Transoral Endoscopic CO_2 Laser Microsurgery for Early Laryngeal Cancers

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Background: The impact of transoral endoscopic CO_2 laser microsurgery (TLM) for the treatment of Tis, T1, and T2 glottic cancer on local disease control, survival, and laryngeal preservation was investigated.

Methods: From October 1999 to Feburary 2008, 48 patients with a previously untreated early laryngeal malignant tumor who had been treated with TLM were enrolled in this study. Overall survival, primary and ultimate local control, and larynx preservation rates were calculated by the Kaplan-Meier method. The impact of anterior commissure involvement on the local control rate after primary TLM was performed was analyzed by the log-rank test. Functional results for postoperative voice were analyzed by patient telephone intelligibility.

Results: The overall 5-year survival rate was 97% (95% CI, 94%-100%), the primary 5-year local control rate was 72% (95% CI, 66%-92%), the local control rate exclusively for TLM was 85% (95% CI, 79%-99%), and the ultimate 5-year local control rate was 100%. Larynx preservation rate was 97% (95% CI, 94%-100%). Anterior commissure involvement in glottic cancer showed no statistically significant difference in primary local control rate (p = 0.9). Regarding the post-operative voice function, 47 patients (97.9%) were able to maintain adequate telephone intelligibility.

Conclusion: In terms of long-term survival and locoregional control, TLM is an optimal primary treatment modality for early laryngeal cancer. With TLM treatment, involvement of the anterior commissure is not a poor prognostic indicator.
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Key words: laryngeal cancer, transoral microsurgery, head and neck, laser, endoscopy

The term *early laryngeal cancer* refers to carcinoma in situ (Tis), T1, and T2 carcinomas of the larynx without positive cervical lymph node metastasis. Early stage laryngeal neoplasms mostly arise from subsites in the glottis or supraglottis, with the subglottic larynx being a less frequent primary tumor site.[1] Many published studies have discussed the efficacy and outcome of various treatment modalities for early glottic malignancies.[2-5] Historically, the definite treatment for laryngeal carcinomas has been

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by performing open laryngeal surgery in order to excise the tumor en bloc and obtain a macroscopic safety margin. Various techniques, including laryngofissure with cordectomy,[6] supracricoid laryngectomy, vertical partial laryngectomy,[7] and total laryngectomy, have been adopted for the radical removal of primary tumors. However, despite providing good oncological control, open laryngectomies also involve a greater detrimental impact on the laryngeal architecture and thus typically result in a poorer functional outcome. Hence, treatments of laryngeal cancer have evolved in order to not only provide oncological control but also to preserve a functioning larynx. With these goals, both external beam radiotherapy and transoral laser microsurgery (TLM) have been introduced for the treatment of early laryngeal carcinomas.[8]

The transoral endoscopic approach for laryngeal carcinomas can be dated back to Lynch during the 1920s.[9] However, since Strong and Jako[10] first introduced the carbon dioxide (CO_2) laser operation for laryngeal carcinoma in 1972,[10] its use for treating early stage laryngeal malignancies has been advocated by many physicians and researchers.[3-5,11] Werner et al. demonstrated the sealing of blood and lymphatic vessels and delayed lymphatic regeneration from laser cutting margins in an animal, suggesting that the resection of malignant tumors by laser might effectively reduce the risk of intraoperative metastases.[12] Over the past two decades, many authors have reported the success of TLM in the treatment of early glottic and supraglottic carcinomas.[3,5,13] It has an oncological outcome comparable with conventional open laryngectomy, but also has the benefits of better laryngeal preservation, less surgical morbidity, and a shorter treatment time.[8]

Another treatment modality aimed at larynx preservation is primary radiotherapy. This approach achieves better voice and higher larynx preservation when compared with open laryngectomy.[2,14] However, if radiotherapy is performed other possible management approaches are precluded and so only salvage treatment in the form of a total laryngectomy is possible.[8] Comparisons between voice results, complications, and cost between TLM and radiotherapy have been infrequently reported.[8,14,15] The selection of treatment modalities is usually based on multiple factors, including patient preferences, clinical evaluation by the surgeon, and the capability to perform TLM or availability of radiotherapy from the facility.[8,16]

The involvement of the anterior commissure in glottic cancer has been reported to correlate with a higher rate of local recurrence.[7,8,17] The insertion of the anterior commissure tendon (Broyle's ligament) into the thyroid cartilage has been suggested as a weak point for protection against tumor spread due to the lack of a perichondrium or periosteum[17] or as a line of resistance against tumor spread.[18] In addition to these different views on the role of this anatomical structure in blocking tumor invasion, the difficulty in complete exposure during the operation has also resulted in suboptimal resection by TLM.[19]

The aim of this study was to evaluate the oncological results of the use of primary TLM in the treatment of patients with Tis, T1, and T2 glottic carcinomas and to investigate the role of the anterior commissure in local control rates for glottic cancer. We also collected the average time of surgery, blood loss from surgery, and days of hospitalization in order to evaluate the cost and risk of TLM. Voice function after treatment was evaluated by self-assessment of telephone intelligibility.

METHODS

From October 1999 to February 2008, 48 patients with previously untreated glottic malignant tumors had transoral endoscopic CO_2 laser excision at the Department of Otolaryngology-Head and Neck Surgery, Chang Gung Memorial Hospital, Taiwan. A total of 47 males (97.9%) and 1 female (2.1%) aged 26 to 86 years (median, 67) enrolled. Postoperative follow-up time ranged from 4.37 to 101.6 months (median, 36.48). All patients had biopsy-verified squamous cell carcinoma primarily located in the glottic larynx. Staging was performed according to the 2002 American Joint Cancer Committee/International Union Against Cancer (AJCC/UICC) classification. Among all patients, 2 tumors (4.2%) were classified as Tis, 30 (62.6%) as T1a, 9 (18.6%) as T1b, and 7 (14.6%) as T2. Patients who were found to have previous radiotherapy or surgery, distal metastasis at the time of initial diagnosis, recurrent disease, or existence of previous malignancy of the head and neck region were excluded from the study.

Following clinical suspicion of a glottic lesion, a

complete physical examination was performed in order to exclude cervical metastasis. Endoscopic biopsy and careful inspection and mapping of the primary lesion were then done. After the initial diagnosis was confirmed pathologically, a routine preoperative examination was conducted that included a head and neck computed tomography scan, abdominal ultrasonography, and a bone scan. During the operation, the patient was placed in the Jackson position with the head extended at the atloid-occipital joint and general anesthesia was achieved through a laser-safe endotracheal tube. Suspension laryngoscopy (Storz Co., Culver City, CA, U.S.A.) was performed with adjustment for optimum exposure of the lesion and anterior glottis under direct visualization. An operating microscope (Wild M695, Leica Microsystems, Wetzlar, Germany) fitted with a 400 mm front lens was used for magnification of the surgical field. A variety of micromanipulators (Storz Co., Nagashima Medical Instruments Co., Tokyo, Japan) were used for tissue retraction, suction, and cauterization. After the glottal lesion was clearly visualized, subepithelial infusion of saline into the superficial lamina propria was performed with a specialized needle. The infusion is helpful for determining the extent and depth of invasion. A CO_2 laser (Model 40C, Sharplan Lasers Inc., Allendale, NJ, U.S.A.) set at the repeated or continuous mode (2-5 watt, spot size 0.1 mm) was used for tumor resection. The perimeter of the lesion was examined and followed by en bloc resection in most cases. Due to difficulties in the full exposure of larger tumors at the beginning of the procedure, these tumors were resected as more than one discrete specimen (mosaic resection) in order to obtain a better surgical field and to facilitate complete removal of the tumor. Surgical margins were sent as frozen sections intraoperatively and an extended resection was performed if a positive margin was reported.

Local recurrence was defined as biopsy-proven cancer originating from the larynx after primary laser surgery with adequate healing and a disease-free interval. Regional recurrence was defined as recurrent disease exclusively within the cervical lymphatics. All patients were scheduled for regular follow-up examinations, including inspection using a flexible fiberoptic laryngoscope and other head and neck physical examinations. If local recurrence was suspected, a laryngoscopic biopsy was performed. Treatment options for local recurrence included further endoscopic laser surgery, radiotherapy, concurrent chemoradiotherapy, and open total laryngectomy. Total laryngectomy was performed if radiotherapy failed to control the primary disease. Operation time, blood loss, and days of hospital stay were recorded for every TLM. Postoperative voice function was assessed by the patients' statement of their ability to communicate by telephone during outpatient follow-ups.

Local control rates and overall survival rates were plotted by the Kaplan-Meier method. The statistical significance of the survival analysis was measured by the log-rank test. All comparison was two-tailed and results were considered significant when $p < 0.05$.

RESULTS

Survival and local control analysis

The treatment paradigm is illustrated in Fig. 1. The estimated 5-year overall survival was 97% (95% confidence interval (CI), 94%-100%). One patient died due to distant metastasis without evidence of local recurrence, but all other patients were healthy and free of disease during their last follow-up. The primary and ultimate 5-year local control rates were 72% (95% CI, 66%-92%) and 100%, respectively (Fig. 2A). The 5-year local control rate exclusively for TLM was 85% (95% CI, 79%-99%). Eighteen patients (37%) had anterior commissure involvement. The 5-year local control rates after primary TLM between patients with and without anterior commissure involvement were 74% (95% CI, 39-63%) and 71% (95% CI, 62%-95%), respectively. These rates were not statistically different ($p = 0.90$) (Fig. 2B). The ultimate local control rates were 100% for both groups. Salvage total laryngectomy was only performed on one patient with a T2 glottic tumor who developed local recurrence 10 months after concurrent chemoradiotherapy. Thus, the 5-year laryngeal preservation rate was 97% (95% CI, 94%-100%). None of the patients with Tis lesions had local recurrence or radiotherapy. The ratios of local recurrence were 17%, 22%, and 43% for T1a, T1b, and T2 glottic tumors, respectively. Radiotherapy was performed in 6 patients. Two of them had suspicious pathologic margins reported after the operation and radiotherapy was performed in order to achieve

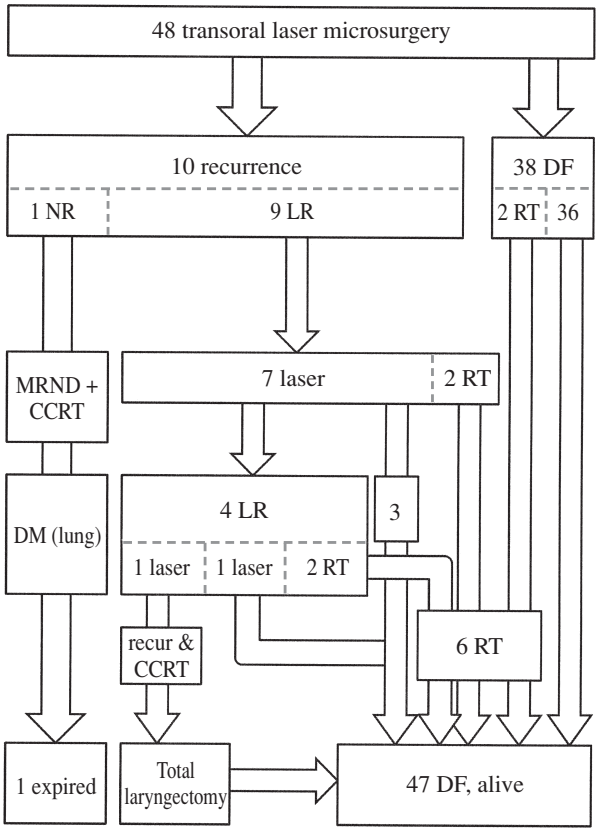

Fig. 1 Treatment algorithm for patients with early laryngeal carcinoma. Abbreviations used: DF: disease free; NR: neck recurrence; LR: local recurrence; RT: radiotherapy; MRND: modified radical neck dissection; CCRT: concurrent chemoradiotherapy; DM: distal metastasis.

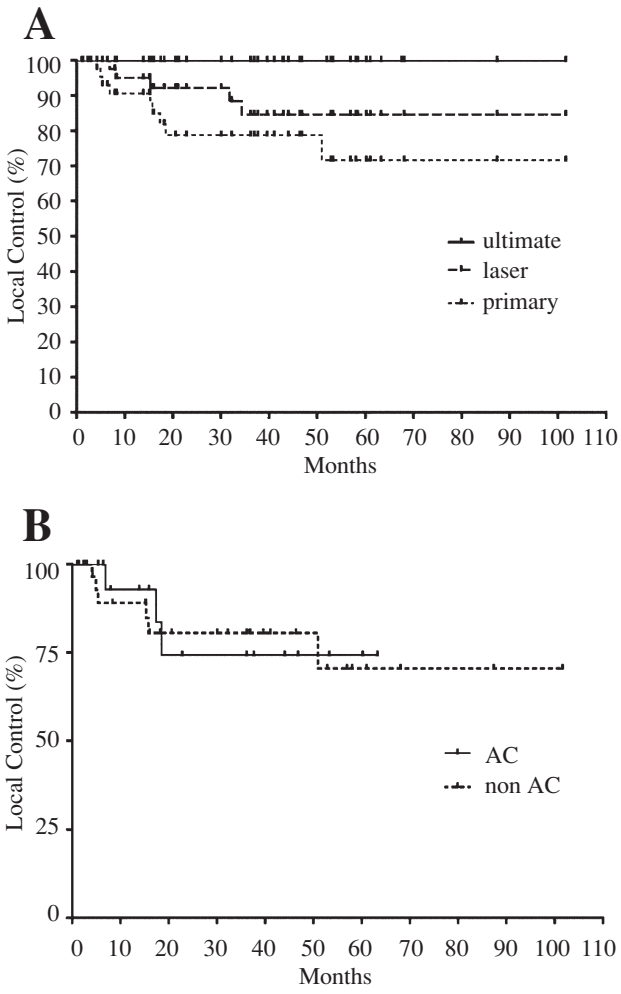

Fig. 2 (A) Local control curves for primary TLM (primary), exclusive TLM (laser), and final after-salvage treatment modalities (ultimate). (B) Primary local control curves for treatment with TLM. Treatment of early laryngeal carcinoma showed no statistically significant difference between the patients featuring or not featuring anterior commissure involvement (p = 0.90). Abbreviations used: AC: anterior commissure involvement; non AC: no anterior commissure involvement.

optimal local control. The remaining 4 procedures were performed due to local recurrences. None of the patients in this cohort underwent tracheostomy or required a persistent feeding tube (Table 1).

Management of recurrences

Recurrence occurred in 10 patients (18.9%, Fig. 1). The interval between TLM and development of recurrence ranged from 1.1 to 50.9 months (median, 12.6). Nine patients had local recurrence and one had neck recurrence. Among nine patients with local recurrences, 7 underwent a second laser resection and 2 had radiotherapy. For the only patient with neck recurrence, type I modified radical neck dissection and postoperative concurrent chemoradiotherapy were administered. Unfortunately, this patient developed distal lung metastasis and expired 15.3 months after the first operation. A second local recurrence occurred in 4 patients. Two of them received irradiation and 2 had salvage TLM. One patient with an initial T2 glottic tumor who had a second TLM after the first local recurrence also developed a second recurrence after 3.1 months. Concurrent chemoradiotherapy resulted in a complete response, but the patient still experienced a third local recurrence after an

additional 9 months. Consequently, salvage total laryngectomy was successfully performed and the patient was alive and free of disease during the last follow-up. Positive margins were documented in 9 cases (18.7%), 7 identified intraoperatively by frozen section and managed with wider resectioning to obtain negative resection margins. The remaining two patients had suspicious postoperative surgical margins by histopathological examination and underwent postoperative radiotherapy for optimal control. The details and paradigm of locoregional recurrence are summarized in Table 2 and Fig. 1.

Operation time, blood loss, hospital stay, and voice

A total of 56 TLMs were performed. There were no operation-related intraoperative or postoperative complications. The mean operation time was 132.9 ± 53.8 (mean ± standard deviation) minutes and the average hospital stay following all laser opera-

Table 1. Treatment Results of CO_2 Laser Microsurgery for Early Laryngeal Carcinoma

	T stage			
	Tis	T1a	T1b	T2
Number of patients	2	30	9	7
Local recurrence (%)	0	17 (5/30)	22 (2/9)	43 (3/7)
Radiotherapy (%)	0	10 (3/30)	22 (2/9)	14 (1/7)
Tracheostomy (%)	0	0	0	0
Feeding Tube (%)	0	0	0	0
Salvage laryngectomy (%)	0	0	0	14 (1/7)

Table 2. Analysis of the Patients with Recurrences

	Iinitial T stage	Site of first recurrence	Time (mo)	Second treatment	Site of second recurrence	Time (mo)	Third treatment	Site of third recurrence	Time (mo)	Fourth treatment	Outcome (mo†)
1	T1b	Right TVC	17.3	RT	–	–	–	–	–	–	DF (67.6)
2	T1b	Left Ventricle	15.8	LE	–	–	–	–	–	–	DF (58.4)
3	T1a	IL, TVC	50.9	LE	–	–	–	–	–	–	DF (58.3)
4	T1a	IL, ventricle	4.1	RT	–	–	–	–	–	–	DF (52.0)
5	T1a	IL, TVC	18.5	LE	–	–	–	–	–	–	DF (42.9)
6	T1a	IL, TVC	4.9	LE	–	–	–	–	–	–	DF (21.2)
7	T1a	IL, neck	9.9	type I MRND + CCRT	lung	6	palliative	–	–	–	DOD (15.3)
8	T2	Right, FF	6.9	LE	Right, FF	4	RT	–	–	–	DF (42.8)
9	T2	Left	1.1	LE	Left	3.1	CCRT	Left	9	TL	DF (17.5)
10	T2	Right	5.4	LE	Left, AC	1.9*	LE		–	–	DF (8.2)

Abbreviations: IL: ipsilateral; TVC: true vocal cord; FF: false fold; AC: anterior commissure; RT: radiotherapy; DF: disease-free and alive; LE: laser excision; DOD: died of disease; MRND: modified radical neck dissection; CCRT: concurrent chemoradiotherapy; TL: total laryngectomy; *: From a different subsite of previous recurrence; †: Months after primary treatment.

tions was 3.4 ± 2.3 days. We pre-defined a "minimal" blood loss as being less than 50 mL during the operation. All operations were recorded "minimal" with the exception of 1 patient (2.1%) who had a total laryngectomy and failed to maintain adequate telephone intelligibility. The other 47 patients (97.9%) maintained fair telephone communicative ability during the 1 month outpatient follow-ups.

DISCUSSION

Although several treatments are currently available for early laryngeal cancer, the optimal treatment has not yet been determined. The local control, laryngeal preservation, and survival rates of patients with glottic cancer were similar after primary radiotherapy and conservative operations, including open partial laryngectomy and TLM.[8] Open partial laryngectomy destroys normal laryngeal anatomy and can impair laryngeal function. Major surgical morbidities such as aspiration pneumonia, fistula, infection, bleeding, subglottic stenosis, and permanent dependence on gastrostomy have been reported.[20,21] TLM has resulted in few documented intraoperative or postoperative major complications and has been generally regarded as a safe procedure.[22,23] Ledda et al. reported no intraoperative or postoperative complications in a series of 103 patients who underwent TLM for Tis to T2 glottic cancer between 1993 and 2001.[23] In our series, no major perioperative complications occurred, which is consistent with the safety of this procedure.

The lymphatic drainage for the glottic larynx is sparse when compared with the supraglottis and subglottis and thus cervical metastasis is rare. Cervical lymph node involvement was present in less than 1% of early T1 glottic carcinomas.[24] Peretti et al. retrospectively reviewed 140 patients with Tis to T2 glottic cancer and the 5-year ultimate local control rate following the laser operation alone was 89%.[5] Gallo et al. evaluated 156 patients with Tis and T1 glottic tumors treated with TLM and found that the local control rates were 100% for Tis, 94% for T1a, and 91% for T1b lesions.[3] In our series, neck recurrence and eventual distal metastasis was found only in 1 patient. Most locally recurrent tumors were successfully controlled by secondary TLM alone or irradiation (Fig. 1). The local control rate exclusively for TLM was 85% and the ultimate local control rate was 100% when combined with other modalities (Fig. 2A). Only one patient required salvage total laryngectomy due to local failure after concurrent chemoradiotherapy. No patients required intraoperative or postoperative tracheostomy.

The involvement of the anterior commissure in glottic carcinomas has been reported as a significant prognostic indicator for local control.[2,8,18] The anterior commissure tendon combines the vocal ligament, thyroid epichondrium, and thyroepiglottic ligament at the level of the vocal fold and is thus regarded as a barrier against cancer spread.[18] However, this barrier has been regarded as questionable just superior to and inferior to the level of the vocal cord.[18] For TLM, the difficulty in exposure of this specific anatomical site by endoscopy has also been suggested as a cause of higher local recurrence after TLM.[18] Mendenhall et al. reported a higher rate of local recurrence in laryngeal cancers involving the anterior commissure treated by TLM, whereas no difference was found when this subgroup received radiotherapy.[8] On the other hand, many authors have suggested that there is no difference in local control following TLM whether or not the anterior commissure was involved.[3,5,23] Steiner et al. retrospectively reviewed 261 patients with T1 to T2 glottic carcinomas treated with TLM and reported the 5-year local control rates according to the involvement of anterior commissure. Among the patients with tumors involving the anterior commissure, the 5-year local control rates ranged from 73% to 84%. In patients with tumors without anterior commissure involvement, the 5-year local control rates ranged from 74% to 92%. It was concluded that TLM was effective for laryngeal cancers regardless of anterior commissure involvement.[25] In a series of patients reported by Peretti et al., 40 out of 138 patients treated with TLM had tumors involving the anterior commissure and no statistical difference in the local control rate was found with respect to anterior commissure involvement.[5] Pearson et al. also reviewed the records of 39 patients with glottic carcinomas involving the anterior commissure treated with TLM and reported no local recurrences for T1 and T2 primary lesions.[26] In our study, anterior commissure involvement was found in 18 out of 48 patients with glottic cancers and there was no statistically significant difference (p = 0.90) in primary local control rates (Fig. 2B). These results indicate that in early glottic cancers,

tumor involvement of the anterior commissure did not affect oncological results in terms of primary local control and survival following treatment with TLM. Thus, anterior commissure involvement does not represent a poor prognostic indicator.

Another demonstrable advantage for TLM is its short treatment course and lower cost. Pearson et al reported an average hospital stay of 3.3 days in his series of 39 patients with T1 to T4 laryngeal cancers treated with TLM, with 12 patients treated on a same-day basis.[26] In our study, the mean operation time and the hospital stay were 132.9 minutes and 3.4 days, respectively. These results are comparable with previous studies. The short operation time directly impacted possible anesthesia-related morbidity and thus made those patients who were not suitable for prolonged general anesthesia, due to underlying systemic diseases, eligible for this treatment modality. Furthermore, all operations had a documented blood loss below 50 mL without major postoperative complications, reflecting the safety of this procedure. The short hospital stay also resulted in lower medical costs and a lessened impact on employment for the patient.

Radiotherapy provides excellent local control for early laryngeal cancers and is still the primary treatment modality for early laryngeal cancer in many hospitals.[8] In our institute, primary radiotherapy was conducted in 134 patients with T1 and T2 glottic cancers from March 1983 to February 2003. A 71% and 83% 5-year initial and final local control rate and a 77% 5-year larynx preservation rate were reported for this series of patients.[2] Comparable results with respect of local control and larynx preservation using TLM have been reported by many authors.[3,5,11,23] Brandenburg compared these two modalities according to the cost of treatment and found that radiotherapy had a significantly higher cost than TLM, suggesting that TLM should be considered as the initial treatment modality.[16] However, other investigators have reported similar costs for these two treatments.[8] In addition to medical costs, laser operations provide a curative treatment only within a few days, whereas a full course of external beam radiotherapy requires at least 7 weeks of continuous treatment. Therefore, the shorter treatment period for TLM may provide a more acceptable alternative for patients with poor compliance. Nevertheless, because radiotherapy successfully treated 5 out of 9 patients with local recurrence after TLM, this treatment should also be considered and suggested under such circumstances.

For evaluation of post-operative vocal function, objective measurements such as acoustic and aerodynamic analyses, the overall grade, rough, breathy, asthenic, and strained (GRBAS) scale, and subjective examinations such as rigid stroboscopy have been used.[27] Self-assessment of voice quality by patients, including a vocal handicap index, can reflect their perception of disability resulting from voice problems.[28] Telephone communication has also been used as a form of self-assessed voice outcome measurement for laryngectomees and is related with overall quality of life.[29] In our study, most patients were able to maintain adequate telephone function after treatment, reflecting a useful voice and hence the ability to communicate with distant individuals. However, this measurement only provides a quick view of a generalized voice outcome instead of the objective data collected as part of a detailed analysis of qualitative vocal function. From literature, voice outcome analyses were comparable after TLM and radiotherapy treatment of early glottic cancers.[8]

In the present patient series, TLM resulted in short hospital stays, extremely low surgical morbidity, and sound oncological results, suggesting that it should be a preferred treatment modality for early laryngeal cancer. Radiotherapy had a significant beneficial role in the adjuvant treatment of selected patients and in the treatment of recurrent cancers. This treatment protocol provides excellent ultimate local control, larynx preservation, and functional outcome. Under this treatment modality, involvement of the anterior commissure is not a poor prognostic indicator in terms of local control and long-term survival.

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經口內視鏡二氧化碳雷射顯微手術治療早期喉癌

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背 景： 探討經口內視鏡二氧化碳雷射顯微手術施行於 Tis, T1, T2 早期喉癌在局部控制，存活率以及喉部保存上的角色。

方 法： 自 1999 年 10 月至 2008 年 2 月，統計 48 位早期喉癌並施行經口內視鏡二氧化碳雷射切除手術 (TLM) 之病人。使用 Kaplan-Meier 氏方法計算整體存活率、最初與最終局部控制率以及喉保存率。腫瘤侵犯前聯合對於局部控制的影響則使用 log-rank test 計算。術後的嗓音功能則以病人之電話交談能力評估。

結 果： 五年整體存活率爲 97% (95% CI 94%-100%)，最初局部控制率爲 72% (95% CI 66%-92%)，僅使用 TLM 治療之局部控制率爲 85% (95% CI 79%-99%)，最終局部控制率爲 100%，喉保存率爲 97% (95% CI 94%-100%)。腫瘤前聯合侵犯對於最初局部控制率並無顯著影響 (p = 0.9)。47 (97.9%) 位病人於術後表示仍具有使用電話交談的能力。

結 論： 根據長期存活率以及局部控制率，經口內視鏡雷射顯微手術爲早期喉癌的最佳初步治療選擇之一。經由此方式，腫瘤喉部前聯合侵犯並不構成較差的預後因素。
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關鍵詞：喉癌，經口顯微手術，頭頸部，雷射，內視鏡

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