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Original Scientific Paper

TREATMENT OF EARLY GLOTTIC CARCINOMA WITH TRANSORAL ENDOSCOPIC LASER SURGERY

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SUMMARY – Laryngeal carcinoma is one of the most common tumors of the head and neck, just after skin cancer. Alongside open surgery, transoral endoscopic laser surgery (TOLS) has become widespread as a treatment method. Our aim was to assess the efficacy of transoral laser cordectomy in a group of patients with early glottic carcinoma. We retrospectively analyzed data on 131 patients who underwent TOLS in the 2017-2021 period. We divided patients into groups according to tumor stage and type of cordectomy performed, and compared outcomes between the groups. Our results revealed a higher number of patients in the group with Tis and T1a than in those with T1b and T2 who underwent type III cordectomy, and also a higher number of those for whom outpatient follow-ups were sufficient after surgery in the same group. We did not observe significant difference in outcomes according to cordectomy type except for type V (a-d), where a higher number of patients had to undergo radiotherapy. This study underlines the importance of careful patient selection for TOLS, as well as the need for close cooperation with pathology and radiology specialists to ensure optimal approach and extent of surgery for each individual patient. It also displayed TOLS as a sound therapeutic option for early stages of glottic carcinoma but also indicated the need for similar studies in a larger number of patients to elucidate the effectiveness in certain glottis areas.

Key words: *Transoral laser surgery; Glottic carcinoma; Cordectomy; Outcomes*

Introduction

Laryngeal carcinoma is one of the most common tumors of the head and neck, just after skin cancer. Histologically, in most cases it is squamous cell carcinoma, and by the time of diagnosing it can be classified in early stages (I and II) and advanced stages (III and IV).

Early stage carcinomas are usually treated with single modality, either surgically or by radiotherapy, while advanced stage tumors require multimodal strategies which include combinations of surgery, radiotherapy, chemotherapy, or other relatively new methods of treatment such as immunotherapy.

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Alongside open surgery, transoral endoscopic laser surgery (TOLS) has become widespread as a treatment method. It was first performed by Strong and Jako in 1972[1]. Numerous advantages of this procedure have been described since, compared to open surgical methods and primary radiotherapy. Laser surgery is oncologically sound with a possibility of achieving a histopathologically free margin with largely preserved laryngeal function. Only one procedure is often required, without the need for tracheostomy and insertion of nasogastric tube. Modern CO_2 lasers are precise and capable of good intraoperative hemostasis. It is possible to repeat laser resection on case of positive or uncertain margin[2,3].

The aim of this study was to assess the efficacy of transoral laser cordectomy in patients with early glottic carcinoma (stages I and II) treated at our department.

Patients and Methods

We analyzed data on 131 patients diagnosed with glottic carcinoma who had undergone TOLS from 2017 to 2021. All patients underwent surgery at the Department of Otorhinolaryngology and Head and Neck Surgery, Zagreb University Hospital Center. Data were analyzed retrospectively using the Department database of oncologic patients. Inclusion criteria were glottic carcinomas stage Tis, T1a, T1b, and selected patients with T2 tumors. All patients with suspected neck lymph node metastases underwent ultrasound and computed tomography scan of the neck preoperatively, and fine needle aspiration biopsy (FNAB) as needed. Exclusion criteria were laryngeal carcinoma previously treated either surgically or with radiotherapy, and existing locoregional or distant metastases. Surgical procedures, that is, cordectomies, were classified according to the current European Laryngological Society classification (I-VI)[4], as follows: subepithelial (type I), subligamental (type II), transmuscular (type III), total cordectomy (type IV), extended cordectomy (type V a-d), and commissure resection with bilateral anterior cordectomy. Type V is further classified as Va (cordectomy encompassing contralateral vocal fold), Vb (encompassing arythenoid), Vc (encompassing ventricular fold), and Vd (encompassing subglottis). TNM staging was made according to the current American Joint Committee on Cancer classification from 2018[5].

Patients were divided into groups according to TNM stage, type of cordectomy performed, and outcome. The possible outcomes were outpatient follow-up, repeated TOLS because of uncertain or positive surgical margin, repeated TOLS because of recurrence, total laryngectomy because of recurrence, total laryngectomy because of residual tumor, and radiotherapy.

Ethics

This study was approved by the Zagreb University Hospital Center Bioethical Board adhering to the Helsinki Declaration of 1983. All patients read and signed the written consent form.

Statistics

Statistical analysis of data among the groups was performed using Mann Whitney U test and χ^2-test. The normality of distribution was tested using Shapiro-Wilk test. The values of p less than 0.05 were considered as statistically significant. Statistical analysis was performed using MedCalc Statistical Software, version 19.4.0 (MedCalc Software Ltd., Ostend, Belgium).

Results

Data on 131 patients were analyzed. There were 88% of men, mean age 67 (range 35-83) years. Clinicopathological characteristics of the whole group are displayed in Table 1. We compared data regarding types of cordectomy that were carried out in the two groups of patients, depending on tumor stage (Table 2). In group A, 2 type I, 3 type II, 47 type III, 9 type IV and 20 type V cordectomies (11 type Va and 9 type Vc) were carried out. In group B, no type I or II cordectomy was performed, while there were 18 type III, 6 type IV and 25 type V cordectomies (12 type Va, 2 type Vb/type Vc and 4 type Vd), yielding a statistically significant difference compared to group A (p=0.00138).

When comparing data on outcomes after certain procedure (Table 3), in group A outpatient follow-up examinations were sufficient after surgery in 58.4% of patients as compared with 32.6% in group B. In group A, TOLS had to be repeated due to uncertain or positive margins in 23.2% of patients *versus* 36.7% in group B. Repeated TOLS due of recurrence was required in 8.5% of group A patients and 4.1% of group B patients. Total laryngectomy due to recurrence was performed in 3.7% of group A patients and 14.3% of group B patients, while due to residual tumor it was performed in 2.4% of group A patients and 8.2% of group B patients.

When observing outcome according to type of cordectomy performed, patients were divided into two groups depending on the extent of the procedure (Table 4). Group A included patients having undergone cordectomy types I-IV, and group B patients having undergone extended cordectomy (types Va-Vd). None of the patients underwent type VI cordectomy. Outpatient follow-ups were sufficient for 48.2% of group A patients compared with 34.1% of group B patients. TOLS had to be repeated due to uncertain or positive margin in 29.9% of group A patients *versus* 25% of group B patients. In case of recurrence, TOLS had to be repeated in 8% of group A patients and 11.36% of group B patients. Total laryngectomy because of recurrence was undertaken in 8% of group A patients and 4.5% of group B patients, while in case of residual tumor it was performed in 4.6% and 4.5%, respectively. Radiotherapy was required after TOLS in 2.3% of group A patients and 13.63% of group B patients.

Table 1. Clinicopathological characteristics of study population

Variable	Result
Age (years)	67 (35-83)
Gender:	
Men Women	88% 12%
Tumor stage: Tis T1a T1b T2	 5 (3.82%) 77 (58.78%) 33 (25.2%) 16 (12.21%)
Type of cordectomy: I II III IV Va Vb Vc Vd VI	 2 (1.52%) 3 (2.3%) 68 (51.9%) 15 (11.45%) 23 (17.56%) 2 (1.52%) 16 (12.21%) 3 (2.3%) 0
Outcome: Outpatient follow-ups Reoperation due to uncertain or positive margin Reoperation due to recurrence Total laryngectomy due to recurrence Total laryngectomy due to residual tumor Radiotherapy	 64 (48.85%) 37 (28.24%) 12 (9.2%) 9 (6.9%) 6 (4.58%) 8 (6%)

Table 2. Type of cordectomy performed depending on tumor type

	A (n=82)		B (n=49)			
Type of cordectomy	Tis (n=5)	T1a (n= 77	T1b (n= 33	T2 (n=16)	p	p
I	2 (2.4%)				NA	<0.01
II					NA	
III	3 (3.66%)	48 (54.9%)	14 (28.57%)	0	0.02	
IV		9 (11%)	4	2	0.83	
Va		11 (13.4%)	12	0	0.1	
Vb			2		NA	
Vc		9 (11%)	3	4	0.57	
Vd				4	NA	

NA = not applicable

Table 3. Outcomes according to tumor stage

	A (n=82)		B (49)			
Outcome	Tis	T1a	T1b	T2	p	p
Outpatient follow-ups	5 (6.01%)	43 (52.4%)	9 (18.3%)	7 (14.3%)	<0.01	0.02
Reoperation due to uncertain or positive margin		19 (23.2%)	16 (32.65%)	2 (4.1%)	0.09	
Reoperation due to recurrence		7 (8.5%)	2 (4.1%)		0.32	
Total laryngectomy due to recurrence		3 (3.7%)	3 (6.1%)	4 (8.2%)	0.02	
Total laryngectomy due to residual tumor		2 (2.4%)	2 (4.1%)	2 (4.1%)	0.13	
Radiotherapy		3 (3.7%)	2 (4.1%)	2 (4.1%)	0.26	

Table 4. Outcomes according to type of cordectomy performed

	A (n=87)				B (n=44)					
	I (n=2)	II (n=3)	III (n=68)	IV (n=15)	Va (n=23)	Vb (n=2)	Vc (n=16)	Vd (n=3)	p	p
Outpatient follow-ups	2	2	33	5	10		5		0.12	0.07
Reoperation due to uncertain or positive margin		1	19	6	7		4		0.55	
Reoperation due to recurrence			7				3	2	0.53	
Total laryngectomy due to recurrence			7				2		0.42	
Total laryngectomy due to residual tumor			2	2	2				0.98	
Radiotherapy				2	4		2		0.01	

Discussion

Correct selection of patients with glottic carcinoma who are candidates for TOLS is one of the most important factors in achieving positive treatment outcome. Tumor characteristics such as dimensions, localization, pattern of spreading alongside with specifics of each patient (age, comorbidities, anatomic features) have a key role when making treatment decision. Thorough preoperative diagnostic workup is necessary to minimize the rate of positive or uncertain margins, which affects the success of surgical treatment, especially in case of TOLS, where it is often difficult to perform tumor resection deep enough in the healthy tissue. In this study, we observed a significantly higher number of patients in the Tis and T1a group for whom outpatient follow-up was sufficient and who

did not develop recurrence or displayed residual tumor, as compared with the T1b and T2 group (Table 4). This could be attributed to the before mentioned difficult visualization in case of advanced stage tumors and therefore more challenging margin control. Another affirmation of significance of workup and adequate visualization is the observed significantly higher proportion of patients in the T1b and T2 groups who needed total laryngectomy. Some earlier studies demonstrated that uncertain or superficial positive margin did not have a notable impact on treatment outcome[6]. This study revealed a relatively high proportion of patients who required repeated TOLS due to uncertain or positive margin (43.5%), but displayed no tumor after histopathological analysis. Laser beam thermically damages the margins of excision and often causes shrinking of tissue, which can complicate the pathologist's assessment and potentially result in a positive margin[7]. Some authors are unsure whether it is always necessary to perform re-excision in case of uncertain or positive margin, and in many cases practice watchful waiting and frequent follow-ups[8]. On the other hand, Osuch-Wójcikiewicz *et al*. report that patients in whom re-excision was performed due to positive or uncertain margin displayed a decreased rate of recurrence compared to those who had negative margins in the first place[9]. This also highlights the importance of detailed preoperative radiological analysis and close cooperation with pathology specialist in case of uncertain or positive margin to minimize the probability of residual tumor. In the future, intraoperative use of narrow-band imaging could ensure more reliable margin control[10].

According to the literature, the viability of local tumor in the 5-year period varies from 76% to 100%[11-13], although some studies with a high proportion of tumors affecting the anterior commissure report lower rates[7]. In this study, local tumor control was observed in 77.1% of patients, which could be attributed to the relatively high proportion of T1b and T2 tumors (25.2%), and a very small percent of Tis stages, compared to other similar studies[10].

One of the prerequisites for efficacy of TOLS is adequate visualization of the glottis. Due to anatomic relationships and constitution, sometimes it is not possible to clearly visualize the whole glottis and therefore to achieve effective tumor resection in total with clear oncologic margins. According to numerous studies, the failure of sufficient visualization of endolarynx with this procedure led to limitations of TOLS in 1.5% to 24% of cases, depending on the institution[10,14]. Adequate visualization of the glottis is often not possible without resection of ventricular folds. Kashima *et al*. describe ventricular fold resection as the first step of the procedure which aims to resect the full length of the vocal cord[15]. Hans *et al*. report on a markedly more frequent use of partial resection of ventricular folds in case of T1b and T2 tumors[10], however, there was no difference in the rate of positive margins compared to studies in which ventricular resection was not performed. Our study showed no statistically significant difference of outcomes in patients having undergone extended cordectomy, which largely included ventricular fold resection (Vc), as compared to those having undergone less radical procedures, except for the case of radiotherapy. Radiotherapy was more often necessary in patients after type V cordectomy (a-d). On the other hand, we observed a strong trend of worse tumor control after type Vc cordectomy, where outpatient follow-up or one reoperation due to uncertain/positive margin was sufficient in 56.3% of patients, while such outcomes were observed in 76.4% of cases after type III cordectomy. In our study, type III cordectomy was much more often performed in Tis and T1a stages (p=0.022) than type Vc, which goes along with the previously described trend.

Anterior commissure involvement is by some authors discarded as nonsignificant in affecting oncologic outcomes[6], while others describe worse local control and laryngeal preservation rates. In case of tumor crossing the anterior commissure in the vertical plane, the possible pathways of spreading are through the thyroid notch, the cricothyroid membrane and the pre-epiglottic space, which jeopardizes the effectiveness of TOLS[16,17]. On the contrary, when the tumor crosses the commissure in the glottic plane, TOLS is considered as oncologically sound therapeutic option. We observed 17.6% of patients to have tumor involvement of the anterior commissure and therefore the same proportion of type Va cordectomies, with no significant difference in laryngeal preservation rate. However, a trend of higher rate of radiotherapy was observed in this group (17.4% *vs*. 3.4%). A larger group of patients would be necessary for more objective evaluation of the impact of anterior commissure involvement on outcomes, but this still indicates the importance of meticulous preoperative radiological assessment.

Today, TOLS represents a reliable therapeutic solution for a wide spectrum of glottic carcinomas. Its continuing development and widespread implementation will surely add to further progress with improved treatment efficacy and functional outcomes. Results of this study underline the advantages of TOLS, and better outcomes observed in early tumor stages point to the importance of thorough patient selection and exact planning of appropriate extent of cordectomy. The potential limitations of this technique, such as inadequate tumor control or unfavorable outcomes, can be overcome by improving preoperative and intraoperative planning and conducting further multicenter studies.

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Sažetak

LIJEČENJE RANOG KARCINOMA GLOTISA TRANSORALNOM ENDOSKOPSKOM LASERSKOM KIRURGIJOM

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Karcinom grkljana ubraja se u najčešće tumore u području glave i vrata, odmah nakon kožnih zloćudnih tumora. Uz otvorene kirurške metode transoralna endoskopska laserska kirurgija je postala vrlo rasprostranjena kao metoda liječenja. Cilj našeg istraživanja bio je utvrditi kolika je uspješnost laserske kordektomije u liječenju bolesnika oboljelih od ranog karcinoma grkljana. U ovoj retrospektivnoj studiji analizirali smo podatke 131 bolesnika koji su podvrgnuti endoskopskoj laserskoj kirurgiji glasnica zbog karcinoma u razdoblju od 2017. do 2021. godine. Bolesnici su podijeljeni u skupine s obzirom na stadij tumora te tip učinjene kordektomije te smo usporedili ishode među skupinama. Rezultati su prikazali veći broj bolesnika s tumorima Tis i T1a (skupinaa A) nego onih s T1b i T2 (skupina B) kojima je učinjena kordektomija tip III. te također veći broj onih kojima su dostatne bile ambulantne kontrole u skupini A. Nije uočena značajna razlika u ishodima s obzirom na tip učinjene kordektomije osim za tip V (a-d), gdje je veći broj bolesnika kasnije podvrgnut radioterapiji. Ovo istraživanje ukazalo je na važnost pažljivog izbora bolesnika koji su kandidati za transoralnu lasersku resekciju te nužnost bliske suradnje sa specijalistima radiologije i patologije, kako bi se osigurao optimalan pristup i opseg za svakog bolesnika. Također dokazuje kako je transoralna laserska resekcija pouzdana terapijska opcija za rane stadije karcinoma glotisa te upućuje na važnost provođenja sličnih istraživanja s većim brojem bolesnika kako bi se rasvijetlila uspješnost ove metoda u određenim dijelovima glotisa.

Ključne riječi: *Transoralna laserska kirurgija; Karcinom glotisa; Kordektomija; Ishodi*