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Nomograms for predicting survival and recurrence in patients with adenoid cystic carcinoma. An international collaborative study

Ian Ganly[a,*], **Moran Amit**[b], **Lei Kou**[c], **Frank L. Palmer**[a], **Jocelyn Migliacci**[a], **Nora Katabi**[a], **Changhong Yu**[c], **Michael W. Kattan**[c], **Yoav Binenbaum**[b], **Kanika Sharma**[d], **Ramer Naomi**[e], **Agbetoba Abib**[f], **Brett Miles**[f], **Xinjie Yang**[g], **Delin Lei**[g], **Kristine Bjoerndal**[h], **Christian Godballe**[h], **Thomas Mücke**[i], **Klaus-Dietrich Wolff**[i], **Dan Fliss**[j], **André M. Eckardt**[k], **Copelli Chiara**[l], **Enrico Sesenna**[l], **Safina Ali**[m], **Lukas Czerwonka**[n], **David P. Goldstein**[n], **Ziv Gil**[b,o], and **Snehal G. Patel**[a]

[a]Head and Neck Surgery Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[b]The Laboratory for Applied Cancer Research, Rambam Medical Center, Rappaport Medical School, The Technion, Israel Institute of Technology, Haifa, Israel

[c]Department of Quantitative Health Sciences, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, USA

[d]Department of Radiotherapy & Oncology, Maulana Azad Medical College and Lok Nayak Hospital, Bahadur Shah Zafar Marg, New Delhi, India

[e]Mount Sinai Medical Center, Department of Pathology, The Mount Sinai School of Medicine, New York, NY, USA

[f]Department of Otolaryngology, The Mount Sinai School of Medicine, New York, NY, USA

[g]Department of Oral and Maxillofacial Surgery, School of Stomatology, The Fourth Military Medical University, Xi'an 710032, PR China

[h]Department of Otolaryngology Head and Neck Surgery, Odense University Hospital, Denmark

[i]Department of Oral and Maxillofacial Surgery, Klinikum rechts der Isar, Technische Universität München, Germany

[j]Department of Otolaryngology Head and Neck Surgery, Tel Aviv Medical Center, Tel Aviv, Israel

[*]*Corresponding author*: Head and Neck Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1233 York Avenue, Rm. SR331, New York, NY 10065, USA. Tel.: +1 212 639 6244; fax: +1 212 396 5560. ganlyi@mskcc.org (I. Ganly).

Conflict of interest statement

None of the authors have any conflict of interest to disclose.

Contributions

Ian Ganly, Snehal Patel – study design, data analysis, data interpretation, writing.
Lei Kou, Changhong Yu, Michael W. Kattan – data analysis and interpretation, manuscript editing.
Frank L. Palmer, Jocelyn Migliacci – data collection, data analysis, data interpretation, manuscript editing.
Moran Amit, Nora Katabi, Yoav Binenbaum, Kanika Sharma, Ramer Naomi, Agbetoba Abib, Brett Miles, Xinjie Yang, Delin Lei, Kristine Bjoerndal, Christian Godballe, Thomas Mücke, Klaus-Dietrich Wolff, Dan Fliss, André M. Eckardt, Copelli Chiara, Enrico Sesenna, Safina Ali, Lukas Czerwonka, David Goldstein, Ziv Gil – data collection, manuscript editing.

Disclosures

None.

[k]Department of Cranio-Maxillofacial Surgery, Hannover Medical School, Hannover, Germany

[l]Maxillo-Facial Surgery, University-Hospital of Parma, Italy

[m]Department of Otolaryngology Head and Neck Surgery, Edinburgh, UK

[n]Department of Otolaryngology Head and Neck Surgery, Princess Margaret Cancer Center, University of Toronto, Canada

[o]Department of Otolaryngology Head and Neck Surgery, Rambam Medical Center, Rappaport Medical School, The Technion, Israel Institute of Technology, Haifa, Israel

Abstract

Background—Due to the rarity of adenoid cystic carcinoma (ACC), information on outcome is based upon small retrospective case series. The aim of our study was to create a large multiinstitutional international dataset of patients with ACC in order to design predictive nomograms for outcome.

Methods—ACC patients managed at 10 international centers were identified. Patient, tumor, and treatment characteristics were recorded and an international collaborative dataset created. Multivariable competing risk models were then built to predict the 10 year recurrence free probability (RFP), distant recurrence free probability (DRFP), overall survival (OS) and cancer specific mortality (CSM). All predictors of interest were added in the starting full models before selection, including age, gender, tumor site, clinical T stage, perineural invasion, margin status, pathologic N-status, and M-status. Stepdown method was used in model selection to choose predictive variables. An external dataset of 99 patients from 2 other institutions was used to validate the nomograms.

Findings—Of 438 ACC patients, 27.2% (119/438) died from ACC and 38.8% (170/438) died of other causes. Median follow-up was 56 months (range 1–306). The nomogram for OS had 7 variables (age, gender, clinical T stage, tumor site, margin status, pathologic N-status and M-status) with a concordance index (CI) of 0.71. The nomogram for CSM had the same variables, except margin status, with a concordance index (CI) of 0.70. The nomogram for RFP had 7 variables (age, gender, clinical T stage, tumor site, margin status, pathologic N status and perineural invasion) (CI 0.66). The nomogram for DRFP had 6 variables (gender, clinical T stage, tumor site, pathologic N-status, perineural invasion and margin status) (CI 0.64). Concordance index for the external validation set were 0.76, 0.72, 0.67 and 0.70 respectively.

Interpretation—Using an international collaborative database we have created the first nomograms which estimate outcome in individual patients with ACC. These predictive nomograms will facilitate patient counseling in terms of prognosis and subsequent clinical follow-up. They will also identify high risk patients who may benefit from clinical trials on new targeted therapies for patients with ACC.

Funding—None.

Keywords

Adenoid cystic cancer; Nomogram

1. Introduction

Adenoid cystic carcinoma (ACC) accounts for less than 1% of all head and neck malignancies and approximately 10% of all salivary neoplasms [1,2]. It is a locally aggressive tumor and surgery remains the mainstay of treatment for these patients since it is relatively resistant to radiation and chemotherapy [3,4]. ACC is characterized by perineural invasion which predisposes patients to local recurrence. In addition these patients have a high prevalence of late distant metastases, usually to lung, which can develop up to 10 years after initial treatment [3,5]. Since ACC is a rare tumor, reports of the clinical and pathological predictors of outcome generally consist of small single-institution retrospective series [6–13]. Most of the reports on ACC are based on cohorts of patients with tumors involving various anatomical locations in the head and neck, and therefore analysis of outcomes on specific tumors or sites have not been possible. Two population based studies on the NCDB and SEER databases have been reported but these studies lack details on many clinicopathological factors as well as details on recurrence [14,15]. This has led to inconsistency in the reported factors which contribute to recurrence and survival. To address this issue we created an international collaborative database with contributions from 10 international institutions recognized as major centers of excellence for the treatment of head and neck cancer.

The current method for predicting outcome for patients with ACC is the American Joint Committee on Cancer (AJCC) TNM staging system. This system stages patients from stage I to stage IV according to the T-status, N-status and M-status of the patient. The TNM system works effectively for a patient population but it is less useful for predicting outcome in an individual patient. In addition, it does not account for other variables which may be important for determining outcomes in individual patients. This includes patient variables such as age, gender, and comorbidities, as well as tumor factors such as the presence of perineural invasion, vascular invasion and margin status. These factors are all important in patients with ACC. Therefore we decided to use this large and unique international dataset to create statistical models (nomograms) and test their capability to predict both recurrence and survival in individual patients with ACC.

Nomograms are statistical tools shown to accurately predict outcome in an individual patient by utilizing multiple variables in addition to the standard TNM variables. These nomograms are created using regression analysis [16], Well-designed nomograms have outperformed the projections of experienced clinicians [17,18], and have been incorporated into clinical trial inclusion criteria and National Comprehensive Cancer Network (NCCN) guidelines [19]. At present, no such predictive tool applicable to individual ACC patients is available. Using clinical and pathological variables we have created the first ACC nomograms that accurately predict overall recurrence, distant recurrence, cause-specific mortality and overall survival. Such tools will help clinicians counsel patients by determining prognosis and the intensity of follow-up.

2. Methods

2.1. Patient, tumor, and treatment data

Our study cohort used to create the nomograms comprised 438 patients treated for ACC between 1985 and 2011 in 10 cancer centers worldwide. Primary surgery was carried out on all patients. Criteria for study population inclusion were histopathologic diagnosis of head and neck ACC with >12 months follow-up or earlier death or recurrence. The study was approved by the local institutional review board (IRB) committees of the participating centers. Pathologic staging was performed using the American Joint Committee on Cancer (AJCC) Staging Manual, 7th edition [20]. Data collection was approved by the MSKCC Institutional Review Board. The 10 centers were Memorial Sloan Kettering Cancer Center (New York), Rambam Medical Center (Israel), Maulana Azad Medical College and Lok Nayak Hospital (India), Mount Sinai Medical Center (New York), Fourth Military Medical University (China), Odense University Hospital (Denmark), Technische Universität München (Germany), Tel Aviv Medical Center (Israel), Hannover Medical School (Germany), University-Hospital of Parma (Italy).

Patient, tumor, and treatment characteristics were extracted for each patient from patient charts. All clinical and pathological factors were taken at baseline. Clinical characteristics included patient age, gender, tumor site and clinical stage. Tumor characteristics included pathological T-status, pathological N-status, M-status, margin status, and presence of perineural invasion (PNI). Margin status was categorized as negative, close (less than 5 mm) or positive. Treatment characteristics included extent of primary surgery, extent of neck dissection and use of postoperative radiation and/or chemotherapy.

2.2. Nomogram design

A cumulative incidence plot was constructed to show the difference between death with disease and death from other causes (Supplementary Fig. 1). Follow-up length was defined as months from treatment to death or censoring. Four multivariable competing risk models were then built to predict the 10-year overall survival, cancer specific mortality, overall recurrence, and distant recurrence free probability of ACC. Log transformation was applied on continuous variables. Restricted cubic splines were used to relax the commonly assumed linear relationship between continuous predictors and the outcome. Eight predictors were investigated using a cox model: age, sex, clinical T-status, M-status, site, pathological N-status, pathologic PNI and margin status. All predictors of interest were added in the starting full models before model selection. Stepdown method was used in model selection to choose predictive variables. Of the multiple variable combinations assessed, factors with the highest predictive value were parsimoniously selected for the scale, limited by the number of events. For the final models, predictive accuracy was assessed by discrimination (the ability of a model to separate patients with different outcomes) and calibration (how far predictions are from actual outcomes). Discrimination was measured with the concordance index, similar to the area under the receiver operating characteristic curve: values range from 0.5 (no discrimination) to 1.0 (perfect discrimination). Calibration was measured by graphically plotting the predicted against the actual probability for tertiles of the predicted probability of recurrence. All the internal validations for cox models were performed by bootstrapping for

1000 times. Internal validation for competing risk model was done by using ten fold cross-validation. R version 3.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses.

2.3. Nomogram validation on external cohort

99 patients treated for ACC at 2 other international centers (Department of Otolaryngology Head and Neck Surgery, Princess Margaret Cancer Center, Canada, n = 75 and Department of Otolaryngology Head and Neck Surgery, Edinburgh, Scotland, n = 24) were used as an external validation dataset. Patient, tumor, and treatment characteristics were extracted for each patient from patient charts. The concordance index for overall recurrence, distant recurrence, overall survival and cancer specific mortality nomograms were calculated using this dataset.

3. Results

3.1. Patient, tumor, and treatment characteristics (Table 1)

Of 438 eligible patients, the median age was 57 years (range 16–91). 184 (42%) were male and 256 (58%) tumors arose from minor salivary glands of the oropharynx, oral cavity or larynx. 177 (40%) had clinical T3–4 tumors, 20 (5%) had distant metastases at presentation and 65 (15%) had positive neck nodes. 201 (46%) had close or positive margins on surgical resection and 215 (49%) had perineural invasion. 278 (63.5%) had postoperative radiation and 84 (19%) had adjuvant chemotherapy. 27.2% (119/438) died from ACC, while 38.8% (170/438) died secondary to other causes. Median follow-up period was 56 months (range 1–306).

3.2. Nomograms for survival

a) 10 year overall survival probability—After testing multiple iterations for predictive accuracy, age, sex, clinical T stage, M-status, tumor site, pathologic N-status, and margin status were selected for the final model as having the highest predictive accuracy with the correct sign of risk for 10 year overall survival probability (Supplementary data). Internal bootstrap validation was performed to correct the over-fitting bias that results from testing on the same patient population. All the internal validations for cox models were performed by bootstrapping for 1000 times. Discrimination and calibration were found to be excellent, with a concordance index of 0.71 (Supplementary Fig. 2). The composite nomogram based on these variables is shown in Fig. 1.

b) 10 year cancer specific mortality—Age, sex, clinical T-status, M-status, tumor site, pathologic N-status were selected for the final model as having the highest predictive accuracy with the correct sign of risk for 10 year cancer specific mortality (Supplementary data). Discrimination and calibration were found to be excellent, with a concordance index of 0.70 (Supplementary Fig. 2). The composite nomogram based on these variables is shown in Fig. 2.

3.3. Nomograms for recurrence

Age, sex, clinical T status, tumor site, pathologic N status, perineural invasion and margin status were selected for the final model as having the highest predictive accuracy with the correct sign of risk for 10 year overall recurrence free probability (Supplementary data). The concordance index was 0.66 (Supplementary Fig. 2). The composite nomogram based on these variables is shown in Fig. 3a. We then developed an individual nomogram for distant recurrence. 6 variables (sex, clinical T-status, tumor site, pathological N-status, perineural invasion and margin status) were selected for the final model (Supplementary data). The concordance index for this nomogram was 0.64 (Supplementary Fig. 2). The composite nomogram is shown in Fig. 3b.

3.4. External validation of nomograms

Patient, tumor, and treatment characteristics of the external validation cohort are shown in Table 1. Of 99 eligible patients, the median age was 51 years (range 23e83). 40 (40%) were male and all tumors arose from major salivary glands. 14 (14%) had clinical T3–4 tumors, 1 (1%) had distant metastases at presentation and 11 (11%) had positive neck nodes. 83 (84%) had close or positive margins on surgical resection and 70 (71%) had perineural invasion. 12% (12/99) died from ACC, while 11% (11/99) died secondary to other causes. Median follow-up period was 74 months (range 5–254). Concordance indices for overall survival, cancer specific mortality, overall recurrence and distant recurrence nomograms for the external validation set were 0.76, 0.72, 0.67 and 0.70 respectively.

4. Discussion

Adenoid cystic cancer is a rare cancer of the major and minor salivary glands [1–4]. It is recognized for its tendency for local recurrence due to perineural invasion as well as frequent positive margin following surgery. It is also well recognized as a tumor which can present with distant metastases late in the disease course, usually in the lungs. Due the rarity of these tumors, most physicians may only treat a handful of patients in their practice. Formulating treatment decisions and counseling patients with these types of rare tumors can therefore be quite challenging. The current TNM staging system can help to predict prognosis for patients but this system applies only to a population and not to an individual patient. A nomogram has the attraction that it applies to an individual patient utilizing several clinical, tumor and treatment related variables to predict outcome. Outside of adenoid cystic cancer, nomograms have been demonstrated in breast and prostate cancer to be superior to conventional staging, scoring systems, and expert opinion [17,18,21,22]. We have also reported the utility of nomograms for management of patients with oral cancer [20] and salivary gland cancer [24,25]. Furthermore, nomograms are arguably most valuable in situations where the potential benefit of added therapy is unclear [22,26,27]. Such tools are therefore extremely useful for individualized risk stratification, helping the physician determine management where no firm guidelines may exist. Here, we have designed models which predict recurrence and survival in individual patients with adenoid cystic cancer. Our models contain far more variables than that used in the TNM staging system illustrating the depth of data utilized in such predictive tools. These nomograms employ easily accessible clinical information and the concordance index for each nomogram compares favorably with

those of widely used nomograms in other fields, which have ranged between 0.64 and 0.81 [22–28]. One of the other major strengths of our study was the use of an external validation cohort [29,30] of 99 patients which had concordance indices of approximately 0.7 for all outcomes. To illustrate the utility of the nomogram Fig. 4a and b show two hypothetical patients. A 30-year old man with a T2N0M0 ACC of the hard palate with negative margins has an 10 year overall survival probability of 80%. (Fig. 4a) In contrast, a 50-year old man with a T2N0M1 ACC of the parotid gland with positive margins and lung metastases has a 10 year overall survival probability of 5%. (Fig. 4b).

It is important to point out that our models may have several limitations which may constrain their use. Firstly, the nomograms have been created from retrospective data from several institutions and therefore this makes it susceptible to the inherent weaknesses of retrospective data collection. Although pathological review was carried out in some institutions, several did not have pathological review. The impact that positive margin status on outcome is likely to be underestimated as we found a large variation in the reporting of positive margin status from 5.9% to 29.4% as well as variation in close margin status ranging from 1.4% to 74.3%. In addition, there are now several papers which report that the solid histological subtype of ACC is more aggressive and has worse outcome. We did not have accurate subtype histology on a significant number of our patients and therefore could not look at the relationship between the solid subtype and outcome. Secondly, although we carried out external validation with appropriate concordances indices, our validation cohort was comprised only of major salivary gland cancers. This is a limitation of the dataset and we therefore suggest further validation on other datasets which have a range of tumor subsites included. Thirdly, the nomograms may not be applicable in areas where management is markedly different from the centers that contributed data to this collaboration. However, the nomograms have been created from data collected from 10 centers worldwide including countries in Europe, India, China and America. Such diversity in geography would mean that any heterogeneity in management policy of ACC among centers would have diluted out, suggesting that the nomograms may be valid for use at any center in the world. However, it is still possible that this could be an area of bias which can impact on outcomes both in terms of recurrence and survival.

In summary, using the strength of international collaboration we have been able to create the first ever set of nomograms to predict overall recurrence, distant recurrence, overall survival and cause-specific mortality in individual patients with ACC. These nomograms will be invaluable to many physicians who treat patients with these rare tumors allowing physicians to better counsel patients on prognosis in terms of overall recurrence risk, distant recurrence risk as well as survival. Such nomograms are also invaluable in helping to identify patients at risk of recurrence, particularly distant recurrence, as they will enable more reliable stratification of patients to clinical trials evaluating new targeted therapies to be designed. Clinical trials on new radiotherapy techniques and modalities may also be carried out on these high risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.09.004.

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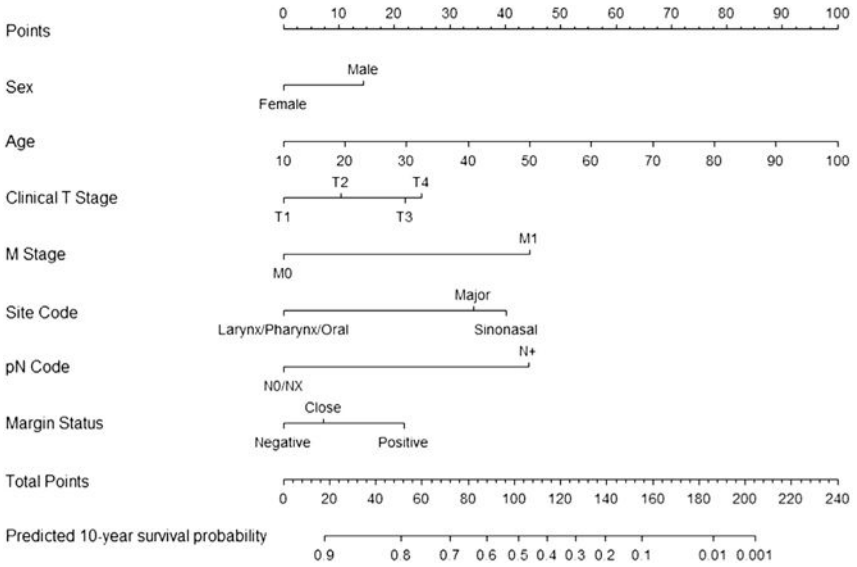

Fig. 1.
Nomogram of 10 year overall survival.

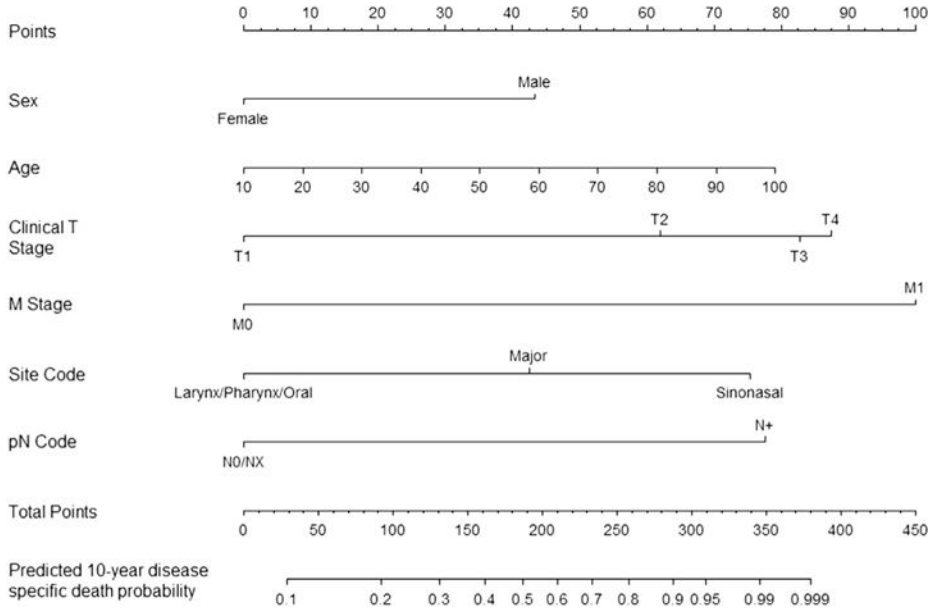

Fig. 2.
Nomogram of 10 year disease specific death probability.

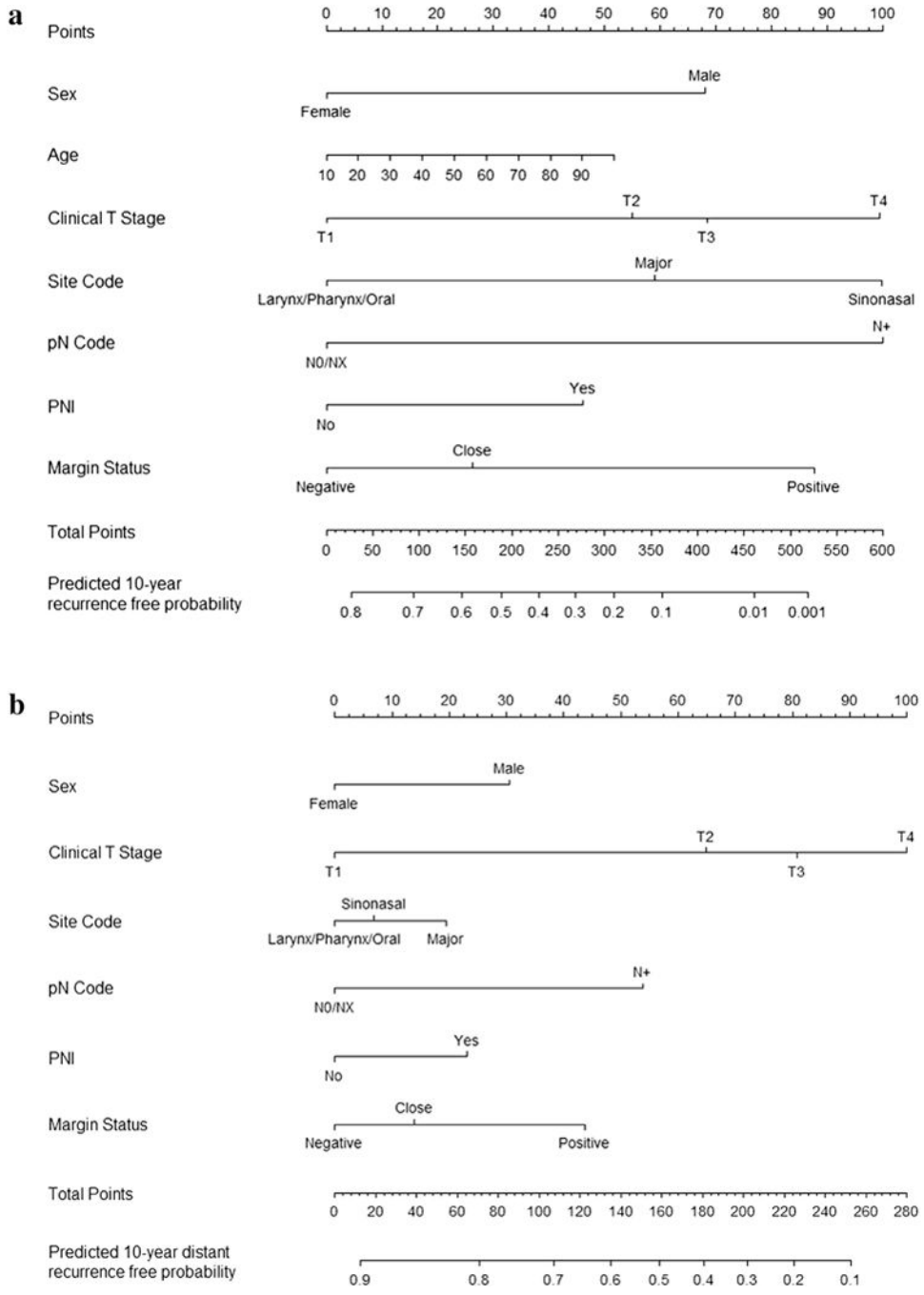

Fig. 3.

a. Nomogram of 10 year recurrence free probability. b. Nomogram of 10 year distant recurrence free probability.

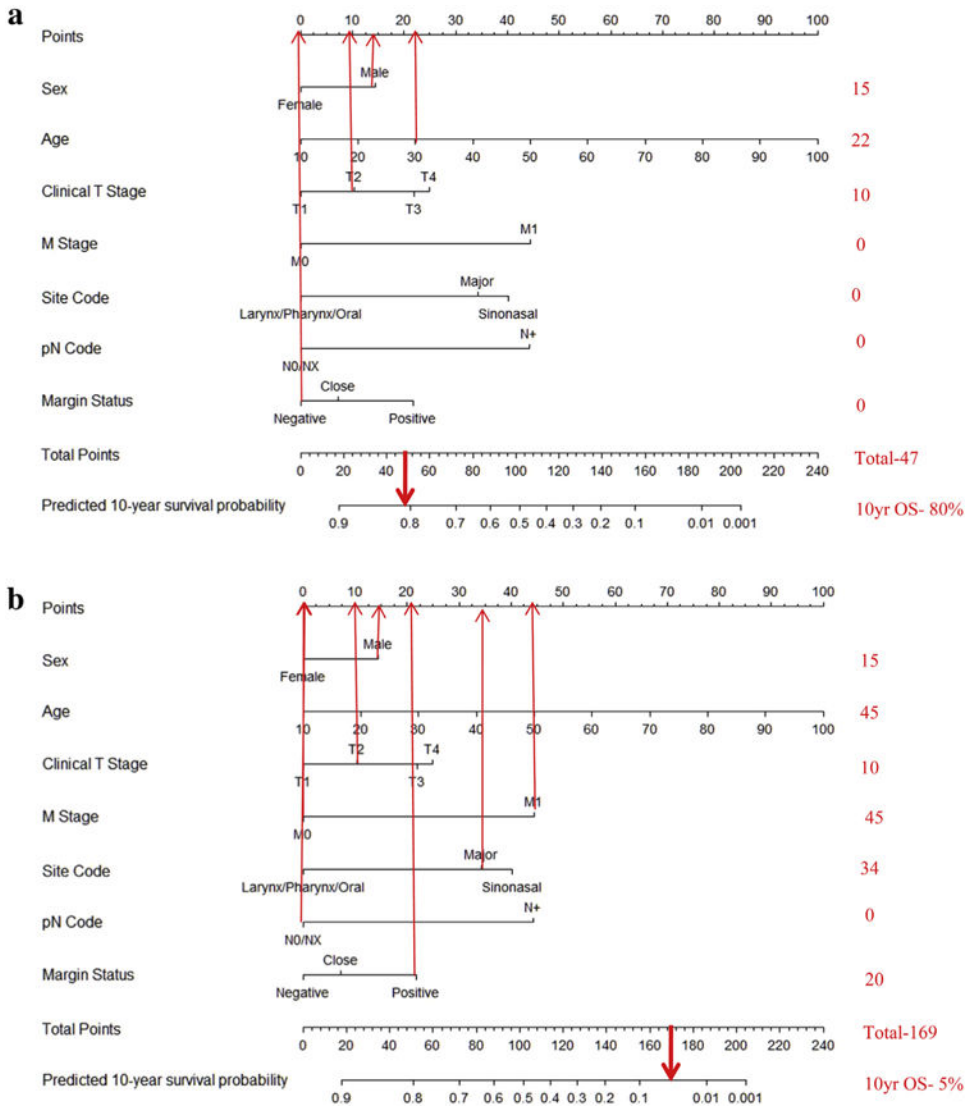

Fig. 4.

a. Nomogram of 10 year overall survival for 30 year man with a T2N0M0 ACC of the hard palate with negative margins. b. Nomogram of 10 year overall survival for 50 year man with a T2N0M1 ACC of the parotid gland with positive margins and lung metastases.

Table 1

Clinical and tumor characteristics of training and validation cohorts.

Variables	Training cohort		Validation cohort	
	No.	%	No.	%
Sex				
Female	254	58%	59	60%
Male	184	42%	40	40%
Site				
Larynx/Pharynx/Oral	256	58%	0	0%
Major	128	29%	99	100%
Sinonasal	54	12%	0	0%
Clinical T stage				
T1	96	22%	42	42%
T2	150	34%	33	33%
T3	58	13%	9	9%
T4	119	27%	5	5%
Unknown	15	3%	10	10%
M stage				
M0	413	94%	98	99%
M1	20	5%	1	1%
Unknown	5	1%	0	0%
Pathological N stage				
N+	65	15%	11	11%
N0/NX	373	85%	85	86%
Unknown	0	0%	3	3%
Pathologic PNI				
No	223	51%	24	24%
Yes	215	49%	70	71%
Unknown	0	0%	5	5%
Margin status				
Negative	204	47%	14	14%
Close	138	32%	17	17%
Positive	63	14%	66	67%
Unknown	33	8%	2	2%