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CLINICAL INVESTIGATION

Survival and Larynx Preservation in Early Glottic Cancer: A Randomized Trial Comparing Laser Surgery and Radiation Therapy

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Purpose: The prognosis of glottic T1a laryngeal squamous cell carcinoma (LSCC) is excellent with both transoral laser surgery (TLS) and radiation therapy (RT). Our aim was to compare TLS and RT treatment results in a randomized study.
Methods and Materials: Of 56 male patients with glottic T1a LSCC, 31 were randomized for TLS and 25 for RT. Survival and larynx preservation data were collected from medical records.
Results: Five-year overall survival (OS) was 87%, disease-specific survival (DSS) was 97%, and recurrence-free survival (RFS) was 81% in patients treated with TLS. Five-year OS was 92%, DSS was 100%, and RFS was 88% in patients treated with RT. The primary treatment method was not associated with OS, RFS, or DSS in a log-rank test. The larynx preservation rate was similar in both groups (TLS, 97%; RT, 92%; $P = .575$).
Conclusions: In a prospective randomized setting oncological outcomes of both treatment modalities (TLS or RT) for T1a LSCC were similar.

Introduction

The prognosis of T1a glottic laryngeal squamous cell carcinoma (LSCC) is excellent regardless of the treatment method.[1-17] However, randomized controlled studies comparing transoral laser surgery (TLS) and radiation therapy (RT) are lacking. A Cochrane review by Warner et al[18] found only 1 randomized study comparing open surgery and RT. In a previous prospective study by Aaltonen et al, 56 male patients with T1a glottic LSCC were randomly assigned to TLS (n = 31) or RT (n = 25). The primary endpoint was voice quality. In the perceptual voice analysis based on grade, roughness, breathiness, asthenia, strain classification, general voice quality was similar. Patients undergoing TLS had a breathier voice and more hoarseness-related inconvenience compared with patients treated with RT at 2-year follow-up.[19]

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To our best knowledge, randomized studies on the treatment of T1a LSCC have not been published since that of Aaltonen et al.[19] Our aim was to report long-term survival and larynx preservation data in the same series after median follow-up of 5.7 years.

Methods and Materials

Patients

The recruitment of patients, their randomization, treatment protocol, and voice analyses have been described in detail previously. Of the 56 male patients with T1a glottic LSCC included in the voice quality study, 31 were randomly assigned to the TLS group and 25 to the RT group (Table 1) at a 1:1 ratio. Only male patients were included in the original study to confirm homogeneity of voice analysis. All patients were treated in the 3 largest university hospitals in Finland between June 1998 and October 2008. The median age at the time of diagnosis was 65 years (range, 46-83). The treatments started within 6 weeks after diagnosis. TLS was performed with CO_2 laser by 7 experienced surgeons and with the patient under general anesthesia. RT was performed with a linear accelerator, and radiation dose was 66 Gy in 2 Gy fractions over 6.5 weeks.[19]

Of 56 patients, 28 (50%) died during follow-up. The median follow-up of surviving patients was 6.6 years (range, 3.9-17.4 years), and 25 of 28 (89%) had a minimum follow-up of 5 years. Overall survival (OS) was defined as the duration from diagnosis to death from any cause and disease-specific survival (DSS) as the duration from diagnosis to death from LSCC. Recurrence-free survival (RFS) was defined as the duration from diagnosis to the first recurrence. Data on LSCC recurrences, laryngectomies, and new primary cancers were collected from the medical records. A new tumor in the larynx was defined as a second primary tumor when diagnosed more than 5 years after the primary T1a tumor. Accordingly, new primary tumors in the other head and neck area or lungs were defined as second primary tumors. The dates and causes of death were provided by Statistics Finland.

The study was approved by the ethics committee at the Hospital District of Helsinki and Uusimaa, and institutional study permission was granted. The patients had provided written consent before study participation in the original study.

Statistical analyses

IBM SPSS Statistics 27.0 (Armonk, NY) was used in statistical analyses. Chi-square and Fisher's tests were used to study a connection between categorical variables, and *t* test and Mann-Whitney U test were used for continuous variables. Survival was analyzed by Kaplan-Meier method and log-rank test. Statistically significant *P* value was set at .05.

Results

Recurrences

Of 56 patients, 9 (16%) had recurrence during the 5-year follow-up. The median time from diagnosis to recurrence was 1.5 years (range, 0.4-2.7 years). The localization of recurrence was larynx in 8 patients and mediastinum in 1 patient. The recurrences of patients primarily treated with TLS (n = 6) were treated with TLS (n = 1), RT (n = 4), and palliative care (n = 1). The recurrences of patients primarily treated with RT (n = 3) were treated with TLS (n = 2) and total laryngectomy (n = 1). For all patients the 5-year RFS was 84%. Five-year RFS was 81% for patients treated with TLS and 88% for patients treated with RT. The primary treatment method was not associated with RFS in a log-rank test. Smoking history, earlier dysplasia, anterior vocal cord involvement, and histologic grade were not related to RFS in a log-rank test.

Total laryngectomies

In total, 3 patients (5%) underwent total laryngectomy, 1 patient was primarily treated with RT after his first recurrence and 2 patients after their second recurrence. Five-year larynx preservation rate was similar in both treatment groups (TLS 30/31 [97%] vs RT 23/25 [92%], $P = .575$). Age, smoking history, earlier dysplasia, anterior vocal cord involvement, and histologic grade were not related to larynx preservation.

Second primary tumors

Ten patients (18%) had a second primary tumor during follow-up. The median time from T1a LSCC diagnosis until detection of a second primary tumor was 8.5 years (range, 3.8-15.4 years). The tumor location was lungs in 5 patients, larynx in 3 patients, and hypopharynx in 2 patients. Two of 3 patients with second primary tumor in larynx were treated with surgery and 1 with RT. Four of these 10 patients (2 with lung cancer and 2 with hypopharyngeal cancer) died of a second primary tumor. The number of second primary tumors was not associated with the primary treatment method of glottic T1a LSCC. Age, smoking history, earlier dysplasia, anterior vocal cord involvement, and histologic grade were not associated with second primary tumors.

OS and DSS

One (2%) patient died of LSCC within 5 years and 1 patient 6 years after the diagnosis. The 5-year DSS was 98% for all patients, 97% in the TLS group, and 100% in the RT group. The corresponding numbers for 10-year

Table 1 Clinical characteristics of all patients with glottic T1a LSCC

Characteristic	n (%)	TLS (n = 3), n (%)	RT (n = 25), n (%)	*P* value
Male sex	56 (100)	31 (100)	25 (100)	1.000
Median age, y (range)	65 (46-83)	69 (46-83)	61 (46-75)	.067
Smoking history				.039
Yes	48 (86)	28 (90)	20 (80)	
No	4 (7)	0 (0)	4 (16)	
NA	4 (7)	3 (10)	1 (4)	
Earlier dysplasia*				.412
Yes	6 (11)	2 (6)	4 (16)	
No	39 (70)	25 (81)	14 (56)	
NA	11 (20)	4 (13)	7 (28)	
Histologic grade				.060
Grade 1	13 (23)	9 (29)	4 (16)	
Grade 2	18 (32)	7 (23)	11 (44)	
Grade 3	3 (5)	3 (10)	0 (0)	
NA	22 (39)	12 (39)	10 (40)	
Anterior involvement of vocal cord				.438
Yes	41 (73)	22 (71)	19 (76)	
No	8 (14)	6 (19)	2 (8)	
NA	7 (13)	3 (10)	4 (16)	
Recurrence†				.716
Yes	9 (16)	6 (19)	3 (12)	
No	47 (84)	25 (81)	22 (88)	
Total laryngectomy‡				.581
Yes	3 (5)	1 (3)	2 (8)	
No	53 (95)	30 (97)	23 (92)	
Second primary tumor§				.738
Yes	10 (18)	5 (16)	5 (20)	
No	46 (82)	26 (84)	20 (80)	
Died of LSCC‖				1.000
Yes	2 (4)	1 (3)	1 (4)	
No	54 (96)	30 (97)	24 (96)	

Abbreviations: LSCC = laryngeal squamous cell carcinoma; NA = not available; RT = radiation therapy; TLS = transoral laser surgery.
* Presence of dysplasia confirmed in laryngeal biopsy before the diagnosis of glottic T1a LSCC.
† Recurrence during 5-year follow-up.
‡ Total laryngectomy during 5-year follow-up.
§ Second primary tumor during follow-up (whole follow-up time included).
‖ Died of LSCC during follow-up (whole follow-up time included).

DSS were 97%, 97%, and 96%, respectively. The 5-year OS was 89% for all patients, 87% for the TLS group, and 92% for the RT group. The corresponding numbers for 10-year OS were 20%, 19%, and 20%, respectively. The primary treatment method did not associate with DSS or OS in a log-rank test. Smoking history, earlier dysplasia, anterior vocal cord involvement, and histologic grade were not related to DSS or OS in a log-rank test.

Discussion

We are not aware of other randomized studies comparing the effect of TLS and RT on recurrence, laryngeal preservation, and survival in glottic T1a LSCC. A recent meta-analysis of 16 studies, including both T1a and T1b tumors, showed that local control between TLS (85%) and RT (89%) groups did not differ significantly. However, laryngeal

preservation in TLS (99%) was significantly superior compared with RT (89%). Accordingly, the TLS group had significantly superior DSS compared with the RT group (99% vs 96%).[17] These differences may be partly explained by the heterogeneity of TLS and RT groups in a retrospective study setting: bulky tumors and those affecting the anterior third of vocal cord, the anterior commissure, or both vocal cords (T1b) are more likely treated with RT. Furthermore, TLS is not suitable for patients with anesthesia contraindications or for those with difficult endoscopic exposure. Treatment decisions are further affected by patient preferences, expectations for posttreatment voice quality, and availability of modalities across different institutions. All these issues may explain why several previous randomized trials have been terminated early because of poor accrual.[18]

In our randomized study, 5-year RFS (81% in TLS; 88% in RT), laryngeal preservation (97% in TLS; 92% in RT), and DSS (97% in TLS; 100% in RT) were comparable to the previous nonrandomized studies.[1-17] However, no significant differences emerged between TLS and RT groups. The accrual in this study lasted for 10 years, and as much as 80% of eligible patients did not enter the study when the T stage distribution and the incidence of LSCC in Finland were considered. Only male patients were included in the original study to confirm homogeneity in voice analysis. Thus, this material may not be representative for all glottic T1a LSCCs. Additionally, the primary endpoint of the original study was voice quality, and survival was a secondary outcome. The results may not be applicable to women regarding voice quality or oncologic outcomes. The RT group included 4 patients without a smoking history, whereas in the TLS group all patients were either previous or current smokers. To reliably assess the effect of smoking on oncologic outcomes, a larger number of study patients is required.

Our previous retrospective study assessing patients treated at all the 5 Finnish university hospitals between years 2003 and 2015 showed similar laryngeal preservation rates (97% in TLS; 94% in RT) and DSS (97% in TLS; 99% in RT) for glottic T1a patients. In that retrospective study, 5-year local control in the T1a RT group (97%) was significantly better compared with the TLS group (87%).[20] Smoking history was not significantly associated with recurrences, laryngeal preservation, or second primary tumor. The number of patients in the present study was small, and mortality for LSCC in patients with glottic T1a was an extremely rare event. Larger series are needed to show significant differences in major endpoints. Nine of 56 patients (16%) had recurrence during follow-up, and only 3 of them died of it. Hence, the treatment of T1a glottic LSCC recurrences seemed beneficial and should always be considered.

When treating patients with T1a LSCC the possibility of disease recurrence and second primary tumor should be considered. The problem with RT is that the curative treatment dose is available only once for each patient because of the increasing risk of adverse effects caused by reirradiation. Contrarily, TLS can be repeated in the case of recurrence.[13] RT should be considered when the location of the tumor is anterior and hard to reach with TLS or the patient is not suitable for general anesthesia.[21] It is notable that the patients with inoperable T1a glottic tumors were excluded from our study, and consequently the series does not represent a real-world setting. Moreover, the costs of RT compared with TLS are higher and finishing RT takes longer.[2,13]

In Finland the causes and dates of death are known reliably for study purposes because the medical record data are updated from the Digital and Population Data Services Agency. In our study, 3 of the 56 (5%) patients of LSCC, 10 (18%) had a second primary tumor, and 4 patients (7%) died of it. In the previous studies the proportion of second primary tumors in patients with LSCC with T1-4 stage varied from 15% to 29%.[22] In our study, the long follow-up time enabled a reliable assessment of second primary tumors. During 10-year follow-up the primary treatment method of T1a LSCC did not affect the mortality in second primary tumors.[20]

Conclusions

The prognosis of T1a LSCC was clearly favorable, and no significant differences in survival or larynx preservation by treatment modality were present in our series. The treatment for each patient with T1a glottic LSCC should be selected individually, and the multidisciplinary tumor board meeting is important in recommending the best suitable treatment option.

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