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Temporal bone carcinoma: Classical prognostic variables revisited and modern clinico-pathological evidence

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ABSTRACT

Aim: Prognostic factors, rational management, and the ongoing investigations regarding temporal bone squamous cell carcinoma (TBSCC) have been critically reviewed.
Background: TBSCC is an uncommon, aggressive malignancy. Although some progress has been made in treating this aggressive tumor, the prognosis in advanced cases remains poor.
Materials and methods: A systematic search of the literature for articles published between 2009 and October 2014 was performed using the PubMed (http://www.pubmed.gov) electronic database.
Results: Given the particular anatomical site of TBSCC, its prognosis is significantly influenced by any direct involvement of nearby structures. The extent of the primary tumor is generally considered one of the most important prognostic factors and it is frequently related to prognosis even more strongly than N stage. For TBSCC, biomarker investigations in surgical specimens are only just beginning to appear in the oncological literature.
Conclusion: Given the particular features of TBSCC, the sub-specialty of otologic oncology seems to be emerging as a defined area of practice involving multidisciplinary team comprising oto-neurosurgeons, head and neck surgeons, plastic surgeons, oncologists, radiotherapists, dedicated radiologists, and pathologists.

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1. Background

Squamocellular carcinoma of external-middle ear is an uncommon (less than 0.2% of head and neck cancers) and aggressive malignancy. It accounts for the 60–80% of tumors arising in the external auditory canal.[1–3]

The reason for this malignancy aggressiveness may be found in the disease biological behavior but also in the various potential routes of diffusion to the surrounding structures. Temporal bone does not protect from tumoral invasion and microscopic invasion seems to be frequent through the intraosseous vessels and Haversian canals. In available literature, the association between the tumor and middle ear chronic inflammatory disease has been reported,[4,5] as well as genetic predisposition.[4] A role has been hypothesized for chlorinated disinfectants in the etiopathogenesis of middle ear carcinoma and for human papillomavirus in cases of temporal bone squamous cell carcinoma (TBSCC) associated with inverted papilloma.[6,7] TBSCC is usually diagnosed with delay[1,4] since clinical signs (otorrhea, polyps or granulation tissue, hearing loss, bleeding) and patients complaints (ear pain) are similar to other common inflammatory diseases of the ear. When present, facial nerve paralysis is a sign of advanced disease.

Perineural invasion and angio-lymphatic diffusion are local features of tumor aggressiveness.[4,8] The temporal bone may be eroded by obvious extension or microscopic undetectable intra-osseus infiltration. Adjoining sites (jugular foramen, dura mater, internal carotid artery, facial nerve, parotid, condyle) may be involved by local tumor growth. Diagnosis is mostly clinico-radiological and necessarily confirmed by local deep biopsies. Cervical lymphnodes metastases are relatively common (10–20%).[4,9,10] Temporal bone contrast-enhanced, high-resolution CT scan and MRI are mandatory. Neck ultrasonography and/or contrast-enhanced CT scan can effectively investigate regional metastases. PET scan can be important to rule out distant metastasis. Differential diagnosis involves[1,4] skull base osteomyelitis, infectious complications of the skull base and other local neoplasms.

Curative treatment is an extensive radical surgery followed by radiotherapy and chemotherapy in advanced stages or if required by postoperative pathological evidence (including involved margins). The anatomical complexity of this area involves technically difficult surgery and the need of extending the surgical field beyond macroscopically free margins in order to obtain oncologically safe margins.

Despite improvements in early diagnosis, surgical techniques and adjuvant therapies, prognosis remains poor, especially for advanced TBSCCs. It has been diffusely reported that several cases recurred even after radical surgical excision with pathologically free margins. Further investigations exploring the biological behavior of the tumor seem nowadays to be mandatory to predict prognosis and promote modern treatments for TBSCC.

2. Aim

Critical review of the current status of knowledge, prognostic factors, rational management and the ongoing investigations regarding primary temporal bone squamous cell carcinoma (TBSCC).

3. Materials and methods

A systematic search of the literature for articles published between 2009 and October 2014 was performed using the PubMed (http://www.pubmed.gov) electronic database; only articles in English were included. The searched terms used were: “temporal bone cancer”, “temporal bone malignancy”, “temporal bone carcinoma”, “ear malignancy”, “ear cancer”, “ear carcinoma”. The “Related articles” option on the PubMed homepage was also considered. Some papers were found in more than one search. The texts of the publications identified were screened for original data and reference lists were checked for other relevant studies.

Studies considered acceptable for inclusion were those addressing TBSCC prognostic factors. All investigations discussing malignancies other than squamous cell carcinoma, case reports, very limited series, and clinical reviews were excluded. Other recent series referring to carcinoma of the parotid skin, retroauricular, preauricular area involving the external-middle ear were also excluded.

4. Results

4.1. *Conventional clinico-pathological variables and prognosis*

Among the considered series, the significant prognostic factors in terms of disease-free survival (DFS) and disease-specific survival (DSS) were critically analyzed.

The pathological status of surgical margins was diffusely reported as the main factor influencing the outcome and the recurrence rate,[10–16] although how reliable “free margins” could be in the bone is still a matter of discussion.[10]

There is quite a general agreement on the significant role of T stage according to the Pittsburgh staging system[10,12,13,15,16] as a factor determining prognosis, since the latter was good in T1–T2 and poor in T3–T4. The different outcome of the group of patients with anterior vs. non-anterior extension of T4 tumors was recently investigated[17] showing a significantly better prognosis in the anterior T4. The proposal of a modified classification system for tumor local extension has been reported in a recent paper by Mazzoni et al.[17] (Table 1). Extensive erosion of the bone was also a negative prognostic factor.[11,13,16,17] The pathological grading of the tumor was reported as a factor related to worse prognosis only in a limited number of series.[10,18] In part, facial nerve involvement continues to be controversial with a significant negative prognostic role found by most[11,12,15,16,19–22] but not all groups.[23] Dura mater infiltration evidence (both radiological and/or pathological) was reported in most of the series[10,11,21,22] as the strongest negative prognostic factor affecting survival.

Different conclusions have been reported about the prognostic value of neck lymph-nodes clinical status (cN). Clinically positive neck has been significantly related with poor prognosis by some groups[10,11,18,21,22] but not by others.[23,8]

Table 1 – SCC of ear temporal bone. A new classification system.

Stage	Site and subsites
T1	Tumor in skin with no bone involvement
T2	Tumor in skin with bone/cartilage involvement, but not full thickness
T3a	Tumor extending <5 mm from cartilage to periauricular soft tissues, or Tumor strictly limited to the anterior bone wall and growing <5 mm into the parotid space
T3b	Same as for T3a, but extending >5 mm
T4a	Tumor growing into the mastoid, without 7th nerve palsy
T4b	Tumor growing into the mastoid with facial palsy, or into the infratemporal space, or the medial wall of the tympanum, or labyrinth, or petrous bone (jugular foramen, internal carotid canal, petrous apex)

Modified by Mazzoni et al.[17]

4.2. *Biomarkers and temporal bone carcinoma prognosis*

Despite the increasing interest and the recent investigations about rational therapeutic approaches and prognosis of TBSCC previously critically analyzed, rare attempts have tried to go beyond clinical studies focusing on the biologic mechanisms behind these malignancies.[6,10] Molecular markers, detectable by means of reliable assays, have to precisely characterize tumor's biological and clinical behavior. Molecular markers are demonstrable cellular alterations which may be genetic, epigenetic or phenotypic, but are in any case the expression of one or more neoplastic steps.[24] One of the goals of biomarker analysis in oncology is to establish a patient's prognosis. Another goal of such analyses is to ascertain the radio- and chemosensitivity profiles of individual temporal malignancies, so that a truly personalized therapy can be administered. The third goal is to find targets for therapeutic agents as Cetuximab (an IgG1 chimeric human/murine monoclonal antibody that binds to EGFR with a high affinity) that is, at the moment, the only molecular targeting agent used in head and neck carcinoma.[25]

Considering that carcinoma cells seem to activate a dormant epithelial–mesenchymal transition program to promote cell migration, invasion and metastasis, Sugimoto et al.[26] retrospectively examined the role of epithelial–mesenchymal transition in 16 cases of TBSCC. Sugimoto et al.[26] reported that statistical analysis failed in confirming significant differences in disease-specific survival between patients with and without epithelial-mesenchymal transition. Recognizing the importance of neoangiogenesis in the growth of solid malignancies, Marioni et al.[27] investigated in a series of 20 consecutive TBSCCs the role of the expression of endoglin (CD105), a proliferation-associated protein expressed in angiogenic endothelial cells.[28] CD105 stained intra-tumor vessels intensively, while there was little or no reaction to CD105 in the vessels of normal healthy tissues adjacent to TBSCC. The recurrence rate was significantly higher and the disease-free survival shorter in TBSCCs with CD105 expression of 9.44% or higher than in TBSCCs where it was less than 9.44%. The crude carcinoma recurrence risk ratio was 5.9 times higher for patients whose CD105 expression was ≥9.44%. The protein MASPIN reveals a unique tumor-suppressing activity and has been found to inhibit tumor growth and metastasis in numerous models and cancer types.[29] In 2013, Marioni et al.[30] studied the role of the tumor suppressor protein MASPIN in TBSCC, finding subcellular cytoplasmic MASPIN expression significantly higher in patients who had experienced no recurrence of their carcinoma. In the same year, Marioni et al.[31] investigated the prognostic role of phosphorylated (activated) signal transducer and activator of transcription 3 (STAT3) in TBSCC. pSTAT3 over-expression occurs in a variety of malignancies, suggesting that STAT3 may be not only prognostically important but also a potential target for therapy, and several strategies are being developed to target the STAT3 signaling pathway. Unfortunately, Marioni et al.[31] found no significant correlations between phosphorylated STAT3 expression in tumor cells and DFS or DSS in TBSCC patients.

5. Conclusions

The homogeneity of a given series is very important when considering the prognostic factors for carcinoma of the external ear-temporal bone. This was at the base of our critical revision of literature.

This tumor carries a worse prognosis than other histotypes in the same sites and subsites.

Prognosis is influenced by the pathological status of the margins, stage of the disease, degree of differentiation, facial nerve and dura mater involvement.

The radicality achieved with extensive surgery is the most important independent factor influencing prognosis[10–16] though it is not clear how surgical margins can be really considered "free" in the bone.[10] The en-bloc resections with lateral or subtotal temporal bone resections (LTBR and STBR), though more likely to ensure gross radicality, encounter the problem of microscopic diffusion in the bone and may explain the relatively high recurrence rate also after surgery with pathologically free margins. The mainstay of treatment is *extensive* radical surgery to ensure negative margins,[10,30] but this is particularly difficult to achieve when the bone is infiltrated. It is definitely controversial to what extent LTBR or STBR should be enlarged beyond the "free" margins.

There is general agreement[10,12,13,15,16] about the poor prognosis of locally advanced stages, although tumors with anterior extension into soft tissues showed better prognosis than other (medial, posterior, inferior) extensions.[17] A new staging system was thus proposed[17] (Table 1) to differentiate these different sites of tumoral infiltration and give them a prognostic value.

At now, there is no widely accepted system for classifying squamous cell carcinoma of the external ear and temporal bone. Different classifications have been proposed,[6] but none have been accepted by the International Union Against Cancer (UICC) or the American Joint Committee on Cancer (AJCC).[32] This makes it difficult to compare results and complicates efforts to identify prognostic factors.

Preoperative involvement of the facial nerve is considered a negative prognostic factor,[11,12,15,16,19–22] although not

universally recognized.[23] Facial nerve sacrifice was also related to poor prognosis,[10] both in the condition of clinical preoperative involvement and in the necessity to sacrifice it for oncological reasons in the surgical approach. Dural infiltration was the strongest reported negative factor affecting survival. The resection of infiltrated *dura*, although technically feasible, did not prevent recurrences and strongly affected poor survival. The opportunity of a curative surgery when *dura* is infiltrated is questionable and the option of palliation may be considered as a reasonable alternative.

Our critical analysis of prognostic factors showed how aggressive the tumor is and how survival is poor in advanced stages. Radical surgery is the mainstay of treatment and the status of the margin is one of the most important aspect determining prognosis. Adjuvant radiotherapy has showed improvement in the loco-regional control of advanced disease[6,13] and it is mandatory also after radical surgery.

But despite the oncological principles being respected in the management of this tumor and the role of adjuvant radiotherapy, the poor prognosis of advanced stages remains a fact.

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 TBSCC and help clinicians to predict the outcome of treatment.[6] For TBSCC such investigations are only just beginning to appear in the oncological literature. Biomarkers could be extremely important to the development of novel, integrated therapeutic strategies (including targeted approaches) capable of improving the DFS and DSS for patients with advanced TBSCC.

Conflict of interest

None declared.

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None declared.

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