Original Article

Retrospective analysis of risk factors for lymph node metastasis in recurrent glottic cancer after primary laser surgery: a cohort study from China

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Background: Although lymph node metastasis is a critical prognostic factor, the indications for neck dissection in recurrent glottic cancer after transoral laser microsurgery (TLM) are unclear. At present, there is no clear standard for simultaneous cervical lymph node dissection at home and abroad.

Methods: We summarize the pattern of regional recurrence in glottic cancer after initial TLM and to evaluate the risk factors for neck metastasis. Seventy-five cases with recurrent glottic cancer after TLM between December 2004 and June 2014 were retrospectively analyzed. Survival, regional control rate, and neck metastasis were analyzed. The Kaplan-Meier method was used for survival analysis. Univariate analysis was performed with the log-rank test and multivariate analysis was completed using Cox regression.

Results: The 5-year overall survival (OS), disease-specific survival (DSS), and regional control rate after the first TLM were 73.6%, 89.1%, and 69.7%, respectively. A total of 22 (29.3%) patients developed cervical metastases during long-term follow-up and showed a significant decline in OS and DSS rates. Multivariate analysis indicated that histological grading and type of TLM were both risk factors for neck metastasis. Patients treated with type Vc cordectomy were more likely to develop regional recurrence than patients treated with type III cordectomy [hazard ratio (HR) =14.737, 95% confidence interval (CI): 2.117–102.610, P=0.007]. No significant correlation was present between rT stage and neck metastasis.

Conclusions: Multivariate analysis indicated that histological grading and type of TLM were both risk factors for neck metastasis. Patients with recurrence after type V cordectomy may have an increased risk of developing cervical lymph node metastasis, especially those with supraglottic spread or high-grade tumors.

Keywords: Laryngeal cancer; cervical lymph node metastasis; transoral laser microsurgery (TLM)

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Introduction

Laryngeal cancer is one of the most common tumors in the head and neck region. In many institutes, transoral laser microsurgery (TLM) is the preferred treatment for early and selective advanced laryngeal carcinoma. The local control and laryngeal preservation rate of T1–T2 glottic carcinoma after TLM is about 80% to 100% (1), equivalent to that after radiotherapy.

Despite the multidisciplinary progress in treatment strategies, the 5-year survival rate for laryngeal cancer has decreased in the past 4 decades (2). Cervical lymph node metastasis is widely considered to be a critical prognostic

factor, and the long-term survival rate is reduced by 50% when it occurs (3). When the risk of lymph node metastasis exceeds 15–20%, elective neck dissection is considered. For primary glottic cancer, the risk of neck metastasis does not exceed 20% until tumors are stage T3 or greater (4). When choosing TLM for cT1–T2N0 glottic carcinoma, neck dissection can be avoided in most cases. In the case of local recurrence, previous treatment might change the innate structure, and whether neck dissection should be performed concurrently is still unclear (4). Recurrent laryngeal cancer can be treated with repeat TLM, partial laryngectomy, total laryngectomy, or radio/chemotherapy, depending on the extent of the disease as well as the patient's wishes. When a salvage operation is planned, lymph node status and relative influencing factors still need to be clarified to determine when neck dissection should take place. At present, there is no clear standard for simultaneous cervical lymph node dissection at home and abroad.

The purpose of this study was to retrospectively analyze the pattern of regional recurrence in glottic cancer after the first TLM. The rate of lymph node metastasis and the risk factors of neck metastasis are presented. We present the following article in accordance with the STROBE reporting checklist (5) (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3385/rc).

Methods

Between December 2003 and June 2012, 838 patients with glottic cancer underwent laser surgery at our hospital. There were 46 cases of TisN0M0, 603 cases of T1aN0M0, 77 cases of T1bN0M0, and 112 cases of T2N0M0. After a mean follow-up of 18 months (range, 1.5–52 months), 75 cases (between December 2004 and June 2014) were diagnosed with local-regional recurrence and received a salvage operation. According to the 2017 American Joint Committee on Cancer (AJCC) TNM system, 4 of the 75 cases were classified as TisN0M0, 42 were T1aN0M0, 9 were T1bN0M0, and 20 were T2N0M0 at the first operation. A total of 27 type III, 16 type IV, 7 type Va, 24 type Vc, and 1 type Vd cordectomies (6) were performed. Frozen sections were examined and further resection was undertaken until negative margins were obtained.

These patients were followed up by outpatient follow-up and telephone follow-up. A total of 70 patients were male and 5 were female, and their mean age was 60 years (range, 39–84 years). Contrast-enhanced CT and stroboscopy were used to evaluate the extent of tumors before surgery. Patients with unresectable locally advanced (rT4b) cancer, distant metastasis or second primary cancer, and patients who had received radiotherapy or chemotherapy were excluded from this study. Among the 75 patients with local-regional recurrence, 5 patients were first diagnosed with lymph node metastasis without local recurrence, and the other 70 patients comprised 18 cases of rT1, 31 cases of rT2, 9 cases of rT3, and 12 cases of rT4. Salvage surgery was performed in each patient, with postoperative radiotherapy performed in cases of rT4, rN2, rN3, positive margins, perineural invasion, or vascular embolism. Twenty-eight of the 70 patients underwent repeat TLM, 21 underwent partial laryngectomy with neck dissection, and 21 underwent total laryngectomy with neck dissection.

Ethics and approvals

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (No. Trecky2014-027). All patients were informed of the purpose of the study and signed informed consent before treatment. All information will be stored securely.

Statistical analysis

Data on treatment and follow-up were analyzed with SPSS, version 26.0 (IBM Corp., Armonk, NY, USA). The Kaplan-Meier method was used for survival analysis. Univariate analysis was performed with the log-rank test and multivariate analysis was performed using the Cox proportional regression model.

Results

During long-term follow-up [average follow-up of 18 months (range, 1.5–52 months)], 22 of the 75 patients (29.3%) diagnosed with regional recurrence developed cervical metastases (*Table 1*), and the remaining patients had local recurrence. Most (16/22) lymph node metastasis occurred on ipsilateral level II–III. Fifteen of the 22 cases had only 1 positive lymph node, 5 patients had 2 positive lymph nodes, 1 patient had 4 positive lymph nodes, and the remaining 1 patient had 8. The average size of the largest metastatic lymph node in each patient was approximately

Table 1 Number of patients with neck metastasis in different rT stages

Stage	No. of patients	Neck metastasis at first relapse, n (%)	Neck metastasis during long-term follow-up, n (%)
rT0	5	5 (100.0)	–
rT1	18	2 (11.1)	4 (22.2)
rT2	31	3 (9.6)	7 (22.6)
rT3	9	1 (11.1)	2 (22.2)
rT4	12	3 (25.0)	4 (33.3)

Table 2 Univariate analysis of variables for primary and recurrent tumors in 75 patients with local-regional recurrence showing OS, DSS, and the RC rate

Variable	P value		
	OS	DSS	RC
Primary tumor			
Unilateral or bilateral	0.743	0.680	0.488
T stage	0.756	0.933	0.014
Histological grading	0.724	0.797	0.000
Involvement of the anterior commissure	0.376	0.873	0.049
Supraglottic spread	0.457	0.905	0.003
Subglottic spread	0.419	0.205	0.390
Type of cordectomy	0.166	0.143	0.001
Recurrent tumor			0.888
rT stage (n=70)	0.401	0.430	
Neck metastasis at first relapse	0.138	0.394	
Neck metastasis during long-term follow-up	0.001	0.001	

OS, overall survival; DSS, disease-specific survival; RC, regional control.

2.4 cm in diameter (range, 0.7–5.1 cm).

Survival and regional control rate

Over a mean follow-up period of 58 months (range, 6–161 months) after the first recurrence, 11 of the 75 patients died from local-regional recurrence, 4 patients died from lung metastasis, and 4 patients died from internal disease. One patient was lost to follow-up in less than 5 years from the last treatment without any evidence of relapse.

The 5-year overall survival (OS), disease-specific survival (DSS), and regional control rate after the first TLM were 73.6%, 89.1%, and 69.7%, respectively. The laryngeal preservation rate after long-term follow-up was 61.3%.

Prognostic factors

Variables associated with the primary tumor and recurrent lesion were assessed with the log-rank test to analyze their effects on prognosis. For OS and DSS, only neck metastasis during long-term follow-up showed a statistically significant negative impact (both P=0.001) (*Table 2*, *Figures 1*,*2*). T stage of the primary tumor, histological grading, involvement of the anterior commissure, supraglottic spread, and type of TLM all showed a statistically significant effect on the regional control rate (*Table 2*). Supraglottic spread refers to the invasion of primary glottic tumors into the supraglottic region, including the upper hyoid epiglottis, arytenoid plica, arytenoid cartilage, inferior hyoid epiglottis, and false vocal cord. Multivariate analysis including the 5 variables

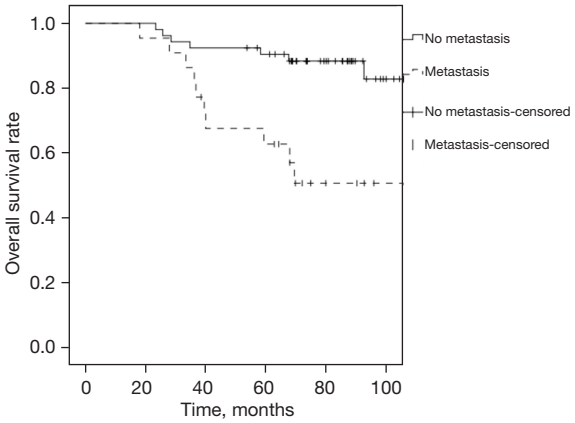

Figure 1 Overall survival curve for patients with (n=22) or without (n=53) regional recurrence (P=0.001) in cases with/without neck metastasis during long-term follow-up.

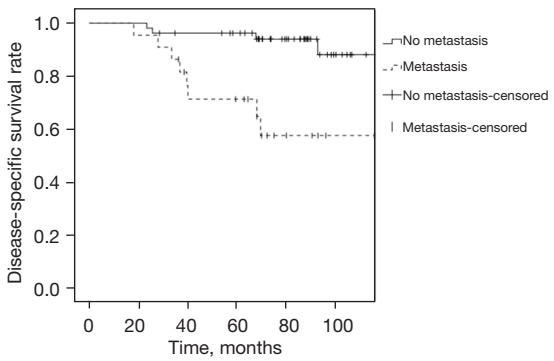

Figure 2 Disease-specific survival curve for patients with (n=22) or without (n=53) regional recurrence (P=0.001) in cases with/without neck metastasis during long-term follow-up.

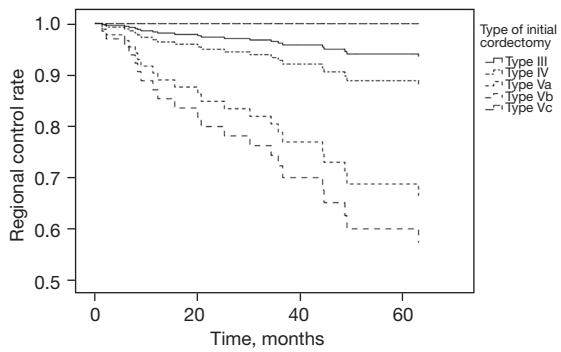

Figure 3 Regional control rate for cases treated with different types of cordectomy.

above indicated that histological grading and type of TLM were both risk factors for neck metastasis. Compared with low-grade tumors, high-grade tumors revealed higher cervical lymph node metastasis [4/4 *vs.* 8/26, hazard ratio (HR) = 3.761, 95% confidence interval (CI): 1.006–14.062, P=0.049]. With regard to the initial treatment, after type V cordectomy, especially Vc cordectomy, patients were more likely to develop regional recurrence than patients treated with type III cordectomy (14/24 *vs.* 2/27, HR =14.737, 95% CI: 2.117–102.610, P=0.007) (*Figure 3*).

Correlation between primary treatment and neck metastasis

To rule out the influence of other factors, the log-rank test was performed in 51 T1 cases (including only 1 case of high-grade tumor) to confirm the influence of initial TLM on neck recurrence. We found no statistically significant correlation between involvement of the anterior commissure and the rate of cervical metastasis (27.3% *vs.* 20%, P=0.552, *Table 3*). The 5-year regional control rates in T1 cases after type III, type IV, type Va, and type Vc cordectomy were 91.3%, 93.8%, 42.9%, and 40.0%, respectively. There were statistically significant differences among the 4 groups (P=0.007, *Table 3*).

In order to determine the potential length of time to the occurrence of lymph node metastasis, the size of the lymph nodes and lengths of time from initial or repeat surgical intervention to neck dissection were estimated in the 22 cases with regional recurrence. Pearson correlation analysis indicated that the maximum metastatic lymph node size was positively correlated with the length of time from the initial TLM to regional recurrence (P=0.047), but not with the length of time from the last treatment to regional recurrence (P=0.099).

Discussion

TLM is a suitable treatment for early laryngeal carcinoma (7). As it causes minimal damage to surrounding tissue and results in faster healing, avoidance of tracheotomy and neck scar, and a lower incidence of aspiration, TLM has been widely used in the treatment of laryngeal carcinoma since 1972 (8). When recurrence is detected, TLM can be performed repeatedly in selected cases and still has a good

Table 3 Rates of neck metastasis during long-term follow-up in T1 cases grouped by type of cordectomy and involvement of the AC

Cordectomy	Involvement of the AC	No involvement of the AC	Total
Type III	0% (0/1)	9.1% (2/22)	8.7% (2/23)
Type IV	16.7% (1/6)	10.0% (1/10)	12.5% (2/16)
Type Va	33.3% (1/3)	75.0% (3/4)	57.1% (4/7)
Type Vc	100.0% (1/1)	50.0% (2/4)	60.0% (3/5)
Total	27.3% (3/11)	20.0% (8/40)	21.6% (11/51)

AC, anterior commissure.

oncological outcome (9-11). It is accurate and an excellent choice for resecting laryngeal lesions, but is inadequate for the exploration of lymph nodes. Early glottic carcinoma rarely presents with nodal metastases because of poor lymphatic drainage in the glottis (4). Neck dissection is not recommended in cT1–2N0 cases according to National Comprehensive Cancer Network (NCCN) guidelines. For recurrent glottic carcinoma, rT1–T2N0 tumors may be treated again with TLM alone since the indications for neck dissection are unclear. However, occult cervical metastasis might be missed. A retrospective study of 123 patients with laryngeal cancer showed that a PET/CT scan altered the treatment plan in 38 (30.9%) patients (12). In another prospective blinded study of 52 patients with head and neck cancer, PET/CT altered the N classification in 12 (23.1%) patients (13). Even though PET/CT displayed up to 33.4% higher sensitivity than CT/MRI in detecting occult cervical metastasis (14), it still cannot replace neck dissection in the diagnosis of cervical metastases for lesions less than 5 mm. The indications for elective neck dissection and the patients who may benefit from surgery need to be further clarified.

In this study, data from 75 patients with recurrences after initial TLM were analyzed retrospectively. The 5-year DSS rate was 89.1%, which is an acceptable oncological result. Univariate analysis demonstrated that the development of neck metastasis was related to poor outcome. This is consistent with previous literature (3). For rT1–T3 tumors, the rates of neck metastasis at first relapse were around 10% (*Table 1*). It seemed that neck dissection was beneficial in only rT4 tumors (25% had cervical metastases). However, unlike the correlation of T stage with neck metastasis in primary tumors, we did not find a strong correlation between rT stage and lymph node metastasis in these recurrent lesions. Instead, the extent of the primary tumor and type of surgery had a significant influence on lymph node recurrence.

High-grade tumors have a tendency to metastasize due to their aggressive biological properties (15). Although there were only 4 cases of high-grade tumor in our study, 2 of them developed neck metastases at first relapse and the other 2 developed neck metastases during several bouts of treatment.

The supraglottic region is rich in lymphatic drainage (16). Recurrences in this area may have a tendency to transfer to cervical lymph nodes, and cervical lymph nodes of supraglottic laryngeal carcinoma have a high rate of occult metastasis. Our study showed that involvement of the anterior commissure and supraglottic spread were related to lower regional control rates in the log-rank test. This changed the T stage of local lesions, and the T stage determines the type of surgery. Univariate analysis also demonstrated a correlation between the T stage of the primary tumor and neck recurrence.

In the univariate analysis, the type of first TLM was found to affect neck recurrence. In the further multivariate analysis, it was one of the only 2 prognostic factors with statistical significance. This may be because the option of operative approach largely depends on the extent of the tumor and depth of invasion. Supraglottic (T2) lesions and high-grade tumors would be treated with type V cordectomies to ensure a safe margin. To exclude the influence of other factors, we analyzed the correlation between the type of first TLM and the regional control rate in T1 cases. We found no significant correlation between involvement of the anterior commissure and the rate of cervical metastasis. Our results showed that regional control rates after type Va and type Vc cordectomies were significantly lower than those after type III and type IV cordectomies (91.3% and 93.8% *vs.* 42.9% and 40.0%). The results indicated that the type of TLM was a more

important factor in predicting neck recurrence than rT stage. A type V cordectomy may compromise the connective tissue barriers within the larynx, such as the conus elasticus, quadrangular membrane, ventricular connective tissue, and Broyles' ligament (commissural tendon) (16). Recurrent tumors could spread from the glottis to the supra/subglottis and paraglottic space, which have a more abundant lymph node basin (17).

In patients with recurrence after radiotherapy, elective neck dissection is also contentious. The reported regional recurrence rates are low (18-20), and some studies indicated that a beneficial effect would only be obtained in a locally advanced or supraglottic recurrence (21,22). When grouping patients according to rT stage, we found that T1–T3 patients had a regional metastasis rate of approximately 10–20%, which will fail to dispel controversy on this issue. When dividing patients into groups based on the first TLM, the rate of regional metastasis was significantly higher in cases after type V cordectomies (much more than 20%) than in cases after type III or type IV cordectomies (about 10% after long-term follow-up). Even early recurrence after TLM could lead to neck metastasis through the compromised barriers.

In our study, since neck metastasis was more likely related to the extent of the primary tumor and type of first surgery, the subsequent neck recurrence might occur insidiously during the first treatment period until it is detected by imaging or elective neck dissection. We further evaluated the size of the largest positive lymph node and the possible duration of its existence. In the 22 cases with neck metastases, the size of the largest metastatic lymph node was correlated with the duration from first TLM to neck metastasis instead of the duration between the 2 adjacent treatments. This provides further support that the extent of the primary lesion may have a strong effect on neck metastasis. For recurrent cases, there could be undetectable residual tumor cells after the first treatment (23,24). We hypothesized that, due to the deficiency of barriers within the larynx after type V cordectomy, the residual tumor cells might result in local relapse and a high risk of neck metastases (up to 60%) through the accessible lymphatics. These potential cervical lesions need regular assessment and timely treatment in patients at high risk of regional recurrence. In this situation, the type of TLM is a better predictor for neck dissection than rT stage.

Conclusions

Recurrence after type V cordectomy may be linked to an increased risk of developing cervical lymph node metastasis, especially in patients with supraglottic spread or high-grade tumors. Patients with supraglottic laryngeal carcinoma should be followed up closely and more attention should be paid to the lymph node status while focusing on recurrent lesions in the larynx.

Methodological limitations

This study has several limitations. First, this was a retrospective study and the sample size was limited. In addition, postoperative radiotherapy may influence neck metastasis. Due to differences in departments, the range of patients we could contact was limited. Some recurrent cases with unresectable tumors or cases treated with radio/chemotherapy were excluded from this study. Moreover, preoperative staging was based on CT and stroboscopy. This could present a bias in pT staging, but discordance between cT and pT staging is an unavoidable drawback of treating laryngeal cancer.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3385/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3385/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3385/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (No. Trecky2014-027). All patients were informed of the purpose of the study and signed informed consent before treatment.

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