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Lymph node ratio-based nomogram for prognosis evaluation and treatment optimization of non-metastatic oral cavity squamous cell carcinoma

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ABSTRACT

Background: Lymph node ratio (LNR) has been increasingly reported as a prognostic factor in oral cavity squamous cell carcinoma (OCSCC). This study aimed to develop and validate a prognostic nomogram integrating LNR and to further assess its role in guiding adjuvant therapy for OCSCC.

Methods: A total of 8703 OCSCC patients treated primarily with surgery in the Surveillance, Epidemiology and End Results (SEER) database were retrieved and randomly divided into training and validation cohorts. The nomogram was created based on the factors identified by Cox model. The value of PORT and chemotherapy was respectively evaluated in each prognostic group according to nomogram-deduced individualized score.

Results: The final nomogram included tumor site, grade, T stage, number of positive lymph nodes and LNR. Calibration plots demonstrated a good match between predicted and observed rates of overall survival (OS). The concordance indexes for training and validation cohorts were 0.720 (95% confidence interval (CI): 0.708, 0.732) and 0.711 (95% CI: 0.687, 0.735), both significantly higher than did TNM stage ($p< 0.001$). According to individualized nomogram score, patients were stratified into three subgroups with significantly distinct outcome. PORT presented survival benefit among medium- and high-risk groups whereas a near-detrimental effect in low-risk group. Chemotherapy was found to be beneficial only in high-risk group.

Conclusion: This LNR-incorporated nomogram surpassed the conventional TNM stage in predicting prognosis of patients with non-metastatic OCSCC and identified sub-settings that could gain survival benefit from adjuvant thearpy.

Introduction

Oral cavity cancer is one of the most common malignant tumors occurring in head and neck, with the dominant histologic type of squamous cell carcinoma (SCC) [1]. Lymph node metastasis is an important prognostic determinant of oral cavity SCC (OCSCC), resulting in reduced locoregional control and overall survival [2–5]. The nodal stage of the 8th edition of the American Joint Committee on Cancer (AJCC) Staging system is determined by the size, laterality, number and extra-nodal extension (ENE) status of regional lymph nodes (LNs). However, some reports have questioned the discriminative ability of current N staging, which is affected not only by surgeons who determines the quality of neck dissection, but also by the pathologist who examined the lymph nodes from the resected specimen [3,5–7].

Lymph node ratio (LNR), namely the ratio of positive LNs to the total number of excised LNs, has been increasingly reported as a prognostic factor in various kind of tumors, including breast cancer [8,9], bladder cancer [10], colorectal cancer [11,12], melanoma [13] as well as OCSCC [14–17]. A high LNR is indicative of an inadequate neck resection, an incomprehensive pathological examination or a more advanced disease, implying a potential higher likelihood of regional recurrence and a subsequent greater benefit from post-operative radiotherapy (PORT)

List of abbreviations: LNR, Lymph node ratio; OCSCC, oral cavity squamous cell carcinoma; PORT, post-operative radiotherapy; SEER, Surveillance Epidemiology and End Results; OS, overall survival; CI, confidence interval; SCC, squamous cell carcinoma; AJCC, American Joint Committee on Cancer; ENE, extra-nodal extension; LNs, lymph nodes; SD, standard deviation; HRs, hazard ratios; C-index, concordance index; AUC, area under the curve; ROC, receiver operating characteristic; PLNs, positive lymphnodes; NSL, nomogram score low; NSM, nomogram score medium; NSH, nomogram score high; SND, selective neck dissection; POF, pattern of failure; LRF, local regional failure.

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[18,19]. A number of studies have verified the superior performance of LNR over AJCC based N-stage with respect to prognosis assessment in OCSCC [14–17]. Limited studies have shown that a high LNR value was associated with more benefits from PORT for OCSCC patients [18,19]. These studies mainly rendered a single cutoff or certain cutoffs of LNR to create prognostic stratification and further guide PORT in high-risk stratum [15].

Nomogram is a reliable tool that creates the graphic presentation of a statistical predictive model. By incorporating multiple prognostic determinants, nomogram based prognostic score is more accurate and comprehensive in predicting individualized oncologic outcome and the value of PORT. Several nomograms have been developed to evaluate prognosis of OCSCC in recent years [20–23]. However, to the best of our knowledge, there is no LNR-based nomogram in predicting the prognosis of OCSCC or adapting PORT in OCSCC so far.

In current study, we aimed to: (1) develop and validate a LNR-incorporated nomogram based on Surveillance, Epidemiology and End Results (SEER) data; and (2) explore the indication and value of PORT as well as adjuvant chemotherapy as per the nomogram-derived stratification.

Materials and methods

Study population

Patients data were primarily extracted from SEER database by using the following criteria: year of diagnosis between 2010 and 2015, with complete AJCC 7th TNM stage, AJCC M0 and primary site of oral cavity including tongue, floor of mouth, gum and other mouth. There were 21216 patients who met these criteria. After excluding those who did not receive primary surgery, had less than 3 LNs examined or harbored T0 or Tx stage of diseases, a total of 8703 patients were finally eligible for analysis. Detailed diagram of patient selection is illustrated in Fig. 1. Selected variables included diagnostic year, age, ethnicity, sex, histology type, AJCC T stage, AJCC N stage, overall AJCC stage, radiation sequence, chemotherapy type, regional node examined, regional node positive, vital status, cause-specific death status and survival months.

Statistical consideration

Continuous variables were presented as mean ± standard deviation (SD) and were compared using Mann-Whitney U test. Chi squared tests was adopted for categorical data comparison between groups. Kaplan-Meier method was used to estimate survival and log-rank test was performed to examine the significance of difference. Cox proportional hazard regression model was rendered to identify factors independently associated with survival and to calculate hazard ratios (HRs). To assess the effect of the continuous LNR value on survival outcome, an additive Cox model was implemented to compute pointwise estimates of HR curves and their corresponding confidence intervals (CI) by using "smoothHR" package. The spline-based approach was used as the smoothing technique [24]. Based on the factors identified by Cox proportional hazard regression model, a nomogram was created to calculate individual's probability of overall survival (OS) by using "rms" package. In the nomogram, each patient was assigned a series of scores corresponding to all involved variables and the final sum of the scores was projected to certain year survival probability. The discriminative performance of the nomogram was measured by Harrell concordance index (C-index) and the area under the curve (AUC) of receiver operating characteristic (ROC) curve. The value of C-index ranges from 0.5 to 1 [25]. The higher the C-index is, the more accurate the prediction is. The AUC value$\geq$ 0.7 was indicative of a good discriminating ability of the nomogram model. Calibration plots were generated by comparing predicted probabilities from the nomogram versus observed Kaplan–Meier estimates of survival probability, with the 45° diagonal representing the perfect concordance in between. Bootstraps with 1000 resamples were applied to these activities [26]. To stratify patients into groups with distinct prognosis, we applied X-tile method to divide the population into low-, medium-, and high-risk groups through selecting the point with minimum p-value in the triangular grid [27]. Statistical analyses were conducted with SPSS 22.0 (IBM Inc.), Graphpad Prism 6.0C (GraphPad Software, Inc.) and R 3.6.2 (R Foundation for Statistical Computing). All tests were two sided and a $p\leq$ 0.05 was considered statistically significant.

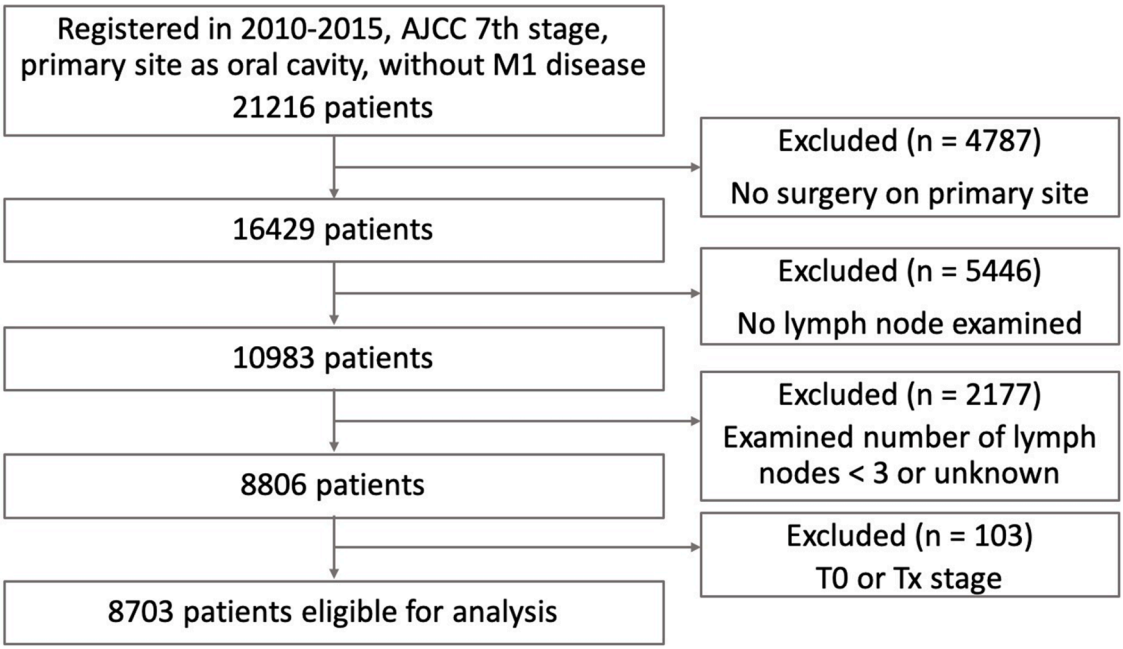

Fig. 1. Diagram of study patient identification.

Results

General characteristics

A total of 8703 patients were identified from corresponding SEER database and were randomly divided into training and validation cohorts with the ratio of 4:1, resulting in 6963 patients in training cohort and 1740 patients in validation cohort. The majority of patients were between 50 and 69 years old, accounting for nearly 60% of the entire population. Most of the patients were male (64.6%) and white (84.4%). More than 40% patients harbored AJCC IVA stage. Most of the tumor located in the tongue (59.9%) and were moderately differentiated (55.5%). More than half of the patients received PORT (54.5%), while only 28.4% received chemotherapy with detail administration timing unavailable. There was no significant difference in the characteristics between training and validation cohort (all p values > 0.05). The median and 5-y rate of OS among entire cohort was 82.0 months and 56%. General characteristics of study patients are summarized in Table 1.

Univariate and multivariate analysis in training cohorts

eFigure 1 depicts the P-splines based smooth log HR estimates with 95% pointwise confidence limits for number of positive lymph nodes (PLNs) to predict the death among the entire cohort and demonstrates a nonlinear association between the number of PLNs and death hazard. According to the trend of the smooth log HR, we observed that the log HR of death linearly increased with the PLNs from 1 to 10 and reached a plateau since the PLN of 11 and more. Thus we considered PLN as a continuous variable including absolute number of 0 to 11, with patients with $\geq$ 11 PLNs being considered as 11 in the following analysis. Other factors were analyzed as categorical variables.

As per univariate analysis results, race, tumor location, tumor Grade, AJCC T stage, N stage, number of PLNs and LNR were found to be significantly correlated with OS. Age, gender and lymph node yield failed to present significant association with OS and were excluded from the subsequent multivariate analysis. The multivariate analysis revealed that tumor site, tumor differentiation grade, AJCC T stage, number of PLNs and LNR were independent prognostic factors of OS (Table 2).

Nomogram development and validation

A nomogram predicting OS was established based on all independent prognostic factors selected by multivariate analysis in the training set (Fig. 2A) Fig. 2.B–C demonstrate the respective calibration plots for training and validation cohorts, with the plots of predictive OS probability versus observed OS hovering near the 45° diagonal.

Table 1
General characteristics and demographics of entire, training and validation cohorts.

Parameters		Entire cohort(n = 8703)		Training cohort(n = 6963)		Validation cohort(n = 1740)		*p*
		Patient number	%	Patient number	%	Patient number	%	
Age	10–19	7	0.1	5	0.1	2	0.1	0.560
	20-29	98	1.1	81	1.2	17	1.0	
	30-39	275	3.2	231	3.3	44	2.5	
	40-49	901	10.4	711	10.2	190	10.9	
	50-59	2438	28.0	1965	28.2	473	27.2	
	60-69	2647	30.4	2117	30.4	530	30.5	
	70-79	1547	17.8	1221	17.5	326	18.7	
	80+	790	9.1	632	9.1	158	9.1	
Race	White	7346	84.4	5879	84.4	1467	84.3	0.472
	Black	586	6.7	477	6.9	109	6.3	
	Other	771	8.8	607	8.7	164	9.4	
Gender	Male	5620	64.6	4504	64.7	1115	64.1	0.629
	Female	3083	35.4	2458	35.3	625	35.9	
Site	Floor of mouth	1267	14.6	1012	14.5	255	14.7	0.868
	Gum and other mouth	2219	25.5	1784	25.6	435	25.0	
	Tongue	5217	59.9	4167	59.8	1050	60.3	
Grade	Well differentiated (Grade I)	1763	20.3	1408	20.2	355	20.4	0.483
	Moderately differentiated (Grade II)	4832	55.5	3886	55.8	946	54.4	
	Poorly to undifferentiated (Grade III-IV)	2108	24.2	1669	24.0	439	25.2	
T stage	T1	3113	35.8	2505	36.0	608	34.9	0.403
	T2	2813	32.3	2255	32.4	558	32.1	
	T3	997	11.5	804	11.5	193	11.1	
	T4	1780	20.5	1399	20.1	381	21.9	
N stage	N0	4351	50.0	3508	50.4	852	49.0	0.746
	N1	1570	18.0	1242	17.8	319	18.3	
	N2	2681	30.8	2134	30.6	547	31.4	
	N3	101	1.2	79	1.1	22	1.3	
AJCC stage	I	1911	22.0	1544	22.2	367	21.1	0.252
	II	1350	15.5	1101	15.8	249	14.3	
	III	1637	18.8	1313	18.9	324	18.6	
	IVA	3601	41.4	2843	40.8	758	43.6	
	IVB	204	2.3	162	2.3	42	2.4	
PORT	Yes	4745	54.5	3799	54.6	946	54.4	0.886
	N0	3958	45.5	3164	45.4	794	45.6	
Chemo	Yes	2476	28.4	1994	28.6	482	27.7	0.117
	No	6227	71.6	4960	71.4	1258	72.3	
ELNs*	median (range)	29 (3, 90)		29 (3, 90)		28 (3, 90)		0.102
PLNs*	median (range)	0 (0, 69)		0 (0, 69)		1 (0, 40)		0.157
LNR*	median (range)	0 (0, 1.0)		0 (0, 1.0)		0 (0, 1.0)		0.581
	0	4407	50.6	3545	50.9	862	49.5	0.285
	≤ 5%	1704	19.6	1343	19.3	361	20.7	
	5-10%	1124	12.9	903	13.0	221	12.7	
	10-15%	567	6.5	440	6.3	127	7.3	
	>15%	901	10.4	732	10.5	169	9.7	

Abbreviations: PORT: post-operative radiotherapy; Chemo: chemotherapy; ELN: examined lymph node; PLNs: positive lymph node; LNR: lymph node ratio.

Table 2
Univariate and multivariate analyses on OS in training cohort (n = 6963).

	Univariate analyses			Multimariate analyses		
Parameters	**HR**	**95% CI**	***p***	**HR**	**95%CI**	***p***
Age				/	/	/
10-19	ref					
20-29	0.468	0.141,1.56	0.217			
30-39	0.358	0.111,1.151	0.085			
40-49	0.479	0.153,1.497	0.205			
50-59	0.550	0.177,1.711	0.302			
60-69	0.663	0.213,2.060	0.477			
70-79	0.863	0.277,2.683	0.799			
80+	1.260	0.404,3.926	0.690			
Gender (male as ref)	0.934	0.860, 1.015	0.109	/	/	/
Race						
White	ref			ref		
Black	1.367	1.188, 1.572	< 0.001	1.130	0.996, 1.283	0.059
Other	1.015	0.879, 1.172	0.841	1.038	0.913, 1.180	0.567
Site						
Tongue	ref			ref		
Floor of mouth	1.480	1.329, 1.649	< 0.001	1.353	1.224, 1.494	< 0.001
Gum and other mouth	1.580	1.445, 1.727	< 0.001	1.332	1.220, 1.454	< 0.001
Grade						
Well differentiated (Grade I)	ref			ref		
Moderately differentiated (Grade II)	1.517	1.354, 1.699	< 0.001	1.243	1.122, 1.378	< 0.001
Poorly to undifferentiated (Grade III-IV)	1.691	1.490, 1.920	< 0.001	1.176	1.046, 1.323	0.007
AJCC T stage						
T1	ref			ref		
T2	1.916	1.718, 2.136	< 0.001	1.657	1.502, 1.828	< 0.001
T3	3.086	2.711, 3.514	< 0.001	2.568	2.282, 2.889	< 0.001
T4	3.465	3.101, 3.871	< 0.001	2.565	2.304, 2.855	< 0.001
AJCC N stage						
N0	ref			ref		
N1	1.902	1.707, 2.120	< 0.001	0.759	0.405, 1.424	0.391
N2	2.450	2.241, 2.679	< 0.001	0.678	0.363, 1.267	0.223
N3	2.392	1.736, 3.296	< 0.001	0.629	0.319, 1.241	0.181
Regional nodes examined				/	/	/
3-5	ref					
6-10	0.948	0.739,1.215	0.673			
11-15	1.074	0.849,1.358	0.552			
16-20	0.975	0.774,1.229	0.833			
21-25	0.831	0.659,1.048	0.117			
26-30	0.912	0.725,1.148	0.433			
31-35	0.786	0.616,1.002	0.052			
36-40	0.913	0.714,1.168	0.469			
41-45	0.876	0.678,1.132	0.310			
46-50	0.985	0.756,1.283	0.909			
51-55	1.100	0.831,1.457	0.506			
56-60	1.114	0.836,1.486	0.460			
> 60	1.191	0.947,1.498	0.135			
*Regional nodes positive	1.183	1.170, 1.197	< 0.001	1.067	1.045, 1.090	< 0.001
LNR						
0	ref			ref		
≤ 5%	1.633	1.464, 1.822	< 0.001	1.830	0.976, 3.431	0.059
5-10%	2.155	1.918, 2.420	< 0.001	2.234	1.190, 4.194	0.012
10-15%	2.377	2.046, 2.762	< 0.001	2.586	1.367, 4.890	0.003
> 15%	3.937	3.521, 4.403	< 0.001	3.462	1.827, 6.559	< 0.001

Abbreviations: HR: hazard ratio; CI: confidence interval; LNR: lymph node ratio.
* As continuous variable

The C-index of OS for training cohort was 0.720 (95% CI: 0.708, 0.732). Correspondingly, the C-index of OS for validation cohort was 0.711 (95% CI: 0.687, 0.735). Additionally, we calculated the C-indexes of TNM staging among training and validation cohort respectively to evaluate its performance in predicting OS. The C-indexes of TNM staging for OS were 0.647 (95%CI: 0.635, 0.659) and 0.649 (95%CI: 0.627, 0.671) in training and validation cohorts respectively, both significantly worse than did the nomogram model ($p< 0.001$). Likewise, the AUCs for predicting OS of total points derived from nomogram model were also significantly superior to those of TNM stage among both training and validation cohorts (Fig. 3). Detailed AUCs of nomogram and TNM stage are provided in eTable 1.

Prognostication of nomogram-derived prognostic score

Fig. 4A and B reveal the linear correlation between the nomogram score and the hazard of death in both training and validation cohorts. On the basis of training cohort, X-tile identified two cutoffs of nomogram score to divide the cohort into 3 subgroups (eFigure 2), namely nomogram score low (≤ 99, NSL), nomogram score medium (99-196, NSM) and nomogram score high (> 196, NSH). The OS curves of the 3 subgroups were significantly separated, with the 5-year OS of 71.6%, 47.2% and 20.6%, respectively ($p< 0.001$) (Fig. 4C). As for the validation setting, Fig. 4D demonstrates similar divergent trend, presenting the 5-year OS of 69.6%, 49.7% and 21.0%, respectively ($p < 0.001$).

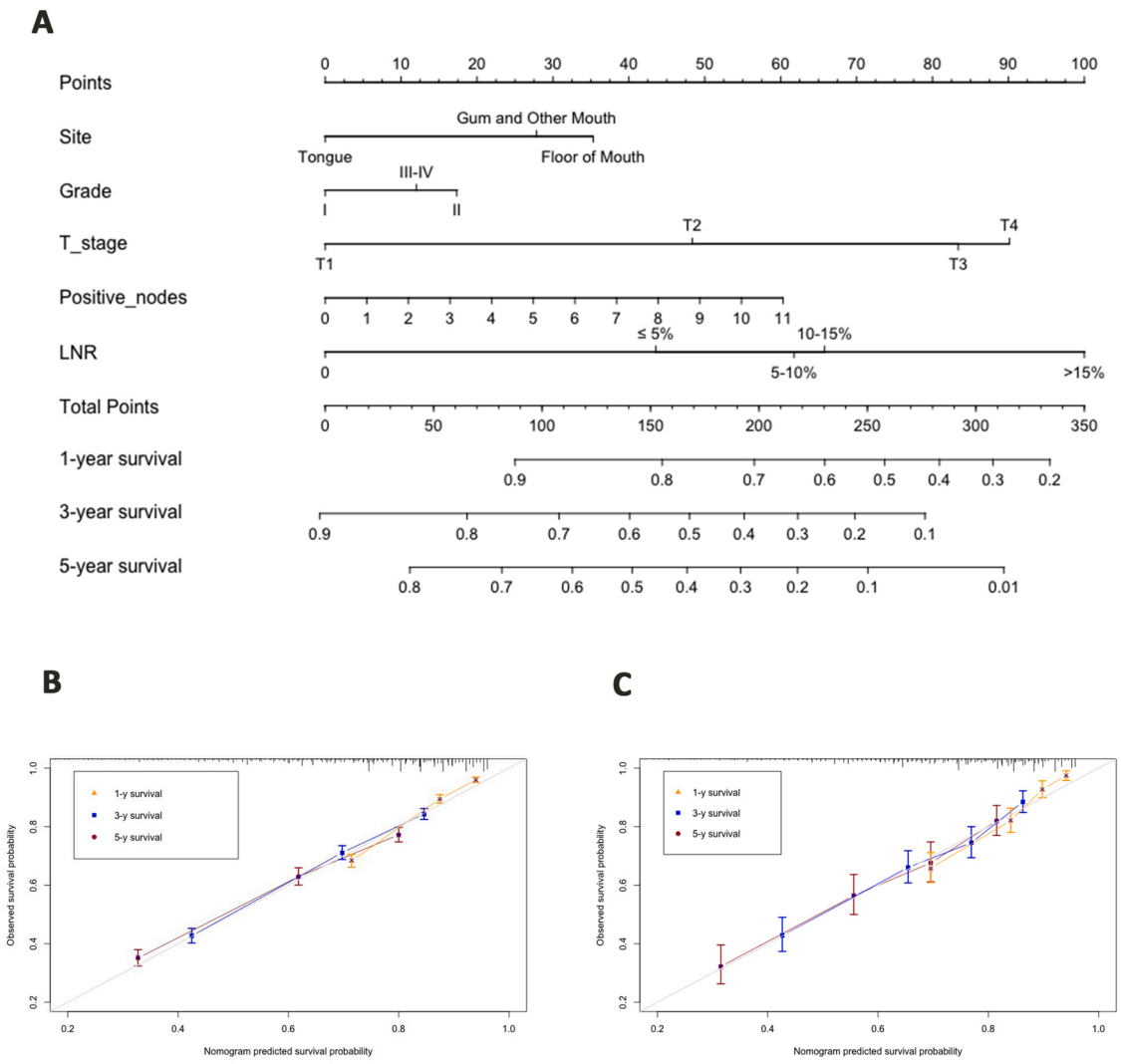

Fig. 2. Nomogram based on training cohort (A) and calibration plots based on training cohort (B) and validation cohort (C). For the variable of positive nodes, 11 indicates $\geq$ 10 metastatic lymph nodes.

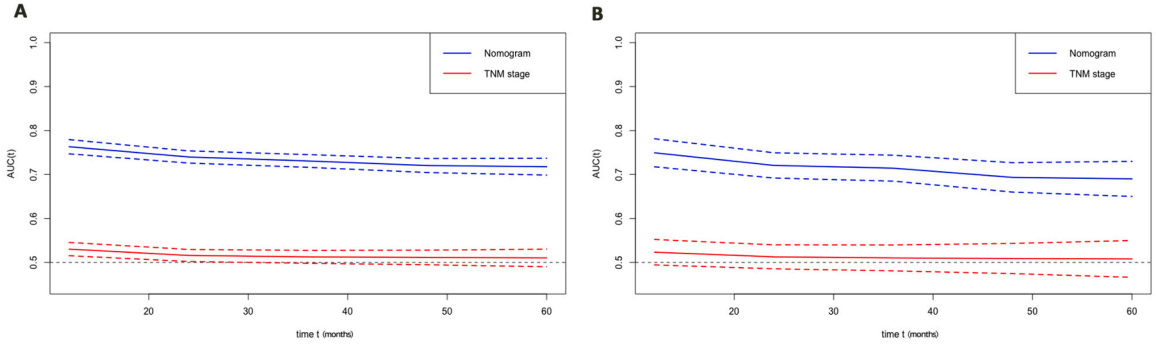

Fig. 3. Comparison of AUC plots between nomogram and TNM stage in training (A) and validation cohort (B). AUC: area under curve.

Nomogram-based adaptive utilization of PORT

Based on the nomogram-derived grouping with different prognosis, we further compared the OS between patients with and without PORT within each stratum to assess the clinical validity of this nomogram in guiding post-operative treatment Fig. 5. displays the survival comparison between patients receiving PORT or not within each risk group among both training and validation population. Detailed survival data are provided in eTable 2. Basically, PORT was associated with improved survival outcome in both NSM and NSH groups, unveiling a more remarkable benefit in NSH group. However, no statistical OS difference between patients with and without PORT was observed in NSL group, with a trend toward detrimental effect of PORT.

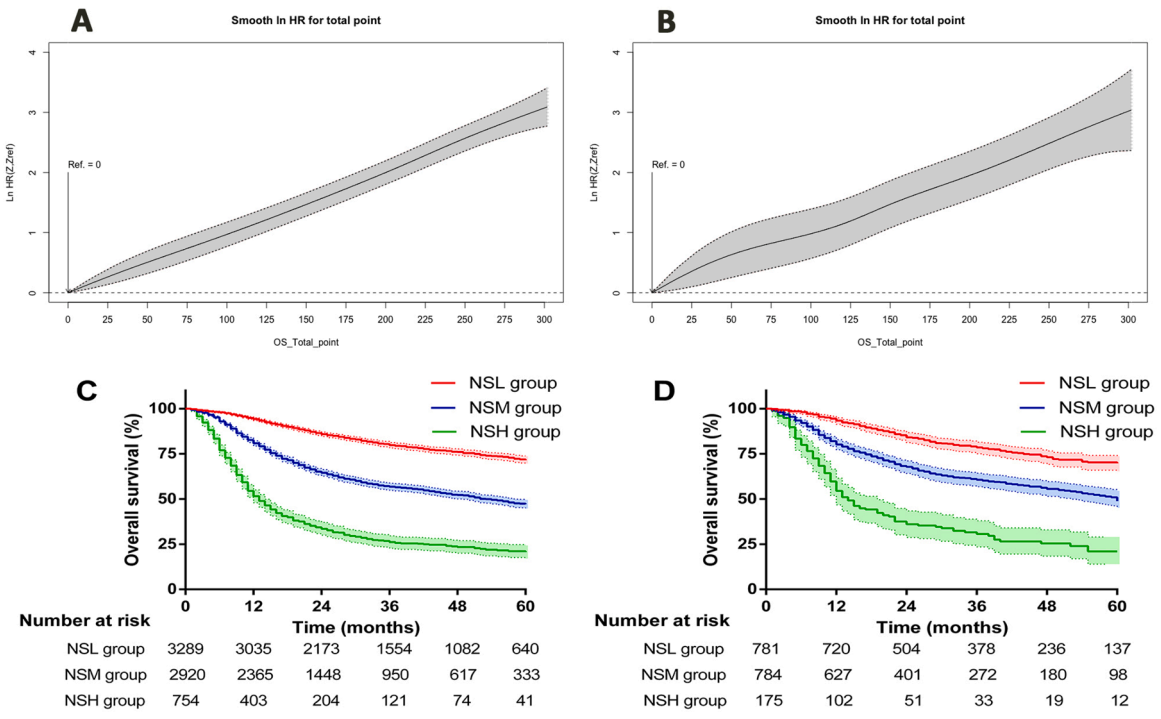

Fig. 4. Correlation between nomogram-derived score and survival outcome. Linear correlation between nomogram-derived prognostic score and hazard of death in training (A) and validation cohort (B). The gray bands indicate 95% confidence interval. Survival curves of three subgroups stratified by nomogram-derived score in training (C) and validation (D) cohort. NSL: nomogram score low; NSM: nomogram score medium; NSH: nomogram score high.

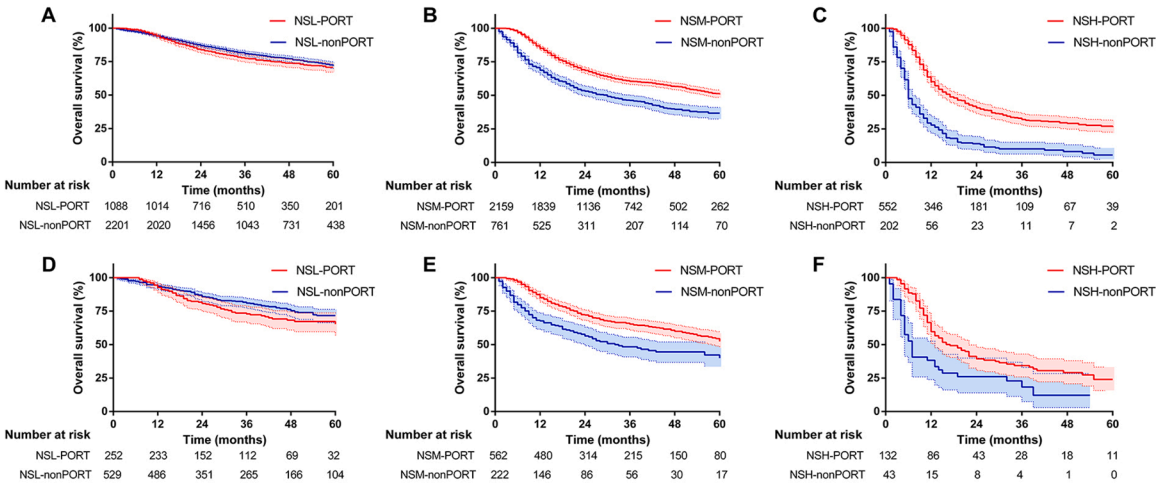

Fig. 5. Impact of PORT within various nomogram-stratified risk groups in training (A-C) and validation cohort (D-F), respectively. NSL: nomogram score low; NSM: nomogram score medium; NSH: nomogram score high; PORT: postoperative radiation therapy.

Nomogram-based adaptive utilization of chemotherapy

We also evaluated the impact of chemotherapy on OS for each nomogram-derived stratum. In training cohort, same scenario was found with that of PORT. Chemotherapy provided significantly beneficial effect for patients in the NSH group and a similar trend in the NSM group whereas without reaching a statistical significance. Notwithstanding, a detrimental effect of chemotherapy was noticed among those in NSL group. Similar pattern was observed in validation cohort. Detailed survival data and survival curves within each risk group are provided in eTable 3 and eFig. 3.

Discussion

In this large population-based study, a LNR-based nomogram was established and validated. This nomogram model demonstrated excellent predictive performance for OS and outperformed the categorical AJCC stage. Moreover, the nomogram-derived prognostic stratification assisted the identification of high-risk patients who are more likely to gain benefit from PORT. To the best of knowledge, this study is the first that incorporating LNR into nomogram to predict the prognosis of OCSCC and to further guide postoperative management.

Nodal status is well accepted as one of the most significant prognostic factors of survival and disease recurrence in patients with OCSCC [17, 28–30]. Selective neck dissection (SND) is the standard approach in OCSCC under the current clinical practice [31]. The number of positive

LNs is based on the quality of neck dissection as well as the pathologic analysis. Limited LN dissection or retrieval will apparently result in pathological underestimation of the current AJCC staging. In recent years, some alternative indicators of lymph node burden, such as LNR, have been increasingly investigated to compensate for the potential bias of the sampling method. A growing amount of evidence supported the prognostic value of LNR in OCSCC [14–17]. In current study, LNR outperformed the traditional N stage and was identified as an independent determinant for prognostication in the multivariate analysis.

According to the results of multivariate analysis in the training cohort, we finally included tumor site, grade, AJCC T stage, number of PLNs and LNR into the nomogram for OS. Although the prognostic significance of tumor site, grade, and AJCC T stage have been reported and presented in the manner of nomogram previously [19,20,23,32–34], our nomogram is the first one that we are aware of to incorporate LNR into the prognostic model. Another notable hallmark of our nomogram is the inclusion of PLNs. Among the previously published nomograms, only one including the lymph node status into the nomogram whilst the LN status was merely defined negative vs positive and lacked more detailed categorization [19]. In current study, we implemented the P-penalized based additive Cox model to reflect the nature of continuous PLNs on survival. The hazard of death was revealed to be linearly associated with the PLNs from 1 to 10 and ultimately reach a plateau since the PLN of 11 and more. Based on this tendency, PLN surpassed the traditional AJCC N stage and sprung up as an independent variable from the MVC model. In terms of the discriminative performance of this nomogram, its C-index and AUC both significantly outperformed AJCC TNM stage and were at least comparable to previous nomograms for OCSCC [20–23]. On the basis of single-institution data with similar cohort identification and potential factors for selection with ours, Chen F et al [19]. established a nomogram including age, smoking status, AJCC stage, histological grade, LN positivity, comorbidity as well as neutrophil to lymphocyte ratio, resulting a suboptimal C-index of 0.687. Based on SEER data from 2004 to 2012, Wang FZ et al [20]. developed a nomogram for OCSCC including age, site, sex, race, grade, surgery (yes or no), radiation (yes or no) and AJCC T, N, M stage. Despite of higher C-index of 0.762, this study included patients with metastatic disease as well as therapeutic management. It is well-known that local therapy such as surgery and radiation should have been administered in selected patients and therefore it may be not rational enough to simply include these factors as yes vs no into nomogram for the entire setting. Our study included a more recent cohort of non-metastatic OCSCC patients registered in SEER database from 2010 to 2015, when AJCC 7th stage and IMRT as the mainstays in OCSCC, leading to a nomogram with more instructive and profound implication for current clinical care. Another notable advantage of this study was that we split the whole cohort into training and validation cohort randomly and performed independent external-validation to corroborate the performance of this nomogram.

Despite a growing amount of evidence supported the prognostic value of LNR in OCSCC, whereas very few integrated LNR-based stratification into adjuvant therapy decision-making from clinical management point of view. The dominant pattern of failure (POF) of isolated local-regional failure (LRF) highlights the importance of PORT to improve the local-regional tumor control in OCSCC patients [35]. As far as we know, among the previously published nomograms for OCSCC, only Chen F's study has analyzed the ability of nomogram model in guiding personalized postoperative management [19]. In current study, we implemented X-tile method to identify 3 subgroups as per the nomogram score, which was more sensible and discriminating than the arbitrary grouping based on median, tertiles or quartiles. Then we revealed that PORT was only associated with improved survival outcome in medium- and high-risk groups whereas provided a trend toward detrimental effect in low-risk group. Furthermore, high-risk group of patients gained most considerable benefit from PORT, with the reduction of death hazard around 60% and 50% in the training and validation cohort, respectively. With regard to the adjuvant chemotherapy, only patients in high-risk group was verified to gain significant survival benefit from chemotherapy. A trend of advantageous OS without approaching significance for medium-risk group and detrimental effect for low-risk group were unveiled with the administration of chemotherapy. These results underline that this nomogram may be sufficiently valid to serve as a practical tool for clinicians to select PORT and chemotherapy candidates for OCSCC patients.

We admit the present study contains typical limitations of SEER based analysis. Some important data were not included in the SEER database, such as patients' comorbidities, performance status, depth of invasion, surgical margin, perineural invasion, ENE and chemotherapy sequence, which may affect the comprehensiveness of this nomogram. In addition, detailed patterns of failure were unavailable from SEER data, which impeded the investigation of direct impact of LNR on regional failure and PORT administration. Moreover, the established nomogram in our study was also validated by using the SEER data instead of the real-world data.

Conclusions

In conclusion, this large population-based study developed and validated a LNR-based nomogram with excellent performance, which surpassed the conventional TNM staging in predicting the prognosis of patients with non-metastatic OCSCC. In addition, a nomogram-based stratification effectively identified patients who were more likely to gain survival benefit from PORT and chemotherapy. Overall, this nomogram is qualified to be applied as a tool for personalized prognosis prediction and treatment decision-making. Further evaluation and validation of this nomogram with real-world data is warranted to further examine and improve its clinical utility.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Study data was publicly available in the SEER database (https://seer.cancer.gov/).

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CRediT authorship contribution statement

Yuchao Ma: Formal analysis, Writing – original draft. **Yang Liu:** Formal analysis. **Gulidanna Shayan:** Formal analysis. **Junlin Yi:** Conceptualization. **Jingbo Wang:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2022.101401.

References

[1] F Bray, M Colombet, L Mery, M Pineros, A Znaor, R Zanetti, et al., Cancer Incidence in Five Continents, Vol. XI, International Agency for Research on Cancer, Lyon, 2017 electronic versionAvailable from, https://ci5.iarc.fr.

[2] S Shingaki, M Takada, K Sasai, R Ribi, C. Saito, Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas, Am. J. Surg. 185 (2003) 278–284, https://doi.org/10.1016/S0002-9610(02)01378-8.

[3] SY Kim, SY Nam, SH Choi, KJ Cho, JL. Roh, Prognostic value of lymph node density in node-positive patients with oral squamous cell carcinoma, Ann. Surg. Oncol. 18 (8) (2011) 2310–2317, https://doi.org/10.1245/s10434-011-1614-6.

[4] CT Liao, C Hsueh, LY Lee, CY Lin, KH Fan, HM Wang, et al., Neck dissection field and lymph node density predict prognosis in patients with oral cavity cancer and pathological node metastases treated with adjuvant therapy, Oral Oncol. 48 (4) (2012) 329–336, https://doi.org/10.1016/j.oraloncology.2011.10.017.

[5] SG Patel, M Amit, TC Yen, CT Liao, Z Gil, Lymph node density in oral cavity cancer: results of the international consortium for outcomes research, Br. J. Cancer 109 (8) (2013) 2087–2095, https://doi.org/10.1038/bjc.2013.570.

[6] MT Agrama, D Reiter, MF Cunnane, A Topham, WM. Keane, Nodal yield in neck dissection and the likelihood of metastases, Otolaryngol. Head Neck Surg. 128 (2) (2003) 185–190, https://doi.org/10.1067/mhn.2003.67.

[7] A Ebrahimi, Z Gil, M Amit, T Yen, C Liao, P Chaturvedi, et al., The prognosis of N2b and N2c lymph node disease in oral squamous cell carcinoma is determined by the number of metastatic lymph nodes rather than laterality: evidence to support a revision of the American Joint Committee on Cancer staging system, Cancer 120 (13) (2014) 1968–1974, https://doi.org/10.1002/cncr.28686.

[8] VV Belle, BV Calster, H Wildiers, SV Huffel, P. Neven, Lymph node ratio better predicts disease-free survival in node-positive breast cancer than the number of positive lymph nodes, J. Clin. Oncol. 27 (30) (2009) e150–e151, https://doi.org/10.1200/JCO.2009.24.0044.

[9] D Liu, Y Chen, M Deng, G Xie, J. Wang, Lymph node ratio and breast cancer prognosis: a meta-analysis, Breast Cancer 21 (1) (2014) 1–9, https://doi.org/10.1007/s12282-013-0497-8.

[10] JH Ku, M Kang, HS Kim, CW Jeong, C Kwak, HH. Kim, Lymph node density as a prognostic variable in node-positive bladder cancer: a meta-analysis, BMC Cancer 15 (2022) 447, https://doi.org/10.1186/s12885-015-1448-x.

[11] MR Zhang, TH Xie, JL Chi, Y Li, ZG. Zhou, Prognostic role of the lymph node ratio in node positive colorectal cancer: a meta-analysis, Oncotarget 7 (45) (2016) 72898–72907, https://doi.org/10.18632/oncotarget.12131.

[12] HB Qiu, LY Zhang, YF Li, ZW Zhou, RP Keshari, RH. Xu, Ratio of metastatic to resected lymph nodes enhances to predict survival in patients with stage III colorectal cancer, Ann. Surg. Oncol. 18 (2011) 1568–1574, https://doi.org/10.1245/s10434-010-1528-8.

[13] AJ Spillane, BLH Cheung, J Winstanley, JF. Thompson, Lymph node ratio provides prognostic information in addition to American joint committee on cancer N stage in patients with melanoma, even if quality of surgery is standardized, Ann. Surg. 253 (2011) 109–115, https://doi.org/10.1097/SLA.0b013e3181f9b8b6.

[14] HJ Son, JL Roh, KJ Cho, SH Choi, SY Nam, SY Lim, Nodal factors predictive of recurrence and survival in patients with oral cavity squamous cell carcinoma, Clin. Otolaryngol. 43 (2) (2018) 470–476, https://doi.org/10.1111/coa.12995.

[15] A Hosni, C McMullen, SH Huang, W Xu, J Su, A Bayley, et al., Lymph node ratio relationship to regional failure and distant metastases in oral cavity cancer, Radiother. Oncol. 124 (2) (2017) 225–231, https://doi.org/10.1016/j.radonc.2017.06.018.

[16] N Subramaniama, D Balasubramaniana, N Kumar, SP Murthy, S. Lyer, Lymph node staging systems in oral squamous cell carcinoma: A comparative analysis, Oral Oncol. 97 (2019) 92–98, https://doi.org/10.1016/j.oraloncology.2019.08.002.

[17] TH Huang, KY Li, WS. Choi, Lymph node ratio as prognostic variable in oral squamous cell carcinomas: Systematic review and meta-analysis, Oral Oncol. 89 (2019) 133–143, https://doi.org/10.1016/j.oraloncology.2018.12.032.

[18] D Urban, I Gluck, MR Pfeffer, Z Symon, YR. Lawrence, Lymph node ratio predicts the benefit of post-operative radiotherapy in oral cavity cancer, Radiother. Oncol. 106 (1) (2013) 74–79, https://doi.org/10.1016/j.radonc.2012.09.022.

[19] F Chen, LS Lin, FQ Liu, LJ Yan, Y Qiu, J Wang, et al., Three prognostic indexes as predictors of response to adjuvant chemoradiotherapy in patients with oral squamous cell carcinoma after radical surgery: a large-scale prospective study, Head Neck 41 (2019) 301–308, https://doi.org/10.1002/hed.25495.

[20] F Wang, H Zhang, J Wen, J Zhou, J. Wei, Nomograms forecasting long-term overall and cancer-specific survival of patients with oral squamous cell carcinoma, Cancer Med. 7 (4) (2018) 943–952, https://doi.org/10.1002/cam4.1216.

[21] KH Fang, CH Lai, CM Hsu, E Huang, YT. Tsai, A retrospective study on the prognostic value of preoperative C-reactive protein to albumin ratio in patients with oral cavity squamous cell carcinoma, PeerJ 8 (12) (2020) e9361, https://doi.org/10.7717/peerj.9361.

[22] ZL Nie, PC Zhao, YS Shang, B. Sun, Nomograms to predict the prognosis in locally advanced oral squamous cell carcinoma after curative resection, BMC Cancer 21 (2021) 372–389, https://doi.org/10.21203/rs.3.rs-137829/v1.

[23] PH Montero, CH Yu, FL Palmer, PD Patel, I Ganly, JP Shah, et al., Nomograms for preoperative prediction of prognosis in patients with oral cavity squamous cell carcinoma, Cancer 120 (2014) 214–221, https://doi.org/10.1002/cncr.28407.

[24] L Meira-Machado, C Cadarso-Suárez, F Gude, A. Araújo, smoothHR: an R package for pointwise nonparametric estimation of hazard ratio curves of continuous predictors, Comput. Math. Methods Med. 2013 (2013) 745742–745753, https://doi.org/10.1155/2013/745742.

[25] J Wang, W Jiang, T Zhang, L Liu, N Bi, X Wang, et al., Increased CYFRA 21-1, CEA and NSE are prognostic of poor outcome for locally advanced squamous cell carcinoma in lung: a nomogram and recursive partitioning risk stratification analysis, Transl. Oncol. 11 (4) (2018) 999–1006, https://doi.org/10.1016/j.tranon.2018.05.008.

[26] A Iasonos, D Schrag, GV Raj, K. Panageas, How to build and interpret a nomogram for cancer prognosis, J. Clin. Oncol. 26 (8) (2008) 1364–1370, https://doi.org/10.1200/JCO.2007.12.9791.

[27] RL Camp, M Dolled-Filhart, Rimm DL. X-Tile, A new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization, Clin. Cancer Res. 10 (21) (2004) 7252–7259, https://doi.org/10.1158/1078-0432.CCR-04-0713.

[28] D Ding, W Stokes, M Eguchi, M Hararah, SD. Karam, Association between lymph node ratio and recurrence and survival outcomes in patients with oral cavity cancer, JAMA Otolaryngol. Head Neck Surg. 145 (1) (2019) 53–61, https://doi.org/10.1001/jamaoto.2018.2974.

[29] TC Zhao, SY Liang, WT Ju, Y Fu, ZH Zhou, LZ Wang, et al., High-risk lymph node ratio predicts worse prognosis in patients with locally advanced oral cancer, Oral Pathol. Med. 49 (8) (2020) 787–795, https://doi.org/10.1111/jop.13043.

[30] S Spoerl, M Gerken, A Mamilos, R Fischer, G. Spanier, Lymph node ratio as a predictor for outcome in oral squamous cell carcinoma: a multicenter population-based cohort study, Clin. Oral Investig. 25 (2021) 1705–1713, https://doi.org/10.1007/s00784-020-03471-6.

[31] SA Koyfman, N Ismaila, D Crook, A D'Cruz, CP Rodriguez, et al., Management of the neck in squamous cell carcinoma of the oral cavity and oropharynx: ASCO clinical practice guideline, J. Clin. Oncol. 37 (20) (2019) 1753–1774, https://doi.org/10.1200/JCO.18.01921.

[32] HK Kao, J Lofstrand, CYY Loh, WWK Lao, JS Yi, YL Chang, et al., Nomogram based on albumin and neutrophil-to-lymphocyte ratio for predicting the prognosis of patients with oral cavity squamous cell carcinoma, Sci. Rep. 8 (1) (2018) 13081–13090, https://doi.org/10.1038/s41598-018-31498-z.

[33] Y Lin, W Kang, B Huang, Z Qiu, L Wei, B Zhang, et al., Nomogram based on clinical characteristics and serological inflammation markers to predict overall survival of oral tongue squamous cell carcinoma patient after surgery, BMC Oral Health 21 (1) (2021) 667–678, https://doi.org/10.1186/s12903-021-02028-7.

[34] F Huang, G Xu, H. Du, A new nomogram for predicting overall survival and assisting postoperative adjuvant treatment decision-making in stage II oral tongue squamous cell carcinoma: a surveillance, epidemiology and end results (SEER) database analysis, J. Oral Maxillofac. Surg. 79 (10) (2021) 2147–2154, https://doi.org/10.1016/j.joms.2021.04.010.

[35] JE Leeman, JG Li, X Pei, P Venigalla, ZS Zumsteg, E Katsoulakis, et al., Patterns of treatment failure and postrecurrence outcomes among patients with locally advanced head and neck squamous cell carcinoma after chemoradiotherapy using modern radiation techniques, JAMA Oncol. 3 (11) (2017) 1487–1494, https://doi.org/10.1001/jamaoncol.2017.0973.