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Journal of the Chinese Medical Association 80 (2017) 452−457

www.jcma-online.com

Original Article

Predictors of local recurrence of glottic cancer in patients after transoral laser microsurgery

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Received August 17, 2016; accepted October 18, 2016

Abstract

Background: Transoral laser microsurgery (TLM) is used to treat early and select cases of moderately advanced glottic cancer, with results equivalent to those of conventional conservative surgery and radiotherapy (RT). As surgeons and researchers become more experienced and familiar with TLM, they can focus on mechanisms to earlier detect local recurrence, to more effectively preserve laryngeal function. This study analyzed the predictors of local recurrence in glottic cancer patients who underwent TLM.
Methods: Our study focused on 93 consecutive patients with glottic cancer who received TLM between 2003 and 2009, and were analyzed retrospectively. All of these patients were treated by the same surgeon. The local control and survival rate were calculated with Kaplan−Meier method and compared using the log-rank test. Additionally, the Cox proportional hazard model was used for multivariate analysis.
Results: The 5-year local control, overall survival, and disease-specific survival rates were 87%, 95%, and 96%, respectively. The final laryngeal preservation rate was 98%. Independent predictors of local recurrence were arytenoid cartilage invasion (hazard ratio [HR], 6.5; 95% confidence interval [CI], 2.1−26.6), difficult laryngeal exposure (HR, 4.6; 95% CI, 1.5−17.3), previous microlaryngoscopic surgery (HR 3.1; 95% CI, 1.3−10.5), positive surgical margin (HR, 2.7; 95% CI, 1.1−9.7), and endophytic tumors (HR, 2.6; 95% CI, 1.1−7.6).
Conclusion: TLM is a reliable modality to treat early and select cases of moderately advanced glottic cancer with good final laryngeal preservation rate. Our study found that independent factors of local recurrence included arytenoid cartilage invasion, difficult laryngeal exposure, previous microlaryngoscopic surgery, positive surgical margin and endophytic tumors. These findings may help to follow-up glottic cancer patients after TLM.

Keywords: Carbon dioxide laser; Glottis; Local recurrence; Squamous cell carcinoma

1. Introduction

In the past decade, transoral laser microsurgery (TLM) has been used to treat early and select cases of moderately advanced glottic cancer.[1−4] The oncologic results of TLM are equivalent to those obtained by conventional conservative surgery and radiotherapy (RT). The advantages of TLM are reduced morbidity, shorter hospital stay, and better postoperative laryngeal function than with conventional conservation surgery. In fact, patients with subepithelial and subligamental cordectomies have been reported to have good voice outcomes.[5]

Compared with RT, patients undergoing endoscopic surgery have lower hidden costs including total travel time, total travel distance and total hours of work lost.[6] The absence of RT-induced tissue toxicity and shorter treatment time also make TLM a more favorable initial treatment. In cases of local recurrence or second primary cancer in the head and neck

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.jcma.2017.04.002

area, TLM can be repeated and provide more treatment options than with initial RT or conventional conservative surgery. In addition, TLM does not interfere with alternative treatments because it preserves the laryngeal framework and vascularization.[2,7,8] Furthermore, two literature reviews indicated that local control and survival rates were similar after TLM, conventional conservative surgery, and RT.[1,9]

Because TLM is widely performed, it is essential to understand the predictors of local recurrence to allow for early diagnosis and optimize the laryngeal preservation rate after salvage treatment. The purpose of this study was to analyze the predictors of local recurrence in patients with glottic cancer who underwent TLM.

2. Methods

2.1. Study population

Ninety-three consecutive patients with glottic squamous cell carinoma who had undergone TLM between 2003 and 2009 were enrolled into this study. Those who underwent TLM for benign vocal fold lesions and palliation of airway obstruction were excluded. All patients were treated by a single surgeon (Dr. PY Chu). The types of TLM were classified in accordance with the classification of the European Laryngology Society.[10,11] For further analysis, patients were grouped as follows: those with limited cordectomy (types I and II), and those with extended cordectomy (types III−VI). The definition of positive margin was less than 1 mm distance from the tumor. Subglottic invasion was defined as 1 cm below the free edge of the vocal fold, based on the patient's clinical finding. Difficult laryngeal exposure (DLE) was defined as when direct laryngoscopy could not provide adequate visualization of the anterior commissure of the vocal fold. The study was conducted in accordance with the principles stated in the Declaration of Helsinki (1964), and its design was approved by the hospital's institutional review board. The IRB waived the requirement for written, informed consent.

2.2. Surgical procedures

When the patient was under general anesthesia, the larynx was suspended and exposed with a rigid laryngoscope. Before the operation, 0°, 30°, and 70° telescopic views were used to examine the tumor extension, including the ventricle, anterior commissure, and subglottic area. Video recording was performed before, during, and after the procedure in all patients prospectively. The procedure was then performed using a CO_2 laser (Compact 30; Lumenis Ltd., Yokneam, Israel) with a micromanipulator (Acuspot 712; Sharplan, Tel Aviv, Israel). The power was set at 2−5 W, in the continuous superpulse mode. En-bloc resection was performed in patients with small lesions, and the piecemeal method with transection of the tumor was performed in those with bulky lesions. The bulky tumors were transected into two to four manageable pieces to identify the depth of invasion. External compression of the neck was used if necessary to improve surgical exposure of the anterior commissure. A frozen section was sent for examination in cases with any suspicion of tumor invasion. Laryngeal videostroboscopic examinations were performed monthly in the first year, and every 2 to 3 months thereafter to evaluate wound healing and monitor for the possibility of tumor recurrence.

2.3. Statistical analysis

Statistical analyses were performed using commercially available computer software (SPSS version 18, SPSS, Inc., Chicago, IL, USA). Descriptive statistical analysis was performed on the patient characteristics. The follow-up interval was calculated by using the number of months from the date of initial surgery until death or the date of last follow-up. Local control, overall survival, and disease-specific survival rates were calculated using the Kaplan−Meier method, and univariate analysis was performed using the log-rank test. The level of statistical significance was set at $p \leq 0.05$. All significant factors were entered into multivariate analysis using a Cox proportional hazard model.

3. Results

In this study, patients were predominantly male (97%), with a median age of 63 years (range 34 to 89 years). Seventy-three patients (78%) had a history of tobacco use and 36 (39%) had a history of alcohol consumption. The characteristics of the 93 patients are shown in Table 1. As classified by the American Joint Committee on Cancer 2002,[12] the primary tumor stage was 18 Tis (19%), 38 T1 (41%), 20 T2 (22%), and 17 T3 (18%). In the 38 T1 patients, 32 (84%) were T1a and 6 (16%) were T1b stage. Seventeen patients (18%) had undergone microlaryngoscopic surgery (MLS) with mucosal stripping within 3 months before this operation. Ten patients (11%) had local recurrence after previous treatment, including 5 TLM and 5 RT. The types of TLM included 18 type I (19%), 31 type II (33%), 20 type III (22%), 3 type IV (3%), 15 type V (16%), and 6 type VI (6%). Five patients (5%) had DLE during TLM even though external compression was performed. Seven patients (8%) received postoperative RT due to positive surgical margin.

The characteristics of the tumors are shown in Table 2. The tumor morphology indicated 69 (74%) exophytic tumors and 24 (26%) endophytic tumors. Forty-five patients (48%) had anterior commissure invasion, and 30 (32%) had tumors extending to the contralateral true vocal fold. Twenty-two patients (24%) had vocal process invasion, and 7 (8%) had tumor invasion to the body of the arytenoid cartilage. Eighteen patients (19%) had vocal fold limitation. Twenty-eight patients (30%) had tumors extending to the ventricle, 9 (10%) had false vocal folds, and 18 (19%) had subglottic invasion. Seventeen patients (18%) had paraglottic invasion, and 8 (9%) had perichondrium of thyroid cartilage invasion. Fourteen patients (15%) had positive surgical margin (including carcinoma in situ and severe dysplasia).

The oncologic results after primary TLM are shown in Table 3. In a median follow-up of 35 months (range

Table 1
Characteristics of patients with glottic cancer.

Characteristics	Number	%
Total cases	93	100
Gender		
Male	90	97
Female	3	3
Age range 34–89 years; median 63 years		
Tobacco		
Yes	73	78
No	20	22
Alcohol		
Yes	36	39
No	57	61
Primary T stage		
Tis	18	19
T1a	32	34
T1b	6	7
T2	20	22
T3	17	18
Previous microlaryngoscopic surgery		
Yes	17	18
No	76	82
Salvage treatment		
Yes	10	11
No	83	89
Type of cordectomy		
Type 1	18	19
Type 2	31	33
Type 3	20	22
Type 4	3	3
Type 5	15	16
Type 6	6	6
Difficult exposure		
No	88	95
Yes	5	5

8–100 months), 11 patients (12%) had local recurrence. Five patients (5%) had second primary malignancies, including four in the head and neck area and one in the lung. The 5-year local control, overall survival, and disease-specific survival rates were 87%, 95%, and 96%, respectively. Ten of the 11 patients with local recurrence underwent salvage treatment, and one patient received only palliative tracheotomy due to advanced age. The 10 patients were salvaged with TLM only (n = 4) or with postoperative RT (n = 6). One patient had total laryngectomy due to paratracheal lymph node recurrence. Ninety-one of the 93 patients still had a preserved larynx at last follow-up, for a final laryngeal preservation rate of 98%.

Table 4 shows the predictors of local recurrence. In univariate analysis, the following were significant factors for local recurrence: primary T stage, previous MLS, salvage treatment, type of cordectomy, tumor morphology, limitation of vocal folds, anterior commissure, arytenoid cartilage, false vocal fold, paraglottic space, perichondrium of thyroid cartilage invasion, positive surgical margin, and difficult exposure during MLS. In multivariate analysis (Table 5), the following were independent factors for local recurrence: arytenoid cartilage invasion, DLE, previous MLS, positive surgical margin, and endophytic tumors. Bilateral vocal fold lesions was not a significant factor of local recurrence (91% vs. 78%, p = 0.104). Patients with arytenoid cartilage extension had a 6.5-fold higher local recurrence rate than those without invasion. Patients with DLE had a 4.6-fold higher rate of local recurrence than those without DLE, and those with previous MLS had a 3.1-fold higher rate of local recurrence than those without previous MLS. Patients with a positive surgical

Table 2
Tumor characteristics of 93 patients with glottic cancer.

Characteristic	Number	%
Morphology		
Exophytic	69	74
Endophytic	24	26
Anterior commissure invasion		
No	59	63
Yes	34	37
Bilateral lesions		
No	63	68
Yes	30	32
Vocal process invasion		
No	71	76
Yes	22	24
Arytenoid cartilage invasion		
No	86	92
Yes	7	8
Vocal cord limitation		
No	75	81
Yes	18	19
Ventricle invasion		
No	65	70
Yes	28	30
False cord invasion		
No	84	90
Yes	9	10
Subglottic invasion		
No	75	81
Yes	18	19
Paraglottic space invasion		
No	76	82
Yes	17	18
Thyroid cartilage perichondrium invasion		
No	85	91
Yes	8	9
Surgical margin		
Positive	14	15
Negative	79	85

Table 3
Oncologic results of patients with glottic cancer receiving transoral laser microsurgery.

Outcomes	Number	%
Local recurrence		
Yes	11	12
No	82	88
Second primary		
Yes	5	5
No	88	95
5-year local control rate		87
5-year overall survival rate		95
5-year disease-specific survival rate		96
Final laryngeal preservation		
Yes	91	98
No	2	2

Table 4
Univariate analysis with log-rank test for predictors of local recurrence of glottic cancer.

Factors	Number	5-year local control rate	P value (log rank)
Primary T stage			
Tis	18	100%	0.024
T1	38	92%	
T2	20	84%	
T3	17	66%	
Previous MLS			
No	76	94%	0.0007
Yes	16	67%	
Salvaged treatment			
No	83	91%	0.0009
Yes	10	60%	
Type of cordectomy			
Limited	49	96%	0.013
Extended	44	78%	
Morphology			
Exophytic	69	95%	<0.0001
Endophytic	24	64%	
Vocal cord limitation			
No	75	91%	0.010
Yes	18	68%	
Anterior commissure invasion			
No	59	95%	0.007
Yes	34	74%	
Arytenoid cartilage invasion			
No	86	91%	<0.0001
Yes	7	38%	
False cord invasion			
No	84	90%	0.009
Yes	9	67%	
Paraglottic space invasion			
No	76	92%	0.005
Yes	17	66%	
Thyroid perichondrium invasion			
No	85	90%	0.005
Yes	8	56%	
Surgical margins			
Negative	79	92%	<0.0001
Positive	14	56%	
Difficult laryngeal exposure			
No	88	91%	<0.0001
Yes	5	20%	

Table 5
Multivariate analysis of factors affecting local recurrence of glottic cancer.

Factors	P value (Cox)	HR* (95% CI†)
Arytenoid cartilage invasion		
No	0.0009	1.0 (reference)
Yes		6.5 (2.1−26.6)
Difficult laryngeal exposure		
No	0.006	1.0 (reference)
Yes		4.6 (1.5−17.3)
Previous MLS‡		
No	0.009	1.0 (reference)
Yes		3.1 (1.3−10.5)
Surgical margin		
Negative	0.046	1.0 (reference)
Positive		2.7 (1.1−9.7)
Morphology		
Exophytic	0.019	1.0 (reference)
Endophytic		2.6 (1.1−7.6)

*HR: hazards ratio.
†CI: confidence Interval.
‡MLS: microlaryngoscopic surgery.

margin had a 2.7-fold higher rate of local recurrence than those with a negative margin, and those with an endophytic tumor had a 2.6-fold higher rate of local recurrence than those with an exophytic tumor.

4. Discussion

In the current study, TLM provided satisfactory oncologic results for patients with early and select cases of moderately advanced glottis cancer. The 5-year local control, overall survival, and disease-specific survival rates were 87%, 95%, and 96%, respectively. Although 11 patients (12%) developed local recurrence after TLM, 91 of the 93 patients (98%) had final laryngeal preservation after salvage treatment. Our results are comparable with a previous report from Schrijvers et al.,[13] who reported a higher laryngeal preservation rate after TLM vs. RT for patients with T1a glottis cancer. TLM can be used multiple times in cases of local recurrence, and postoperative RT can still be administered later in those patients with positive surgical margin.

Our results showed that arytenoid cartilage extension, DLE, previous MLS, positive surgical margin, and an endophytic tumor were independent predictors of local recurrence in patients with glottic cancer who underwent TLM. The other factors, such as anterior comissure invasion and bilateral vocal fold lesions, were not independent predictors in patients who underwent TLM if exposure was good during operation. Patients with arytenoid cartilage extension had a 6.5-fold higher rate of local recurrence than those without invasion, and the 5-year local control rates were 38% and 91% in patients with or without arytenoid cartilage extension, respectively. Once tumors invade into this area, they grow close to the cricoarytenoid joint and may impair the mobility of the arytenoid cartilages, making it difficult to complete the resection. Peretti et al.[2,14] also mentioned that posterior paraglottic involvement in close proximity to the cricoarytenoid joint was generally associated with local persistence of the tumor. Moreover, failure in this area can dramatically jeopardize the laryngeal preservation rate after partial laryngectomy. Special techniques and experience are needed to improve the surgical field for resection, and surgeons are recommended to employ wide resection of the primary tumor as well as the inner perichondrium of the thyroid lamina and the cricoid arch. The piecemeal technique may improve exposure of the posterior paraglottic space, and facilitate tumor depth and margin estimation. Postoperative RT is indicated for patients without adequate surgical margin.

Patients with DLE had a 4.6-fold higher rate of local recurrence than those without DLE. The 5-year local control rates were 20% and 91% in patients with and without DLE, respectively. DLE creates serious problems not only in inserting the endotracheal tube but also in performing MLS in patients under general anesthesia. The condition may result

from anatomic characteristics or trauma to the neck, and prevent visualization of the glottis. Patients with limited mouth opening, a receding lower jaw, a short or stiff neck, marked obesity, or a large tongue may also be at high risk of DLE. However, such problems can be difficult to predict preoperatively. Although rigid laryngoscopes and specialized surgical instruments have been developed for use in patients with DLE, it is still difficult to expose the anterior commissure of the vocal fold for TLM. Zeitels and Vaughan[15] reported that the use of both external counter-pressure and internal distention as an adjunct to microlaryngoscopy may be helpful in the surgical management of lesions located near the anterior commissure. However, if these methods cannot achieve an adequate surgical margin, postoperative RT is recommended.

Patients with previous MLS by simple removal of the mucous membrane (mucosal stripping) before TLM had a 3.1-fold higher rate of local recurrence than those without a previous biopsy. The 5-year local control rates were 67% and 94% in patients with and without a previous biopsy before TLM, respectively. In our series, most of the patients (15/17) with a previous biopsy were referred from local hospitals. The biopsy was performed with small or no surgical margin by cold instruments or a CO_2 laser. It was therefore more difficult to identify the margin during TLM in these patients due to inflammation or scarring of the surgical bed. In our experience and according to the recommendations of other studies,[8,16] both biopsy and treatment can be accomplished in one endoscopic procedure. When malignancy is strongly suspected, resection with margin exceeding 1 mm is oncologically adequate.[17] Such patients do not need to receive a second surgery under general anesthesia, thus reducing surgical time, cost of treatment, and trauma. Therefore, for those patients with minimally invasive carcinoma of the vocal fold, resection with type I or type II cordectomy performed simultaneously during biopsy is recommended for both diagnosis and treatment. No significant differences have been reported in vocal parameters between patients undergoing subepithelial cordectomies (type I), subligamental cordectomies (type II), and controls.[5]

Patients with positive surgical margin had a 2.7-fold higher rate of local recurrence than those with negative margin. The 5-year local control rates were 56% and 92% in those with positive and negative margin, respectively. These findings are similar to those of previous studies which reported 5-year local control rates of positive margin ranging from 51.3% to 81.9%, and negative margin from 78.4% to 95%.[2,17–20] Local recurrence has been reported to be significantly correlated with the presence of positive margin.[3,17–19] The management of positive margin after TLM depends on institutional policy, and repeated TLM, postoperative RT and watchful observation are all reasonable treatments after TLM. Laser re-excision is suggested by most studies at 2 weeks to 6 months postoperatively.[5,14,20,21] RT can be administered in cases with more than 2 positive margins, persistent positive margin after repeated TLM, paraglottic space involvement or upon the patient's preference.[2,17,18] If experienced surgeons have confidence in the safety of the margin during TLM, watchful observation is another way to manage positive margin after TLM. However, watchful observation is suggested for patients with good compliance who receive close and regular follow up.[2,19,22,23] In our institute, watchful observation is our policy for positive margin if the surgeon has confidence and patients have good compliance. Regardless of whether patients receive a second operation or adjuvant RT, the local recurrence rate has still been reported to be higher than for those with negative margin.[2] Therefore, it is important to provide wide resection of the primary tumor with adequate margin during the first surgery. Removal of large glottic tumors by en bloc resection is not necessary. Transecting tumors by the piecemeal method may be useful in evaluating deep margin. The carbonization of tumors after cutting by CO_2 laser is different from the carbonization of normal mucosa and submucosa of the glottis.[23] This difference may suggest that laser surgery can be used to recognize the contours of glottic tumors and obtain adequate margin.

Patients with endophytic tumors had a 2.6-fold higher rate of local recurrence than those with exophytic tumors. The 5-year local control rates were 64% and 95% in those with endophytic and exophytic lesions, respectively. The correlation of tumor morphology with local recurrence in patients with early glottic cancer who underwent TLM has rarely been reported. Franchin et al.[24] analyzed the prognostic factors of 412 patients with T1–T2 glottic cancer treated with RT, and found borderline significance of local control in patients with exophytic lesions versus infiltrative lesions (hazard ratio, 2.2; $p = 0.07$). In other sub-sites of the head and neck area, Spiro et al.[25] found that endophytic tumors were significantly more likely to recur locally than exophytic tumors in patients with oral tongue cancer (32% vs. 10%, $p < 0.04$). In our experience, it is more difficult during TLM to identify deep margin in patients with endophytic tumors than in those with exophytic tumors. The piecemeal method with transection of the tumor may help delineate the tumor and healthy tissue interface[23] and identify the depth of tumor invasion.

In conclusion, TLM is a reliable modality to treat early and select cases of moderately advanced glottic cancer with good local control and disease specific survival rate. In this study, arytenoid cartilage extension, DLE, previous MLS, positive surgical margin, and endophytic tumors were independent predictors of local recurrence. With these findings, we may identify local recurrence earlier and arrange salvage TLM or RT as soon as possible. Therefore, we may finally be able to more reliably preserve laryngeal function.

Acknowledgments

This study was sponsored by the National Science Council (grant number 100-2314-B-075-017-MY3) and Taipei Veterans General Hospital (grant number V98C1-135).

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