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CT Imaging–Based Preoperative Nomogram for Predicting Early-Stage Glottic Cancer Recurrence after Transoral Laser Microsurgery

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Abstract

Objective: To explore the differences between clinical features and computed tomography (CT) findings of early-stage glottic cancer (EGC) with or without recurrence after transoral laser microsurgery (TLM), and to establish a preoperative nomogram for predicting postoperative recurrence.

Methods: The clinical and CT features of 168 consecutive EGC patients with or without recurrence were analyzed retrospectively. Multivariate Logistic regression analysis was used to determine the independent predictors for recurrence. A nomogram was constructed to preoperatively predict recurrence. C-index and calibration plot were used to assess the performance of nomogram.

Results: EGCs with and without recurrence differed significantly in T-stage, depth, normalized CT value in arterial phase (NCTAP) and venous phase (NCTVP) (all $P<0.05$). T-stage, depth and NCTVP were independent predictors of recurrence in EGCs (all $P<0.05$). C-index (0.765, 95%CI: 0.703-0.827) and calibration plot show that nomogram has good prediction accuracy. Nomogram based on T-stage and CT variables provided numerically predicted recurrent rate, and were better than did only T-stage (C-index of 0.765 vs. 0.608).

Conclusions: Using clinical and CT variables, we developed a novel nomogram to predict the recurrence of EGC patients before TLM, which may be a potential non-invasive tool to guide personalized treatment.

Keywords: Tomography; X-Ray Computed; Nomograms; Neoplasm Recurrence; Risk Factors; Laryngeal Neoplasms

Abbreviations

EGC: Early-Stage Glottic Cancer; TLM: Transoral Laser Microsurgery; NCT: Normalized CT Value; ROI: Region of Interest

Introduction

Glottis is the most common origin site of laryngeal squamous cell carcinoma (SCC), accounting for about 60% of new cases [1], and most of them are diagnosed at early stage (T1-T2 and N0) [2,3]. During these 40 years, transoral laser microsurgery (TLM) for larynx has gained followers all over the world and has become the gold standard for almost all early-stage glottic cancer (EGC) [4]. The cure rate of patients for early-stage patients ranges from 80% to 90%. However, recurrence is still a problem for EGC, which will inevitably affect the patient's quality of life [5].

Many studies have been carried out to find out the recurrent factors of EGC, such as age, gender, smoking, alcohol abuse, and TNM stage [6-9]. However, it is still a challenge for clinicians to reliably identify high-risk patients with EGC which hinders the decision-making process of individualized treatment. Some molecular markers have been found in head and neck tumors, but these markers have not reached relatively high specificity and sensitivity [10]. Therefore, it is necessary to further explore other prognostic indicators in order to better carry out individualized treatment.

Previous studies on the prognosis of laryngeal cancer mainly focused on the pathological results of surgical specimens or clinical features and ignored the imaging findings, which may play an important role. According to the National Comprehensive Cancer Network (NCCN) guidelines [11], the preoperative determination of glottis cancer was recommended by using CT (with contrast and thin angled cuts) and/or enhanced MRI examination of primary focus and neck, among which enhanced CT was the most commonly used imaging modality in daily clinical practice. Clinicians can evaluate images to determine location of lesions, tumor progression, and metastasis [12]. As an imaging biomarker, CT quantitative parameters may be important prognostic factors in patients with EGC. However, as far as we know, the prognostic value of preoperative CT imaging in EGC patients had not been reported. Therefore, the purpose of this study is to construct and internally validate a predictive model for predicting recurrence using CT imaging–based variables in patients with EGC after TLM.

Materials and Methods

Patient Selection

This retrospective study was approved by our institution's ethics committee (No. 2021-007) and the requirement for written informed consent was waived.

In this study, we consecutively analyzed the data of all patients with laryngeal SCC admitted to our institution from January 2014 to December 2018. The cancer staging was confirmed based on 8th edition AJCC-TNM stage [13]. All patients were obtained by searching our institutional database and medical record system and confirmed by postoperative histopathological diagnosis.

The inclusion criteria were as follows: 1) confirmed SCC by histopathology; 2) the primary site was glottis; 3) T1-2N0 staging; 4) the initial treatment was TLM and no other preoperative or/and postoperative treatment; 5) TLM within 4 weeks after CT scanning; 6) no history of other tumors except laryngeal carcinoma, and 7) the clinical data were complete and the image quality was excellent to show the extent of the lesions. The exclusion criteria were as follows: 1) non-SCC patients; 2) T3-4Nx staging; 3) other treatment modalities before or/and after TLM; 4) other tumors except laryngeal carcinoma; 5) loss to follow-up; 6) the quality of the image was too poor to determine the extent of the lesion or have serious artifacts; 7) the lesion was so small that there was not enough area to delineate region of interest (ROI). The details of the patient recruitment pathway are shown in Figure 1. Finally, 168 patients were enrolled and divided into two groups: 1) with recurrence (37 cases), and 2) without recurrence (131 cases).

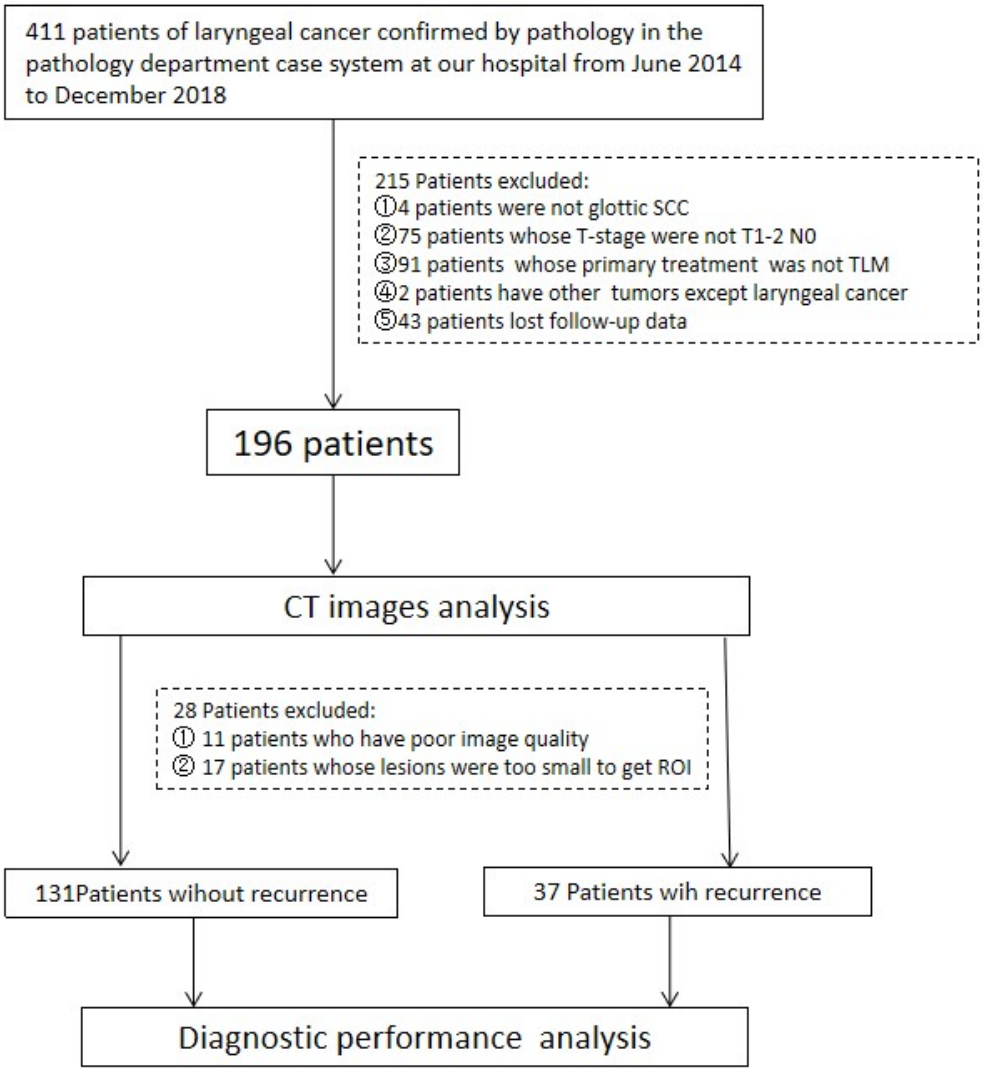

Figure 1: Flowchart of the study population. SCC, squamous cell carcinoma; TLM, transoral laser microsurgery; CT, computed tomography; ROI, region of interest

The final follow-up period of our study is December 2020, so all patients had a follow-up period of at least 2 years. We investigated recurrence status of the tumor based on their electronic medical records and telephone follow up. Recurrence is defined as the first treatment failure caused by primary lesion or metastasis from the other site (including lymph nodes or distances). The recurrence was diagnosed comprehensively according to the follow-up images and the progress of the lesions confirmed by pathology.

CT Examination

Contrast-enhanced neck CT images were obtained via a SOMATOM Definition Flash CT (Siemens Healthcare, Erlangen, Germany) when suspicious malignant lesion was detected in the vocal fold by laryngoscope. The scanning parameters were as follows: dual energy fusion coefficient is 0.3, helical thickness, 6 mm; pitch, 0.9; rotation speed 0.28 s; detector width 40 mm; collimation, 64*0.6 mm; Tube A was operated at a peak voltage of 100 kVp and tube B was operated at Sn140 kVp (Sn = additional tin filtration). Reconstruction layer thickness 1 mm, interval 0.7 mm, axial scan mode. Real-time automatic tube current modulation (CARE dose 4D; Siemens Healthineers) was used to reduce radiation exposure. Images were obtained from skull base to aortic arch level. For contrast-enhanced scanning, an iodinated nonionic contrast agent (iohexol; 350 mg/dl iodine) was administered through the right elbow median vein by a dual-head injector. The dosage was 1 ml/kg with a flow rate of 3 ml/sec, the total injection dose was 60 - 70 ml, followed by a bolus injection of 40 ml saline given at the same flow rate. The timing of arterial phase scanning

was determined by automatic trigger technique, and the scanning delay was 25 s at the beginning of arterial phase scanning. The delay time of venous scan was 20 s after the end of arterial. The mean CTDIvol and DLP were 11.19±0.61 mGy (range, 8.98–14.78 mGy) and 277.36±26.75 mGycm (range, 236.07–365.11 mGycm).

CT Imaging Analysis

All preoperative CT images analysis was respectively conducted by two radiologists with 8 (reader 1) and 10 (reader 2) years of experience in head and neck image diagnosis. Image analysis was done after the TLM. The clinical--pathologic and follow-up data of the lesions was blinded to the two radiologists.

The CT images were reviewed using a picture archiving and communication system (PACS). ROI was drawn in the highest density area of the lesion and in the center of the common carotid artery (CCA) at the same level (Figure 2), avoiding the area of cystic degeneration, necrosis, bone and air. Recording the CT value of lesion and CCA in arterial (CT_{AP}, CCA_{AP}) and venous phase (CT_{VP}, CCA_{VP}). CT variables (length, depth, CT value of lesion and CCA) were respectively measured and then taken average if they have good repeatability. Then, we were able to calculate the normalized CT value (NCT): $NCT=CT_{tumor}/CT_{CCA}$. Tumor length and depth were measured at the arytenoid cartilage vocal process level.

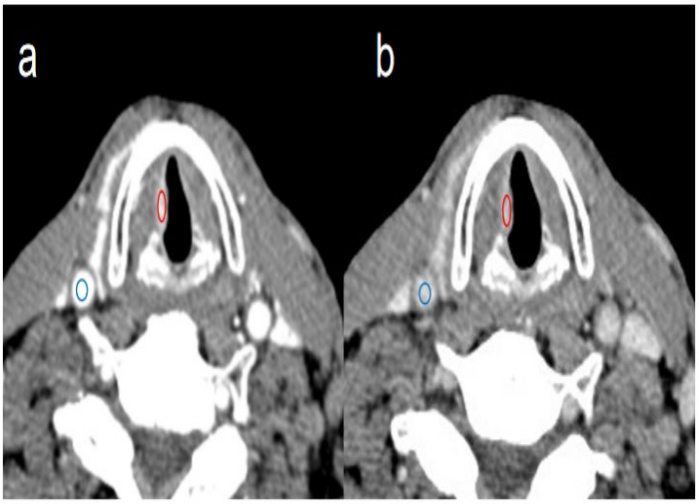

Figure 2: A 47-year-old man with T1 staging right glottic cancer. Axial CT image of arterial (a) and venous (b) phase. Tumor (red circle) limited to the right vocal cord. Blue circle show the center of the common carotid artery at the same level

Statistical Analysis

All statistical analyses were conducted by using R software (version 3.6.3) and SPSS (version 25.0). Continuous variables were described as medians and ranges meanwhile categorical variables as frequencies and percentages. We used Student's t test or the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, which were used comparing recurrent group with non-recurrent group. Using package "pROC", we determined the cut-off value for continuous variables and convert continuous variables to categorical variables. All variables with P < .1 in univariate analysis were included in the multivariate logistic analysis to investigate the independent predictors of recurrence. Package "foreign" and "rms" were used to perform univariate and multivariate Logistic analysis, draw a nomogram, calculate C-index, and drat calibration plot. The interobserver reproducibility of feature extraction was evaluated using the interclass correlation coefficient (ICC). P value < .05 was considered to be statistically significant.

Results

Clinicopathological Characteristics

A total of 168 patients were enrolled: 155 males (92.3%) and 13 females (7.7%); the mean age of the patients at the time of TLM was 62.4 ± 8.6 years, range, 44-86 years.

The detailed characteristics of the 168 patients were summarized in Table 1. According to the 8th edition of TNM staging criteria of laryngeal cancer established by AJCC, 116 patients (69.0%) were classified as stage T1 and 52 (31.0%) with T2. There was significant difference in tumor T-staging between non-recurrent group and recurrent group (P=0.043). The poorly differentiated patients in recurrent group (14.8%) were slightly higher than those in non-recurrent group (7.8%), but there was no significant difference just as those in age, gender, smoking and drinking history. The mean interval between the last CT examination and surgery was 7.54 ±4.40 days (range, 1 to 13 days).

Table 1: Clinicopathological and CT Characteristics

Parameter	Total (n=168)	Non-recurrence group (n=131)	Recurrence group(n=37)	P value
Age (year)	62.4 ± 8.6	62.3 ± 8.5	62.7 ± 9.1	.806
Gender				.924
Male	155 (92.3)	121 (92.4)	34 (91.9)	
Female	13 (7.7)	10 (7.6)	3 (8.1)	
Smoke				.974
Yes	132 (78.6)	103(78.6)	29 (78.4)	
No	36 (21.4)	28 (21.4)	8(21.6)	
Alcohol				.449
Yes	101 (60.1)	81 (61.8)	20 (54.1)	
No	67 (39.9)	50 (38.2)	17 (45.9)	
Pathological differentiation				.422
Low	15 (8.9)	11 (7.8)	4 (14.8)	
Moderate-High	153 (91.1)	130 (92.2)	23 (58.2)	
T-stage				.043
T1	116 (69.0)	96 (73.3)	20 (51.4)	
T2	52 (31.0)	35 (26.7)	17 (45.9)	
CT variables				
Length (mm)	11.3 ± 3.7	11.2 ±3.6	11.8 ± 3.9	.339
Depth (mm)	2.4 (1.7, 3.4)	2.4 (1.7, 3.1)	2.8 (2.0, 4.2)	.041
NCTAP	0.237 (0.163, 0.283)	0.213 (0.155, 0.266)	0.285 (0.219, 0.315)	.000
NCTVP	0.609 (0.447, 0.806)	0.587 (0.396, 0.787)	0.709 (0.554, 0.916)	.009

Note: Unless indicated otherwise, data are number of patients, with percentages in parentheses.

* Recurrence: isolated local recurrence (n = 35), synchronous local and regional recurrence (n = 1), synchronous regional and distant recurrence (n = 1).

** T1: the tumor was confined to the vocal cords with normal vocal cord activity, T2: the tumor invaded the supraglottic and/or subglottic, and/or vocal cord movement was restricted; according to the 8th AJCC staging systems.

NCTAP=normalized CT value in arterial phase

NCTVP=normalized CT value in venous phase

Treatment Outcome and Follow-up

The median follow-up period was 23.4 months (range, 1.5–54.5 months) and all patients had a follow-up period of at least 2 years. Recurrence was observed in 22.02% (37/168) patients at the last follow-up (35 were isolated local recurrence, 1 was synchronous local and regional recurrence, 1 was synchronous regional and distant recurrence), meanwhile 77.98% (131/168) patients without recurrence. The median time to recurrence was 10.3 months (range, 3–42 months). Among them, 64.9% (24/37) patients recurred within 12 months, 86.5% (32/37) patients recurred within 24 months, and only 13.5% (5/37) patients had relapsed after 24 months. Most recurrences of EGC occur within the first 2 years [14,15].

CT variables Between Groups with and without Recurrence

Interobserver consistency of CT variables between the two radiologists with intraclass correlation coefficients from 0.822 to 0.931. As shown in Table 1, the recurrence group presented a larger involved depth and length, but only the depth had statistically significant difference (2.8mm vs. 2.4mm, 11.8mm vs. 11.2mm; P=0.041, 0.339, respectively). Normalized CT value in arterial phase (NCTAP) and venous phase (NCTVP) in recurrence group were significantly higher than non-recurrence group (0.285 vs. 0.213, 0.709 vs. 0.587; P<0.001, P=0.009, respectively).

Univariate and Multivariate logistic Regression Analysis and Construction of a Nomogram

We calculated the cut-off values (62.5 years old, 11.35 mm, 3.80 mm, 0.27 and 0.51 for age, length, depth, NCTAP and NCTVP, respectively). Then, univariate analysis indicated 4 variables as risk factors of recurrence in EGC patients, including T-stage, depth, NCTAP, and NCTVP (all P<0.05). As shown in Table 2, multivariate logistic regression analysis identified T-stage, depth, and NCTVP as independent predictors of recurrence in EGCs (all P<0.05). A nomogram was constructed based on the above three significant variables, which providing a practical tool for clinicians (Figure 3). Draw a vertical line and connect the value of each variable with the score at the top of the chart to get the score for each variable. Then add the scores of each variable to get the total score, which is drawn along the "total score" line at the bottom of the nomogram. This line reflects the probability of recurrence in patients with EGC. C-index was used to evaluate the predictive accuracy (discrimination) of the nomogram, which was 0.765 (95%CI: 0.703-0.827). In addition, 1000 repetitions bootstrapped calibration plot (consistency) show that nomogram has good prediction accuracy for EGC recurrence (Figure 4). Nomogram based on T-stage and CT variables provided numerically predicted recurrent rate, and were better than did only T-stage (C-index of 0.765 vs. 0.608).

Table 2: Multivariate analysis of recurrence after TLM in early-stage glottic cancer patients

Variables	Multivariate analysis		
	Odds ratio	95% CI	P value
T2 stage (T1)	8.578	2.593-28.360	<0.001
Depth ≥ 3.8mm (< 3.8mm)	4.664	2.818-7.721	0.002
NCTAP ≥0.27 (< 0.27)	2.135	0.202-2.734	0.128
NCTVP ≥0.51 (< 0.51)	6.097	2.544-14.614	<0.001

Note: The reference category for each variable is presented in parenthesis.

TLM = transoral laser microsurgery;

CI = confidence interval;

NCTAP = normalized CT value in arterial phase;

NCTVP = normalized CT value in venous phase

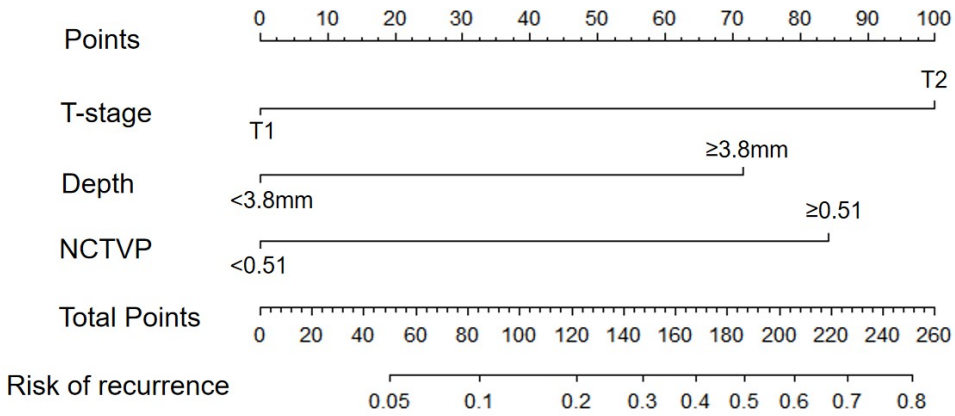

Figure 3: The nomogram for predicting recurrence. Predictor points ("Points" scale; top) correspond to each variable. Points for all three variables are added and translated into the probability of recurrence ("Risk of recurrence" scale; bottom). NCTVP = normalized CT value in venous phase

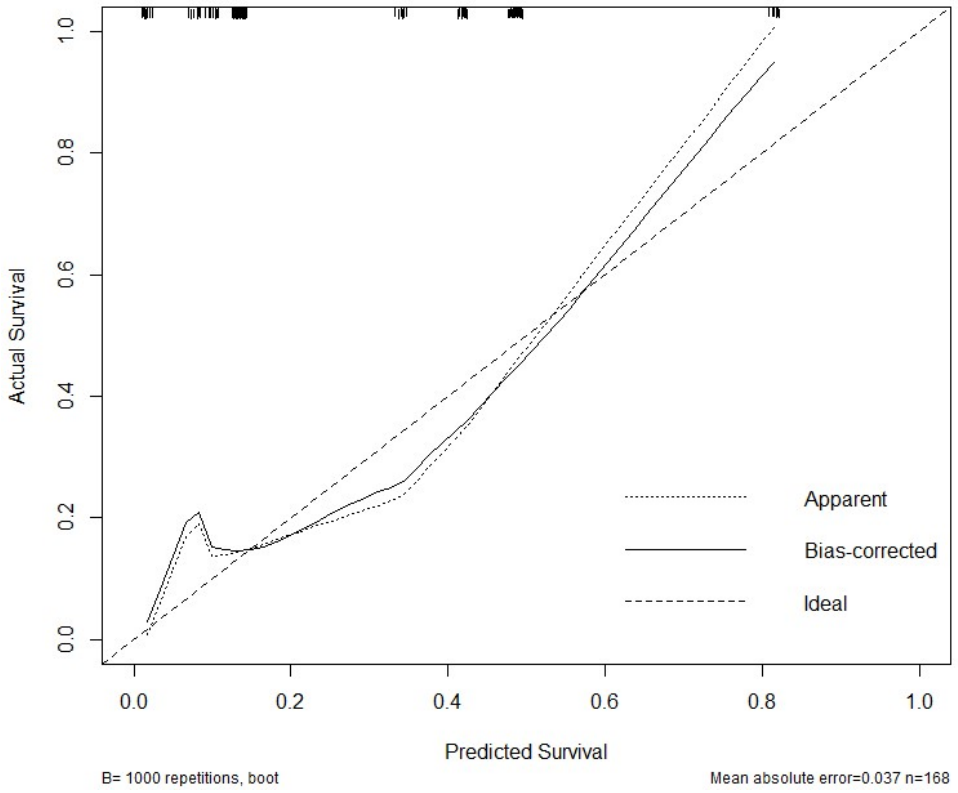

Figure 4: Calibration plot for the patients with EGC. Expected survival and actual survival exhibit good agreement

Discussion

In this study, we found that in addition to T-stage, preoperative CT variables were also useful for predicting recurrence after TLM in EGC patients. We have developed a nomogram based on T-stage (OR 8.58) and CT variables (depth, OR 4.64; NICVP, OR 6.01), which can calculate the probability of recurrence of EGC individuals with excellent predictive accuracy. We hope that this nomogram will help to more accurately select the EGC patients who plan to undergo TLM surgery should undergo other treatment management.

With regard to the analysis of the factors found in our model, we firstly found that T-stage was a significant predict factor, which was in line with the previous study [6,16]. At present, TNM staging is a common factor in evaluating the risk of recurrence in tumor [17]. The treatment mode of EGC was commonly based on the 8th edition of Tumor, Node, and Metastasis staging of the American Joint Committee on Cancer (AJCC)/International Union against Cancer system. However, even among the patients of the same stage, there were significant differences in postoperative recurrence in individual EGC patients, which often leaded to treatment failure. In the present study, we found that, with the increase of T-stage, the frequency of successful outcome decreases, as shown in the study of Yan F et al [18]. As shown in our study, T2 tumor had a more obvious tendency of recurrence than T1, which seemed to be consistent with the previous literature [19]. It was hypothesized that some patients classified as T2 stage may actually T3 stage (have minor para-glottic and pre-epiglottic space invasion), which are difficult to identify on CT scan [20].

The second factor of the nomogram was tumor depth. Tumor depth or thickness of invasion was not easy to measure with endoscope alone. CT was a feasible method to detect the depth of laryngeal carcinoma. A study by Son et al. has showed that there was a significant correlation between the tumor thickness measured by CT and pathology [21]. They also found that tumor depth measured by CT was a prognostic factor. The mechanism may be that submucosal invasion means aggressive tumor behavior, while protruding lesions that do not infiltrate into the deep structure behave differently, just as the study of Ebrahimi et al. reveals [22]. Therefore, when deep involvement of the vocal cords was suspected, the scope of TLM should be expanded to ensure safe removal of the edge, so as to improve local control. According to NCCN guideline [11], the factors affecting the oncological outcome of early glottic carcinoma treated with TLM were tumor location and extent without depth or thickness. Our study may provide a choice for the selection of patients on this in the future.

NCTVP based on CT images was the third independent predictor in the present study. These has not been mentioned in previous studies. In contrast, univariate analysis showed that NCTAP was associated significantly with recurrence of EGC, which was not included in the nomogram because a significant difference was not observed in multivariate analysis. Quantitative enhanced CT can improve the diagnostic evaluation of cancer patients by providing markers of tumor angiogenesis [23]. To prevent different individual circulation levels, we calculated the ratio of lesion to CCA at same phase and slice. We found that the NCT values in venous phase in the recurrent group were higher than those in the non-recurrent group. The reason may be that the higher NCTVP values reflect that the tumor has entered the period of rapid neovascularization from the period of slow growth of blood vessels (pre-vascular phase) to the period of rapid neovascularization (vascular phase). After entering the vascular phase, the growth of the tumor was accelerated and it was more likely to recur, which was similar to some previous studies [24,25].

Our study has the several limitations. First, the retrospective instinct is the major limitation. Some patients' data were lost or incomplete during follow-up, resulting in censored data and possible bias. Second, the analysis of radiological variables was from the maximum cross-sectional area of the tumor rather than the whole tumor was one-sided, which may not result in the most representative area of the tumor. Third, this study was an exploratory study to build a model, lack of external data verification before putting into clinical application. We still need to obtain more evidence from multiple centers to verify the predictive effectiveness of the model.

Conclusion

The nomogram combined with clinical and CT variables may predict the recurrence of EGC patients after TLM and the predicted accuracy better than only clinical variable (T-stage), which provide new useful information for pre-clinical judgment of EGC patients, and help clinicians to make a more appropriate operation plan.

Ethical Statement

This retrospective study was approved by our institution's ethics committee (No. 2021-007) and the requirement for written informed consent was waived.

Declaration of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

Huanlei Zhang: Manuscript writing; Conception and design;Provision of study materials or patients; Data analysis and interpretation; Collection and assembly of data; Administrative support; Final approval of manuscript

Yuanyuan Li: Manuscript writing;Provision of study materials or patients;Data analysis and interpretation;-Collection and assembly of data;Final approval of manuscript

Xiuli Zhao: Collection and assembly of data; Data analysis and interpretation; Final approval of manuscript

Xuelin Zhu: Conception and design; Administrative support; Collection and assembly of data; Data analysis and interpretation; Final approval of manuscript

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