Original article

Prognostic Model to Predict Overall Survival for Patients with Middle Ear Cancer:

A Population-based analysis

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ABSTRACT

Background:

The purpose of this study was to evaluate the survival outcome for middle ear cancer and to construct a prognostic model to provide patients and clinicians with more accurate estimates of individual survival probability.

Patients and methods

Patients diagnosed with middle ear cancer between 1983 and 2010 were selected for the study from the Surveillance Epidemiology and End Results Program. We used the Kaplan-Meier product limit method to describe overall survival and the log-rank test to assess differences between patient groups. Cox proportional hazards model were fitted to model the relationships between patient characteristics and overall survival. A nomogram for predicting survival was built using the Cox model established.

Results:

The entire cohort comprised 283 patients with malignant middle ear cancer. Median duration of follow-up until censoring or death was 32 months (range, 0-307 months). Five-year and ten-year overall survival were 43.0% (95% CI, 37.2% to 49.7%) and 35.6% (95% CI, 29.5% to 42.9%), respectively. In multivariable analysis, age, histological subtype, stage, and surgery were predictive of overall survival.
Conclusion:

The model represents an objective analysis of all currently available data. The resulting model demonstrated good accuracy in predicting survival, with a bootstrap-corrected concordance of 0.75. The nomogram should thus be considered as a useful tool for clinical prognosis prediction.

Key words: Middle ear cancer; nomogram; overall survival.

Background

Malignant tumors of the temporal bone are rare and account for less than 0.2% of all tumors of the head and neck [1]. The most common tumors include squamous cell carcinoma (SCC), basal cell carcinoma, adenoid cystic carcinoma, rhabdomyosarcoma, and Langerhans histiocytosis X (LHX). Primary carcinoma of the middle ear represents a small subset of temporal bone carcinomas [2]. The incidence of middle ear cancer was approximately 0.26 per million people in the United States in 2010, according to the Surveillance Epidemiology and End Results (SEER) [3]. The diagnosis is often delayed because the disease may be masked by other ear symptoms. The complex anatomy of the temporal bones, delayed presentation and diagnosis make the surgical management difficult [1]. Although treatment has been improving over the decades, the
Because of the rarity of malignant tumors of the middle ear, most reports published previously were based on case series from single institution, and most of the literature does not separate carcinomas of the external auditory canal (EAC) from primary carcinomas of the middle ear. The prognostic results therefore lack uniformity. To make advances in the management of patients with middle ear cancer, we should improve our understanding of this disease process.

The SEER is a large population-based database that has been used to provide epidemiological and prognostic information about many types of cancers. Using a population-based database can avoid the limitations of a small sample size and the selection or treatment bias associated with analysis of a single institution’s clinical data. The purpose of this study was to evaluate the survival outcomes of middle ear cancer using the SEER database and to determine prognostic factors for this rare cancer. We also developed a simple nomogram based on the prognostic model established.

**Methods**

The SEER program of the National Cancer Institute is the largest population-based cancer registry in the United States. The SEER registries collect data on patient
demographics, primary tumor site, stage, tumor morphology, and treatment for all cancer patients, covering approximately 26% of the US population. For this research, the recently released SEER (1973-2010) database was used for case extraction [4]. All patients diagnosed with middle ear cancer (site code C30.1) were selected. Patients were excluded from the study if the tumor was identified on the death certificate only. Middle ear lymphomas and rhabdomyosarcomas were also excluded. Because there is no SEER stage information before 1983, we also excluded patients diagnosed between 1973 and 1982. Detailed data selection is shown in Figure 1.

Variables in the analysis included: age at diagnosis; sex; race; histological subtype; cancer stage; surgery and radiotherapy. The American Joint Committee on Cancer (AJCC) has not yet produced a staging system for ear and temporal bone cancer. Here, the clinical stage of cancer was grouped using the historical stage coded by SEER: ‘localized’ was defined as a tumor confined to the organ; ‘regional’ was defined as a neoplasm that had extended into surrounding organs or tissues, or into regional lymph nodes or by a combination of extension and regional lymph nodes, and ‘distant’ was defined as a tumor that had spread to parts of the body remote from the primary tumor. The histological subtype was re-grouped as squamous cell carcinoma, adenocarcinoma and others. For patients diagnosed up to 1997, surgery was defined as
“Site-specific surgery (1983-1997)” codes of 40, 60 90. For patients diagnosed in 1998 or later, surgery was defined as “RX Summ-Surg Prim Site (1998+)” codes between 30 and 90. Item “RX-Summ-Radiation” was used to define radiation treatment. We grouped codes 0 and 7 as no radiation and codes 1 to 6 as radiation. Other codes (8 and 9) were regarded as missing.

Missing values were imputed with the ‘tanscan’ function of the rms package [5].

Patients in the cohort were followed for vital status until the earliest of the following dates: death; last contact if before December 31, 2010 or December 31, 2010 if the date of last contact was after December 31, 2010.

Median follow-up was defined as the median observed survival time among all patients. Overall survival was measured as the time from diagnosis to death, data of last follow-up, or December 21, 2010. We used the Kaplan-Meier product limit method to describe overall survival and the log-rank test to assess for differences between patient groups. The Cox proportional hazards model was fitted to model the relationships between patient characteristics and overall survival. We tested the proportional hazard assumption for each variable in the model. The restricted cubic splines with three knots at the 10%, 50% and 90% empirical quantiles were fitted to model age variables. Interaction between histological type and surgery was evaluated in the model. To avoid
overfitting, we used a model selection technique based on Bayesian information criteria to reduce variable in the model. The Wald test was conducted to find which predictors were significant in the model. A nomogram was developed on plain paper based on the reduced model.

The prediction model was internally validated by measuring both discrimination and calibration. Discrimination means the ability of a model to separate subject outcomes. Discrimination is quantifiable with the c-index, an index of the probability of concordance between predicted probability and response. The c-index is defined as the proportion of all evaluable ordered patient pairs for which predictions and outcomes are in concordance [5]. Calibration is the ability of the predictive model to make unbiased estimates of outcome. The calibration curve compares the predicted value with the actual value. In the survival model, patients are grouped by predicted survival and then plotted as actual versus predicted survival. Both discrimination and calibration were estimated from the original data using bootstrapping with 200 re-samples.

All statistical analysis was performed using R version 3.0.0 software (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org)[6]. The R package rms was used for modeling and developing the nomogram [7]. All P values presented in this article were calculated based on a two-sided statistical test.
Results

Overall survival

A total of 283 cases of middle ear cancer were eligible for inclusion in this analysis. Table 1 shows patients and tumor characteristics. Seventy-three patients (25.8%) were younger than 50 years, 104 patients (36.7%) were 50 to 69 years, and 106 patients (37.5%) were 70 years or older. Overall, 53% of the study population was male, and 82.0% was white.

Median patient age was 64 years. Median follow-up for these patients was 32 months (range 0–307 months). Five- and 10-year overall survival rates were 43.0% (95% CI, 37.2% to 49.7%) and 35.6% (95% CI, 29.5% to 42.9%), respectively. Actuarial 5- and 10-year overall survival for all patients is also shown in Table 1.

Age was found to be a predictor of prognosis with the log-rank test, and decreasing survival was observed with increasing age (log rank P <0.001). The 5-year overall survival was 68.2% for younger patients, 42.6% for the sub-group aged 50 to 69 years, and 26.1% for the oldest group aged 70 years or older.

Squamous cell carcinoma was present in approximately 58.0% of all patients with the poorest 5-year overall survival (26.9%). Other histological subtypes included
adenocarcinoma (13.4%), and others (28.6%) with 5-year overall survival of 70.7%, and 62.9%, respectively. A significant survival difference was found between histological subtypes (log rank $P < 0.001$).

Distant disease exhibited the worst prognosis, with 5-year survival being 21.4%, compared with localized and regional disease, with 5-year survival of 70.1% and 38.0%, respectively (log rank $P < 0.001$).

Around 76% patients accepted surgery. There was a clear survival benefit associated with surgery. Five-year survival was 46.3% with surgery and 32.4% without surgery (log rank $P < 0.001$).

Patients who received radiation had a worse prognosis than those who did not. The 5-year overall survival was 28.0% and 61.7% for radiation and no radiation, respectively (log rank $P < 0.001$). Actuarial overall survival grouped by histological subtype, stage, surgery and radiation is shown in Figure 2.

**Multivariable mode and nomogram**

We pre-specified nonlinear for continuous variable and considered the additivity of the model. Hazard ratios and $P$ values of the multivariate regression model are listed in Table 2.

The assumption of a proportional hazard was supported. Statistically significant
covariates were age, histological subtype, stage and surgery in full model, according to the Wald test (P <0.001). Histological subtype showed a significant interaction effect with surgery. This means that the influence of histological subtype varies according to whether the patient receives surgery or not.

After model selection, age, stage of tumor, histological type and surgery were left in the reduced model. The nomogram was developed based on beta coefficients from this model. To use the nomogram, first draw a vertical line up to the points row to assign points for each variable, then add up the points for each variable to obtain the total points, and drop a vertical line from the total points row to obtain the 5- and 10-year overall survival.

Model performance was evaluated by internal validation. The discrimination (concordance index) was 0.75 (95%CI, 0.71 to 0.78). This implies that the models are reasonably accurate. The calibration plot for 5-year overall survival is shown in Figure 3. Points close to the 45-degree line show good agreement between predicted and observed outcomes.

Discussion

We estimated the overall survival of primary middle ear cancer and developed
a prognostic model to predict 5- and 10-year overall survival using a SEER dataset. A simple nomogram was constructed based on the prognostic model, which included four variables available from the cancer registry or routine clinical practice.

Individual estimation of survival probability for cancer patients is useful for treatment selection and clinical counseling. An individual predictive value of prognosis can also be used to identify and stratify patients for clinical trials. A nomogram based on a statistical model provides clinicians and patients with a practical tool for prognostic prediction [8]. A number of important cancer prognostic models and nomograms have been developed and are in use today for prostate, pancreas, breast, and thyroid cancer and other cancer sites [9-14]. To our knowledge, the present nomogram is the first to use the SEER database to predict the prognosis of middle ear cancer.

Because of the rarity of middle ear cancer, evaluation of prognosis can be challenging. Most of the literature reports results combining malignancies of EAC with primary tumors of the middle ear. So far, middle ear cancer as a subgroup of malignant tumor of the temporal bone has not been well studied. In addition, most published studies involving the temporal bone originate from the experiences of single institutions and the results are heterogeneous. Due to short follow-up periods and rare cases and events, reports from a single institution often do not have sufficient power to identify true
prognostic factors. A population-based study can provide more reliable analysis, and the results are likely to be more generally applicable. The SEER data are a powerful tool for exploring prognostic factors, especially for unusual and rare tumors. The current study, which included 283 middle ear cancer patients, had the largest cohort among middle ear cancer studies. There were 170 deaths in this study, and only 9 predictor d.f. in the reduced model. This is about 1/20 as many predictor d.f. as there are deaths, so we think that this model could provide reliable predictions.

The simplicity of our prognostic model is also a strength. In clinical practice, complex models may not be well accepted and implemented. Our nomogram is based on few predictors, which are all available from routine clinical work. We therefore believe that it can be easily used by clinicians to make accurate individualized prognosis estimates.

Richard first reported the prognosis of middle ear cancer using the SEER database [2], showing 5-year survival by stage, histology and treatment of patients diagnosed between 1973 and 2004. The limitation of this previous study is that confounding factors were not adjusted when evaluating the prognosis, making some results difficult to explain. For example, they identified that treatment with surgery and radiation had a poor survival compared with surgery alone. However, the true effect of
treatment approaches on survival might have been misestimated due to the failure to account for disease characteristics in univariate analysis. In this article, we updated their results to 2010 and added a multivariable model process to control for confounding.

Older patients had lower 5-year survival than younger patients. The increased perioperative risk in the elderly may have precluded some older patients from surgery. Using less aggressive therapy to avoid increased drug toxicity from chemotherapy in elderly patients with more comorbidities is another possible explanation for the poor prognosis among older patients.

Histology was a main prognostic factor, with squamous cell carcinoma (SCC) carrying the worst prognosis. Compared with SCC of EAC, SCC of the middle ear seem have a worse outcome. The overall 5-year survival of SCC has varied in different studies that focused on prognosis of EAC around 50% [15-17]. The difference in cancer prognosis between two sites of the temporal bone suggested that carcinomas of the middle ear have different clinical behavior from those of EAC.

Stage was found to be an independent prognosis factor of overall survival, with local patients having better survival than regional and distant patients. We did not use a staging system currently used for temporal bone malignancy, such as the Pittsburgh
staging system, which provides a comprehensive means of assessing temporal bone
tumors according to imaging and preoperative clinical information. The Pittsburgh
staging system is based on external auditory canal malignancies, [1] and therefore was
not suitable for staging cancer in this study. Stell and McCormick proposed a staging
system in 1985 that can be used for staging both EAC and middle ear cancer [18].
Nevertheless, the Stell and McCormick staging system also could not be used in this
study because of the limited SEER dataset.

Surgical resection with the purpose of achieving a negative margin and
decreasing morbidity or mortality is considered to be the standard of care for middle ear
cancer. It is agreed that all patients who are able to tolerate an operation should be
treated with surgery, except those who are diagnosed with histiocytosis X, which is
treated primarily with radiation only or adjuvant chemotherapy [1]. Surgical approaches
used in clinical practice include local canal resection, sleeve resection, en bloc resection
of the EAC, lateral temporal bone resection, subtotal temporal bone resection and total
temporal bone resection [19]. Whether radical surgery is necessary remains under
debate [1]. Unfortunately, SEER does not provide data regarding the detailed surgery
approach and margin status. Further evaluation of surgery management for middle ear
cancer needs other cohort or series.
Radiotherapy is advocated as an adjunct to surgery or for palliation, rather than as a curative approach. T2 and higher-staged tumors, recurrent tumors, positive margins, perineural spread, positive lymph nodes, or extracapsular spread are indications for postoperative radiotherapy. The effectiveness of adjuvant radiation remains controversial. Some studies have demonstrated an improvement in terms of the survival rate and local control in patients with positive surgical margins who underwent adjuvant radiotherapy compared with patients who underwent surgery only [20-22]. In contrast, other authors concluded that a positive surgical margin was the major cause of recurrence, and adjuvant radiotherapy showed no more effect on survival. In our study, univariate analysis suggested that radiotherapy may be an adverse prognostic factor for overall survival; however, after adjusting for other demographic and disease characteristics, radiotherapy showed an insignificant hazard ratio in the multivariable model. In limited analysis of patients who received surgery, we obtained similar results (data not shown). This implied that patients treated with surgery and radiotherapy have similar survival to those who receive surgery alone. However, because this study was limited to predictive factors available from SEER database, some other factors could not be adjusted in our model. New sources of data which consider a more detailed extent of disease or stage will be important to address this
issue. Furthermore, due to the lack of data on local recurrence, the survival benefit of adjuvant radiotherapy for loco-regional control may have been missed.

There are several limitations of this study. First, some factors impacting survival are not included in the current model. For example, it appears that positive margins and promontory or facial nerve involvement are negative prognostic makers. However, this surgery information cannot be found in the SEER registry. In addition, chemotherapy data cannot be obtained from the public SEER database. Second, patients were enrolled in the database over three decades. It is therefore possible that improvements in multiplanar imaging, IMRT, and chemotherapy, along with advances in skull base surgical techniques have combined to improve overall survival. Thus, our nomogram might have a low estimate of survival probability. Finally, we used internal validation in the model because of relative small sample size. Independent external validation is still necessary to confirm efficacy. Despite its limitation, SEER still provides the largest cohort of middle ear cancer patients available, which is a valuable resource for providing valid statistical comparison and building predictive models for this rare lesion.

Conclusions

In conclusion, we analyzed prognostic data on middle cancer using the SEER
database, a high quality reliable cancer cohort. Survival outcome specific to histology, stage, surgery, radiation therapy and other prognostic factors are described. We then built a survival model to predict 5- and 10-year survival rates. The model provides an objective analysis of all currently available data. The performance of the model is good, with a c-index of 0.75. This nomogram should thus be considered as an accurate tool for clinical prognosis prediction.

**List of abbreviations**

squamous cell carcinoma (SCC); Langerhans histiocytosis X (LHX); the Surveillance Epidemiology and End Results (SEER); external auditory canal (EAC); Intensify-modulated radiation therapy (IMRT); adenocarcinoma(A); others (O); Overall survival (OS)

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors have no potential conflicts of interest.

**Authors' contributions**

L.Y. designed and performed analyses and drafted the paper; W.S prepared data and created the figure; N.S. edited the paper and commented on the interpretation of the results. All authors read and approved the final draft of the paper.

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Funding

This project did not receive any grant funding

REFERENCES


FIGURE LEGENDS

Fig. 1. Flow chart for creation of the Surveillance Epidemiology and End Results (SEER) data set.

Fig. 2. Overall survival by disease characteristics and treatment. (A) Histological subtype; (B) Stage of tumor; (C) Surgery; (D) Radiation.

Fig. 3. Nomogram for predicting 5- and 10-year overall survival. Abbreviations: Race: W, white; NonW, Nonwhite. Stage: L, localized; R, regional; D, distant. Sex: M, male; F, female. Radiation: R, radiotherapy. Histological subtype: S, squamous cell carcinoma; A, adenocarcinoma; O, others. Instructions: Locate the patient’s characteristic on the variable row and draw a vertical line straight up to the points row to assign a value of points for the variable. Repeat this process to obtain points for each variable. Add up the total points and drop a vertical line from the total points row to obtain the 5- and 10-year overall survival.

Fig. 4. Calibration plot. Solid line represents equality between the predicted and observed 5-year overall survival probability.
Table 1. Patient characteristics and 5- and 10-year overall survival

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<th>No. of Events</th>
<th>%</th>
<th>To 5 years</th>
<th>To 10 years</th>
<th>P-value</th>
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Abbreviations: SCC Squamous cell carcinoma; A, Adenocarcinoma; O, Others; OS, Overall survival.

*Significant overall difference: P <0.05
Table 2. Cox proportional hazards multivariate regression analysis results

<table>
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<th>Covariate</th>
<th>Full model</th>
<th>Reduced model</th>
<th>Full model</th>
<th>Reduced model</th>
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<td>P-value</td>
<td>HR 95% CI</td>
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<td>1.94 1.44-2.61</td>
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<td>2.38 1.56-3.63</td>
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<td>Histology × Surgery</td>
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| Abbreviations: SCC, Squamous cell carcinoma; HR: Hazard Ratio
| Hazard ratios are not shown for Histology type and surgery because the significant interaction between these two covariates implies that hazard ratios for surgery are different by histology type. Accordingly, hazard ratios for surgery by histology type are presented.
| * P <0.05

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Figure 1. Flow chart for the creation of the Surveillance Epidemiology and End Results (SEER) data set.

Patients diagnosed with middle ear cancer (C30.1) between 1973 and 2010  
$n = 373$

Exclude reporting resource code 7 (death certificate only)  
$n = 366$

Exclude behavior code 0 (benign) , 1 (malignant potential, and uncertain malignant potential) or 2 (Carcinoma in situ)  
$n = 365$

Exclude middle ear lymphomas  
$n = 349$

Exclude rhabdomyosarcomas  
$n = 326$

Exclude diagnosed between 1973 and 1982  
$n = 283$
Figure 2
Figure 4

Fraction Surviving 5 years

c-index: 0.75 (0.71-0.78)

Predicted 5 years Survival