Radiotherapy Versus Surgery—Which Is Better for Patients With T1-2N0M0 Glottic Laryngeal Squamous Cell Carcinoma? Individualized Survival Prediction Based on Web-Based Nomograms

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Background: Both radiotherapy and surgery are now recommended for early stage glottic laryngeal squamous cell carcinoma (LSCC), and both have their own advantages in patients with different characteristics. For each patient, it is hard to determine whether radiotherapy or surgery is more appropriate.

Methods: Patients with T1-2N0M0 glottic LSCC who received radiotherapy or surgery in the 2004–2016 SEER database were reviewed, then randomly divided into training and validation cohorts. Propensity score matching was used to eliminate the baseline variations, and competing risk analyses helped to exclude the effects of other causes of death. Based on univariate and multivariate analyses, we built two nomograms to visually predict the survival of each patient with different characteristics who received radiotherapy or surgery, then validated the accuracy in both training and validation cohorts. Using nomogramEx, we quantified the algorithms of the nomograms and put the nomograms on the websites.

Results: A total of 6538 patients in the SEER database were included. We found that therapy (p = 0.004), T stage (p < 0.001), age (p < 0.001), race (p < 0.044), grade (p = 0.001), and marital status (p < 0.001) were independent prognostic factors. Two nomograms were built to calculate the survival for each patient who received radiotherapy (C-index = 0.668 ± 0.050 in the training cohort and 0.578 ± 0.028 in the validation cohort) or underwent surgery (C-index = 0.772 ± 0.045 in the training cohort and 0.658 ± 0.090 in the validation cohort). Calibration plots showed the accuracy of the nomograms. Using the nomograms, we found that 3872 patients (59.22%) had no difference between the two therapies, 706 patients (10.80%) who received radiotherapy had better survival outcomes, and 1960 patients (29.98%) who underwent surgery had better survival outcome.
INTRODUCTION

Laryngeal cancer occurs more frequently in head and neck cancers, and approximately 95% of which are laryngeal squamous cell carcinomas (LSCCs) (1). In China, the incidence of laryngeal cancer is approximately 1.86 per 100,000 annually (2). A total of 23,400 new cases occurred in 2014 (3), most of which were diagnosed in the early stage.

The recommended treatment for early glottic LSCC includes surgery and radiotherapy (4–7). Glottic LSCC is the main site of laryngeal squamous cell carcinomas. In our previous research, we found that the survival of patients with T1a glottic cancer, well-differentiated tumors, who were married, and who received radiotherapy were worse. For patients who had T1b glottic cancer, undifferentiated tumors, and who were unmarried, radiotherapy was not preferable to surgery (8). Individual patients have a complex combination of clinical characteristics, and further exploration of individualized treatment methods for patients with early stage glottic LSCC is warranted to personalize treatment (9–11).

The Surveillance, Epidemiology, and End Results (SEER) program is a source for long-term population-based incidence data. In recent years, nomograms have frequently been used to calculate the proportion of various factors for each patient, and comprehensively consider the impact of multiple factors on survival, which may offer guidance for individual treatment. In this manuscript, we attempted to determine which therapy (radiation or surgery) is a better choice for a patient with T1-2N0M0 glottic LSCC using SEER data and a nomogram.

MATERIALS AND METHODS

Ethics Statement

The Ethics Committees of Jinshan Hospital and the Eye and ENT Hospital of Fudan University exempted the study because no personal information is included in the SEER database.

Data Selection

We obtained SEER (Incidence – SEER 18 Regs Custom Data with additional treatment fields, November 2018 Sub, 1975 – 2016 varying) data via the SEER*Stat software (version 8.3.6)\(^1\). The selection process to acquire data from the database is shown in Figure 1A. In brief, we selected patients who had early stage glottic LSCC and underwent only radiotherapy or surgery. The old version to the 8th AJCC TMN staging system was converted manually.

Characteristics, including race, age, gender, grade, TMN stage, T stage, marital status, and insurance, were included in the analyses.

Conclusion: Nomograms were used to comprehensively calculate independent factors to determine which treatment (radiotherapy or surgery) is better for each patient. A website was used to offer guidance regarding surgery or radiation for patients and physicians.

Keywords: glottic laryngeal squamous cell carcinoma, radiotherapy, surgery, SEER, nomogram

\(^{1}\)http://seer.cancer.gov/seerstat/

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with radiation or underwent surgery at 3 and 5 years were calculated.

RESULTS

Patient Characteristics
As shown in Figure 1A, 6538 patients with glottic LSCC (4759 patients treated with radiation and 1779 patients who underwent surgery) were included in our study. A total of 4576 patients were randomly divided into the training cohort. Patients who were excluded after propensity score matching comprised the validation cohort. The baseline characteristics of all participants in the training cohort are summarized in Table 1 and Supplementary Table S1. Compared to the patients who underwent surgery, the patients who underwent radiotherapy were characterized as follows: older ($p = 0.071$); worse tumor differentiation ($p = 0.259$); higher $T$ ($p < 0.001$) and TMN stage ($p < 0.001$); less likely to be white ($p < 0.001$); less likely to have insurance ($p < 0.001$), and less likely to be married ($p = 0.134$).

Propensity Score Matching Analyses
After matching, 1245 pairs of patients were selected; one-half received radiotherapy, and the other half underwent surgery. As shown in Table 1 and Supplementary Table S1, there were no significant differences between the radiotherapy and surgery groups after matching. The $p$-values for variables, including age, race, year of diagnosis, grade, stage, $T$ stage, insurance, and marital status, had been greatly improved. The absolute values of the standardized differences (SD) after matching were all $<10\%$, suggesting that the baseline characteristics were well-balanced. The matched groups had similar propensity score distributions, and the mirror histograms of propensity scores for patients are shown in Figures 1B, C.
Survival Analyses

As shown in Figure 2, patients who received radiation therapy had significantly worse overall survival outcomes compared with patients who underwent surgery (p = 0.0035; Figure 2A). Competing risk analysis also illustrated that the patients who received radiation had a higher risk of cancer-specific mortality (p = 0.003), while there was no apparent difference in the probabilities of other causes of death (p = 0.351; Figure 2B).

We further analyzed the connection between cancer-specific survival and variations. Multicollinearity was detected to test the independence of the variables included in the regression model, and variance inflation factors (VIF) of all variables were far less than ten indicates there was no multicollinearity problem. As Table 2 and Supplementary Table S2 shows, univariate analyses demonstrated that therapy, age, race, grade, stage, T stage, and marital status were significant predictors of glottic LSCC-specific survival. Gender, year of diagnosis, and insurance status had no significant differences between the two groups. Based on multivariate analysis for patients with glottic LSCC, therapy, race, age, grade, T stage, and marital status were independent prognostic predictors and stage, which were not independent of T stage and not included in the multivariate analysis.

To better compare the difference of treatment on cancer-specific survival in glottic LSCC patients, we stratified the patients after matching by variables in univariate analysis. As is shown in Supplementary Figures S1–S8, glottic LSCC patients with a worse cancer-specific survival had the following characteristics: not black; male; insurance; T1a stage; well-differentiated tumor; married, 51–60 or 71–80 years of age. For glottic LSCC patients

### TABLE 1 | Patient characteristics according to the therapy status before and after propensity score matching.

| Characteristics          | Before matching | After matching | Radiation | Surgery | SD (%) | p-value | Radiation | Surgery | SD (%) | p-value |
|--------------------------|----------------|---------------|------------|---------|---------|---------|-----------|---------|---------|---------|
| Total number             | 3331           | 1245          |            | 1245    |         | 0.431   |           |         |         | 0.315   |
| Sex                      |                |               | Male       | 2954    | 1093    | −2.766  |            | 1110    | 1093    | −4.277  |
|                          |                |               | Female     | 377     | 152     | 2.766   |            | 135     | 152     | 4.277   |
| Age                      |                |               |            | 0.111   |         |          |           |         |         | 0.966   |
| ~50                      | 268            | 127           | 7.490      |          |         |          |           | 123     | 127     | 1.069   |
| 51–60                    | 821            | 309           | 0.399      |          |         |          |           | 322     | 309     | −2.401  |
| 61–70                    | 1091           | 378           | −5.148     |          |         |          |           | 375     | 378     | 0.525   |
| 71–80                    | 802            | 289           | −2.034     |          |         |          |           | 279     | 289     | 1.914   |
| 81~                      | 349            | 142           | 2.974      |          |         |          |           | 146     | 142     | −1.005  |
| Race                     |                |               | White      | 2785    | 1075    | 7.666   |            | 1084    | 1075    | −2.129  |
|                          |                |               | Black      | 421     | 103     | −14.304 |            | 92      | 103     | 3.289   |
|                          |                |               | Others     | 125     | 67      | 7.808   |            | 69      | 67      | −0.707  |
| Year at diagnosis*       |                |               |            | < 0.001 |         |          |           | 0.987   |         |         |
| Grade                    |                |               |            | 0.253   |         |          |           | 0.896   |         |         |
| Well differentiated      | 728            | 299           | 5.141      |          |         |          |           | 289     | 299     | 1.891   |
| Moderately differentiated| 1516           | 530           | −5.928     |          |         |          |           | 548     | 530     | −2.918  |
| Poorly or undifferentiated| 254             | 92            | −0.895     |          |         |          |           | 93      | 92      | −0.306  |
| Unknown                  | 833            | 324           | 2.332      |          |         |          |           | 315     | 324     | 1.655   |
| Stage                    |                |               | I          | 2451    | 1099    | 38.066  |            | 1099    | 1099    | 0.000   |
|                          |                |               | II         | 880     | 146     | −38.066 |            | 146     | 146     | 0.000   |
| T stage                  |                |               | T1a        | 1439    | 736     | 32.252  |            | 745     | 736     | −1.473  |
|                          |                |               | T1b        | 355     | 88      | −12.654 |            | 96      | 88      | −2.456  |
|                          |                |               | T1 not specified | 657   | 275   | 5.817  |            | 258     | 275     | 3.330   |
|                          |                |               | T2         | 880     | 146     | −38.066 |            | 146     | 146     | 0.000   |
| Insurance status at diagnosis |                |               | Any        | 2442    | 987     | 14.063  |            | 989     | 987     | −0.397  |
|                          |                |               | None or unknown | 889       | 258    | −14.063 |            | 256     | 258     | 0.397   |
| Marital status at diagnosis |                |               | Married    | 1969    | 767     | 5.102   |            | 776     | 767     | −1.489  |
|                          |                |               | Others     | 1362    | 478     | −5.102  |            | 469     | 478     | 1.489   |

Asterisk *** refers to the year the patient was diagnosed with the disease.
with other characteristics, radiotherapy and surgery had equivalent efficacy.

**Construction and Validation of the Nomogram**

The final multivariate model uncovered six independent variables, including therapy, age, race, grade, T stage, and marital status. As shown in Figures 3A, 4A, the nomograms were developed based on the variables.

A total of 4576 patients were randomly divided into the training cohort and patients excluded after propensity score matching comprised the validation cohort. As shown in Figures 3B,C, 4B,C, the calibration plots are based on internal validation of the training cohort. The C-index for the prediction of cancer-specific survival in glottic LSCC patients who underwent surgery and received radiotherapy was 0.772 ± 0.045 and 0.668 ± 0.050, respectively. In addition, external validation of the nomograms was performed in the validation cohort. The C-index for surgery (0.658 ± 0.090) and radiotherapy (0.578 ± 0.028) was calculated based on the calibration plots shown in Figures 3D,E, 4D,E. The C-index for internal and external validation indicated that the nomograms have a good fit with the actual observations. Therefore, the 3- and 5-year cancer-specific survival rates predicted by the nomograms were reliable.

**Nomogram Analyses and Website Application**

We used the nomogramEx function in R software to calculate the specific algorithms for the above two nomograms and uploaded the algorithms to our website<sup>2</sup>. Patients and physicians can enter age, grade, marital status, and other personal details on our website, which automatically calculates the predicted 3- and 5-year survival rates of patients who received radiotherapy or underwent surgery. The patients and physicians can compare outcomes of radiation and surgery to determine which is the better treatment option. For example, an 82-year-old Chinese patient with a stage T1a moderately differentiated glottic LSCC who is divorced can use our website to find out that the 3- and 5-year survival rates for surgery are 98.16 and 94.78%, respectively, while the corresponding rates for radiotherapy are 78.40 and 68.45%, respectively. At this time, surgery may be a better choice for this patient.

We predicted the prognosis of patients with early glottic LSCC who underwent surgery and radiotherapy. Greater than 6000 patients in the SEER databases were included in this study, and we listed the results as a histogram in Figure 5.

The average difference between the 3-year cancer-specific survival rates assuming all patients received radiotherapy or underwent surgery was −4.29 ± 3.94%. The difference between the 5-year cancer-specific survival rates assuming all patients received radiotherapy or underwent surgery was −2.04 ± 6.74%.

Based on the SEER database, the 5-year survival rate for surgery for 1960 patients (29.98%) was >5% higher than the 5-year survival rate for radiotherapy. The 5-year survival rate for 706 patients undergoing surgery was <5% than the 5-year survival rate for patients who received radiotherapy. The difference in the 5-year survival rate between 3872 patients (59.22%) who underwent surgery or received radiotherapy was between −5 and 5%; thus, this group of patients may choose surgery or radiotherapy.

**DISCUSSION**

In this study, we compared the cancer-specific survival of 6538 patients with early stage glottic LSCC, who received radiotherapy
or underwent surgery. We built and validated two web-based nomograms to predict the cancer-specific survival for each patient who received radiotherapy or underwent surgery. Patients can input relevant information, such as age, grade, T stage, and marital status, on our website and estimate which treatment is superior. Our findings will be of great benefit to help patients and physicians to make treatment decisions.

We showed that radiotherapy and surgery each have their own advantages in the glottic LSCC population (17). Of the 6538 patients from the SEER database, surgery was superior in 29.98%, radiotherapy was superior in 10.80%, and operation and radiotherapy had similar efficacy in 59.22%. Patients and physicians can use our web-based nomograms to predict which therapy is more appropriate for them.

A nomogram is a simple graphical representation of a statistical prediction model that is frequently applied to patients and has gained popularity among oncologists and patients participating in clinical trials (18–23). In the current study, we used two nomograms to visually and individually predict the survival of glottic LSCC patients with different clinicopathologic characteristics to help them choose a superior treatment modality. We believe that our nomogram-based method can be used to compare the outcomes of several therapies and can play an increasingly significant role in future clinical analyses.

Inverso et al. (24) reported that marital status has a positive effect on metastatic laryngeal cancer. Common symptoms of laryngeal cancer included hoarseness, otalgia, dysphagia, and voice changes (25). Such symptoms can attract the early attention

| Characteristics | Univariate analyses | Multivariate analysis |
|-----------------|---------------------|----------------------|
|                | HR 95% CI p-value VIF | HR 95% CI p-value |
| Therapy        | 0.004 1.001         | Reference 0.002 |
| Radiation      | Reference           | Reference           |
| Surgery        | 0.795 0.680–0.928 0.004 | 0.783 0.670–0.915 0.002 |
| Sex            |                      | Not included |
| Male           | Reference            | Reference           |
| Female         | 1.122 0.886–1.422 0.340 | 1.128 0.886–1.422 0.340 |
| Age            | <0.001 1.005         | <0.001              |
| <50            | Reference            | Reference           |
| 51–60          | 2.803 1.726–4.551 <0.001 | 2.756 1.696–4.80 0.001 |
| 61–70          | 3.541 2.205–5.688 <0.001 | 3.679 2.289–5.913 0.001 |
| 71–80          | 6.119 3.820–9.802 <0.001 | 6.296 3.928–10.960 0.001 |
| 81–          | 11.341 6.998–18.379 <0.001 | 11.318 6.980–18.350 0.001 |
| Race           |                      |                      |
| White          | Reference            | Reference           |
| Black          | 1.026 0.774–1.359 0.859 | 0.933 0.700–1.244 0.638 |
| Others         | 0.525 0.336–0.820 0.005 | 0.568 0.363–0.889 0.013 |
| Year at diagnosis* | 0.809 1.564 Not included |                    |
| Grade          | 0.009 1.005         | 0.001               |
| Well differentiated | Reference         |                       |
| Moderately differentiated | 1.117 0.911–1.368 0.287 | 1.126 0.917–1.382 0.257 |
| Poorly or undifferentiated | 1.655 1.233–2.221 0.001 | 1.794 1.334–2.413 0.000 |
| Unknown        | 1.144 0.913–1.432 0.242 | 1.184 0.943–1.485 0.145 |
| Stage          | <0.001 Not included | Not included |
| I              | 1.476 1.203–1.810 <0.001 | <0.001 |
| II             | <0.001 1.013         | <0.001              |
| T stage        |                      |                      |
| T1a            | Reference            | Reference           |
| T1b            | 1.227 0.907–1.660 0.184 | 1.279 0.943–1.734 0.114 |
| T1 not specified | 1.200 0.988–1.458 0.066 | 1.180 0.971–1.434 0.097 |
| T2             | 1.573 1.271–1.949 <0.001 | 1.641 1.323–2.035 0.001 |
| Insurance status | 0.120 1.557 Not included |                    |
| Any            | Reference            | Reference           |
| None or unknown | 1.149 0.965–1.367 0.120 | 0.676 0.577–0.792 0.001 |
| Marital status |                      |                      |
| Married        | Reference            | Reference           |
| Others         | 1.509 1.292–1.763 <0.001 | 1.509 1.292–1.763 <0.001 |

Asterisk *** refers to the year the patient was diagnosed with the disease.
of partners or spouses, who may urge patients to receive timely
diagnosis and treatment. Investigators have reported that patients
who have fee-for-service insurance are more likely to undergo
cancer screening tests that may affect stage at the time of
diagnosis (26). Our analysis showed that insurance was not an
independent factor in patients with early stage laryngeal cancer.
The relationship between insurance and survival outcome needs
further exploration.

Our study had several limitations. First, the information
in the SEER database is not detailed, such as radiation
technology, radiation dose, and surgery regimen. We were
not able to calculate the influence of these factors. Second,
owing to the absence of life quality data in the SEER
database, we only focused on survival outcome rather than
assess functional outcomes, while a trial revealed that patients
with radiotherapy had less hoarseness-related inconvenience
(27, 28). Du et al. (2) reported that surgery had preferable
fundamental frequency values over radiotherapy in T1aN0M0
glottic carcinoma (29). With the development of surgery in
recent years, the effect of surgery on pronunciation and other
functions has greatly improved (7, 30–34). Third, the results
might not be applicable to other populations because patients
included in this research were from the United States. The
last, we only analyzed the clinical characteristics but didn’t
include several molecular factors such as HPV, or TP53
mutations since such information was not included in the SEER
database. The last, but most important limitation was that
it should be noted that our results may not be a reference
before prospective trials are conducted because the study
was retrospective.
FIGURE 4 | Nomogram analyses for patients with surgery (A) A nomogram for prediction of 3- and 5-year CSS rates of patients (B) Calibration curve of the nomogram predicting 3-year CSS rates in training cohort. (C) Calibration curve of the nomogram predicting 5-year CSS rates in training cohort. (D) Calibration curve of the nomogram predicting 3-year CSS rates in validation cohort (E) Calibration curve of the nomogram predicting 3-year CSS rates in validation cohort.

FIGURE 5 | The histogram of the difference between CSS rates (radiotherapy-surgery) (A) the difference between 3-year CSS rates (B) the difference between 5-year CSS rates.
CONCLUSION
In our study, we analyzed the independent prognostic factors for early stage glottic LSCC patients and built nomograms to comprehensively calculate independent factors and help determine which treatment, radiotherapy, or surgery, is better for each patient. A website is also available to offer guidance about surgery or radiation for patients and physicians.

DATA AVAILABILITY STATEMENT
All datasets generated for this study are included in the article/Supplementary Material.

ETHICS STATEMENT
The Ethics Committees of Jinshan Hospital and the Eye and ENT Hospital of Fudan University exempted the study because no personal information is included in the SEER database.

AUTHOR CONTRIBUTIONS
YD, SS, and ML: conception and design. YD, LY, and YZ: administrative support. YD, TQ, and SS: provision of study materials or patients. YD and ML: collection and assembly of data. LY, YZ, and TQ: data analysis and interpretation. All authors: manuscript writing and approval of final manuscript.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.01669/full#supplementary-material

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