

Age as Indicator in the Selection of Surgery Modalities in Early Glottic Cancer

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Purpose: Local failure after endoscopic laryngeal surgery (ELS) for early glottic cancer mounts a challenge to researchers to investigate risk factors of recurrence. The present study was therefore designed to explore the prognostic factors in patients who underwent ELS for early glottic cancer.

Patients and Methods: We reviewed 328 patients with T1-2N0 glottic cancer who were treated with either ELS or open surgery between 2007 and 2018 at our institution. Survival, univariate and multivariate analyses were performed in different groups (ELS vs open surgery; < 65 vs ≥ 65 years).

Results: Age was discovered to be the independent prognostic factor of DFS for patients treated with ELS (HR = 3.673, $p = 0.003$), but not for patients who underwent open surgery. Survival analysis performed on young patients (< 65 years) showed that survival outcomes between different surgery modalities were significantly different (ELS vs open surgery: five-year DFS: 72.5 vs 84.7%, $p = 0.034$). Univariate and multivariate analyses further confirmed the finding, whereas these results did not appear in old patients (≥ 65 years).

Conclusion: Young patients (< 65 years) treated with ELS had less favorable oncologic outcomes than those treated with open surgery. Young patients (< 65 years) are advised to consider open surgery over ELS.

Keywords: early glottic cancer, age, recurrence, prognostic factor, surgery

Introduction

Laryngeal squamous cell carcinoma is one of the most common cancers in head and neck.¹ Patients with laryngeal cancer are disproportionally males, and the most common subsite is glottis.^{2,3} Patients with glottic cancer often present with obvious hoarseness, which was conducive to early diagnosis and clinical intervention. Early glottic cancer, according to the extent of tumor and affected vocal cord, is subdivided into Tis, carcinoma *in situ*, T1a, confined to one cord, T1b, affects both cords, and T2, spreads beyond vocal cord or has cord mobility limited. For patients with early glottic cancer, organ-preserving treatment strategies such as radiotherapy and surgery are amenable.⁴ Five-year disease-free survival and overall survival of this population ranged between 74.9–92.8% and 80.0–96.0%, respectively.^{4–8} The wide variety of survival outcomes is primarily attributed to the distinction of T stage, treatment modality, comorbidity, etc.

Surgical larynx-preserving modalities mainly included endoscopic laryngeal surgery (ELS), open cordectomy and partial laryngectomy, and surgery can be provided as a single treatment modality for patients with early glottic cancer.⁹ Although most patients with early glottic cancer can achieve a satisfactory local

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control rate and overall survival, recurrence is still a major issue and keeps deviating patients from normal life. There are abundant studies aiming to investigate the prognostic factors of patients treated with radiotherapy,^{5,10–12} while studies in regard to the relationship of factors and relapse of patients treated with surgery are comparatively rare.

In our institution, laryngeal cancer has been mainly and primarily managed by ELS (mainly transoral CO₂ laser microsurgery) or partial laryngectomy. Since the superior vocal cord function can be achieved by ELS without the disruption of laryngeal surrounding anatomy, ELS has grown in popularity in recent years. We designed this study to find out the risk factors of recurrence for patients who underwent ELS for early glottic cancer, and we also investigated whether the risk factors were significant in patients treated with open laryngeal surgery.

Patients and Methods

We reviewed and collected the clinical information of patients who were diagnosed with early glottic cancer and treated with primary surgery between April 2007 and December 2018 in our institution. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the ethics committee of our institution. The enrollment criteria of our study were: (1) biopsy-proven squamous cell carcinoma; (2) glottic cancer; (3) treated with ELS or open surgery; (4) stage I or II disease; (5) negative surgical margin; (6) previously untreated. In total, we extracted information of 915 patients who were diagnosed with laryngeal cancer. With regard to exclusion criteria, we first excluded patients diagnosed with supraglottic or subglottic cancer (174), then patients with stage III or IV disease (270), and then those histologically confirmed with sarcoma (25), as well as those with missing follow-up information (107) and those with positive surgical margin (11). Finally, we incorporated 328 patients in this study (312 males and 16 females; mean age, 64 years; range, 22–83 years). The staging of tumor-node-metastasis (TNM) of patients was on the grounds of preoperative and operative findings, as well as post-operative pathological results. TNM was determined according to the 7th edition of the American Joint Committee on Cancer (AJCC) for glottic cancer.

Treatment of Patients

Treatment of patients was based on the conditions and willingness of patients, and the recommendation of the multidisciplinary team. Patients treated with surgery were able to tolerate general anesthesia and laryngoscopy

procedures. For tumor of T1a, T1b and selected T2 that could be exposed and visualized completely, ELS was preferred. For patients treated with ELS, a self-retaining laryngoscope was able to expose the whole lesion, and all of the tumor boundaries were included in the vision. Excision of the tumor was in accordance with the principles of surgical oncology. ELS was performed by a CO₂ laser combined with the operating microscope. The quantity of CO₂ laser power varied from 5 to 8 W.¹³ Laryngeal endoscopic cordectomy was in line with the classification as well as the revision suggested by the European Laryngological Society.¹⁴ The modalities of open surgery mainly included cordectomy, vertical partial laryngectomy, and supracricoid partial laryngectomy. The greater part of open neck partial laryngectomies in our institution were vertical partial laryngectomy and supracricoid partial laryngectomy. Negative margins were achieved in all of the patients enrolled in this study.

Follow-Up

After the completion of treatment, patients were followed up closely until December 2020 or until death for those who died. Recurrence was determined as locoregional recurrence and distant metastasis. In our study, recurrence was defined as recurrence that happened at any time after primary surgery without a date limit, and usually required re-resection. Disease-free survival (DFS) was calculated as the time from the day of pathology-confirmed diagnosis to the day of recurrence or the date of last follow-up for those freed from recurrence; OS was the time from the day of pathology-confirmed diagnosis to the date of death of any causes or the date of last follow-up; Locoregional recurrence-free survival (LRFS) was the time from diagnosis to the day of locoregional recurrence or the date of last follow-up for those freed from locoregional recurrence.

Statistical Analysis

All statistical analyses were performed by using SPSS software (IBM, version 25.0). We first carried out univariate and multivariate analyses in patients treated with ELS, and then in patients treated with open laryngeal surgery. Afterward, we divided all the patients into two groups (age, < 65 vs \geq 65 years), and performed survival, univariate and multivariate analyses in both groups. The relevance between classified variables and surgical modalities were analyzed by chi-square test. Factors including patient-related (age, gender, smoking history, drinking history), tumor-related (T stage, pathological grade) and

treatment-related (surgical modality) were analyzed. A two-sided P-value ≤ 0.05 was viewed as statistical significance.

Results

Univariate and Multivariate Analyses of DFS of Patients Treated with ELS

Among 328 patients, 220 were treated with ELS, 206 were males (93.6%) and 14 were females (6.7%). The median age of this group was 61 years (range 22–83 years). T1 was in 176 patients and T2 was in 44 patients. One hundred and fifty-three patients had a history of smoking, 59 patients had a history of drinking, while 58 patients were both smokers and drinkers. Forty-five patients developed locoregional recurrence, among them, five developed cervical lymph nodes metastases. Three patients progressed with distant metastasis (lung). Seven patients were diagnosed with other cancers synchronously or asynchronously (including esophageal, breast, rectal, lung, liver cancer, and non-Hodgkin lymphoma).

Univariate and multivariate analyses of DFS were carried out in patients treated with ELS. The results showed that age (< 65 vs ≥ 65 years, hazard ratio (HR) of 3.673, 95% confidence interval (CI): 1.557–8.664, $p = 0.003$) was an independent prognostic factor of DFS, while gender, T stage, pathological grade, smoking history and drinking

history were not related with DFS (Table 1). We then proceeded to establish whether age played the same role in patients who were treated with open surgery.

Univariate and Multivariate Analyses of DFS of Patients Treated with Open Laryngeal Surgery

Among 328 patients, 108 underwent open laryngeal surgery; 106 were men (98.1%) and two were women (1.9%). The median age of this population was 62 years (range 31–81 years). T1 was in 45 patients and T2 was in 63 patients. Eighty-two patients were heavy smokers, 40 patients were heavy drinkers, while 38 patients were both. Locoregional recurrence appeared in 15 patients, and three developed cervical lymph nodes metastases among them. One patient emerged with distant metastasis (bone). Seven patients were diagnosed with second cancer asynchronously (including esophageal cancer, lung cancer, pancreatic cancer, and nasopharyngeal cancer).

Univariate and multivariate analyses of DFS were conducted. The results showed that age, gender, T stage, pathological grade, smoking history and drinking history were not related with DFS of patients treated with open laryngeal surgery (Table 2).

Table 1 Univariate and Multivariate Analyses of DFS in Patients Treated with ELS

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, year				
< 65 vs ≥ 65	3.673 (1.557–8.664)	0.003	3.67 (1.557–8.664)	0.003
Gender				
Female vs male	2.032 (0.803–5.145)	0.135	NA	
T stage^a				
T1 vs T2	0.733 (0.372–1.445)	0.370	NA	
Pathological grade				
Good vs poor	0.774 (0.107–5.620)	0.800	NA	
Smoking				
Yes vs no	1.338 (0.679–2.636)	0.400	NA	
Drinking				
Yes vs no	1.841 (1.018–3.330)	0.043	NA	

Notes: ^aTumor-node-metastasis staging system proposed by the 7th edition American Joint Committee on Cancer (AJCC).

Abbreviations: ELS, endoscopic laryngeal surgery; DFS, disease-free survival; CI, confidence interval; HR, hazard ratio.

Table 2 Univariate and Multivariate Analyses of DFS in Patients Treated with Open Laryngeal Surgery

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, year				
< 65 vs \geq 65	1.257(0.399–3.965)	0.696	NA	
Gender				
Female vs male	NA		NA	
T stage^a				
T1 vs T2	1.654(0.562–4.871)	0.361	NA	
Pathological grade				
Good vs poor	0.392(0.087–1.759)	0.222	NA	
Smoking				
Yes vs no	1.943(0.437–8.641)	0.383	NA	
Drinking				
Yes vs no	1.992(0.722–5.494)	0.183	NA	

Notes: ^aTumor-node-metastasis staging system proposed by the 7th edition American Joint Committee on Cancer (AJCC).

Abbreviations: DFS, disease-free survival; CI, confidence interval; HR, hazard ratio.

Analyses above showed that age was an independent risk factor of DFS only for patients treated with ELS. The results illustrated that younger patients who underwent endoscopic procedures have an increased risk of recurrence. Furthermore, recurrence hazard of younger patients was the same as the older patients in open surgery group. Based on the results, we proposed a hypothesis that open laryngeal surgery can erase the effect of age. We then performed more analyses to confirm this hypothesis. The whole population was separated into two groups (age, < 65 vs \geq 65 years), and survival, univariate and multivariate analyses were conducted.

Survival, Univariate and Multivariate Analyses of Young Patients (< 65 Years)

We first extracted young patients (< 65 years) from the whole study population, and 216 patients were eligible for analysis. The median follow-up time was 68 months (range 2–155 months). The median age of this population was 57 years (range: 22–64 years). It was not a surprise to see that T stage was strongly correlated with surgery modality. Patients with T2 were predisposed to be treated with open laryngeal surgery, while patients with T1 were predisposed to be treated with ELS. However, the relationship between

smoking history and surgery modality was unexpected. The baseline characteristics were listed in Table 3.

Survival analysis showed that survival outcomes (DFS and LRFS) between the two groups (ELS vs open surgery) were significantly different in young patients (< 65 years). Five-year DFS was 72.5% in ELS group and 84.7% in open surgery group ($p = 0.034$), and five-year LRFS was 73.1% in ELS group and 84.7% in open surgery group ($p = 0.042$). However, the distribution of OS in two groups was similar (Table 4, Figure 1).

We further performed univariate and multivariate analyses in young patients, and the results demonstrated that surgery modality (ELS vs open surgery) was an independent prognostic factor of DFS, with hazard ratio of 2.027 (95% CI: 1.040–3.953, $p = 0.038$). While gender, T stage, smoking and drinking history etc. were not related with recurrence (Table 5).

Survival, Univariate and Multivariate Analyses of Old Patients (\geq 65 Years)

Afterward, we proceeded to investigate whether surgery modality exerts a prognostic influence on old patients. We then selected old patients (\geq 65 years) from the whole study population, and 112 patients were selected and analyzed. The median follow-up time of this population was

Table 3 Baseline Characteristics of Young Patients (< 65 Years)

Variable	ELS (N=144)	Open Surgery (N=72)	P value
Gender			0.345
Male	134	70	
Female	10	2	
T stage^a			0.000
T1	117	31	
T2	27	41	
Pathological grade			0.225
Well differentiated	141	68	
Poor differentiated	3	4	
Smoking history			0.039
Yes	99	59	
No	45	13	
Drinking history			0.216
Yes	42	27	
No	102	45	

Notes: ^aTumor-node-metastasis staging system proposed by the 7th edition American Joint Committee on Cancer (AJCC).

Abbreviation: ELS, endoscopic laryngeal surgery.

52.5 months (range 5–155 months). The median age was 70 years (range 65–83 years). The results showed that the relationship between T stage and surgery modality was robust. The baseline characteristics of old patients (≥ 65 years) are listed in Table 6.

Kaplan-Meier analysis indicated that the survival distribution of the two groups (ELS vs open surgery) was not significantly different in old patients (Table 4). Further univariate and multivariate analyses conducted in old patients also put forward negative results (Table 7). These results validated our hypothesis that open surgery can erase the effect of age.

Discussion

Endoscopic laryngeal surgery (ELS, mainly transoral CO₂ laser microsurgery), endowed with minimally invasive technology, is one of the valid surgical approaches for early glottic cancer. In contrast to conventional open laryngectomy and primary radiotherapy, the competitive edges of ELS include excellent local control, survival outcomes, and voice quality, as well as shorter hospital admission and lower mortality.^{15–18} Another benefit of ELS as reported by Moreau was that ELS facilitated the refinement of the TNM classification as certain carcinomas *in situ* were discovered to be invasive in

Table 4 Kaplan-Meier Analysis of Young and Old Patients

Young Patients (< 65 Years)					
Group	ELS (N=144)		Open Surgery (N=72)		P value
	3-Year	5-Year	3-Year	5-Year	
DFS	79.5%	72.5%	88.4%	84.7%	0.034
OS	97.2%	95.0%	98.6%	94.5%	0.509
LRFS	80.2%	73.1%	88.4%	84.7%	0.042
Old Patients (≥ 65 Years)					
Group	ELS (N=76)		Open Surgery (N=36)		P value
	3-Year	5-Year	3-Year	5-Year	
DFS	94.5%	90.4%	91.5%	91.5%	0.529
OS	93.0%	82.0%	82.4%	79.0%	0.114
LRFS	94.5%	90.4%	91.5%	91.5%	0.529

Abbreviations: ELS, endoscopic laryngeal surgery; DFS, disease-free survival; OS, overall survival; LRFS, locoregional recurrence-free survival.

endoscopic excision.¹⁹ Moreover, studies showed that in respect of cost-utility, ELS prevailed over RT for T1 glottic cancer.^{20,21} However, the limitations of ELS lie in the additional perioperative risks of general anesthesia, as well as relatively poor voice outcomes compared with RT.^{21,22} Based on the Surveillance, Epidemiology, and End Results (SEER) database, a study investigated the risks of second primary laryngeal cancer after initial surgery or RT, and showed a relative increased risk in the surgery group. However, the difference was not statistically significant.²³ The theory of field cancerization illustrates that nearby organ tissue (e.g. aerodigestive tract mucosa) are normally exposed to the same carcinogens such as alcohol, tobacco and HPV infection, and thus possess similar precancerous lesions as the primary. The presence of field cancerization inevitably increases the event of locoregional recurrence and second primaries.²⁴ Therefore, the single excision of the tumor performed by ELS may not be adequate to remove the lesion possessing similar genetic/epigenetic mutations.

Different from ELS, tissue resection in open surgery is complete and not confined by the extent of the tumor.⁹ Open partial laryngectomy is competent in obtaining excellent locoregional control without compromising the whole function of the larynx. A study showed that endoscopic excision succeeds in producing a decent survival outcome in most of cT2, but fails in tumor that upstaged as pT3 for involvement of the paraglottic space.²⁵ The failure in exposing the lesion adequately with direct laryngoscopy

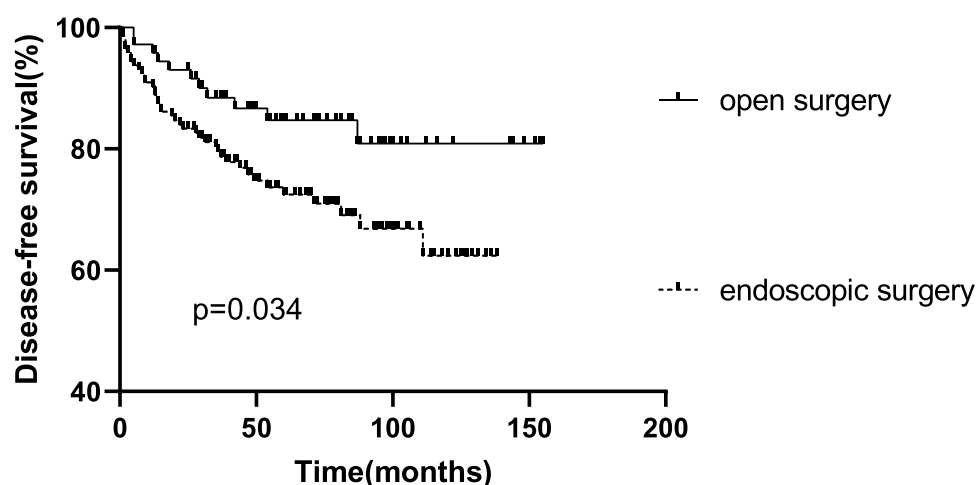


Figure 1 Kaplan-Meier curve of patients < 65 years.

and the involvement of anterior commissure hinder the use of endoscopic surgery for T2 glottic cancer and support open partial laryngectomy.^{26,27} The outstanding oncological outcomes achieved by open partial surgery justify its role in selected cT2 patients.²⁸ However, the inherent qualities of open surgery such as prolonged recovery and hospitalization duration, higher mortality, requirement of tracheostomy, worse quality of life after operation and deteriorated voice mean that this treatment option is

currently being supplanted.²⁸ Open surgery is now reserved for treatment of advanced stage laryngeal carcinoma, locoregional failure of radiation or ELS for early stage cancer. Before being relegated by endoscopic procedures, open laryngectomy had been the standard treatment for early glottic cancer for almost half a century.²⁹ We should wonder, with the overwhelming preference toward ELS over open surgery, whether the pendulum may have swung too far in the direction of endoscopic approaches.

Table 5 Univariate and Multivariate Analyses of Young Patients (< 65 Years) of DFS

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Surgery modality				
ELS vs open surgery	2.027(1.040–3.953)	0.038	2.027(1.040–3.953)	0.038
Gender				
Female vs male	2.265(0.898–5.714)	0.083	NA	
T stage ^a				
T1 vs T2	0.962(0.532–1.739)	0.898	NA	
Pathological grade				
Good vs poor	0.468(0.145–1.505)	0.203	NA	
Smoking				
Yes vs no	1.227(0.629–2.394)	0.548	NA	
Drinking				
Yes vs no	1.492(0.854–2.606)	0.160	NA	

Notes: ^aTumor-node-metastasis staging system proposed by the 7th edition American Joint Committee on Cancer (AJCC).

Abbreviations: DFS, disease-free survival; CI, confidence interval; HR, hazard ratio.

Table 6 Baseline Characteristics of Old Patients (≥ 65 Years)

Variable	ELS (N = 76)	Open Surgery (N = 36)	P value
Gender			0.303
Male	72	36	
Female	4	0	
T stage^a			0.000
T1	59	14	
T2	17	22	
Pathological grade			0.209
Well differentiated	73	32	
Poor differentiated	3	4	
Smoking history			0.445
Yes	54	23	
No	22	13	
Drinking history			0.125
Yes	17	13	
No	59	23	

Notes: ^aTumor-node-metastasis staging system proposed by the 7th edition American Joint Committee on Cancer (AJCC).

Abbreviation: ELS, endoscopic laryngeal surgery.

Our study unveiled that age was an independent prognostic factor of DFS of patients treated with ELS, and not in patients treated with open laryngeal surgery.

Furthermore, survival analysis showed that recurrence tendencies of the two groups (ELS vs open surgery) significantly differed in young patients (< 65 years), but did not differ in old patients (≥ 65 years). Therefore, we drew an intriguing conclusion that patients with early glottic cancer who are under 65 years old may be justified in choosing open laryngeal surgery, for it had a more satisfactory oncology outcome in terms of DFS.

Incorporating 1616 patients with laryngeal squamous cell carcinoma, a cohort study indicated that old patients (> 70 years) had a significantly lower risk of recurrence in both glottic and supraglottic cancer,³ which was coincident with our study. Another study enrolled a total of 590 patients with early-intermediate (cTis-cT3) glottic cancer who received transoral laser microsurgery, and discovered that age (< 60 vs ≥ 60 years) was significantly associated with recurrence-free survival, and the recurrence risk of young patients (< 60 years) was higher than old patients (≥ 60 years) specifically.³⁰ Analogously, Nomura et al. reported that relapse in the groups of T1b, T2, and T1-2 had a younger average age compared with the non-relapse groups, and age was independent of the other indicators and may be a useful prognostic factor.¹⁰ In contrast, a study of Rutkowski et al. suggested the opposite.³¹ The

Table 7 Univariate and Multivariate Analyses of Old Patients (≥ 65 Years) of DFS

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Surgery modality				
ELS vs open surgery	1.499(0.421–5.338)	0.532	NA	
Gender				
Female vs male	NA		NA	
T stage ^a				
T1 vs T2	0.445(0.126–1.578)	0.210	NA	
Pathological grade				
Good vs poor	NA		NA	
Smoking				
Yes vs no	1.811(0.383–8.558)	0.454	NA	
Drinking				
Yes vs no	2.927(0.846–10.124)	0.090	NA	

Notes: ^aTumor-node-metastasis staging system proposed by the 7th edition American Joint Committee on Cancer (AJCC).

Abbreviations: DFS, disease-free survival; CI, confidence interval; HR, hazard ratio.

different result may be attributed to the fact that Rutkowski et al. enrolled only patients with T2 cancer.

It is important to mention that patients afflicted with early glottic cancer are not a single entity, but a quite heterogeneous group with great complexity and possibility,³² and thus the treatment selection between open surgery and endoscopic approach of this population is intricate. Meticulous selection of the ideal patients who can benefit the most from ELS, and offering rigorous follow-up procedures to detect recurrence in time are recommended. More importantly, it is critical to cautiously evaluate the most suitable patients who can take the best advantage of open laryngeal surgery, and prevent the occurrence of a Pyrrhic victory. Although many recurrences at the glottis can be managed by endoscopic surgery repeatedly,³³ and open laryngectomy for early glottic cancer is being gradually substituted by endoscopic procedures, primary open surgery may still be the better choice for particular patients.²⁵ It is necessary to establish rigorous selection criteria on the grounds of tumor-related factors (size, extent, surgical margin status etc.), patient-related factors (age, gender, expectation, general condition etc.) and treatment-related factors (cost, efficacy, relevant sequelae etc.), so as to deliver patients with early glottic cancer pleasant oncological and functional results.

Since surgery is the standard care for early glottic cancer in our institution, as well as the inclination of patients toward endoscopic procedures when provided both ELS and RT, we lacked patients who were treated with radiotherapy in particular. Our study therefore failed to evaluate the prognostic factors of patients treated with radiotherapy, as well as to investigate the comparison of radiotherapy and surgery in respect of oncologic and functional outcomes. Furthermore, due to the retrospective nature of our study and the lack of relevant medical records, other risk factors such as anterior commissure involvement, HPV status, tumor size and vocal cord immobility could not be evaluated.

Conclusion

The results of this study suggested that young patients with early glottic cancer should choose surgical alternatives (ELS vs open surgery) cautiously. Patients who are under 65 years are advised to choose open laryngectomy over endoscopic approaches, but more prospective studies are required to draw any concrete conclusions.

Ethics Statement

This study was conducted under the principle of the Institutional Review Board at Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University (ethics approval number: SYSEC-KY-KS-2021-059). The present study was conducted retrospectively and did not interfere in the treatment of patients. The paper contains no patients' identifiable features, thus informed consents of the participants in the study were waived.

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Disclosure

The authors report no conflicts of interest in this work.

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