Temporal Bone Squamous Cell Carcinoma: Analyzing Prognosis With Univariate and Multivariate Models

Elisabetta Zanoletti, MD*; Gino Marioni, MD*; Paola Stritoni, MD; Marco Lionello, MD; Luciano Giacomelli, BD; Alessandro Martini, MD; Antonio Mazzoni, MD

Objectives/Hypothesis: Temporal bone squamous cell carcinoma (SCC) is an uncommon malignancy accounting for less than 0.2% of head and neck cancers. Despite advances in its early diagnosis, skull base microsurgery, radiotherapy, and integrated treatments, prognosis in advanced SCCs remains dismal. The present study aimed to analyze the clinicopathological variables potentially influencing outcome in a series of temporal bone SCCs.

Study Design: The prognosis of 41 patients with temporal bone SCC was assessed retrospectively using univariate and multivariate statistical approaches.

Patients and Methods: Twenty-two women and 19 men consecutively operated for primary temporal bone SCC with a curative intent at a tertiary referral center between 1980 and 2008.

Results: On univariate analysis, cT stage correlated with disease-free survival in months (DFS) (P = 0.037), and pT stage correlated with recurrence rate (P = 0.038), DFS (P = 0.013), and disease-specific survival (DSS) (P = 0.025). Lymph node status (cN0 or pN0 vs. pN+) was associated with DFS (P = 0.025). SCC grading correlated significantly with recurrence rate (P = 0.005), DFS (P = 0.004), and DSS (P = 0.0036). Dura mater involvement was significantly associated with a higher recurrence rate (P = 0.001), a shorter DFS (P = 0.00001), and a lower DSS (P = 0.0001). On multivariate analysis, only dura mater involvement (P = 0.001) and N status (P = 0.012) remained independently prognostic of DFS.

Conclusion: Recurrences occurred despite obtaining block resections according to the tumor’s clinical stage and pathologically free margins in all cases. Further analyses are mandatory to investigate hidden microscopic pathways of tumor diffusion, particularly in bone. Multi-institutional protocols are needed to facilitate comparisons between studies and enable meaningful meta-analyses.

Key Words: Temporal bone carcinoma, prognosis, dura mater involvement, lymph node, multivariate analysis.

Level of Evidence: 2b.

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INTRODUCTION

Squamous cell carcinoma (SCC) of the temporal bone is an uncommon malignancy, accounting for less than 0.2% of head and neck cancers. SCC is the most common oncotype, occurring primarily in the temporal bone.

Temporal bone SCC has an aggressive course, invading adjacent structures. The reasons for its aggressiveness lie in the nature of the disease itself and the numerous pathways along which the tumor can spread from this site. Instead of creating a barrier to the tumor’s diffusion, the temporal bone acts as a medium for microscopic diffusion through bony canals and intra-osseous vessels. Curative treatment is feasible, but good oncological results are only achieved in loco-regionally limited tumors. Despite advances in the disease’s early diagnosis, skull base microsurgery, radiotherapy, and integrated treatments, the prognosis remains dismal for advanced SCCs, even if they are managed with combined treatments.

The present study involved a retrospective univariate analysis of several clinicopathological variables potentially affecting the outcome of a series of consecutively operated temporal bone SCCs. Using a dedicated model, a multivariate analysis was subsequently performed on this clinically and pathologically very homogeneous series to calculate the prognostic significance of the variables considered (in terms of disease-free survival). The multivariate statistical approach has rarely been applied to this particular oncological setting, probably partly because of the limited number of cases involved in most of the available series.

MATERIALS AND METHODS

The study was conducted on 41 patients (22 women and 19 men, with a mean age of 61.1 ± 11.2 years) consecutively operated for primary temporal bone SCC by the same surgeon (A. Mazzoni) with a curative intent at the Bergamo (Italy) ENT Unit, a tertiary referral center between 1980 and 2008. Preoperatively, all patients underwent microotoscopy with biopsy.
temporal bone computerized tomography, and/or contrast-
enhanced magnetic resonance imaging (MRI), neck ultrasonogra-
phy (with or without fine needle aspiration cytology), chest X-
ray, and liver ultrasonography. Positron emission tomography
(PET) was used in selected cases.

According to the revised Pittsburgh staging system,8,9 the
primary temporal SCCs were classified as cT1 in 7 cases, cT2 in
6 cases, cT3 in 15 cases, and cT4 in 13 cases. No distant metast-
tases (M) were detected at diagnosis.

Statistical Analysis

For our univariate model, the statistical method applied
was Fisher’s exact test. Disease-free survival (DFS) was
expressed as the number of months from the date of ending the
treatment up until a locoregional recurrence was identified.
Disease-specific survival (DSS) was expressed as the percentage
of participants in the study who survived the SCC from diagno-
sis to latest follow-up. The log-rank test was also used to com-
pare DFS (in months) and DSS, stratified according to the
different clinicopathological variables analyzed.

In the multivariate analysis, Cox’s Proportional Hazards
Regression identified significant predictors of DFS. After cre-
ating a full model with the variables of interest, that is, pT (pT1–
2 vs. pT3–4), N status (N0 vs. N+), grade (G1 vs. G2-G3), neck
dissection (1/0), parotidectomy (1/0), facial nerve surgical sacri-
fice (1/0), postoperative radiotherapy (RT) (1/0), and dura mater
involvement (1/0), and checking for multicollinearity, a back-
ward variable selection modality was used to derive a new
model. Then a p-exclusion value of P > 0.20 in the log-rank test
was used and a final multivariate model was generated.

A P value < 0.05 was considered significant, while values
in the range of 0.10 > P > 0.05 were assumed to indicate a sta-
tistical trend. The STATA 8.1 (Stata Corp, College Station, TX)
statistical package was used for all analyses.

RESULTS

Temporal Bone SCC Prognosis: Univariate
Analysis

Lateral temporal bone resection (LTBR) was
performed in 30 cases (partial in 2), and subtotal temporal
bone resection (STBR) in 11 cases. Thirty-three patients
underwent cervical lymph node dissection, and 37 patients
had ipsilateral parotidectomy. Postoperative RT
was administered in 23 cases (in conventional once-daily
fractions of 2 Gy, for a total dose ranging from 50 to 70
Gy, median 60 Gy). The facial nerve was sacrificed dur-
ing surgery in 15 of the 41 patients because there was
intraoperative clinical evidence of its involvement or due
to the need in STBR to allow for en-bloc radical excision
of the SCC. Pathological T-staging identified pT1 in six
cases, pT2 in six cases, pT3 in eight cases, and pT4 in
21 cases. Dura mater specimens were sent for frozen sec-
tion during the surgical procedure to ensure clear mar-
gins: the dura mater was involved in seven of the 41
cases.

All cases who had radiological and/or intraoperative
evidence of dura mater infiltration were treated with ex-
tensive dura resection (furthermore 5 out of 7 cases
with dura mater involvement confirmed by frozen sec-
tion underwent postoperative RT). On final histopatho-
logical examination, the surgical margins were negative in
cases. The regional lymph nodes were pathologi-
cally classified in 33 cases and were: pN0 in 24 cases,
and pN+ in nine cases (pN1 in 4 cases, pN2a in 4, and
pN2b in 1). The pathological grade was G1 in 22 cases
of the 41 cases, G2 in 17 cases, and G3 in two cases.

The mean follow-up was 70.1 ± 65.0 months
(median: 41.0 months; range: 1–220 months). The tem-
poral bone SCC recurrence rate, DFS (in months), and
DSS, stratified according to the clinicopathological vari-
ables considered, are summarized in Table I. Eighteen
patients developed local recurrences of their temporal
SCC after a mean 15.8 ± 38.4 months (median 6
months). Sixteen of the 41 patients died of their dis-
ease, and 13 died of other causes while still disease-
free. All the patients alive with no evidence of SCC had
a follow-up of at least 5 years (mean 132.9 ± 40.7
months; range 60–220 months). Fisher’s exact test
revealed a difference in the distributions for cT (cT1-T2
vs. cT3-T4) (statistical trend, P = 0.09), pT (pT1-T2 vs.
pT3-T4) (P = 0.038), and pathological grade (P = 0.005),
but not for lymph node status (cN0 or pN0 vs.
pN+, P = 0.14), once patients had been divided into
two groups according to whether or not their disease
recurred locally after treatment. Dura mater involve-
ment and sacrifice of the facial nerve both correlated
significantly with a higher likelihood of temporal bone
SCC recurrence (Fisher’s exact test, P = 0.001 and P =
0.049, respectively).

The 21 cases of pT4 SCC were binarized according
to the direction of the tumor’s spread, that is, anterior
(parotid space and preauricular region [8 cases]) or oth-
erwise (posterior, superior, inferior, or medial [13 cases]).
There was a significant association between the direc-
tion in which the SCC spread and the recurrence rate
(Fisher’s exact test, P = 0.003). The log-rank test also
showed a significant difference in DFS (in months)
when patients were stratified by cT according to the
revised Pittsburgh staging system (P = 0.037), and by
pT (P = 0.013) [Fig. 1A]. There was also a significant
difference in DFS when patients were stratified by lymph
node status (log-rank test, P = 0.025) [Fig. 1B], and
pathological grade (log-rank test, P = 0.004) [Fig. 1C].

The log-rank test likewise identified a difference in
DSS when patients were classified by cT (statistical
trend, P = 0.07), pT (P = 0.025), or grade (P = 0.0036),
but not by lymph node status (P = 0.14). Patients stratifi-
ced by dura mater involvement strongly differed in
terms of DFS (log-rank test, P = 0.00001) [Fig. 1D] and
DSS (log-rank test, P = 0.001). Facial nerve sacrifice
correlated with DFS (log-rank test, P = 0.006) and DSS
(log-rank test, P = 0.007). When the preferred therapeu-
tic approach was considered, parotidectomy, neck dissec-
tion, and postoperative radiotherapy did not correlate
significantly with the recurrence rate (Fisher’s exact
test, P = 0.30, P = 0.71 and P = 0.53, respectively), or
DFS (log-rank test, P = 0.36, P = 0.96, and P = 0.33,
respectively), or DSS (log-rank test, P = 0.39, P = 0.81,
and P = 0.27, respectively). In the sub-cohort of pT4
cases, anterior vs. other directions of SCC spread corre-
lated with DFS (log-rank test, P = 0.001) and DSS (log-
rank test, P = 0.0004).

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Multivariate Analysis

Our multivariate DFS estimates were based on a Cox’s proportional hazards model and on the assumption that there were no interactions between significant variables in the final model. No multicollinearity was found. As mentioned previously, the cutoff for selecting the variables for inclusion in the multivariate analysis coincided with a $P < 0.20$ in the univariate analysis. This removed the following variables: neck dissection (1/0), parotidectomy (1/0), and postoperative RT (1/0). The resulting new model is shown in detail in Table II. Only dura mater involvement (relative risk 7.19, 95% confidence interval 2.32–22.27, $P = 0.001$) and N status (relative risk 4.35, 95% confidence interval 1.38–13.74, $P = 0.012$) retained their independent prognostic significance in relation to DFS.

DISCUSSION

Developing an appropriate treatment strategy for temporal bone SCC demands a combination of personal and institutional experience with data gathered from reports published by other oncological centers. Because of this malignancy’s rarity, it has been difficult for any single institution to establish an optimal diagnostic and treatment strategy by analyzing its own data alone. The clinicopathological studies dealing with temporal bone malignancies available in English-language reports published between 2000 and 2013 in the PubMed database, and concerning series of at least 20 patients staged according to the Pittsburgh classifications have been considered (Table III).

In terms of their general clinical features, the patients’ age at diagnosis ranged from 53 to 68 years, and their mean follow-up reportedly ranged from 10 to 97 months. In the studies analyzed for our purposes, surgery was considered the first choice in most cases; only patients with specific contraindications received palliative chemo-radiotherapy. On the other hand, there was no consensus concerning the indications for ipsilateral neck dissection, parotidectomy, or adjuvant radiotherapy. While some authors planned and performed neck dissection and parotidectomy in all cases, others recommended neck treatment only for cN$^+$ cases, and parotidectomy only in the event of clinically or radiologically suspected parotid involvement. The indications for postoperative RT have yet to be generally agreed upon.

Only Moncrieff et al. and Leong et al. recommended postoperative RT for all patients, while adjuvant treatments were only administered to variously selected patients in most series. Histopathological evidence of positive resection margins was not uncommon. This was probably due to inadequate resections and justified by the difficulty of surgery at this anatomical site, which could also explain the significant local recurrence rate emerging from our literature review.

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>SCC Recurrence (No. of Cases)</th>
<th>Mean Disease-Free Survival ($ \pm$ SE) in Months</th>
<th>Disease-Specific Survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1</td>
<td>7</td>
<td>6, 1</td>
<td>90.6 $\pm$ 68.8</td>
</tr>
<tr>
<td>cT2</td>
<td>6</td>
<td>4, 2</td>
<td>98.5 $\pm$ 88.8</td>
</tr>
<tr>
<td>cT3</td>
<td>15</td>
<td>7, 8</td>
<td>60.0 $\pm$ 64.3</td>
</tr>
<tr>
<td>cT4</td>
<td>13</td>
<td>5, 8</td>
<td>39.4 $\pm$ 50.6</td>
</tr>
<tr>
<td>pT1</td>
<td>6</td>
<td>5, 1</td>
<td>90.6 $\pm$ 63.7</td>
</tr>
<tr>
<td>pT2</td>
<td>6</td>
<td>5, 1</td>
<td>117.0 $\pm$ 76.4</td>
</tr>
<tr>
<td>pT3</td>
<td>8</td>
<td>6, 2</td>
<td>92.2 $\pm$ 65.2</td>
</tr>
<tr>
<td>pT4</td>
<td>21</td>
<td>7, 14</td>
<td>30.6 $\pm$ 43.7</td>
</tr>
<tr>
<td>pT4 with SCC spreading anteriorly</td>
<td>8</td>
<td>6, 2</td>
<td>66.9 $\pm$ 49.3</td>
</tr>
<tr>
<td>pT4 with SCC spreading elsewhere</td>
<td>13</td>
<td>1, 12</td>
<td>7.1 $\pm$ 10.2</td>
</tr>
<tr>
<td>Dura mater involved</td>
<td>7</td>
<td>0, 7</td>
<td>6.4 $\pm$ 3.7</td>
</tr>
<tr>
<td>Dura mater uninvolved</td>
<td>34</td>
<td>23, 11</td>
<td>74.7 $\pm$ 67.0</td>
</tr>
<tr>
<td>pN$^+$</td>
<td>9</td>
<td>3, 6</td>
<td>36.7 $\pm$ 50.3</td>
</tr>
<tr>
<td>N0 (cN$^+$ + pN$^+$)*</td>
<td>32</td>
<td>20, 12</td>
<td>70.4 $\pm$ 68.3</td>
</tr>
<tr>
<td>Facial nerve sacrificed</td>
<td>15</td>
<td>5, 10</td>
<td>42.9 $\pm$ 67.3</td>
</tr>
<tr>
<td>Facial nerve spared</td>
<td>26</td>
<td>18, 8</td>
<td>74.7 $\pm$ 62.7</td>
</tr>
<tr>
<td>G1</td>
<td>22</td>
<td>17, 5</td>
<td>92.7 $\pm$ 69.5</td>
</tr>
<tr>
<td>G2</td>
<td>17</td>
<td>6, 11</td>
<td>31.6 $\pm$ 42.3</td>
</tr>
<tr>
<td>G3</td>
<td>2</td>
<td>0, 2</td>
<td>4.0 $\pm$ 2.0</td>
</tr>
</tbody>
</table>

* cN$^+$ 8 cases and pN$^+$ 24 cases. 
SCC = squamous cell carcinoma.
Our brief analysis brought to light the considerable difficulty of comparing the oncological results reported by different institutions. The most evident bias seen in several studies related to the histological heterogeneity of the temporal bone malignancies. Among 19 studies considered, only 13 referred exclusively to SCC (Table III). Oncological outcome (in terms of survival) was expressed in different ways in the available studies. Bacciu et al.\textsuperscript{19} reported long-term results, but there were disease-free survivors with less than a year of follow-up and a considerable number of cases who had a follow-up of less than 5 years. Advanced clinical T and N stages and positive margins seem to be generally accepted as negative prognostic factors.

Our brief literature review confirmed that published data on the oncological outcomes are reported using different parameters. Every effort needs to be made to standardize the format used in staging, presenting the clinical outcome, and assessing the prognosis of patients with temporal bone SCC. Multi-institution studies are also needed to allow larger series, facilitate interstudy comparability, and enable meaningful meta-analyses.

Although the prognostic value of the available clinicopathological systems for staging temporal bone SCC is often debated, and temporal bone cancer has no recognized American Joint Committee on Cancer (AJCC) or International Union Against Cancer (UICC) staging system of its own, the revised Pittsburgh staging system\textsuperscript{2,3} proved quite consistent when applied to the patients considered in the present series: cT stage correlated with recurrence rate (statistical trend, $P = 0.09$), DFS ($P = 0.037$), and DSS (statistical trend, $P = 0.07$), and pT stage correlated with recurrence rate ($P = 0.038$), DFS ($P = 0.013$), and DSS ($P = 0.025$). A different prognosis emerged for pT4 tumors extending into the anterior soft tissues (parotid and condyle), as opposed to pT4
TABLE III.
Clinicopathological Variables and Their Correlation with Prognosis.

<table>
<thead>
<tr>
<th>Clinicopathological Variables</th>
<th>Variables Potentially Correlated with Prognosis</th>
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<tbody>
<tr>
<td>Authors, year</td>
<td>No.</td>
</tr>
<tr>
<td>----------------</td>
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<tr>
<td>Moody et al., 2000</td>
<td>32</td>
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<tr>
<td>Nyrop et al., 2002</td>
<td>20</td>
</tr>
<tr>
<td>Moffat et al., 2007</td>
<td>37</td>
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<tr>
<td>Nakagawa et al., 2006</td>
<td>25</td>
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<tr>
<td>Yin et al., 2006</td>
<td>95</td>
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<tr>
<td>Macneil et al., 2007</td>
<td>42</td>
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<tr>
<td>Moore et al., 2007</td>
<td>35</td>
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<tr>
<td>Ogawa et al., 2007</td>
<td>87</td>
</tr>
<tr>
<td>Kunst et al., 2008</td>
<td>28</td>
</tr>
<tr>
<td>Madsen et al., 2008</td>
<td>68</td>
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<tr>
<td>Dean et al., 2009</td>
<td>65</td>
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<tr>
<td>Gidley et al., 2010</td>
<td>71</td>
</tr>
<tr>
<td>Chi et al., 2011</td>
<td>75</td>
</tr>
<tr>
<td>Morris et al., 2012</td>
<td>72</td>
</tr>
<tr>
<td>Zhang et al., 2012</td>
<td>43</td>
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<tr>
<td>Marioni et al., 2012</td>
<td>20</td>
</tr>
<tr>
<td>Bacci et al., 2013</td>
<td>45</td>
</tr>
<tr>
<td>Leong et al., 2013</td>
<td>35</td>
</tr>
<tr>
<td>Current study</td>
<td>41</td>
</tr>
</tbody>
</table>

*= Moody’s revised Pittsburgh staging system; – = no correlation with prognosis; + = correlation with prognosis; DFS = disease-free survival; DSS = disease-specific survival; ND = no data; OS = overall survival; RT = radiotherapy; 2YS = 2-year survival rate; 5YS = 5-year survival rate.
tumors spreading medially, posteriorly, and inferiorly. Although the number of cases was very limited in both our pT4 sub-cohorts, univariate statistical analysis showed a significant association between a better prognosis and an anterior dissemination of pT4 SCCs in terms of recurrence rate ($P = 0.003$), DFS ($P = 0.001$), and DSS ($P = 0.0004$). This difference might be taken into account when novel staging systems are being designed.

Moffat et al.\textsuperscript{7} emphasized the prognostic role of the degree of temporal bone SCC differentiation, saying that no meaningful comparisons can be drawn between different series unless the degree of histopathological differentiation is taken into account. In our series, it was only in the univariate setting that the relationships between SCC grade and recurrence rate, DFS, and DSS were significant. Moffat and Wagstaff\textsuperscript{22} also said that lymph node involvement was a strong indicator of a poor prognosis in temporal bone SCC, even though the lymphatics of the auditory canal are not well developed and the parotid gland contains the first echelon of nodes draining the external auditory canal.

In our series, lymph node status (cN0 or pN0 vs. pN+) was associated with a shorter DFS in months ($P = 0.025$). This evidence was confirmed by our multivariate model in which N status retained its independent prognostic significance ($P = 0.012$). It is worth adding that, although dura mater involvement was diagnosed on histopathological examination in a limited number of cases, univariate analysis found this feature significantly associated with a higher recurrence rate ($P = 0.001$), a shorter DFS in months ($P = 0.00001$), and a lower DSS ($P = 0.0001$). In our current series of temporal bone SCCs, dura mater involvement was the clinicopathological feature that retained the strongest role as an independent prognostic factor of a short DFS ($P = 0.001$) on multivariate analysis.

The same findings in a multivariate statistical setting were also reported very recently by Bacciu et al.\textsuperscript{19} Morris et al.\textsuperscript{16} studied the clinical intracranial extent of SCC using multivariate analysis as well. However, their conclusions are unfortunately of limited value because of the histological heterogeneity of the series they considered, which included epithelial, salivary, and mesenchymal tumors, given the well-known diversity of different histotypes’ tumor behavior, local invasiveness, and metastatic pathways. Morris et al.\textsuperscript{16} also used the revised Pittsburgh classification system, regardless of a tumor’s histology, although it was originally proposed only for SCC.\textsuperscript{2} The conclusions drawn by Morris et al.\textsuperscript{16} with regard to prognostic factors might also be misleading because the sites of the primary malignancies analyzed varied considerably (including the auricle, concha, parotid gland, periauricular skin, etc.).

**CONCLUSION**

The main strengths of the present study lies in the homogeneity of the series of patients considered: 1) all tumors originated in the temporal bone (SCCs in the periauricular area and adjoining sites were excluded); 2) all patients underwent primary temporal bone surgery; 3) their surgical treatment was performed consecutively by the same team; 4) the histological diagnosis was SCC in all cases; and 5) on final histopathological examination, the surgical margins were negative in all cases. On the other hand, the main weaknesses of the present study relate to the retrospective setting and the relatively limited number of cases considered.

In the present series, well-codified surgical procedures (LTBR and STBR) were planned and performed in all patients, aiming for the radical en-bloc removal of their temporal bone SCC. As already reported in a larger series’ radical SCC resection to achieve pathologically free margins in 17 cases, Bacciu et al.\textsuperscript{19} found positive margins to be a significant negative prognostic factor in terms of DFS and DSS. Although our patients all had pathologically free margins, based after block resections of the temporal bone performed according to the clinical stage of the tumor, some experienced recurrences. This reasonably raises the question of how “free” negative margins must be in order to be considered oncologically safe in the case of temporal bone SCC, to what extent surgery should be enlarged beyond the presumably free margins to ensure oncological radicality, and whether “free” margins can really be considered negative in bone.

Histopathological accuracy has improved over the years, but analyzing margins in bone is still demanding. More sections of the specimen are probably needed, and further analyses are mandatory to investigate hidden microscopic pathways of tumoral diffusion. The Haversian canals (as loci minoris resistantiae) and angiolymphatic invasion are just two of the aspects accounting for the tumor’s potential aggressiveness. Molecular changes occur in malignancies some time before any morphological changes become visible, and the former are responsible for the disease’s biological behavior, prognosis, and response to primary therapy. It is crucial to search for biomarkers that might reflect the biological characteristics of temporal bone SCC and help clinicians to predict the outcome of treatment.\textsuperscript{18} For temporal bone SCC, such investigations are only just beginning to appear in the oncological literature.\textsuperscript{18,23–25} Biomarkers could be extremely important to the development of novel, more effective, integrated therapeutic strategies (including targeted approaches) capable of improving the DSS for patients with advanced temporal bone SCC.\textsuperscript{24}

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**BIBLIOGRAPHY**


