plays the main role. Tumor extent includes more than quantitative data, as malignancy growth is also affected by involved subsites and varying temporal bone architecture. Thus, the meaning of “extent” as an index of severity relates to (i) extent, (ii) subsites involved, (iii) bone architecture. Current staging AJCC and Pittsburgh follows the association tumor-treatment-outcome, but each of these categories has a precarious basis in advanced cases (T3-T4). “Tumor” relates to the pitfall of dubious extent; “treatment” implies variable surgical techniques and heterogeneous procedures, in which crucial steps for radicality are not standardized and differ from one surgeon to another; “outcome” lacks information on undetected microscopic diffusion and subsites where recurrence occurs. Inconsistency of both extent and surgery add up to hinder the foundation of current classifications. It seems to us that an ideal classification should be based on safe categories not liable to errors. The recent Padova scoring system on advanced tumor proposed a classification on easy assessable categories (Table 4). It preliminarily showed a promising prognostic predictivity, deserving further prospective trials, though including some of the weaknesses of the Pittsburgh and AJCC staging systems.
From our viewpoint, the basic step of histopathological study with TBSCC serial sections of the autopsy temporal bone or undivided en bloc resection specimens is expected to provide the picture of tumor extent by adding the potential microscopic growth to the macroscopic extent given by imaging. In particular, it could (i) assess the tumor extent and obtain reliable data on margins status; (ii) provide information on the modalities of tumor growth in the various sites of the bone; (iii) set the relation between preoperative imaging and histopathological evidence; (iv) verify the rationale of appropriateness of a surgical resection approach; and (v) explore the sites of missed removal and the nature of persistence/recurrence.

The main strengths of this study lie in the homogeneity of the series of patients considered: (i) all tumors originated in the temporal bone (SCCs in the periauricular area and adjoining sites were excluded); (ii) all patients underwent primary temporal bone en bloc surgery; (iii) their surgical treatment was performed consecutively by the same team; (iv) the histological diagnosis was SCC in all cases. On the other hand, the main weaknesses of the study are related to the retrospective setting and the relatively limited number of cases considered.

5 | CONCLUSION

The poor outcome in advanced TBSCC occurred because of local recurrence due to defective resection. Defective resection reasonably depended on the erroneous diagnosis of tumor extent as supplied by clinical, radiological and intraoperative data. It appeared that this pitfall hindered the tumor–treatment–outcome canon on which the oncological directions depend. The result of surgery, as explored by imaging, did not provide adequate details on the site/subsite of recurrence from which the erroneous step could be deducted. The fundamental pitfall of surgery on advanced TBSCC appeared to be the insufficient knowledge of microscopic tumor growth in the different sites and subsites of the temporal bone. A serial histopathological study of the en bloc surgical specimen and autopic temporal bones definitely seems to represent a way to enhance our understanding of these tumors.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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