Observational Study

Medicine®

OPEN

Prognostic factors of patients with initially diagnosed T1a glottic cancer

Novel nomograms and a propensity-score matched cohort analysis

Meng-Si Luo, MS[a], Guan-Jiang Huang, MD[b], Hong-Bing Liu, BS[c,*]

Abstract

The option of T1a glottic cancer treatments remarkably varied in different countries. This study aimed to construct predictive models to predict overall survival (OS) and cancer-specific survival (CSS) of patients with initially diagnosed T1a glottic cancer. And we used propensity score matching (PSM) to reassess the effect of treatments.

Data of patients with initially diagnosed T1a glottic cancer were extracted from the Surveillance, Epidemiology, and End Results database. Patients with complete information were randomly divided into the training and the validation cohorts (7:3). Cox regression was conducted to screen significant predictors of the OS and the CSS. PSM was performed to mimic randomized controlled trials. Survival analyses were performed by Kaplan–Meier survival methods, and log-rank tests were utilized.

A total of 2342 patients met the inclusion criteria. Survival analyses showed that patients who underwent primary site surgery would have better OS and CSS. Univariate analyses and multivariate analyses proved that stage, N stage, primary site surgery, and chemotherapy significantly affected both the OS and the CSS. Predictive nomograms were established to predict patients' prognosis. Finally, the OS and the CSS for patients who underwent primary site surgery alone were significantly longer than those who underwent radiation alone before and after PSM.

We constructed nomograms predicting the OS and the CSS of patients with initially diagnosed T1a glottic cancer. Compared to our previous studies, this study indicated that primary site surgery may be superior to radiation and chemotherapy. At present, chemotherapy should be not recommended for T1a glottic cancer patients.

Abbreviations: AJCC = American Joint Committee on Cancer, CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, OS = overall survival, PSM = propensity score matching, SEER = The Surveillance, Epidemiology, and End Results.

Keywords: glottis, neoplasms, nomograms, SEER program, survival

1. Introduction

Laryngeal cancer is one of the most common types in the malignancies of head and neck,[1–3] which often occurs in the glottis.[4,5] Because lymph node metastasis was rare, especially in T1a glottic cancer, patients' prognosis was often satisfactory.[6,7] However, there is still a fierce controversy that the option of T1a glottic cancer treatments varied remarkably in different countries because of its relative rarity.

To date, frequently-used treatment options for T1a glottic cancer are primary site surgery and radiation. These 2 methods have their special advantages and disadvantages, and many published studies proved that there is still no consensus on the specific indication.[8–10] Our previous study proved that no statistical difference was identified between surgery and radiation groups in terms of local control, overall survival (OS), and cancer-specific survival (CSS). And T1a glottic cancer patients who underwent surgery may benefit from increased larynx preservation rate compared with radiation.[11] Over the past years, some studies indicated the positive role of chemotherapy in the treatment of advanced laryngeal cancer patients.[12–14] Nevertheless, an obvious limitation was that previous studies of T1a glottic cancer were mainly conducted based on small, single-institutional patient cohorts, strongly influencing the reliability of their conclusions. Currently, it is noteworthy that the choice of therapeutic strategy is still left to the discretion of

Editor: Sorush Niknamian.

M-SL and G-JH contributed equally to this paper.

The authors declare that they have no conflicts of interest.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are publicly available.

[a] Department of Anesthesiology, Zhongshan Hospital of Traditional Chinese Medicine, Affiliated to Guangzhou University of Chinese Medicine, Zhongshan, Guangdong, [b] Department of Otorhinolaryngology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, [c] Department of Otolaryngology-head and neck Surgery, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China.

[*] Correspondence: Hong-Bing Liu, Department of Otolaryngology-head and neck Surgery, The Second Affiliated Hospital of Nanchang University. No 1, Minde Road, Donghu District, Nanchang 330006, Jiangxi, China (e-mail: liuhb1992@163.com).

How to cite this article: Luo MS, Huang GJ, Liu HB. Prognostic factors of patients with initially diagnosed T1a glottic cancer: Novel nomograms and a propensity-score matched cohort analysis. Medicine 2020;99:45(e23004).

Received: 25 June 2020 / Received in final form: 24 September 2020 / Accepted: 1 October 2020

http://dx.doi.org/10.1097/MD.0000000000023004

doctors (surgeon or radiotherapist) and patients. Thus, the effect of various treatments in T1a glottic cancer patients remains contentious and a multicenter study with a larger sample size would be eagerly needed.[15,16]

The Surveillance, Epidemiology, and End Results (SEER) database, covers about 34.6% of the US population, which provides data of cancer incidence, patient demographics, primary tumor site, stage at diagnosis, treatments, and survival.[16,17] Data collection continues to expand with a large multicenter sample. Thus, we utilized the SEER database to screen the prognostic factors and determine the optimal treatment for T1a glottic cancer patients. In our study, we concentrated on prognostic factors of age, sex, race, marital status, Grade, stage, N stage, M stage, and treatments on the OS and the CSS.

Nomography, a visual and convenient tool to quantify risk by significant clinical factors, has been widely applied to predict survival rates of individual patients.[18,19] Nomogram has shown good accuracy, which could be helpful in clinical decision making, individual treatment, and clinical trial design.[20] Therefore, after performing Cox hazards regression analyses to screen significant prognostic factors affecting the OS and the CSS of T1a glottic cancer, we developed nomograms to predict the prognosis for T1a glottic cancer patients.

Propensity score matching (PSM), an optimal matching algorithm, can help us reduce selection bias in retrospective studies and strengthen the credibility of our research.[21,22] Imbalanced distributions of the confounding factors and selection bias always existed in a retrospective observational study or the research based on national cancer registries, which may result in flawed outcomes.[21,23] PSM was performed to mimic randomized controlled trials and reduce selection bias. Therefore, we conducted PSM to create a new sample and then compare the effect of treatments.

To our knowledge, our study is the first attempt to draw prognostic nomograms for T1a glottic cancer. And it is a multicenter study with a larger sample size and large-scale. Therefore, it could assist in T1a glottic cancer patients' counseling and guide clinical treatment decision making.

2. Materials and methods

2.1. Study population

The data of eligible patients initially diagnosed as T1a glottic cancer was extracted from the SEER database (SEER ID: 18065-Nov2018). SEER*stat software version 8.3.6 (National Cancer Institute, www.seer.cancer.gov/seerstat) was applied to grab the data from the SEER 18 registry (a population-based cancer surveillance registry from 18 geographic regions) with additional treatment from 1975 to 2016.

Patients initially diagnosed as T1a glottic cancer that have met the inclusion criteria for this study were included. For all included patients in the SEER database, tumor stages were given according to the 7th American Joint Committee on Cancer (AJCC). Variables included age, sex, race, marital status, Grade, stage (AJCC, 7th edition, 2010), N stage, M stage, primary site surgery, radiation, chemotherapy, and year of diagnosis. According to the age at diagnosis, patients were divided into 2 groups of <65 and ≥ 65 years old. The race contained black, white, and other (American Indian/AK Native and Asian/Pacific Islander).

The exclusion criteria:

1. not the initial tumor or the only one tumor;
2. without complete information (age, race, sex, marital status, Grade, stages, treatments, cause of death, status, and survival months)
3. stages were not accessed (for example, NX and MX).

The patient consent and ethical approval for this study were not applicable since the data of the SEER database are publicly available.

2.2. Statistical analysis

Survival analyses were performed by Kaplan–Meier survival methods, and log-rank tests were utilized to detect whether differences were statistically of significance or not. All the eligible T1a glottic cancer cases were randomly divided into either the training or the validation cohorts (the split ratio was 7:3). And the training cohort was used to establish predictive models and construct nomograms. Validation of predictive models was conducted using the validation cohort.

Cox proportional hazards regression model was conducted to calculate the hazard ratio (HR) and 95% confidence interval (CI). Univariate Cox proportional hazards models were performed to assess each parameter's power in predicting the OS and the CSS. Then factors with $P<.05$ in univariate analyses were further assessed in multivariate Cox proportional hazards models to determine significant prognostic factors. Afterward, variables with $P<.05$ and special variables with the clinical importance were finally included to build the nomogram. The nomogram performance was quantified by calibration curves. Calibration curves were graphically drawn to show the relationship between actual probabilities[24].

The difference of the count data was tested by the Chi-square test or Fisher exact tests. Statistical analysis was conducted using R (Version 3.6.0, R Foundation, http://www.r-project.org/). $P<.05$ (2 sides) was considered statistically of significance.

2.3. Propensity score matching (PSM)

PSM can reduce selection bias and balance distributions of confounding factors [21,25]. Thus, we performed a 1:1 match for each patient. A propensity score is the conditional probability of assignment to a specific treatment given a vector of covariates, which was calculated using the "MatchIt" package of R. Matching results were created through the "nearest" matching method and a caliper of 0.05. Every case of the surgery group would be matched to the radiation group according to the closest propensity score. After PSM, Chi-squared tests or Fisher exact tests were applied to detect the statistical difference of each factor between 2 treatment groups.

3. Results

3.1. Patients characteristics

A group of 3008 patients with T1a glottic cancer were identified. The flow diagram for our study about screening and grouping is shown in Figure 1. Thus, the original data containing a total of 2342 eligible patients with initially diagnosed T1a glottic cancer were finally analyzed in the current study (Supplementary Table 1, http://links.lww.com/MD/F132).

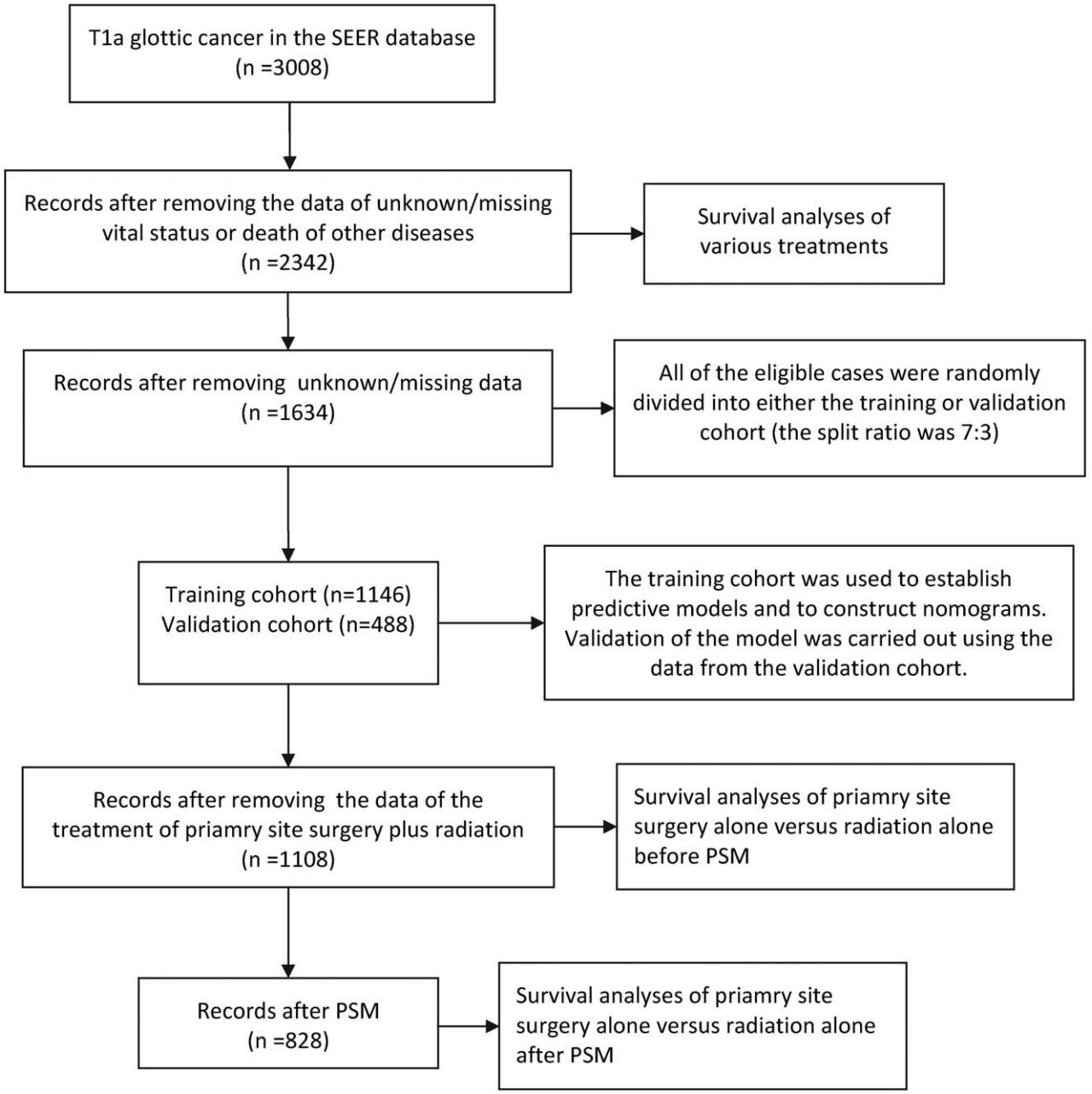

Figure 1. The flow diagram for our study about screening and grouping.

In terms of age, the larger distribution of patients was the age of ≥65 years old. The ratio of males to females was approximately 7.3:1; 88% and 12% were male and female, respectively. Among terms of race and marital status, white and married were the majority, with 1976 (84.37%) and 1452 (62%), respectively. As for Grade and TNM stage, 1045 (44.62%) patients were Grade II, 2294 (97.95%) patients were stage I, 2294 (97.95%) patients were N0 stage, and 2339 (99.87%) patients were M0 stage. As for treatments, 1234 (52.69%) patients underwent primary site surgery, 1605 (68.53%) patients underwent radiation, whereas only 46 (1.96%) patients underwent chemotherapy.

3.2. Survival analyses of various treatments based on the original data

Of the 2342 patients in the current study, survival analyses of various treatments were performed. OS and CSS curves were shown in Figure 2. Figure 2A, 2B showed that patients who underwent primary site surgery would have better OS ($P < .001$) and CSS ($P = .002$). However, Figure 2C,2D showed that patients who underwent radiation may suffer worse OS ($P = .047$) and CSS ($P = .104$). Moreover, Figure 2E, 2F showed that patients who underwent chemotherapy would suffer worse OS ($P < .001$) and CSS ($P < .001$). Furthermore, Figure 2G, 2H

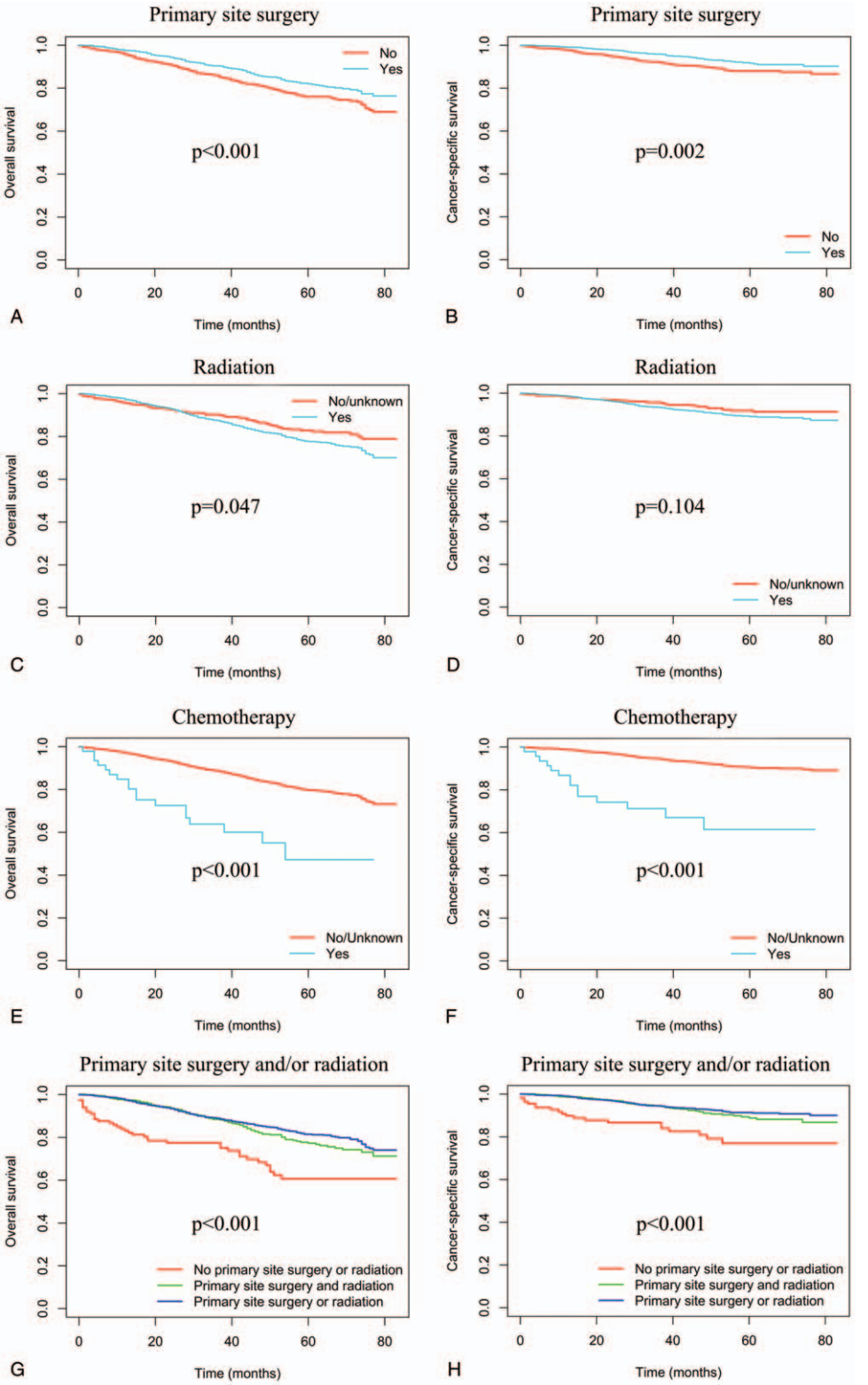

Figure 2. Survival analyses of various treatments of T1a glottic cancer patients based on the original data.

showed that the treatment of primary site surgery or radiation may be superior to the treatment of primary site surgery and radiation in terms of patients' OS ($P < .001$) and CSS ($P < .001$).

3.3. Patients characteristics of the training and the validation cohorts

After removing unknown/missing data, 1634 eligible patients from 2010 to 2015 were finally identified. All eligible patients

Table 1

Baseline characteristics and treatments of all patients and those in the training and the validation cohorts after deleting unknown/missing data.

Variable	All cohorts (N = 1634)	%	Training cohort (N = 1146)	%	Validation cohort (N = 488)	%
Age, years						
<65	712	43.57%	478	41.71%	234	47.95%
≥65	922	56.43%	668	58.29%	254	52.05%
Sex						
Female	185	11.32%	127	11.08%	58	11.89%
Male	1449	88.68%	1019	88.92%	430	88.11%
Race						
Black	154	9.42%	107	9.34%	47	9.63%
White	1406	86.05%	995	86.82%	411	84.22%
Other (American Indian/AK Native, Asian/Pacific Islander)	74	4.53%	44	3.84%	30	6.15%
Marital status						
Unmarried	567	34.70%	404	35.25%	163	33.40%
Married	1067	65.30%	742	64.75%	325	66.60%
Grade						
Grade I&II	1473	90.15%	1034	90.23%	439	89.96%
Grade III&IV	161	9.85%	112	9.77%	49	10.04%
Stage (AJCC, 7th edition, 2010)						
I&II	1575	96.39%	1136	99.13%	439	89.96%
III&IV	59	3.61%	10	0.87%	49	10.04%
N						
N0	1616	98.90%	1136	99.13%	480	98.36%
N1&N2	18	1.10%	10	0.87%	8	1.64%
M						
M0	1634	100.00%	1146	100.00%	488	100.00%
Primary site surgery						
No	762	46.63%	530	46.25%	232	47.54%
Yes	872	53.37%	616	53.75%	256	52.46%
Radiation						
No/Unknown	588	35.99%	428	37.35%	160	32.79%
Yes	1146	70.13%	818	71.38%	328	67.21%
Chemotherapy						
No/Unknown	1599	97.86%	1125	98.17%	474	97.13%
Yes	35	2.14%	21	1.83%	14	2.87%
Year of diagnosis						
2010–2012	842	51.53%	608	53.05%	234	47.95%
2013–2015	792	48.47%	538	46.95%	254	52.05%

were randomly divided into the training (1146, 70%) and the validation cohorts (488, 30%). The baseline characteristics and treatments of all patients were summarized in Table 1.

3.4. Univariate and multivariable analyses

Cox proportional hazards models were performed in the training cohort to detect each variable's power in predicting the OS and the CSS (Table 2).

As for OS, univariate analyses suggested that factors such as age, race, marital status, stage, N, primary site surgery, radiation, and chemotherapy were likely associated with patients' prognosis. Then multivariate analyses indicated that factors such as age, race, marital status, stage, and chemotherapy were identified as independent predictors of OS and included in the predictive model. Primary site surgery ($P = .10$) and radiation ($P = .16$) were also included in the predictive model due to their clinical importance (Fig. 3A). Because the data of N stage was the same as the data of stage, they were considered as 1 homogenous factor in multivariate analyses and N stage was excluded from nomograms.

As for CSS, univariate analyses suggested that factors such as Grade, stage, N, primary site surgery, and chemotherapy were likely associated with patients' prognosis. Then multivariate analyses indicated that factors such as Grade, stage, N, primary site surgery, and chemotherapy were identified as independent predictors of CSS and included in the predictive model (Fig. 3B). Radiation ($P = .24$) was also included in the predictive model due to its clinical importance. Because the data of N stage was the same as the data of stage, they were considered as 1 homogenous factor in multivariate analyses and N stage was excluded from nomograms.

3.5. Building and validating novel nomograms

Predictive models were virtually plotted in the form of nomograms, which were validated using the validation cohort. For every individual patient, lines of significant prognosis factors were drawn upward to determine points. The sum of these points would be

Table 2

Cox regression analyses of prognostic factors affecting T1a glottic cancer patient survival in the training cohort.

	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P
Age, years								
<65	Reference		Reference		Reference			
≥65	1.67 (1.23–2.28)	.001	1.73 (1.27–2.37)	.001	1.00 (0.66–1.51)	1		
Sex								
Female	Reference				Reference			
Male	0.89 (0.58–1.38)	.60			1.30 (0.63–2.68)	.48		
Race								
Black	Reference		Reference		Reference			
White	0.75 (0.49–1.17)	.20	0.83 (0.53–1.29)	.40	0.86 (0.44–1.65)	.64		
Other (American Indian/AK Native, Asian/Pacific Islander)	0.21 (0.05–0.91)	.04	0.27 (0.06–1.16)	.08	0.24 (0.03–1.90)	.18		
Marital status								
Unmarried	Reference		Reference		Reference			
Married	0.62 (0.47–0.83)	.001	0.65 (0.49–0.87)	.003	0.68 (0.45–1.02)	.06		
Grade								
Grade I&II	Reference				Reference		Reference	
Grade III&IV	1.25 (0.80–1.94)	.33			2.15 (1.27–3.63)	.004	2.07 (1.22–3.51)	.007
Stage (AJCC, 7th edition, 2010)								
I&II	Reference		Reference		Reference		Reference	
III&IV	5.19 (2.29–11.74)	<.001	3.47 (1.48–8.15)	.004	8.53 (3.45–21.12)	<.001	6.09 (2.31–16.09)	<.001
N								
N0	Reference		Reference		Reference		Reference	
N1&N2	5.19 (2.29–11.74)	<.001	NA*		8.53 (3.45–21.12)	<.001	NA*	
M								
M0	NA†				NA†			
Primary site surgery								
No	Reference		Reference		Reference		Reference	
Yes	0.68 (0.51–0.90)	.007	0.77 (0.57–1.05)	.10	0.61 (0.41–0.92)	.02	0.61 (0.41–0.93)	.02
Radiation								
No/Unknown	Reference		Reference		Reference			
Yes	1.62 (1.14–2.30)	.007	1.31 (0.90–1.90)	.16	1.33 (0.83–2.15)	.24		
Chemotherapy								
No/Unknown	Reference		Reference		Reference		Reference	
Yes	3.55 (1.75–7.22)	<.001	3.12 (1.49–6.56)	.003	5.51 (2.40–12.61)	<.001	3.35 (1.37–8.21)	.008
Year of diagnosis								
2010–2012	Reference				Reference			
2013–2015	0.79 (0.56–1.13)	.20			0.96 (0.59–1.54)	.85		

* Because the number of N stage was the same as the data of stage (AJCC, 7th edition, 2010), they were considered as one homogenous factor in multivariate analyses.
† After delecting unknown/missing data, no patientof M1 stage were finally included.

located on the "Total Points" axis. Besides, the other lines were drawn downward to determine the possibility of 3- and 5-year OS (Fig. 4A) or CSS (Fig. 4B) for patients according to total points.

Calibration curves showed good consistency between the actual observation and the nomogram prediction in the probability of 3- and 5-year OS and CSS (Fig. 5).

3.6. Patients' characteristics of primary site surgery alone and radiation alone groups before and after PSM

Before PSM, the data of 1108 patients contained 417 patients who underwent primary site surgery alone, and 691 patients who underwent radiation alone (Table 3). Comparing the primary site surgery alone and radiation alone groups, there were statistically significant differences in patients characteristics, including marital status ($P=.006$), stage ($P=.03$), and chemotherapy ($P=.02$).

After PSM, 414 pairs of patients were successfully matched (Table 3). Characteristics such as age ($P=.68$), sex ($P=.74$), race ($P=.99$), marital status ($P=.70$), Grade ($P=1$), stage ($P=1$), N ($P=1$), M ($P=1$), chemotherapy ($P=1$), and year of diagnosis ($P=.78$) were all without a significant difference.

3.7. Survival analyses of primary site surgery alone vs radiation alone before and after PSM

OS and CSS curves before and after PSM were plotted in Figure 6. Before PSM, patients who underwent primary site surgery alone would have better OS ($P<.001$) and CSS ($P=.003$) than patients who underwent radiation alone (Figure 6A, 6B). After PSM, Figure 6C, 6D also proved that patients who underwent primary site surgery alone would have better OS ($P=.019$) and CSS ($P=.032$) than patients who underwent radiation alone.

4. Discussion

Glottic cancer is common and represented approximately 52.03% of laryngeal cancer in the SEER database, in which

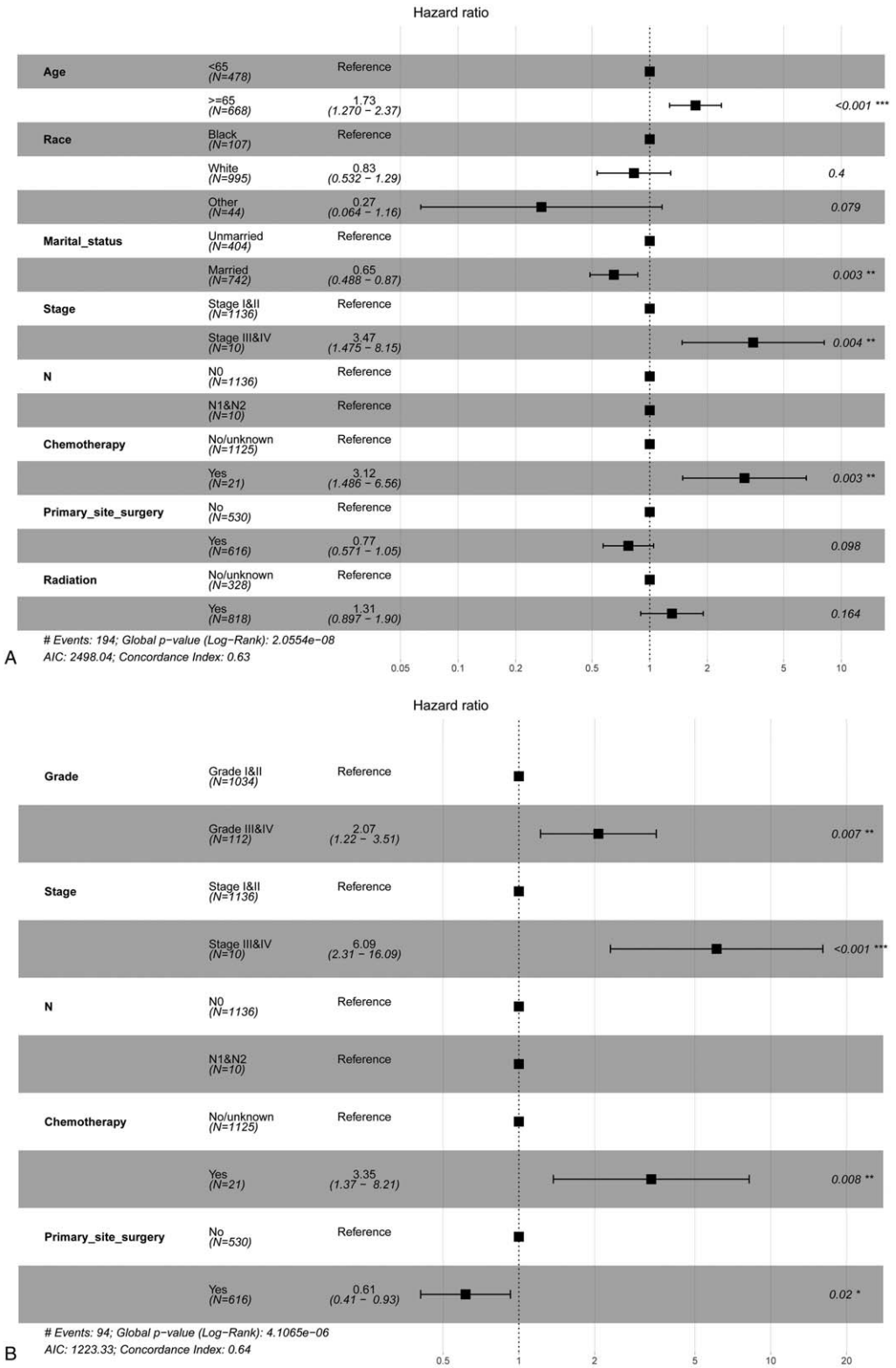

Figure 3. Forest plots for OS (A) and CSS (B) in multivariable analyses based on patients' characteristics. CSS = cancer-specific survival, OS = overall survival.

T1a glottic cancer represents about 7.38% of laryngeal cancer. T1a glottic cancer is one of early-stage glottic cancer and often has an excellent prognosis.[6,7,26] However, owing to its high discrepancy in treatment options for different patients, survival rates of T1a glottic cancer still varied significantly. To date, predictive models of T1a glottic cancer for predicting the prognosis is blank. There are also no reliable guidelines for the treatment of T1a glottic cancer. Therefore, developing prognostic

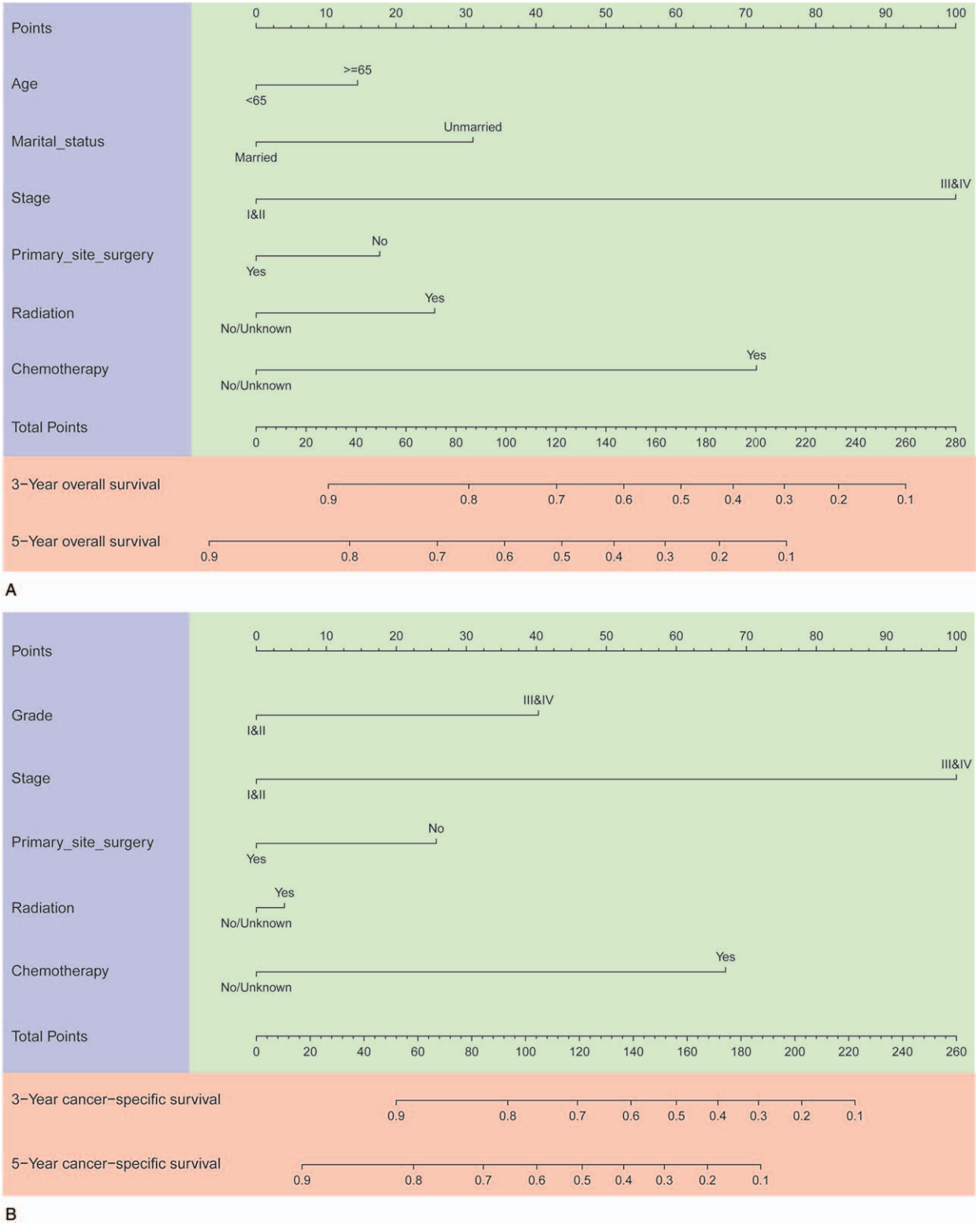

Figure 4. Nomograms for predicting patients OS (A) and CSS (B). CSS = cancer-specific survival, OS = overall survival.

models is 1 meaningful approach to predict patients' outcomes and determine better therapeutic strategies.

With survival analyses of treatments based on the original data, we found that primary site surgery would indicate better OS and CSS compared with non-surgery, whereas radiation may decrease patients' OS compared with non-radiation. And chemotherapy would lead to worse OS and CSS. Understandably, primary site surgery would improve patients' prognosis.

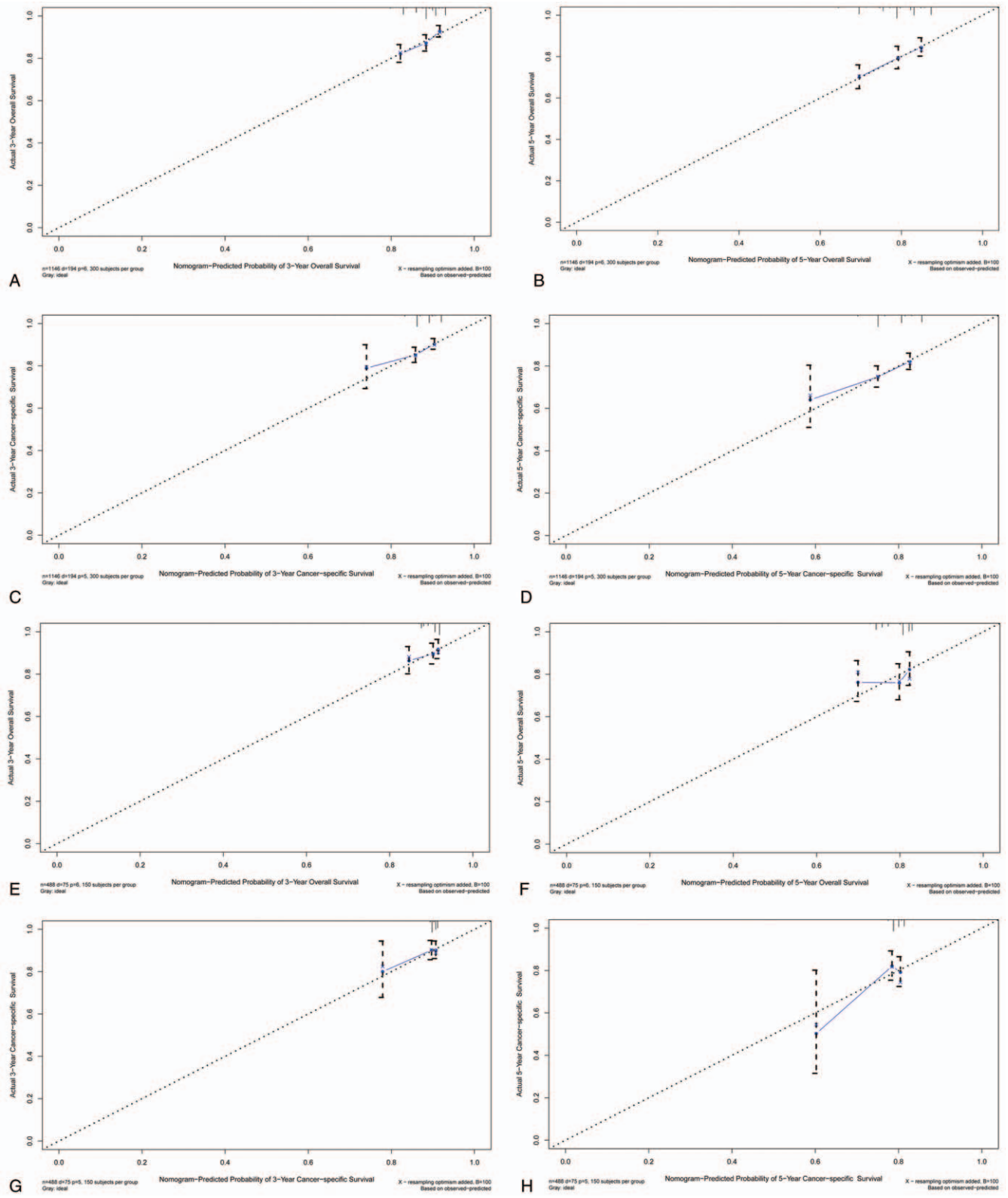

Figure 5. The calibration curves for predicting patients' prognosis. (A) 3-year OS in the training cohort. (B) 5-year OS in the training cohort. (C) 3-year CSS in the training cohort. (D) 5-year CSS in the training cohort. (E) 3-year OS in the validation cohort. (F) 5-year OS in the validation cohort. (G) 3-year CSS in the validation cohort. (H) 5-year CSS in the validation cohort. CSS = cancer-specific survival, OS = overall survival.

Table 3

Patients' characteristics of primary site surgery alone and radiation alone groups before and after propensity score matching (PSM).

	Before PSM			After PSM		
Variable	**Primary site surgery alone (N = 417)**	**Radiation alone (N = 691)**	***P***	**Primary site surgery alone (N = 414)**	**Radiation alone (N = 414)**	***P***
Age, years			.16			.68
<65	201	302		199	192	
≥65	216	389		215	222	
Sex			.80			.74
Female	50	78		47	43	
Male	367	613		367	371	
Race			.16			.99
Black	33	76		33	32	
White	362	588		361	362	
Other (American Indian/AK Native, Asian/Pacific Islander)	22	27		20	20	
Marital status			.006			.70
Unmarried	126	267		125	119	
Married	291	424		289	295	
Grade			1			1
Grade I&II	378	627		376	376	
Grade III&IV	39	64		38	38	
Stage (AJCC, 7th edition, 2010)		.03			1	
I&II	417	683		414	414	
III&IV	0	8		0	0	
N			.14			1
N0	417	683		414	414	
N1&N2	0	8		0	0	
M						
M0	417	691		414	414	
Chemotherapy			.02			1
No/Unknown	416	676		413	413	
Yes	1	15		1	1	
Year of diagnosis			.68			.78
2010–2012	201	343		200	205	
2013–2015	216	348		214	209	

Surprisingly, patients who underwent radiation or chemotherapy may suffer worse patients' prognosis. After screening literature, we found studies cannot set a blank control group (patients without primary site surgery, radiation, or chemotherapy) to assess the effect of treatments.[27–29]

Both primary site surgery and radiation have benefits and drawbacks. Primary site surgery is quick, inexpensive, and repeatable after the event of recurrence.[28,30] But it requires a foundation of solid surgical expertise and the feasibility of surgery will depend on patients anatomy. While, radiation can avoid general anesthesia and lead to a possibility of better functional outcomes, but is actually a longer treatment and may lead to adjacent tissues with some sequelae such as fibrosis, mucosal edema, and laryngeal chondronecrosis.[27,29] In terms of chemotherapy, a recent ten-year study also pinpointed that the curative effect of chemotherapy for LC patients remained uncertain, and the toxicity profile would possibly be significant.[15] Thus, chemotherapy was often recommended for advanced glottic cancer patients in some studies and practice guidelines, such as the NCCN (National Comprehensive Cancer Network) Clinical practice guideline.[14,31,32] And chemotherapy would likely be not suitable for T1a glottic cancer. Furthermore, patients who underwent primary site surgery or radiation would have a better OS and CSS than patients who underwent primary site surgery and radiation. It may indicate that primary site surgery alone may likely be the preferred treatment and may have no need to perform the combination therapy.

With univariate and multivariate analyses of the training cohort, we confirmed that age, marital status, stage, N, and chemotherapy are associated with patients' OS, while Grade, stage, N, primary site surgery, and chemotherapy are associated with patients' CSS. It also proved that primary site surgery was a independent prognostic factor, whereas chemotherapy was a vital independent prognostic factor decreasing patients OS and CSS. And then we established and validated nomograms to predict 3- and 5-year OS and CSS of T1a glottic cancer patients visually and intuitively based on these significant factors and treatments with clinical importance. The validation of models using different statistical methods demonstrated its great performance.

It is noteworthy that one of the most important risk factors impacting patients' prognosis is chemotherapy, which is considered as a significant predictor of decreasing OS and CSS. Vokes et al indicated that the rates of acute toxic effects were higher in chemotherapy groups.[33] Consequently, the poor prognosis may be primarily due to the toxicity of chemotherapy. However, there are still 2 concerns regarding chemotherapy in T1a glottic cancer that remain to be solved. The most vital concern is that there is no generally accepted standard regimen of chemotherapy for T1a glottic patients. Additionally, in the current study, because the

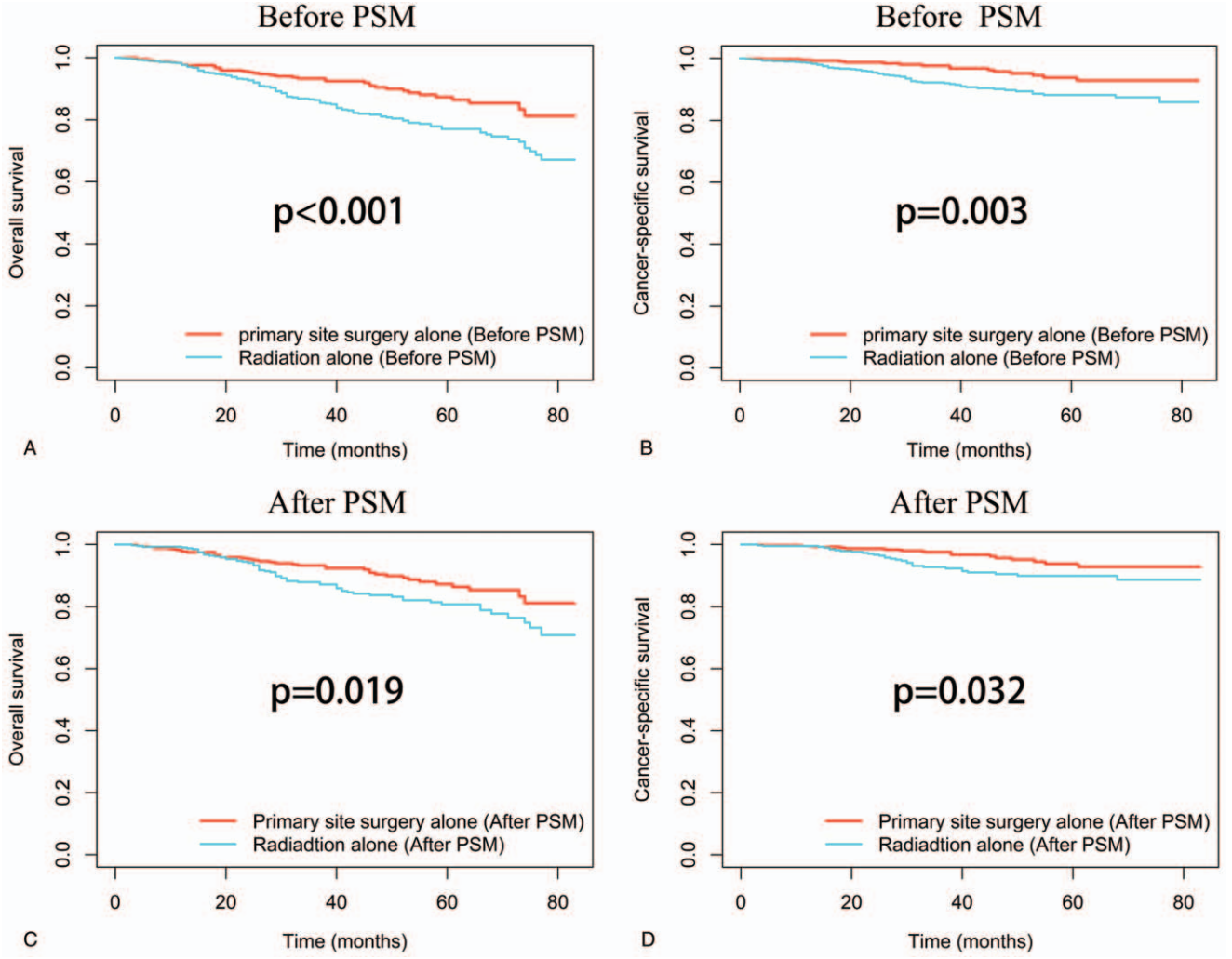

Figure 6. Survival analyses of primary site surgery alone versus radiation alone before and after PSM. (A) Patients OS before PSM. (B) Patients CSS before PSM. (C) Patients OS after PSM. (D) Patients CSS after PSM. CSS = cancer-specific survival, OS = overall survival, PSM = propensity score matching.

details of chemotherapy for patients can not be acquired from the SEER database, subgroup analyses according to specific chemotherapy regimen can not be conducted.

Another significant factor was primary site surgery. The CSS of patients who underwent primary site surgery is far better than patients without primary site surgery. Canis et al included 400 T1a glottic cancer to assess the effect of transoral laser microsurgery. Transoral laser microsurgery has advantages of a low complication rate, an excellent functional outcome, and a high rate of organ preservation.[28] Moreover, Landolfo et al reported that transoral laser surgery showed similar oncologic outcomes compared with open cordectomy.[34]

As shown in Table 3, patients characteristics of primary site surgery alone and radiation alone groups (after deleting unknown data) were distributed unevenly, and several vital variables were proved as independent prognostic factors. Hence, PSM was applied to reduce selection bias and balance distributions of the confounding factors. After PSM, the variables distribution between primary site alone and radiation alone groups were well balanced. Figure 5 showed that patients who underwent primary site surgery alone had significantly a better OS and CSS compared with patients who underwent radiation alone before and after PSM. Low et al reported that the 5-year OS for T1a glottic cancer patients treated with surgery vs radiation was 86% vs 85%, and laryngectomy-free CSS was 100% vs 88% ($P = .03$).[35] Thurnher et al also proved that 5-year, 10-year, and 15-year CSS for laser-treated T1a glottic cancer patients were all 100%, for conventional surgery were 100%, 98%, and 98%, and for radiation were 96%, 92%, and 91%, respectively.[36] Moreover, the mortality rate caused by the laryngeal tumor was significantly higher in the radiation group ($P = .003$). Vaculik eal's meta-analysis suggests that transoral laser microsurgery is superior to radiation for T1 glottic cancer in terms of the OS, the CSS, and laryngeal preservation rate.[26]

There are several limitations in our study. Our study was a retrospective study with inherent biases, although we used PSM to control the bias. Moreover, predictive models were developed based on data obtained from the SEER database, potentially limiting the generalizability of our conclusions. Thus, even though we did internal verifications, larger prospective studies are still required. Besides, due to the limitations of the SEER database, the details of the chemotherapy regimens and

radiotherapy doses could not be obtained, which hindered further prognostic analyses based on detailed treatment schemes. Finally, despite the OS and the CSS, the cost, the risk of a second location, the duration of treatment, and quality of life (including voice quality) may better be taken into account to determine the optimized choice for T1a glottic cancer.[6,37] The SEER database also lacked information about these above factors. Compared with surgery, our previous meta-analysis confirmed that patients undergoing radiation may have the advantage of increased voice quality, including the maximum phonation time and decreased fundamental frequency.[38]

5. Conclusion

We built nomograms for predicting the OS and the CSS of patients with initially diagnosed T1a glottic cancer. The current results can be useful for T1a glottic cancer patients' counseling and guide clinical treatment decision making. Compared to our previous studies, this study indicated that primary site surgery may be superior to radiation and chemotherapy. At present, chemotherapy should be not recommended for T1a glottic cancer patients.

Acknowledgments

We are grateful to Dr. Hui-Zi Li for his statistical support for the study.

Author contributions

Conceptualization: Meng-Si Luo, Hong-Bing Liu.
Data curation: Meng-Si Luo, Guan-Jiang Huang.
Formal analysis: Guan-Jiang Huang.
Funding acquisition: Hong-Bing Liu.
Investigation: Meng-Si Luo.
Methodology: Guan-Jiang Huang, Hong-Bing Liu.
Project administration: Hong-Bing Liu.
Resources: Meng-Si Luo, Hong-Bing Liu.
Software: Guan-Jiang Huang.
Supervision: Hong-Bing Liu.
Validation: Meng-Si Luo, Guan-Jiang Huang.
Visualization: Meng-Si Luo, Guan-Jiang Huang.
Writing – original draft: Meng-Si Luo, Guan-Jiang Huang, Hong-Bing Liu.
Writing – review & editing: Hong-Bing Liu.

References

[1] Steuer CE, El-Deiry M, Parks JR, et al. An update on larynx cancer. CA Cancer J Clin 2017;67:31–50.
[2] Silen S, Haapaniemi A, Dickinson A, et al. Presentation of second primary cancers in young laryngeal carcinoma patients. Acta Otolaryngol 2019;139:85–9.
[3] Breda E, Catarino R, Monteiro E. Transoral laser microsurgery for laryngeal carcinoma: Survival analysis in a hospital-based population. Head Neck 2015;37:1181–6.
[4] Lucioni M, Lionello M, Machin P, et al. Sclerosis of the arytenoid cartilage and glottic carcinoma: a clinical-pathological study. Head Neck 2019;41:72–8.
[5] Puram SV, Bhattacharyya N. Surgery versus radiation for T1 glottic carcinoma: Second primary considerations. Laryngoscope 2019;129:2713–5.
[6] Fakhry N, Vergez S, Baumstarck K, et al. Multicentric evaluation of strategies for treatment of T1a glottic carcinomas. Eur Arch Otorhinolaryngol 2015;272:143–8.
[7] Mendenhall WM, Amdur RJ, Morris CG, et al. T1-T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. J Clin Oncol 2001;19:4029–36.
[8] Warner L, Chudasama J, Kelly CG, et al. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. Cochrane Database Syst Rev 2014;CD002027.
[9] Yoo J, Lacchetti C, Hammond JA, et al. Role of endolaryngeal surgery (with or without laser) compared with radiotherapy in the management of early (T1) glottic cancer: a clinical practice guideline. Curr Oncol 2013;20:e132–5.
[10] Yoo J, Lacchetti C, Hammond JA, et al. Role of endolaryngeal surgery (with or without laser) versus radiotherapy in the management of early (T1) glottic cancer: a systematic review. Head Neck 2014;36:1807–19.
[11] Huang G, Luo M, Zhang J, et al. Laser surgery versus radiotherapy for T1a glottic carcinoma: a meta-analysis of oncologic outcomes. Acta Otolaryngol 2017;137:1204–9.
[12] Popovtzer A, Burnstein H, Stemmer S, et al. Phase II organ-preservation trial: Concurrent cisplatin and radiotherapy for advanced laryngeal cancer after response to docetaxel, cisplatin, and 5-fluorouracil-based induction chemotherapy. Head Neck 2017;39:227–33.
[13] Divi V, Worden FP, Prince ME, et al. Chemotherapy alone for organ preservation in advanced laryngeal cancer. Head Neck 2010;32:1040–7.
[14] Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–8.
[15] Laccourreye O, Marret G, Rubin F, et al. Ten-year outcome of curative "exclusive" chemotherapy in N0M0 squamous cell carcinoma of the larynx and pharynx with complete clinical response. Head Neck 2019;41:2190–6.
[16] Lim H, Devesa SS, Sosa JA, et al. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. JAMA 2017;317:1338–48.
[17] Katz SJ. Cancer Care Delivery Research and the National Cancer Institute SEER Program: Challenges and Opportunities. JAMA Oncol 2015;1:677–8.
[18] Liang W, Zhang L, Jiang G, et al. Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer. J Clin Oncol 2015;33:861–9.
[19] Li H, Wang Z, Yang F, et al. Development and validation of a nomogram for predicting cancer-specific survival of surgical resected stage I-II adenosquamous carcinoma of the lung. J Surg Oncol 2020;121:1027–35.
[20] Iasonos A, Schrag D, Raj GV, et al. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 2008;26:1364–70.
[21] Morgan CJ. Reducing bias using propensity score matching. J Nucl Cardiol 2018;25:404–6.
[22] Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 2016;17:174–83.
[23] Jones EA, Shuman AG, Egleston BL, et al. Common pitfalls of head and neck research using cancer registries. Otolaryngol Head Neck Surg 2019;161:245–50.
[24] Kramer AA, Zimmerman JE. Assessing the calibration of mortality benchmarks in critical care: The Hosmer-Lemeshow test revisited. Crit Care Med 2007;35:2052–6.
[25] Lu B, Cai D, Tong X. Testing causal effects in observational survival data using propensity score matching design. Stat Med 2018;37:1846–58.
[26] Vaculik MF, MacKay CA, Taylor SM, et al. Systematic review and meta-analysis of T1 glottic cancer outcomes comparing CO2 transoral laser microsurgery and radiotherapy. J Otolaryngol Head Neck Surg 2019;48:44.
[27] Chung SY, Lee CG. Feasibility of single vocal cord irradiation as a treatment strategy for T1a glottic cancer. Head Neck 2020;42:854–9.
[28] Canis M, Ihler F, Martin A, et al. Transoral laser microsurgery for T1a glottic cancer: review of 404 cases. Head Neck 2015;37:889–95.
[29] Nomiya T, Nemoto K, Wada H, et al. Long-term results of radiotherapy for T1a and T1bN0M0 glottic carcinoma. Laryngoscope 2008;118:1417–21.
[30] Zhang Y, Wang B, Sun G, et al. Carbon dioxide laser microsurgery versus low-temperature plasma radiofrequency ablation for T1a glottic cancer: a single-blind randomized clinical trial. Biomed Res Int 2018;2018:4295960.
[31] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers (Version 1, 2020). 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

[32] Jones DA, Mendenhall CM, Kirwan J, et al. Radiation therapy for management of t1-t2 glottic cancer at a private practice. Am J Clin Oncol 2010;33:587–90.
[33] Vokes EE, Stenson KM. Therapeutic options for laryngeal cancer. N Engl J Med 2003;349:2087–9.
[34] Landolfo V, Gervasio CF, Riva G, et al. Prognostic role of margin status in open and CO2 laser cordectomy for T1a-T1b glottic cancer. Braz J Otorhinolaryngol 2016;S1808-8694:30240–3.
[35] Low TH, Yeh D, Zhang T, et al. Evaluating organ preservation outcome as treatment endpoint for T1aN0 glottic cancer. Laryngoscope 2017; 127:1322–7.
[36] Thurnher D, Erovic BM, Frommlet F, et al. Challenging a dogma–surgery yields superior long-term results for T1a squamous cell carcinoma of the glottic larynx compared to radiotherapy. Eur J Surg Oncol 2008;34:692–8.
[37] Qian W, Zhu G, Wang Y, et al. Multi-modality management for loco-regionally advanced laryngeal and hypopharyngeal cancer: balancing the benefit of efficacy and functional preservation. Med Oncol 2014; 31:178.
[38] Huang G, Luo M, Zhang J, et al. The voice quality after laser surgery versus radiotherapy of T1a glottic carcinoma: systematic review and meta-analysis. Onco Targets Ther 2017;10:2403–10.