

Oncological and vocal outcomes of patients with stage T1 glottis squamous cell carcinoma: open surgery vs. radiofrequency ablation

Shuguang Li¹, Xiaoli Zhu¹, Yingying Zhu¹, Wenwen Diao¹, and Xingming Chen¹

¹Peking Union Medical College Hospital

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Abstract

Objectives: The optimal treatment for stage T1 glottis squamous cell carcinoma remains controversial. We compared the oncological and vocal outcomes of patients who received endoscopic surgery with radiofrequency ablation (RFA) or open surgery. **Design&Setting&Participants:** Data were retrospectively collected for 93 patients who received primary treatment by RFA (n = 65) or open surgery (n = 28) from 2008 to 2014. **Main outcome measures:** Their characteristics were compared using the chi-square test. The 5-year disease-free survival (DFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. Prognostic factors were assessed by univariate analysis using the log-rank test and by multivariate analysis using Cox models. Subjective vocal outcomes were evaluated by Voice Handicap Index-30 (VHI-30) questionnaire. The VHI scores of the two groups were compared using Mann-Whitney U test. **Results and Conclusions:** The 5-year DFS was 72.3%(47 / 65) for the RFA group and 92.9% (26 / 28) for open surgery group. The open surgery group had a significantly better 5-year DFS (P=0.03), but the two groups had comparable OS (RFA: 86.2%; open surgery: 78.6%; P=0.26). Open surgery led to significantly worse voice quality (P<0.001). Among patients who received open surgery, those with involvement of the anterior commissure had higher total VHI scores (P=0.02). RFA and open surgery were both effective surgical treatments for stage T1 glottis squamous cell cancer. Open surgery was associated with a lower local recurrence rate but a worse VHI score. Among patients receiving open surgery, those with tumors involving the anterior commissure had poorer vocal outcomes.

INTRODUCTION

Laryngeal carcinoma accounts for 30 to 50% of all head and neck cancers worldwide. In China, the mortality rate from laryngeal cancer is 14.5% [1,2] and 56–75 % of these patients are diagnosed with early-stage (T1/T2) cancer, which mostly arises from the glottis [3]. Most patients diagnosed with early-stage laryngeal cancer present with a main symptom of hoarseness. The treatment modalities used for these patients can affect oncological and vocal outcome.

The therapeutic modalities used for early glottis carcinomas (Tis, T1, and selected T2 cases) include open surgery, endoscopic resection, and radiotherapy, or a combination of these [4]. The optimal treatment to be used for early-stage glottis cancer is still disputed, and depends on oncological and functional outcomes, cost, duration of hospitalization, doctor-patient communication, religious beliefs, and other factors [5,6]. The anterior commissure of the larynx is a weak point that easily permits invasion of tumors into the thyroid cartilage because of the missing perichondrium/periosteum at the insertion of the Broyles' ligament [7]. However, the anterior commissure is a clinical rather than an anatomical term, and the impact of anterior commissure involvement in laryngeal carcinoma has been controversial for many years. Even in patients with early-stage glottis cancer, anterior commissure involvement was considered a poor prognostic factor in some studies but not in others [8].

In the present study, we used radiofrequency ablation (RFA) with endoscopic surgery, which has the same surgical principle and margin as the CO₂ laser microsurgery. However, RFA has the benefit that it works at

a temperature of 60°C and therefore protects against peripheral soft tissue injury [9].

Very few previous retrospective case-series compared RFA with open surgery for the treatment of stage T1 glottis squamous cell cancer. The present retrospective single-center study evaluated the oncological and vocal outcomes of patients who received RFA or open surgery for stage T1 glottis squamous cell cancer, with a special focus on patients with involvement of the anterior commissure.

METHODS

Ethics statement

Removed for blind peer review.

Participants

The study group consisted of adult patients with pathologically proven T1/N0/M0 glottis squamous carcinoma who were treated and followed at the Ear-Nose-Throat (ENT) Department of one hospital from October 2008 to October 2014. All the surgeries were performed by 3 specialists, each with more than 10 years of surgical experience. Patients were excluded if they had a second primary tumor, were younger than 18 years old, received primary radiotherapy, had a repeated cancer, or if data were missing or insufficient for analysis.

Tumors were staged according to the American Joint Committee on Cancer (AJCC) TNM cancer staging system (sixth edition, 2002) [10]. Involvement of the anterior commissure was defined as visible spread of the tumor to the anterior-most extent of a single membranous vocal fold or continuously from one vocal fold to the other. For each patient, the surgeons explained the detailed benefits and disadvantages of each kind of therapy, including the effect on voice quality. In our institution, RFA is always the primary surgical option. But, we choose open surgery if the patient's larynx cannot be sufficiently exposed, if there is deep infiltration of the tumor into the anterior commissure, or if there is a large stage T1b tumor involving the anterior commissure. The surgeon's determinations of deep infiltration and tumor stage were based on evaluation of preoperative electronic laryngoscopy and computed tomography (CT) images.

Operative techniques

RFA [11] was used for endoscopic surgery (Coblator II surgery system, EVac70, EIC-7070-01 Radiofrequency Ablation Cutter, Arthrocare Company, U.S.). First, a suspension laryngoscope was inserted, and the lesion was examined under a microscope (LEICA, M520) and using a 0- and 70-degree endoscope. Intraoperative rapid frozen sections were collected during each surgical procedure to identify tumor-free margins. The recent Proposal for Revision of the European Laryngological Society Classification of Endoscopic Cordectomy classified surgical procedures as type I to VI [12]. Among the 65 enrolled patients, there were 31 type III, 17 type IV, 8 type Va, and 9 type VI procedures. External partial surgery was chosen in 28 patients, including 14 Tucker's reconstructive laryngectomies [13] and 14 larynx-cleaved vocal cord resections.

Subjective voice assessment

Vocal outcomes were evaluated using the Mandarin Chinese version of the Voice Handicap Index-30 (VHI-30) questionnaire. It is a self-evaluation form adapted from the American Speech Language Hearing Association [14] that has 30 questions in 3 domains (functional, physical, and emotional). This form was translated and validated in Mandarin Chinese [15]. The possible response to each of the 30 questions is: never (0 points), almost never (1 point), sometimes (2 points), almost always (3 points), and always (4 points). A total score of 10 or less was considered normal, and a score higher than 10 indicated a poor voice-related outcome.

Endpoints

Local recurrence was defined as at least carcinoma in situ of the laryngeal mucosa on the ipsilateral or contralateral laryngeal side after complete removal of tumor with microscopically and histologically negative margins at the initial surgery. The 5-year overall survival (OS) was defined as the interval between surgery and the date of the last consultation or death. The 5-year disease-free survival (DFS) rate was defined as the percentage of patients who were alive and cancer-free at 5 years after the date of the initial surgery.

Statistical analysis

Baseline data were compared using the chi-square test. OS and 5-year DFS were estimated by the Kaplan-Meier method. Prognostic factors were assessed in univariate analysis using the log-rank test and in multivariate analysis using Cox models. Statistical calculations were performed using SPSS (version 23.0; SPSS, Inc. an IBM Company, Chicago, Illinois). The VHI-30 scores of the two groups were compared using the Mann-Whitney U test. P value less than 0.05 was defined as statistically significant.

RESULTS

Patient characteristics

There were 93 patients (91 men, 2 women), the median age was 65 years (range: 54 to 69 years), and 52 patients (55.9%) had anterior commissure invasion (Table 1). The median post-surgical follow-up time was 82 months (range: 20 to 138 months). Fifty-four patients (58%) were smokers and 49 (53%) drank alcohol. Tumor stage classification indicated that 62 patients (66.7%) had stage T1a and 31 (33.3%) had stage T1b. Sixty-five patients (69.9%) received RFA and 28 (30.1%) patients received open surgery.

Oncological outcomes

The 5-year DFS was significantly worse in the RFA group than in the open surgery group (72.3% *vs.* 92.9%, $P = 0.03$; Figure 1). Similarly, the RFA group also had a higher rate of local recurrence (27.7% *vs.* 7.1%, $P = 0.03$). However, the two groups had similar 5-year OS rates (86.2% *vs.* 78.6%; $P = 0.26$). (Table 2)

Analysis of patients with invasion of the anterior commissure indicated the two groups had no significant difference in 5-year DFS, although there was a trend for poorer survival in the RFA group (67.6% *vs.* 88.9%, $P = 0.09$; Figure 2). The 5-year OS rates of the two groups were also comparable (88.2% *vs.* 83.3%, $P = 0.58$; Table 3).

Factors affecting oncological outcomes

We performed multivariate analysis with Cox models to identify factors associated with OS and 5-year DFS (Table 4). This analysis of multiple factors (gender, age, smoking, alcohol abuse, clinical T stage, surgery pattern, involvement of anterior commissure, and resection margins) indicated that only type of surgery had a significant impact on 5-year DFS ($P = 0.02$; HR: 6.35, 95% CI: 1.31 to 30.74). Involvement of the anterior commissure had no significant impact on outcome.

Vocal outcomes

We analyzed data from the VHI-30 after 1 year of DFS. Seventy-six patients (82%) returned questionnaires. The RFA group had a median total VHI-30 score of 11 (range: 9 to 15) and the open surgery group had a median total VHI-30 score of 50 (range: 17 to 55). The Mann-Whitney test indicated the RFA group had significantly better functional, physical, emotional, and total scores ($P < 0.001$ for all comparisons; Table 5). Analysis of the open surgery group indicated that patients with anterior commissure invasion had a worse VHI-30 total score ($P = 0.02$) and emotional score ($P = 0.01$; Table 6). Analysis of the RFA group indicated a worse VHI emotional score ($P = 0.02$; Table 6) in patients with anterior commissure invasion.

Salvage treatment

The RFA group had 18 recurrences (28%). One of these patients was lost to follow-up, and the other patients received RFA endoscopic partial laryngectomy ($n = 8$), external partial laryngectomy ($n = 5$), or total laryngectomy ($n = 4$). After retreatment, the larynx preservation rate was 76.5% (13 of 17). Recurrences (2 of 28) of the open surgery group were treated by total laryngectomy ($n = 2$).

DISCUSSION

The optimal treatment for early-stage glottis cancer must include accurate evaluation of the range of the cancer, multidisciplinary consultation, consideration of patient expectations, analysis of surgical pattern, and expertise in surgical techniques [16]. Voice quality is also an important consideration. In this study,

we reviewed 93 patients with stage T1 glottis cell carcinoma who received RFA endoscopic surgery or open surgery, 52 of whom had anterior commissure invasion.

Our open surgery and RFA groups had similar OS, although the 5-year DFS was better in the open surgery group. This outcome was comparable to previous studies [9,17,18]. More specifically, Zhang et al. [17] conducted a single-blind randomized clinical study that compared treatment of stage T1a glottis cancer using RFA and a CO₂ laser, and reported a 3-year OS of 96%, similar to our result. Shuang et al. [9] performed a retrospective study and reported the local recurrence rate in patients with anterior commissure involvement who received RFA was 31.2%, also comparable to our results (32.4%). Philipp et al. [18] compared the oncological results of open surgery and trans-oral laser micro-resections (TLM) in patients with early-stage glottis squamous cell carcinoma. The local recurrence rate was 20.4% (10 of 49) for TLM and 10.7% (3 of 28) for open surgery. Similarly, our results indicated that open surgery provided a reduced recurrence rate. However, the considerable disadvantages associated with open procedures must be considered, especially poor preservation of voice quality, increased risk for complications, and greater costs.

Previous researchers have considered tumor involvement of the anterior commissure as an important parameter affecting the oncologic outcomes of patients with early-stage glottis carcinoma. However, we found that the impact of anterior commissure involvement had no significant impact on outcome, in contrast to several previous studies [18, 19, 20]. In particular, a recent study of 130 patients who received radiation therapy for stage T1/2/N0 glottis tumors reported that anterior commissure involvement was the main factor affecting local control [19]. Wolber et al. [18] compared patients who received trans-oral laser micro-surgery or open surgery and found a significant difference in local recurrence rate only for tumors invading the anterior commissure; based on endoscopy, the recurrence rate of tumors with involvement of the anterior commissure was 38.1%, but the recurrence rate without involvement was 7.1%. Steiner et al. [20] reviewed 263 patients with stage T1a, T1b, or T2a glottis lesions and reported that local recurrence was more common if there was initial involvement of the anterior commissure (14% in T1a tumors with involvement *vs.* 5% in T1a tumors without involvement).

There are several possible explanations for our discrepant results. First, we used a 0- and 70-degree endoscope and had the advantage of an RFA cutting blade that could be bent and provide better exposure in the laryngoscope. There is good evidence that tumors with involvement of the anterior commissure can be treated effectively using endoscopy. For example, Peretti et al. [21] reported that an adequately designed laryngoscope optimizes effective surgery in this region when the patient is placed in the Boyce-Jackson position and multiple perspectives of the lesion can be provided at 0°, 30°, 70°, and 120°. Besides, resection of the anterior portion of the false vocal cords can provide better visualization of the anterior commissure and allows evaluation of tumor invasion of the underlying cartilage framework. RFA also has a hemostatic function, making the operation field very clear [17]. Second, to reduce the risk of positive margins, some surgical teams use frozen section analysis [22, 23]. Surgeons in our study also maintained a safe margin during surgery especially when anterior commissure was invaded, because we believed that tumor involvement of the anterior commissure was an important parameter affecting oncologic outcome of these patients.

As mentioned above, the preservation of voice quality is also an important consideration. Our analysis of vocal outcomes indicated that open surgery led to poorer voice quality than RFA. Our further analysis of the open surgery group indicated that patients who had anterior commissure invasion had poorer vocal outcomes than those without invasion, similar to the results of Taylor et al. [24]. The poorer vocal outcome in these patients is due to the extended resection and injury to both vocal folds. A study by Demir et al. [25] compared voice-related quality of life for patients treated by RFA, CO₂ laser, and radiation. Their RFA group had the worst voice outcome, and the CO₂ laser and radiation groups had comparable outcomes. To our knowledge, no previous study has directly compared the VHI-30 scores of patients who received open surgery or RFA.

CONCLUSIONS

In conclusion, RFA and open surgery have comparable efficacy and both are suitable surgical options for

treatment of stage T1 stage glottis squamous cell carcinoma. Open surgery is associated with a lower local recurrence rate but worse VHI-30 score. Involvement of the anterior commissure was associated with increased recurrence and poorer voice quality in patients who received open surgery.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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Table 1. Characteristics of patients with stage T1 glottis cancer who received RFA or open surgery.

Variable	RFA (N/%)	Open surgery (N/%)	P-values
Cases	65/69.9%	28/30.1%	-
Age, years			0.981
>65years	35/53.8%	15/53.6%	
<65years	30/46.2%	13/46.4%	
Gender			0.535
Male	64/98.5%	27/96.4%	
Female	1/1.5%	1/3.6%	
Smoking status			0.002
Smoker	36/55.4%	18/64.3%	
Non-smoker	29/44.6%	10/35.7%	
Alcohol use			0.309
Yes	32/49.2%	17/60.7%	
No	33/50.8%	11/39.3%	
T stage			0.025
T1a	48/73.8%	14/50%	
T1b	17/26.2%	14/50%	
Grade			0.010
Highly differentiated	53/81.5%	15/53.6%	
Moderately differentiated	11/16.9%	13/46.4%	
Poorly differentiated	1/1.5%	0/0%	
Anterior commissure			0.286

Variable	RFA (N/%)	Open surgery (N/%)	P-values
Invasion	34/52.3%	18/64.3%	
Not invasion	31/47.7%	10/35.7%	
Resection margins			
Positive	2/3.1%	0/0%	0.348
Negative	63/96.9%	28/100%	

RFA, radiofrequency ablation.

Table 2. Oncologic outcomes of the RFA and open surgery groups

	RFA	Open surgery	P- value
5-year OS	86.2%(56/65)	78.6%(22/28)	0.26
5-year DFS	72.3%(47/65)	92.9%(26/28)	0.03
Local recurrence	27.7%(18/65)	7.1%(2/28)	0.03

OS, overall survival; DFS, disease free survival.

Table 3. Oncologic outcomes of the RFA and open surgery groups among patients with anterior commissure involvement.

	RFA	Open surgery	P- value
5-year OS	88.2%(30/34)	83.3%(15/18)	0.58
5-year DFS	67.6%(23/34)	88.9%(16/18)	0.09
Local recurrence	32.4%(11/23)	11.1%(2/18)	0.09

RFA, radiofrequency ablation; OS, overall survival; DFS, disease free survival

Table 4. Multivariate analysis of the impact of different factors on the 5-year OS and 5-year DFS.

	Factor	P	HR	95%CI
5-year OS	Type of surgery	0.25	0.47	0.13, 1.69
	AC involvement	0.46	1.68	0.41, 6.18
5-year DFS	Type of surgery	0.02	6.35	1.31, 30.74
	AC involvement	0.11	0.42	0.14, 1.22

AC, anterior commissure; OS, overall survival; DFS, disease free survival

Table 5. VHI-30 scores of patients in the RFA and open surgery groups.

	VHI-F	VHI-E	VHI-P	VHI-T
RFA	5(range 4~7)	3(range2~4)	3(range2~5)	11(range9~15)
Open surgery	23(range7~27)	9(range4~11)	16(range6~18)	50(range17~55)
P	<0.001	<0.001	<0.001	<0.001

RFA, radiofrequency ablation;

VHI-F, Voice Handicap Index- functional; VHI-E, Voice Handicap Index- emotional;
 VHI-P, Voice Handicap Index- physical; VHI-T, Voice Handicap Index- total

Table 6. VHI-30 scores of patients in the RFA and open surgery groups who did or did not have anterior commissure involvement.

		VHI-F	VHI-E	VHI-P	VHI-T
RFA	AC+	5(range 4~7)	4(range 2~5)	3(range 3~5)	12(range 10~15)
	AC-	5(range 3~7)	3(range 2~3)	3(range 2~5)	10(range 8~14)
	P	0.43	0.02	0.31	0.08
Open surgery	AC+	24(range 20~28)	9(range 8~12)	16(range 13~18)	52(range 46~57)
	AC-	13(range 3~25)	5(range 2~9)	8 (range 2~18)	26(range 7~51)
	P	0.10	0.01	0.18	0.02

AC+, involvement of anterior commissure; AC-, no involvement of anterior commissure RFA, radiofrequency ablation; VHI-F, Voice Handicap Index- functional; VHI-E, Voice Handicap Index- emotional; VHI-P, Voice Handicap Index- physical; VHI-T, Voice Handicap Index- total



