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Survival analysis of distant metastasis of laryngeal carcinoma: analysis based on SEER database

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Abstract

Background The purpose of this study was to investigate the prognostic factors and the value of surgical treatment of patients with newly diagnosed laryngeal cancer with distant metastasis (DM).

Methods The Surveillance, Epidemiology and End Result database (SEER) was used to analyze 446 patients with laryngeal cancer with DM at the time of initial diagnosis from 2010 to 2014.The survival prognosis of patients with DM was performed by using Kaplan–Meier and log-rank test. The prognostic factors and the effect of surgery were analyzed using the Cox regression analysis and R-language data package.

Results The incidence of DM was 3.21% (446/13865). Lung was the most common distant metastatic site of laryngeal cancer (62.6%), and brain metastases had the worst prognosis in patients at 2 months. T stage and brain metastasis were independent risk factors affecting the survival ($P < 0.05$). The hazard ratio (HR) of DM in T4 stage was nearly twice than that in T1 stage. Surgical treatment of primary and metastatic tumors can cause better survival for patients. Patients who didn't underwent primary tumor surgery were approximately twice as likely to die from cancer as those who did. The nomogram model was constructed to visually present the 1-, 2- and 3-year survival rates of patients.

Conclusions T stage, brain metastasis and surgical treatment are prognostic factors of patients with M1 stage laryngeal cancer. Surgical treatment of primary tumors and metastases can lead to better survival for patients.

Trial registration Not applicable.

Keywords Laryngeal cancer · Distant metastasis · SEER · Prognosis · Surgical treatment

Abbreviations

DM	Distant metastasis
SEER	The Surveillance, Epidemiology and End Result database
OS	Overall survival
CSS	Cancer-specific survival
HR	Hazard ratio
95% CI	95% confidence interval
MST	Median survival time
KPS	Karnofsky score

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Introduction

In the past 20 years, with the advancement of medical technology and the reduction of smoking population, the incidence of laryngeal cancer has decreased year by year, but the mortality rate has increased [1, 2]. As a localized disease, the incidence of distant metastasis (DM) of laryngeal cancer is low. But once it occurs, it will be an important factor affecting the outcome of the disease. Researches on DM of laryngeal cancer have been relatively scarce. Previous studies were almost all based on small, single-institutional patient cohorts for case review, which obviously restricted

the subgroup analyses and stratified studies. As we know, the epidemiological data on initial laryngeal cancer with DM are basically blank.

This study was intended to use the Surveillance, Epidemiology and End Result database (SEER) to identify the prognostic factors that influence the outcome of DM patients. Among the factors, we focused on the impact of surgical and non-surgical treatment on patients' survival for the first time. Finally, we attempted to quantify the patient's individual survival with the nomogram visualization model. Therefore, it will be helpful for the clinical treatment decision and basic research on this part of special population.

Materials and methods

Study population

First, a total of 14,706 patients with a confirmed diagnosis of laryngeal cancer were screened out from the SEER database from 2010 to 2014. With the exclusive cases of an unknown origin and survival time, incomplete follow-up time, unknown diagnostic source information and non-squamous cell carcinoma, there were still 13,865 cases. Among them, there were 446 patients with DM. The follow-up time ranged from 12 to 60 months.

Variables' analysis included diagnosis of age, gender, race, marital status, insurance status, tumor location, TNM classification system (AJCC, 7th edition, 2010), Fuhrman grade, metastatic sites and treatment measures. According to tumor location, patients were divided into five groups: "Glottis", "Supraglottis", "Subglottis", "Larynx, NOS" and "Other". Fuhrman grade was divided into five groups: "Well differentiated (Grade I)", "Moderately differentiated (Grade II)", "Poorly differentiated (Grade III)", "Undifferentiated (Grade IV)" and "Unknown". Treatment modality was divided into surgical group and non-surgical group. Surgical treatment included primary tumor surgery and metastasectomy. Distant metastatic sites included bone, brain, liver and lung. The subsequent information on survival status, survival duration and causes of death was extracted from the database.

In terms of racial classification, it was mainly divided into black, white and others, considering there were a few ethnic groups that had fewer cases, such as Asian and Latino. They were no longer subdivided and merged into the other groups. Among the code, larynx cartilage and overlapping lesion of larynx were not the focus of discussion, because they were not common in clinical classification and with the less number of cases that were classified in the other items. According to the surgery codes, primary tumor surgery includes "local tumor destruction or excision", "subtotal or partial laryngectomy" and "total or radical laryngectomy".

Statistical analysis

Univariate analysis of the above variables was performed by Kaplan–Meier method, and the survival curves of overall survival (OS) and cancer-specific survival (CSS) were calculated. The variables with P value < 0.1 of OS in the log-rank test were included in the multivariate analysis. Cox proportional hazards regression model was performed to evaluate independent risk factors of tumors and the hazard ratio (HR) and 95% confidence interval (CI) calculated. P value < 0.05 was considered statistically significant. The above analysis was performed by using the SPSS 20.0 software package (IBM Corporation, Armonk, NY, USA).

When there was a competitive risk event in the data, the risk model could analyze the survival data of multiple potential outcomes, which was better than the K–M method and Cox regression model to some extent. We constructed the competitive risk model to objectively compare survival differences between surgical and non-surgical patients. Furthermore, the nomogram visualization model was established to present patients with 1-, 2- and 3-year survival rates. The above analysis was performed by using the R-language data package (Version 3.4.3 R Foundation).

Results

Patients' statistical characteristics

There were a total of 446 patients in the SEER database that met the screening criteria during 2010–2014. With 65-year-old as the dividing line, the distributions of the upper and lower intervals were roughly similar. The ratio of males to females was about 4.1:1; 80.3 and 19.7% were male and female. Among the cohort with metastatic disease, white, married and insured were the majority, with 332 (74.4%), 290 (65.0%) and 415 (93.0%), respectively. As for the tumor location and TNM stage, 257 (57.6%) was supraglottic type, 163 (36.5%) was T4 stage and 236 (52.9%) was N2 stage. Among the entire cohort, Fuhrman grade was mainly in the middle and low differentiation, 168 (37.7%) patients were on Grade II stage and 137 (30.7%) patients were on Grade III stage.

On K–M analysis, the differences in age, gender, tumor location, T stage (Fig. 1a), N stage and Fuhrman grade were statistically significant on OS ($P < 0.1$) (Table 1). On multivariate analysis, age, gender and T stage were independent prognostic factors for OS ($P < 0.05$), including under 65-year-old (VS ≥ 65-year-old; HR, 1.246, 95%

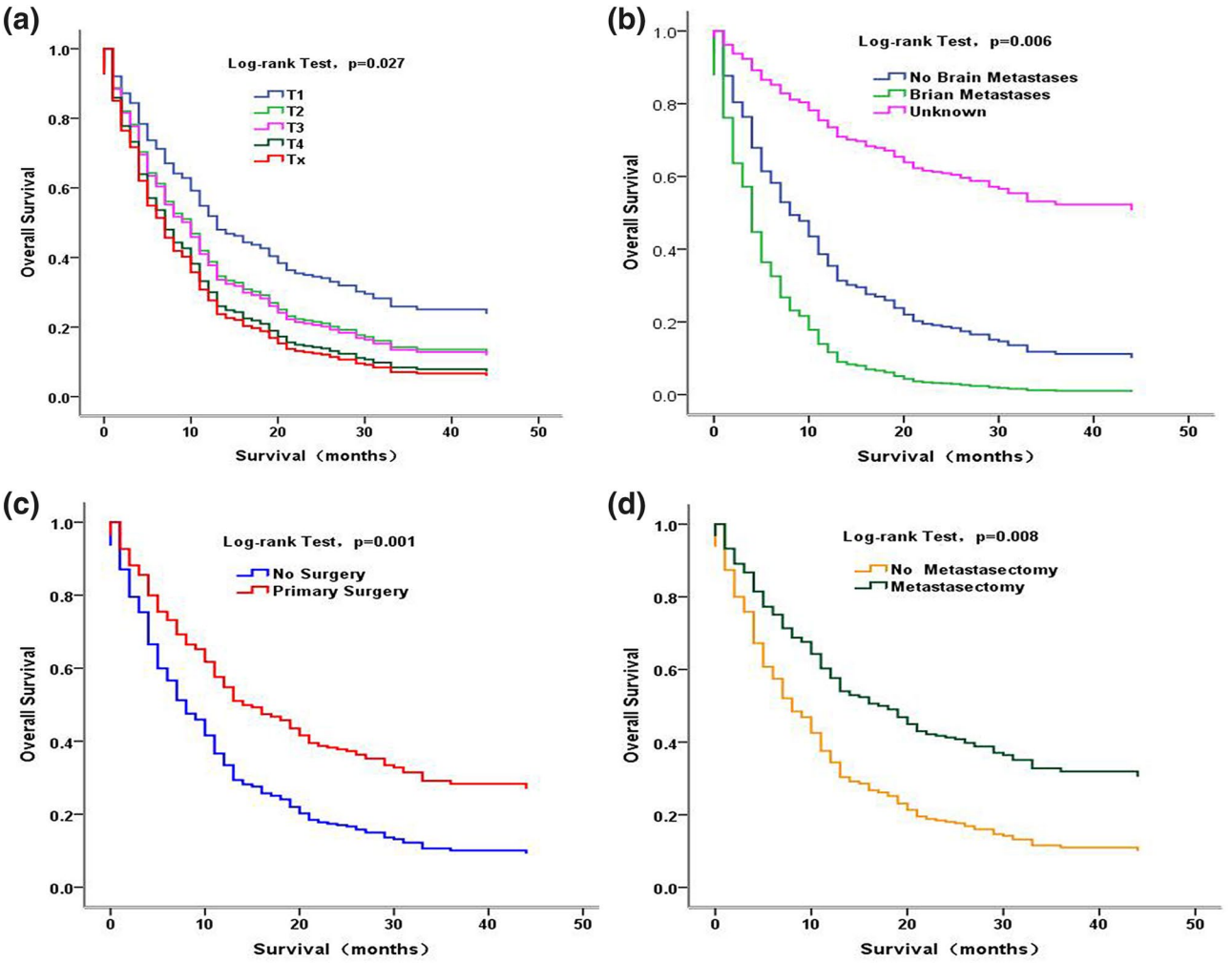

Fig. 1 Kaplan–Meier curves of overall survival among patients with laryngeal cancer and distant metastases at diagnosis. **a** Survival stratified according to the T stage of tumor. **b** Survival stratified according to having or not having brain metastases. **c** Survival stratified according to whether or not primary tumor surgery has been done for patients. **d** Survival stratified according to whether or not metastasectomy has been done for patients

CI 1.00–1.55, $P=0.049$), female (VS male; HR, 0.717, 95% CI 0.54–0.96, $P=0.025$), T2 stage (VS T1 stage, HR, 1.433, 95% CI 0.91–2.27, $P=0.123$), T3 stage (VS T1 stage, HR, 1.471, 95% CI 0.94–2.31, $P=0.093$) and T4 stage (VS T1 stage, HR, 1.939, 95% CI 1.26–2.99, $P=0.003$). Results revealed that only T stage was the independent risk factor on CSS ($P=0.013$), including T2 stage (VS T1 stage, HR, 1.378, 95% CI 0.85–2.22, $P=0.189$), T3 stage (VS T1stage, HR,1.441, 95%CI,0.90–2.30, $P=0.126$) and T4 stage (VS T1 stage,HR, 1.864, 95% CI 1.19–2.93, $P=0.007$) (Table 2).

Distribution and survival analysis of distant metastases sites

The incidence of DM of laryngeal cancer was 3.21% (446/13,865). The most common site of metastasis was lung with 279 (62.6%) cases, 72 (16.1%) patients were diagnosed with bone metastases, 47 (10.5%) patients were with liver metastases, and only 6 (1.3%) patients had brain metastases. Most of the patients in the cohort had only one metastatic site, 301 (67.5%), 42 (9.4%) and 6 (1.3%) patients had one, two and three metastatic sites, respectively. No patients

Table 1 Incidence proportion and median survival of patients with distant metastases of laryngeal carcinoma (Kaplan–Meier method and log-rank test)

Variable	Incidence proportion of distant metastases $N=446$ (n%)	Median survival time of OS[a], months 95% CI[c]	P (OS)	Median survival time of CSS[b], months 95% CI	P (CSS)
Age at diagnosis, years			0.094		0.155
< 65	221 (49.7%)	10.00 (7.93–12.07)		11.00 (8.832–13.168)	
> 65	225 (50.4%)	8.00 (5.74–10.26)		9.00 (7.058–10.942)	
Gender			0.033		0.076
Male	358 (80.3%)	8.00 (6.61–9.39)		9.00 (7.651–10.349)	
Female	88 (19.7%)	12.00 (9.77–14.23)		13.00 (11.397–14.606)	
Race			0.812		0.798
Black	98 (22.0%)	8.00 (5.60–10.40)		10.00 (6.295–13.705)	
White	332 (74.4%)	9.00 (7.48–10.52)		10.00 (8.357–11.643)	
Other	16 (3.6%)	8.00 (6.68–9.32)		10.00 (6.304–13.696)	
Marital status			0.532		0.557
Unmarried	139 (31.2%)	9.00 (6.80–11.20)		10.00 (7.272–12.728)	
Married	290 (65.0%)	8.00 (6.26–9.74)		10.00 (8.427–11.573)	
Unknown	17 (3.8%)	7.00 (5.76–8.24)		7.00 (5.759–8.241)	
Insurance status			0.770		0.717
Uninsured	24 (5.4%)	8.00 (3.31–12.70)		10.00 (6.573–13.427)	
Insured	415 (93.0%)	9.00 (7.53–10.47)		10.00 (8.503–11.497)	
Unknown	7 (1.6%)	7.00 (6.25–7.75)		7.00 (6.246–7.754)	
Tumor location			0.040		0.114
Glottis	76 (17.0%)	11.00 (7.246–14.75)		12.00 (8.742–15.258)	
Supraglottis	257 (57.6%)	8.00 (6.10–9.90)		10.00 (8.170–11.830)	
Subglottis	13 (2.9%)	12.00 (6.49–17.51)		12.00 (7.349–16.651)	
Larynx, NOS	78 (16.7%)	7.00 (4.64–9.36)		8.00 (5.535–10.465)	
Other	22 (4.7%)	6.00 (0.00–12.10)		10.00 (6.472–13.528)	
Fuhrman grade			< 0.001		< 0.001
Grade I	15 (3.4%)	20.00 (0.00–41.80)		20.00 (0.00–41.80)	
Grade II	168 (37.7%)	10.00 (7.57–12.43)		12.00 (9.81–14.19)	
Grade III	137 (30.7%)	8.00 (6.01–9.99)		9.00 (6.89–11.11)	
Grade IV	2 (0.4%)	NA[d]		NA	
Unknown	124 (27.8%)	7.00 (4.35–9.65)		9.00 (6.394–11.606)	
T stage			0.027		0.035
T1	44 (9.9%)	13.00 (7.51–18.50)		16.00 (1.71–30.29)	
T2	98 (22.0%)	10.00 (7.25–12.75)		11.00 (7.56–14.44)	
T3	116 (26.0%)	11.00 (7.67–14.34)		11.00 (7.71–14.29)	
T4	163 (36.5%)	7.00 (5.73–8.27)		8.00 (6.31–9.69)	
Tx	25 (5.6%)	10.00 (6.59–13.41)		10.00 (6.59–14.41)	
N stage			0.047		0.066
N0	85 (19.1%)	11.00 (9.12–12.88)		12.00 (9.54–14.46)	
N1	84 (18.8%)	11.00 (7.52–14.48)		11.00 (7.78–14.23)	
N2	236 (52.9%)	7.00 (5.63–8.37)		8.00 (6.13–9.88)	
N3	33 (7.4%)	7.00 (3.95–10.05)		7.00 (3.95–10.05)	
Nx	8 (1.8%)	10.00 (6.21–13.79)		10.00 (6.21–13.79)	
Primary tumor surgery			0.001		0.002
No	392 (87.9%)	8.00 (6.62–9.38)		9.00 (7.62–10.38)	
Yes	54 (10.4%)	19.00 (10.79–27.21)		19.00 (10.21–27.79)	
Metastasectomy			0.008		0.005
No	418 (93.7%)	8.00 (6.676–9.324)		9.00 (7.59–10.41)	

Table 1 (continued)

Variable	Incidence proportion of distant metastases *N* = 446 (*n*%)	Median survival time of OS[a], months 95% CI[c]	*P* (OS)	Median survival time of CSS[b], months 95% CI	*P* (CSS)
Yes	28 (6.3%)	14.00 (10.05–17.95)		16.00 (0.47–31.54)	
Metastasis sites					
Bone	72 (16.1%)	5.00 (3.59–6.42)	< 0.001	6.00 (2.88–9.12)	< 0.001
Brain	6 (1.3%)	2.00 (0.00–6.80)	0.006	2.00 (0.00-6.80)	0.004
Liver	47 (10.5%)	6.00 (3.22–8.78)	0.017	7.00 (0.92–13.08)	0.040
Lung	279 (62.6%)	8.00 (6.53–9.47)	0.009	9.00 (7.45–10.55)	0.011
Metastases			< 0.001		< 0.001
One site	301 (67.5%)	8.00 (6.66–9.34)		10.00 (8.60–11.40)	
Two sites	42 (9.4%)	4.00 (0.61–4.77)		4.00 (3.11–4.89)	
Three sites	6 (1.3%)	4.00 (0.61–7.40)		4.00 (0.00–14.80)	

[a]Overall survival

[b]Cancer-specific survival

[c]95% confidence interval

[d]No applicable

Table 2 Multivariate Cox regression analysis of independent prognostic factors affecting patient survival (forward LR method)

	OS[a]		CSS[b]	
	P	HR (95% CI)[c]	*P*	HR (95% CI)[c]
Age at diagnosis, years	0.049	1.246 (1.001–1.551)	NA	
Gender	0.025	0.717 (0.537–0.958)	NA	
T stage	0.014	NA[e]	0.013	NA
T1	NA	Reference	NA	Reference
T2	0.123	1.433 (0.907–2.265)	0.189	1.378 (0.854–2.222)
T3	0.093	1.471 (0.938–2.307)	0.126	1.441 (0.902–2.300)
T4	0.003	1.939 (1.259–2.985)	0.007	1.864 (1.187–2.927)
Surgery[d]	0.001	0.530 (0.360–0.780)	0.007	0.573 (0.383–0.856)
Brain metastases	0.001	1.267 (1.107–1.451)	0.008	1.176 (1.043–1.326)
Liver metastases	0.016	1.129 (1.023–1.245)	NA	

[a]Overall survival

[b]Cancer-specific survival

[c]Hazard ratio (95% confidence interval)

[d]Primary tumor surgery

[e]Not applicable

were found to have four metastatic sites at the same time (Table 1).

On univariate analysis, four metastatic sites were statistically significant on OS and CSS ($P < 0.1$). Among the cohort, lung metastasis in patients experienced the longest median survival time (MST) and the prognosis of brain metastasis was the worst, experiencing the shortest MST (Fig. 1b). On multivariable Cox regression (Table 2), brain metastasis and liver metastasis were independent risk factors affecting OS, brain metastasis (VS without brain metastasis, HR, 1.267, 95% CI 1.11–1.45, $P = 0.001$) and liver metastasis (VS without liver metastasis,HR, 1.129, 95% CI 1.02–1.25, $P = 0.016$). For CSS, only brain metastasis was the independent risk factor among patients with metastatic cancer, brain metastasis (VS without brain metastasis, HR, 1.176, 95% CI 1.04–1.33, $P = 0.008$).

Survival outcomes of surgeries to primary sites and metastatic sites

Among the entire cohort, 54 (12.1%) patients received primary tumor surgery and 28 (6.3%) patients had metastasectomy. For primary tumor surgery, 23 patients had local tumor destruction or excision, 5 patients had subtotal

or partial laryngectomy and 26 patients had total or radical laryngectomy. From K–M analysis (Fig. 1c), results revealed that the prognosis of patients undergoing primary tumor surgery was significantly better than the patients who did not receive surgery. It was also confirmed that patients undergoing surgery had better CSS from the data in Table 1. On multivariate analyses, it was shown that primary tumor surgery was a protective factor for CSS (VS without primary tumor surgery: HR, 0.573, 95% CI 0.38–0.86, $P=0.007$).

Although on multivariable Cox regression, metastasectomy was not an independent factor for laryngeal cancer patients with DM ($P>0.05$), we found that the survival outcomes of patients who received metastasectomy were much better than those who did not undergo metastasectomy (Table 1). The K–M analysis (Fig. 1d) also demonstrated a significant survival advantage in patients who underwent metastasectomy.

On the competitive risk model of primary tumor surgery (Fig. 2a), patients who did not receive surgery were associated with significantly higher cancer-specific mortality than surgical patients ($P=0.007$). Also, compared with patients who underwent metastasectomy, the cumulative mortality rate of patients who did not undergo metastasectomy was higher ($P=0.007$) (Fig. 2b).

Construction of prognosis model for distant metastasis of laryngeal cancer (nomogram model)

According to the results of multivariable Cox regression and clinical experience, we selected meaningful and easily accessible factors to construct the nomogram model. The influencing factors incorporated in the nomogram model were age, gender, tumor classification, T/N stage and primary surgery. The classification of each factor has its own corresponding score. For example, the female in the gender scores 0 points, male's score is 53 points and the total score for all factors is 450 points. According to the corresponding scores, 1-year survival rate, 2-year survival rate and 3-year survival rate can be obtained, respectively. If the score is 200, the 1-year survival rate is 56%, the 2-year survival rate is 40% and the 3-year survival rate is 30% (see Fig. 3).

Discussion

In our study, we found that: (1) the incidence of newly diagnosed laryngeal cancer with DM was 3.21%; (2) the majority of patients were of supraglottic type and N2 stage, with 257 (57.6%) and 236 (52.9%), respectively, but tumor location and N stage were not independent risk factors influencing the prognosis of M1 stage laryngeal cancer; (3) on multivariate analysis, only T stage, brain metastasis and primary tumor surgery were independent factors affecting the prognosis of patients with DM.

On multivariate analysis, age and gender were the prognostic factor of OS ($P<0.05$), with elderly patients and female patients obtaining a longer overall survival. However, the differences in the influence on CSS were not statistically significant ($P>0.05$). Equivalency of CSS was likely explained by correction for differences in grade and stage

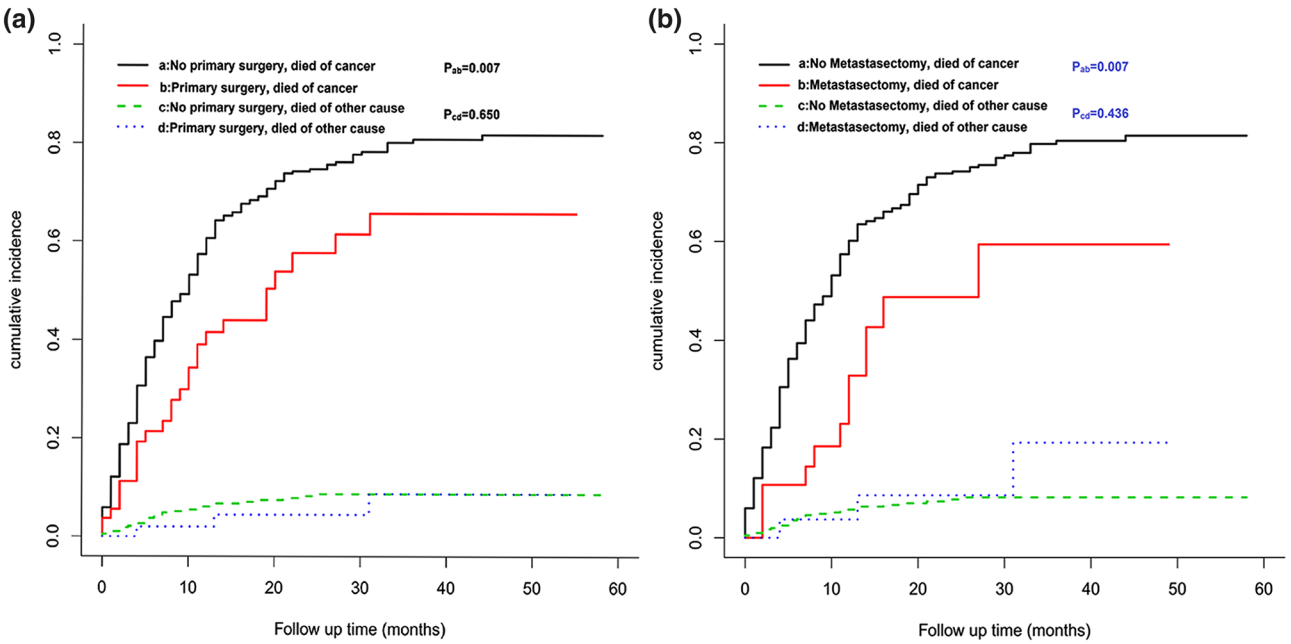

Fig. 2 Competing risk curve of cancer-specific survival among patients with laryngeal cancer and distant metastases at diagnosis

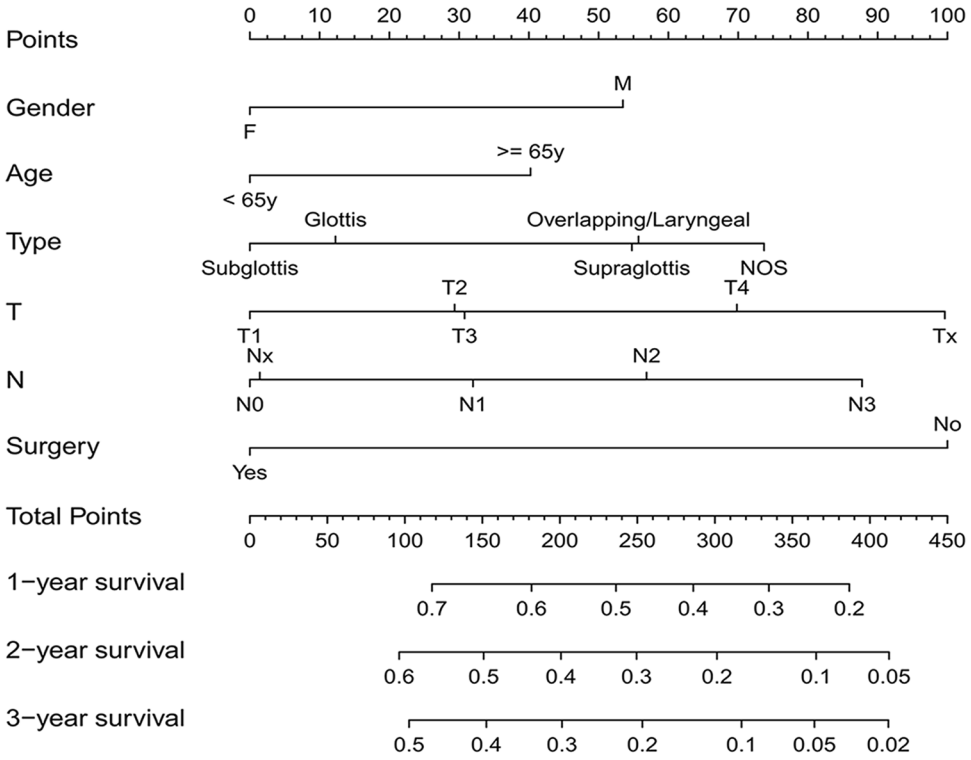

Fig. 3 Nomogram model of patients with laryngeal cancer and distant metastases at diagnosis

with multivariate analysis. Therefore, we speculated that the effect of age and gender on the prognosis of laryngeal cancer with DM is more due to the lower Karnofsky score (KPS), lifestyle, cerebrovascular accident and other non-tumor factors, rather than the tumor itself.

Consistent with the results of other studies, supraglottic type was the most common site among patients with metastatic cancer [3–6], with 257 cases (57.6%). Steuer et al. suggested that patients with supraglottic type was more likely to die from tumor than other types, and the survival rate was reduced due to the high incidence of regional metastases [6]. In the analysis of laryngeal carcinoma with DM, both OS and CSS of supraglottic type were poor. Unlike most studies which indicated that the location of tumor was a determinant of DM of laryngeal cancer [5–8], the effect of tumor location on the prognosis of CSS was not statistically significant on K–M analysis ($P = 0.114$) in our study. On multivariate analysis, tumor location was not an independent risk factor for OS either ($P > 0.05$). Therefore, it could be concluded that the location of laryngeal cancer had little effect on the survival and prognosis of patients with DM.

Most studies have proposed a similar viewpoint that the later the T stage and the greater the depth and extent of tumor, the more likely it was that the patient would have DM in laryngeal cancer [7, 9–14]. On multivariable Cox regression, T stage was an important factor affecting OS and CSS ($P < 0.05$), with metastases being more common in T4 and T3 stage. In addition, we also found that T4 tumors were an absolute risk factor for DM. Once diagnosed with T4 tumors, the relative risk of DM is two times that of patients with T1 tumors. This was one of the few evidences of objectively quantifying the risk of T4 stage.

Some studies have reported that N2 and N3 patients had a threefold increased rate of DM compared with the early N stage. N stage was an important risk factor for determining whether or not laryngeal cancer had DM [7, 9, 10, 13–17]. There were other opinions that the traditional N stage was not applicable to assess the risk of DM in patients. The number of cervical metastatic lymph nodes was the predictor of DM of laryngeal cancer, especially when the number of pathologically positive lymph nodes was more than 3 [4, 5, 18, 19]. In our study, we found that N2 and N3 stages accounted for more than 60% of M1 stage patients. However, N stage was eliminated early on Cox regression analysis (follow: LR method), which indicated that N stage had no value for the survival and prognosis of M1 stage patients.

For patients with DM, surgery has been controversial and the standard treatment in the guidelines was chemoradiotherapy rather than surgery. At present, there is still no relevant study to clearly indicate whether there is difference between surgical and non-surgical methods for the survival of patients with DM of laryngeal cancer. Among the 446 patients in our study, 54 (12.1%) had primary tumor surgery. We found that compared to non-surgical patients, patients undergoing primary tumor surgery showed a clear survival advantage. On multivariate

analysis, primary tumor surgery was also a good protection factor for cancer-specific survival. The relative risk of death of surgical patients was only half that of non-surgical patients.

Shiono et al. analyzed 114 patients with primary lung metastases of head and neck squamous cell carcinoma and determined that the MST of patients receiving resection of lung metastases was extended by 26 months and the 5-year OS rate increased by 26.5% [20]. Although metastasectomy was not a protective factor for patients of laryngeal cancer with DM, patients undergoing metastasectomy had better CSS than non-metastasectomy patients. With the extension of follow-up time, the survival advantage was more obvious. Therefore, we believe that patients who have been screened through certain conditions are entirely likely to have a better survival outcome.

In addition to assessing the risk of DM in patients with laryngeal cancer, we also included these factors into the nomogram model for further analysis to better determine the prognosis in the clinical work. This was the first known quantitative estimate of the survival rate of M1 stage laryngeal cancer. In the model, we could estimate the specific 1-, 2- and 3-year survival rate according to the clinical data of patients, thus providing assistance for clinical decision-making.

Limitations

The limited information provided in the SEER database has limited our research. First of all, we were able to identify only the patients with DM of laryngeal squamous cell carcinoma at initial diagnosis, some of whom were merely a part of the DM. The SEER database did not provide information about disease recurrence or subsequent sites of disease involvement; thus, we were unable to analyze patients who developed DM after treatment or later in their disease course. Therefore, some patients who developed DM during subsequent illnesses could not be captured in our analysis. Secondly, the KPS of patients were unrecorded in the SEER database, and the performance status will inevitably bring about a certain bias to the prognosis of the surgical patients.

Author contributions YP: formal analysis, project administration, writing original draft, and writing review and editing. YH: design of the epidemiological investigation and formal analysis. ZL: conceptualization, supervision, data curation and validation. WZ: data curation, methodology, software, project administration, and writing review and editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate All procedures performed in studies involving human participants conform to the standards of the institutional and national ethics committees, as well as to the 1964 Helsinki Declaration and subsequent relevant ethics. Patient informed consent is not required to extract data from the SEER database.

Consent for publication All authors are informed and consent for publication.

Availability of data and material All data were acquired from the SEER database. We obtained the authorization to access the SEER database with the number 14260-Nov2016.

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