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Original Article

Long-term efficacy of transoral endoscopic plasma resection in the treatment of early glottic laryngeal cancer and analysis of prognostic factors

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Abstract: This study aimed to evaluate the efficacy of transoral endoscopic plasma resection (TEPR) in treating early glottic laryngeal cancer (GLC) and identify prognostic factors. A retrospective analysis was conducted on the medical records of 212 patients with early GLC treated with TEPR between February 2015 and September 2018 at Dongying People's Hospital. Clinical characteristics, objective voice function changes, and clinical outcomes of the patients were analyzed. Meanwhile, Kaplan-Meier curve was plotted to assess the impact of TERP on 3- and 5-year survival in GLC patients. Additionally, univariate and multivariable logistic regression analyses were performed to assess prognostic factors for GLC recurrence, and Receiver Operating Characteristic (ROC) curves were generated to assess their predictive value for patients' prognosis. After surgery, Patients' Jitter (%), Shimmer (%) showed significant improvement from pre-surgery, in contrast to Harmonic noise ratio and maximum phonation time, which underwent a significant decrease. The study assessed success and recurrence rates over 3- and 5-year follow-up periods, revealing a disease control rate of 86.79%, with 3- and 5-year recurrence rates of 14.62% and 20.28%, respectively. Patients were categorized into favorable and unfavorable prognosis groups based on the 3-year recurrence. Univariate analysis identified significant risk factors for recurrence, including age, tumor-node-metastasis (TNM) stage, clinical stage, and cumulative anterior commissure involvement ($P < 0.05$). Further multivariate logistic regression confirmed the above indexes as independent risk factors impacting patient prognosis. In conclusion, TEPR effectively treats early GLC, though recurrence risk persists, with age, TNM stage, clinical stage, and anterior commissure involvement identified as prognostic risk factors, suggesting the need for targeted preventive measures in clinical practice.

Keywords: Transoral endoscopic plasma resection, glottic laryngeal cancer, prognosis, risk factor

Introduction

Laryngeal malignant tumors rank among the most common malignancies in head and neck cancers. According to statistical data, there were approximately 184,615 newly diagnosed cases and 99,840 deaths attributed to laryngeal malignancies in 2020 [1]. The majority of cases were laryngeal squamous cell carcinoma, accounting for approximately 25% of all head and neck cancers [1, 2]. Within laryngeal squamous cell carcinomas, glottic laryngeal cancer (GLC) constitutes the largest proportion, accounting for approximately 60%-70% of cases. Moreover, GLC exhibits fewer occurrences of cervical lymph node metastasis in the early stages. However, the issue of recurrence in patients with early-stage GLC after treatment remains a significant concern [3-5].

Currently, the primary treatment methods for early GLC include open surgery, plasma surgery, and radiotherapy [6, 7]. Open surgery offers distinct advantages by providing clear exposure of the lesion, facilitating a wider resection range, and ensuring thorough removal of the affected area, thereby reducing the recurrence rate [8]. However, it also presents significant drawbacks, such as substantial damage to laryngeal structures and poorer post-

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operative voice quality and swallowing function, which severely impact the patients' quality of life. Consequently, clinicians have progressively decreased the utilization of open laryngeal surgery in recent years [9].

Low-temperature plasma refers to a high-speed ionized gas capable of breaking molecular bonds in tissues at lower temperatures, leading to tissue necrosis and tumor removal [10]. Due to the multi-functional capabilities of the plasma scalpel, such as low-temperature cutting, hemostasis, irrigation, and suction, it has been widely used in otolaryngology-head and neck surgery [11]. Compared to traditional laryngeal support laryngomicroscopy, transoral endoscopy significantly enhances patient comfort. Additionally, it provides superior exposure of the surgical field and enables complete lesion removal, facilitating detailed examination of areas such as the anterior commissure, laryngeal chamber, glottic region, and subglottic region [12, 13]. During the procedure, frequent adjustment of focal length is not necessary, reducing operation time and preventing compression of soft tissues caused by laryngeal support [14]. Moreover, the endoscope's light source delivers strong illumination through the fiber optic bundle, eliminating dark areas. Advances in endoscopic technology have effectively addressed the limitations of narrow surgical fields and incomplete tumor exposure associated with traditional transoral approaches. Consequently, an increasing number of experts endorse transoral endoscopic-assisted resection for treating GLC [15].

Currently, there is limited literature on the long-term efficacy of transoral endoscopic plasma resection (TEPR) in the treatment of early GLC. Therefore, this study analyzed data from 212 cases of early GLC treated with TEPR, with follow-up periods exceeding 3 years, to provide detailed insights into its long-term efficacy. Additionally, we conducted a comprehensive analysis of various factors influencing patient prognosis, aiming to advance early GLC treatment techniques and enhance long-term patient outcomes.

Data and methods

Research subjects

This retrospective analysis involves subjects treated at Dongying People's Hospital between February 2015 and September 2018, based on medical records, outpatient visits, and follow-up examinations. The study was conducted in accordance with the Helsinki Declaration and received approval from the Dongying People's Hospital. A total of 212 cases met the selection criteria were finally included in this study.

Case screening criteria

Inclusion criteria: (1) patients diagnosed with early GLC [16]; (2) patients whose preoperative imaging data ruled out lymph node metastasis or distant metastasis; (3) patients whose preoperative or intraoperative clinical pathological diagnosis confirmed squamous cell carcinoma; (4) patients who had undergone TEPR for the first time at our hospital; (5) patients with complete case data available.

Exclusion criteria: (1) patients who received chemotherapy or radiation therapy before or after surgery; (2) patients combined with other pharyngeal or laryngeal diseases; (3) patients combined with other types of malignant tumors.

Characteristic

The following basic information and clinical characteristics were collected from the medical records: gender, age, weight, tumor-node-metastasis (TNM) staging, smoking status, clinical staging, cumulative anterior commissure involvement, and cumulative vocal cord process.

Surgical treatment

After anesthesia, the patient was placed in the supine position, and the self-retaining laryngoscope was inserted orally. Subsequently, the endoscope was used to accurately locate the vocal folds area, and the low-temperature plasma surgical system (SM-D380C, Xi'an Surgical Medical Technology Co., Ltd., China) was used to perform the ablation cutting and electrocoagulation hemostasis operation for GLC in the vocal folds position, in which the ablation power was adjusted to 7 levels, and the electrocoagulation power was adjusted to 3 levels. During the procedure, Tis and T1 stage tumors were resected by lifting the tumor tissue using forceps and subsequently removing the tumor tissue and part of the vocal cords using a plasma knife approximately 3 mm outside the base of

the tumor. For stage T2 tumors, the affected ventricular band and laryngeal ventricle need to be removed and the entire affected vocal cord, including the anterior commissure, needs to be resected down the thyroid cartilage. Meanwhile, part of the affected arytenoid cartilage and the contralateral anterior vocal cords were also removed if necessary. Subsequently, the tissue at the margins was sent for pathological freezing, and a decision was made as to whether the extent of the resection should be further extended based on the freezing results. After removal of the tumor, the area of the vocal folds was examined and repaired, e.g. hemostasis and suturing to ensure wound healing.

Outcome measures

Objective voice function assessment: Before surgery and at 1 month after surgery, patients' voices were collected in an examination room (background noise < 45 dB) and analyzed using Praat software for objective voice function indicators, including Jitter (%), Shimmer (%), and Harmonic noise ratio (HNR). In addition, the patients were instructed to take a deep breath and continue to make the "a" sound until they were unable to continue, and the maximum phonation time (MPT) was recorded. The above indicators were tested three times and the average value was taken, while maximum MPT among the three times was taken as the final value.

Clinical efficacy: Clinical efficacy was assessed by imaging and video laryngoscopy results using the efficacy evaluation criteria for solid tumors (version 1.1) [17]: complete response (CR), complete disappearance of the original tumor foci; partial response (PR), > 30% reduction in the volume of the original foci compared with the pre-treatment; stable disease (SD), < 30% reduction in the volume of the original foci or no increase; progressive disease (PD), 20% increase in the volume of the foci or the appearance of new foci; disease control rate (DCR) = (CR+PR+SD)/total number of cases ×100%.

Survival prognostic indicators: Progression free survival (PFS) time was recorded as from surgery to local, regional or distant appearance of new metastases.

Postoperative follow-up: Postoperatively, patients were instructed by phone, WeChat, etc. to go to the hospital for regular review, three times a year to the outpatient clinic in the first two years, twice in the third year, and once a year in the later years, with video laryngoscopy during the outpatient follow-ups, and imaging every 6 months in the first two years, and once a year in the third to fifth years. Local, regional and distant recurrence during the follow-up period was recorded. The follow-up period was 5 years, and the follow-up ended in September 2023.

Statistical analyses

Quantitative data were input, coded, and cleaned using Microsoft Excel, and SPSS 23 was used for analysis. Descriptive statistics, such as mean ± standard deviation (SD), percentages, and frequencies, were calculated to analyze the participants' basic information and clinical characteristics. Mean and SD were calculated for continuous variables. The ability of age, TNM stage, clinical stage, and cumulative anterior commissure to predict 3-year recurrence in patients was evaluated using receiver operating characteristic curve (ROC) analysis. Kaplan-Meier survival analysis was conducted to examine the 3-year and 5-year recurrence status of patients, and the log-rank test was used for analysis. The patients were divided into favorable prognosis and unfavorable prognosis groups based on whether they experienced recurrence within 3 years after surgery, univariate and multivariate logistic regression analyses were performed to assess prognostic factors for recurrence. $P < 0.05$ suggests a significant difference.

Results

Basic data and clinical characteristics of patients

The basic information and clinical characteristics of the 212 patients are presented in **Table 1**. There were 58 cases in Tis stage (27.36%), 116 cases in T1 stage (54.72%), and 38 cases in T2 stage (17.92%). Histologically, 141 cases (66.51%) were highly differentiated, while 71 cases (33.49%) were moderately or poorly differentiated. Anterior commissure invasion was noted in 38 cases (17.92%), and 33 cases (15.57%) exhibited vocal cord involvement.

Table 1. Clinical features (n = 212)

Characteristic	n/Means	%/SD
Sex		
Male	184	86.79
Female	28	13.21
Age (years)	60.5	7.4
Weight (kg)	60.77	9.08
TNM staging		
Tis period	58	27.36
T1a period	68	32.08
T1b period	48	22.64
T2 period	38	17.92
Smoking history	56	26.41
Clinical stages		
High differentiation	141	66.51
Moderate differentiation	48	22.64
Low differentiation	23	10.85
Cumulative anterior commissure	38	17.92
Cumulative vocal cord process	33	15.57

Note: TNM: tumor-node-metastasis.

Objective assessment of voice function after surgery

After surgery, patients' Jitter (%), Shimmer (%) showed significant improvement from pre-surgery, in contrast to HNR and MPT which underwent a significant decrease (**Table 2**).

Treatment efficacy and 3-year recurrence status after surgery

Among the patients, 184 achieved disease control after surgery, resulting in a DCR of 86.79%. Within the 3-year post-operative period, 31 patients experienced recurrence, resulting in a 3-year recurrence rate of 14.62% (**Table 3** and **Figure 1A**). Of the 203 patients followed for 5 years post-surgery, an additional 12 patients experienced recurrence, resulting in a 5-year recurrence rate of 20.28% (**Figure 1B**).

Univariate analysis

Patients were divided into favorable and unfavorable prognosis groups based on recurrence within 3 years post-surgery. Univariate analysis indicated that age, TNM staging, clinical staging, and cumulative anterior commissure involvement significantly influenced patient prognosis (**Table 4**).

Predictive efficacy of age, TNM stage, clinical stage, and cumulative anterior commissure on prognosis

ROC curves were constructed to assess the predictive value of age, TNM stage, clinical stage, and cumulative anterior commissure involvement for prognosis. The area under the curve (AUC) for age was 0.687, with an optimal cutoff value of < 62.50, sensitivity of 65.22%, and specificity of 73.33% (**Figure 2A**). For TNM stage, clinical stage, and cumulative anterior commissure involvement, the AUCs were 0.655, 0.805, and 0.622, respectively, with sensitivities and specificities of 85.64%, 75.14%, 85.64%, and 38.71%, 83.87%, 38.71%, respectively (**Figure 2B-D**).

Multivariate analysis

Multivariate analysis was conducted on the factors that showed significant differences in the univariate analysis. It was found that older age (P = 0.044), higher TNM staging (P = 0.016), lower differentiation (P = 0.005), and cumulative anterior commissure involvement (P = 0.009) were independent risk factors for unfavorable prognosis in patients (**Table 5**).

Discussion

Glottis take a crucial part in regulating and protecting the voice [18]. Patients diagnosed with GLC often present with early symptoms such as throat pain, hoarseness, and swallowing difficulties, greatly impacting their quality of life. Therefore, early surgical intervention is recommended for patients with early-stage GLC [19]. Plasma resection, a common surgical approach for laryngeal cancer, depends heavily on the exposure of the glottis during surgery, which directly influences surgical outcomes [20]. Transoral endoscopy, employing an endoscope and specialized instruments, allows direct observation and manipulation of throat lesions through the oral cavity. This technique is particularly effective for early-stage GLC localized to the vocal cords and glottic area, without spreading to deeper tissues or lymph nodes. Transoral endoscopy provides excellent exposure of the glottis during surgery, allowing the physician to clearly visualize and manipulate the glottic area. Transoral endoscopy provides a wide field of view, enabling the physician to examine the subtle structures of the vocal

Table 2. Objective assessment of voice function before and after surgery

Index	Before surgery	1 month after surgery	t	P
Jitter (%)	0.92 ± 0.21	1.24 ± 0.37	-10.952	< 0.001
Shimmer (%)	4.34 ± 1.21	6.32 ± 1.35	-15.902	< 0.001
Harmonic noise ratio	13.67 ± 2.06	11.83 ± 2.62	8.038	< 0.001
Maximum phonation time (s)	19.12 ± 2.93	12.56 ± 2.83	23.448	< 0.001

Table 3. Efficacy

	CR	PR	SD	PD	DCR
n	25	61	98	28	184
%	11.79	28.77	46.23	13.20	86.79

Note: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; DCR: disease control rate.

cords and glottis. This helps determine the extent and depth of the tumor and allows for appropriate resection planning [21, 22].

This study investigated the therapeutic efficacy of TEPR as a primary treatment method. First, we conducted an objective assessment of the postoperative voice function changes in patients. TEPR might result in vocal fold damage and scar formation, which can affect the morphology, tension, and symmetry of the vocal folds, leading to irregular vibration and decreased stability. Jitter and Shimmer, which reflect the stability of the vocal fold vibration cycle and amplitude, respectively, showed significant postoperative increases. Additionally, TEPR might cause incomplete glottic closure, leading to reduced airflow control during phonation, increased noise components, and difficulty sustaining phonation for prolonged periods, resulting in decreased HNR and MPT. Meanwhile, a complete remission was achieved in 184 cases postoperatively, resulting in a DCR of 86.79%. Additionally, the recurrence rate was evaluated over a 3- or 5-year period. Within the 5 years following the surgery, a total of 43 patients experienced recurrence, resulting in a 5- and 3-year recurrence rate of 20.68% and 14.62%, respectively. This finding is in line with prior research [23]. TEPR, characterized by minimally invasiveness and precise lesion visualization via transoral endoscopy, enables targeted ablation of affected tissues while minimizing damage to normal structures. Zhu et al. have highlighted TEPR's benefits, including reduced pain, shorter surgical durations, minimal intraoperative bleeding, shorter hospital stays, and lower complication rates, contributing to enhanced recovery and restoration of vocal fold function [24].

There are various factors that can influence postoperative recurrence in laryngeal cancer. Apart from the biological characteristics of the cancer cells themselves, factors such as tumor staging, pathological grading, surgical approach, involvement of adjacent structures, and margin status may also play a role [25, 26]. However, there is some controversy regarding the factors that affect the postoperative recurrence rate in minimally invasive surgery for early-stage GLC. The use of different surgical tools may introduce variations in the factors that impact recurrence, which requires further research and investigation. Univariate analysis in our study identified age, TNM stage, clinical stage, and cumulative anterior commissure involvement as potential predictors of recurrence within 3 years postoperatively. Subsequent multivariate analysis confirmed these factors as independent risk factors influencing patient prognosis. Lesions in stage T2 often extend beyond the glottic area, involving either the supraglottis or subglottis. These two locations have abundant lymphoid tissue, and the subglottis is a relatively concealed site, making it difficult to detect and expose under endoscopy. The high local recurrence rate observed in T2 stage cases may be related to these factors [27, 28]. In addition, we found that cumulative anterior commissure was also a risk factor affecting the prognosis of GLC patients. The reasons considered are that the lack of abundant submucosal tissue and barrier in the anterior coalition region makes it easy for the tumor to expand along the anterior coalition directly to the thyroid cartilage membrane and outside, forming local progression or invasion. Moreover, the complex location of the anterior commissure increases the difficulty of surgical resection, and the critical role of the anterior commissure for the preservation of vocal cord function makes it difficult for the operator to

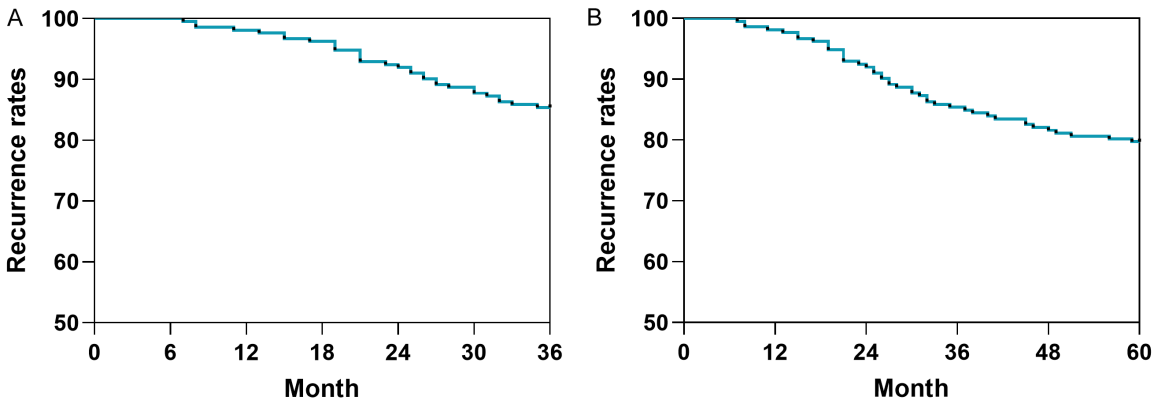

Figure 1. Kaplan-Meier survival analysis. A: 3-year recurrence rate after operation; B: 5-year recurrence rate after operation.

Table 4. Univariate analysis

	Favorable prognosis (n = 181)	Unfavorable prognosis group (n = 31)	P
Sex			0.232
Male	160 (88.40)	25 (80.65)	
Female	21 (11.60)	6 (19.35)	
Age (years)	59.4 ± 7.2	62.8 ± 7.0	0.016
Weight (kg)	60.43 ± 8.93	57.75 ± 9.47	0.127
TNM staging			0.004
Tis period	53 (29.28)	5 (16.13)	
T1a period	61 (33.70)	7 (22.58)	
T1b period	41 (22.65)	7 (22.58)	
T2 period	26 (14.36)	12 (38.71)	
Smoking history	43 (23.76)	13 (41.94)	0.215
Clinical stages			< 0.001
High differentiation	136 (75.14)	5 (20.00)	
Moderate differentiation	32 (17.68)	16 (46.67)	
Low differentiation	13 (7.18)	10 (33.33)	
Cumulative anterior commissure	26 (14.36)	12 (38.71)	0.001
Cumulative vocal cord process	26 (14.36	7 (22.58)	0.244

Note: TNM: tumor-node-metastasis.

balance between complete resection and functional preservation. Mannelli et al. [29] found a 7.31-fold and 9.45-fold increased risk of recurrence in T1b and T1a tumors with cumulative anterior commissure, respectively. Therefore, for patients with these risk factors, efforts were made during surgery to maximize tumor resection range, which potentially reduced the likelihood of recurrence to some extent.

This study has several limitations. Firstly, the sample size was small, and there were insufficient numbers of patients in each stage, which may have resulted in a lack of representativeness. Secondly, the surgical outcomes of this procedure can be influenced by the surgeon's experience, but it remains unclear whether this factor significantly affects the results. Lastly, the follow-up period was limited, and for longer-term prognostic outcomes of patients, further studies with extended follow-up durations are needed to explore these aspects.

In conclusion, the application of TEPR in the treatment of early GLC has shown definite efficacy; however, there is still a risk of recurrence.

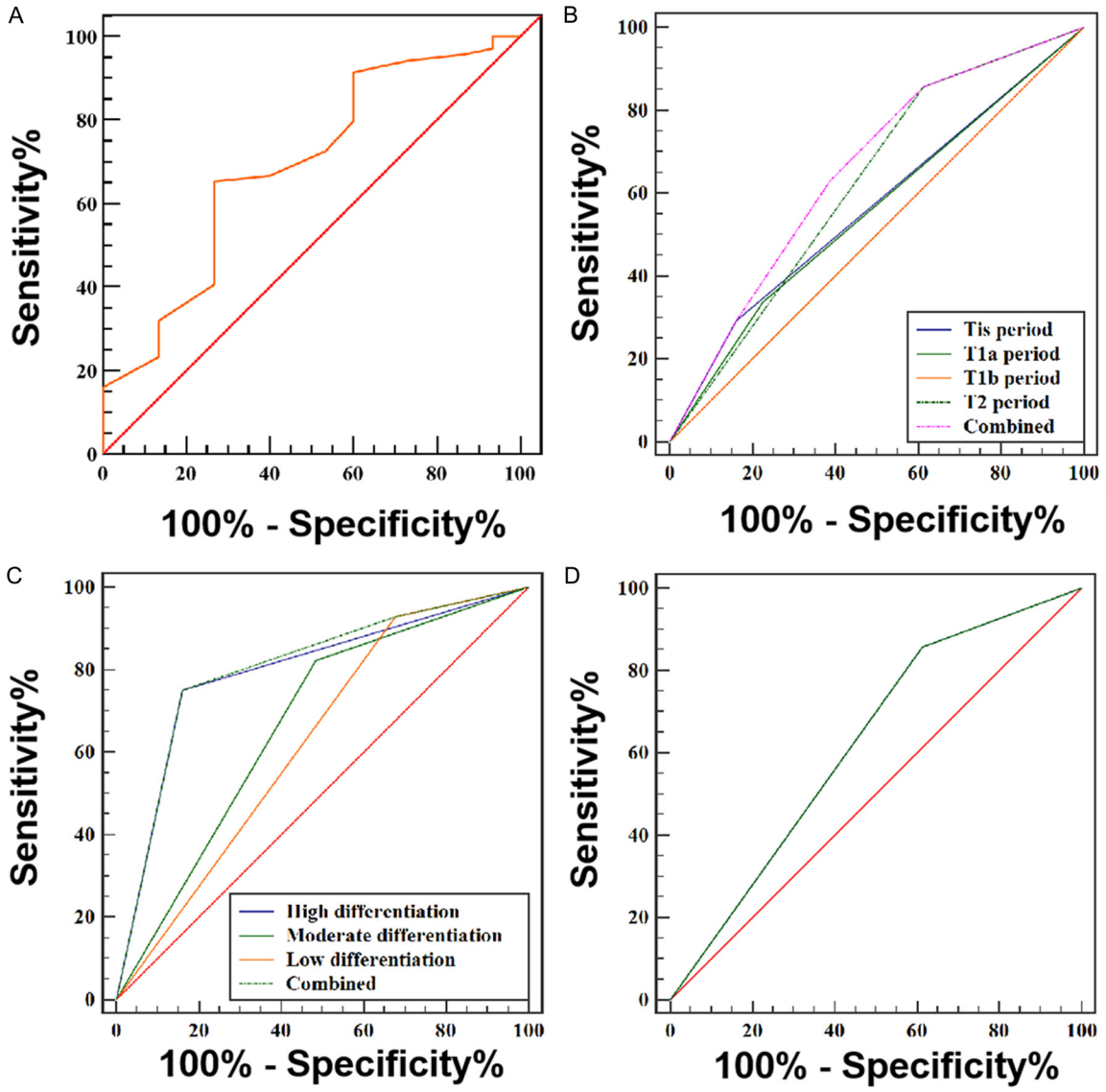

Figure 2. ROC curves for predicting prognosis in glottic laryngeal cancer patients. A: ROC curve of age in predicting prognosis; B: ROC curve of TNM stage in predicting prognosis; C: ROC curve of clinical stage in predicting prognosis; D: ROC curve of cumulative anterior commissure in predicting prognosis. Note: ROC: Receiver Operating Characteristic.

Table 5. Multivariate analysis results

	B	P	EXP (B)	Lower limit	Upper limit
Age	1.848	0.044	6.350	1.053	38.271
TNM staging	1.046	0.016	2.846	1.217	6.655
Clinical stages	1.708	0.005	5.516	1.679	18.122
Cumulative anterior commissure	2.790	0.009	16.284	1.995	132.95

Note: TNM: tumor-node-metastasis.

Age, TNM stage, clinical stage, and cumulative anterior commissure involvement were identified as prognostic risk factors for GLC recurrence. Based on these findings, appropriate preventive and control measures can be implemented in clinical practice.

Disclosure of conflict of interest

None.

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