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Survival and larynx preservation in early glottic cancer: a randomized trial comparing laser surgery and radiotherapy

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Abstract

Purpose: The prognosis of glottic T1a laryngeal squamous cell carcinoma (LSCC) is excellent with both transoral laser surgery (TLS) and radiotherapy (RT). Our aim was to compare TLS and RT treatment results in a randomized study.

Methods and Materials: Of the 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) 97% and recurrence-free survival (RFS) 81% in patients treated with TLS. Five-year OS was 92%, DSS 100% and RFS 88% in patients treated with RT. The primary treatment method was not associated with OS, RFS or DSS in a log-rank test. Larynx preservation rate was similar in both groups (TLS 97%, RT 92%, p=0.575).

Conclusions: In a prospective randomized setting oncological outcome 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 radiotherapy (RT) are lacking. A Cochrane review by Warner et al. found only one randomized study comparing open surgery and RT.[18] In a previous prospective study by Aaltonen et al. 56 male patients with T1a glottic LSCC were randomly assigned for TLS (n=31) or RT (n=25). The primary endpoint was voice quality. In the perceptual voice analysis based on GRBAS classification general voice quality was similar. Patients undergoing TLS had more breathy voice, and more hoarseness-related inconvenience compared to patients treated with RT at 2-year follow-up.[19]

To our best knowledge, randomized studies on the treatment of T1a LSCC have not been published after 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 in the TLS group and 25 in 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 occurred in general anesthesia with CO2 laser performed by 7 experienced surgeons. 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) to the death caused by 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 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 in the Hospital District of Helsinki and Uusimaa and the 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, USA) 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 0.05.

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 (Figure 1A). The primary treatment method was not associated with RFS in a log-rank test. Smoking history, earlier dysplasia, anterior vocal cord involvement or histological grade were not related to RFS in a log-rank test.

Total laryngectomies

In total, 3 patients (5%) underwent total laryngectomy, 1 patient 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=0.575). Age, smoking history, earlier dysplasia, anterior vocal cord involvement or histological 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 was treated with surgery and 1 with RT. Four of these 10 patients (2 with lung cancer, and 2 with hypopharyngeal cancer) died of 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 or histological grade were not associated with second primary tumors.

Overall survival and disease-specific survival

One (2%) patient died of LSCC within 5 years, and 1 patient 6 years after the diagnosis. For all patients the 5-year DSS was 98%, 97% in TLS group and 100% in RT group. The corresponding numbers for 10-year DSS were 97%, 97% and 96%, respectively (Figure 1B). For all patients the 5-year OS was 89%, 87% for TLS group and 92% for RT group. The corresponding numbers for 10-year OS were 20%, 19% and 20%, respectively (Figure 1C). The primary treatment method did not associate with DSS or OS in a log-rank test. Smoking history, earlier dysplasia, anterior vocal cord involvement or histological 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 to RT (89%). Accordingly, the TLS group had significantly superior DSS compared to 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 those with difficult endoscopic exposure. Treatment decisions are further affected by patient preferences, expectations for post-treatment 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 non-randomized 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 secondary outcome. The results may not be applicable to women regarding voice quality or oncologic outcomes. RT group included 4 patients without a smoking history, whereas in TLS group all patients were either previous or current smokers. To reliably assess the effect of smoking on oncologic outcomes requires a larger number of study patients.

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 T1a RT group (97%) was significantly better compared to 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 T1a LSCC patients 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 tumor is anterior and hard to reach with TLS or the patient is not suitable for general anesthesia.[21] It is noticeable 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 to TLS are higher and to finish off RT takes longer.[2,13]

In Finland the causes and dates of death are known reliably for study purposes since the medical record data are updated from Digital and Population Data Services Agency. In our study 3 of the 56 (5%) patients died in LSCC, 10 (18%) had a second primary tumor and 4 patients (7%) died due to it. In the previous studies the number of second primary tumors in LSCC patients with T1-4 stage varies between 15-29%.[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]

In conclusion, 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 T1a glottic LSCC patient should be selected individually, and the multidisciplinary tumor board meeting is important in recommending the best suitable treatment option.

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Table 1. Clinical characteristics of all patients with glottic T1a LSCC.

Characteristic	N (%)	TLS (n=31 (%))	RT (n=25 (%))	p value
Male gender	56 (100)	31 (100)	25 (100)	1.000
Median age, y (range)	65 (46-83)	69 (46-83)	61 (46-75)	0.067
Smoking history				0.039
Yes	48 (86)	28 (90)	20 (80)	
No	4 (7)	0 (0)	4 (16)	
NA	4 (7)	3 (10)	1 (4)	
Earlier dysplasia[1]				0.412
Yes	6 (11)	2 (6)	4 (16)	
No	39 (70)	25 (81)	14 (56)	
NA	11 (20)	4 (13)	7 (28)	
Histological grade				0.060
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				0.438
Yes	41 (73)	22 (71)	19 (76)	
No	8 (14)	6 (19)	2 (8)	
NA	7 (13)	3 (10)	4 (16)	
Recurrence[2]				0.716
Yes	9 (16)	6 (19)	3 (12)	
No	47 (84)	25 (81)	22 (88)	
Total laryngectomy[3]				0.581
Yes	3 (5)	1 (3)	2 (8)	
No	53 (95)	30 (97)	23 (92)	
Second primary tumor[4]				0.738
Yes	10 (18)	5 (16)	5 (20)	
No	46 (82)	26 (84)	20 (80)	
Died of LSCC[5]				1.000
Yes	2 (4)	1 (3)	1 (4)	
No	54 (96)	30 (97)	24 (96)	

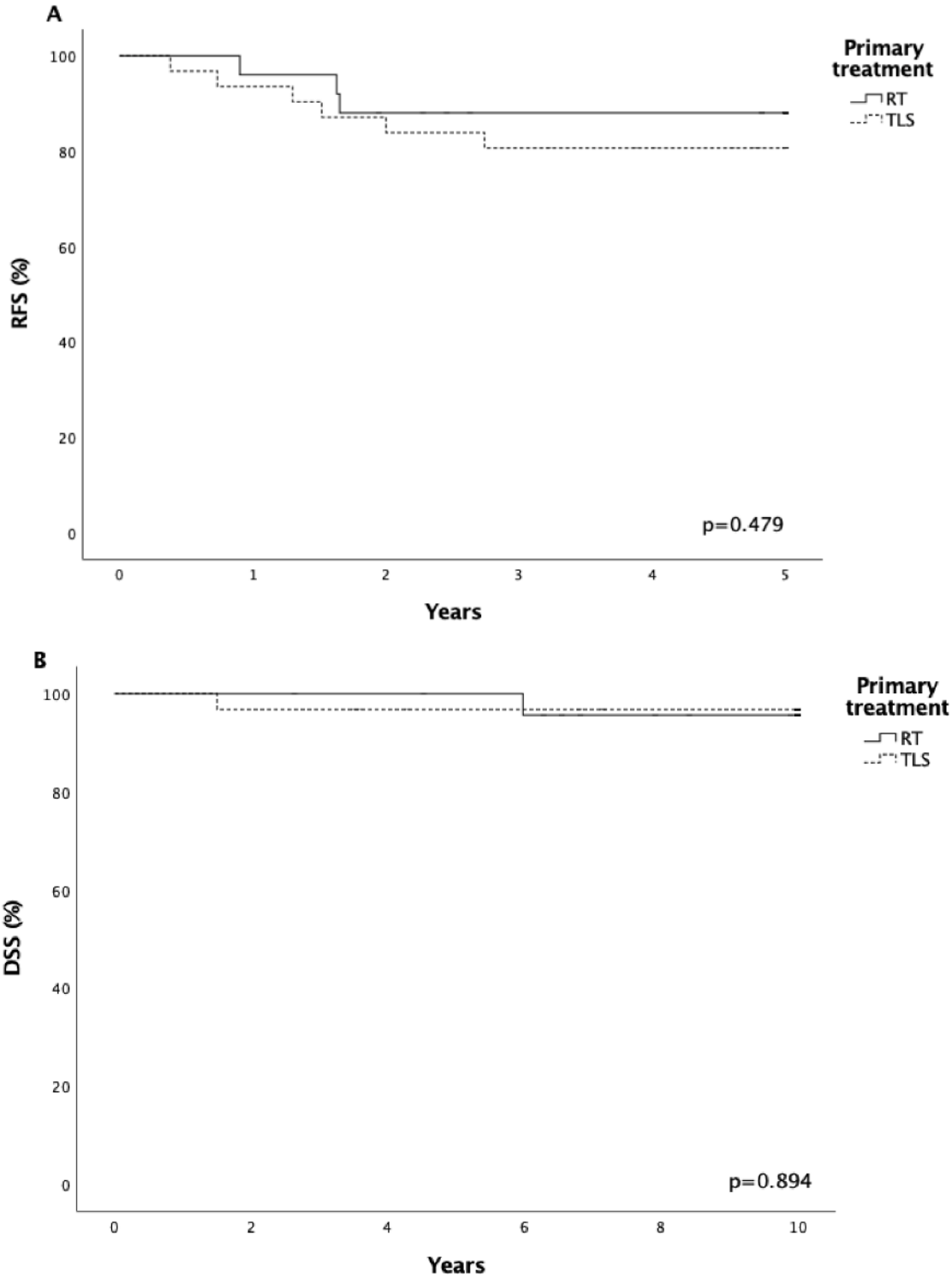
Abbreviations: LSCC, laryngeal squamous cell carcinoma; NA, not available; TLS, transoral laser surgery; RT, radiotherapy

[1] presence of dysplasia confirmed in laryngeal biopsy before the diagnosis of glottic T1a LSCC

[2] recurrence during 5-year follow-up

[3] total laryngectomy during 5-year follow-up

[4] second primary tumor during follow-up (whole follow-up time included)
[5] died of LSCC during follow-up (whole follow-up time included)


A
RFS (%)
100
80
60
40
20
0
0
1
2
3
4
5
Years
p=0.479
Primary treatment
RT
TLS
B
DSS (%)
100
80
60
40
20
0
0
2
4
6
8
10
Years
p=0.894
Primary treatment
RT
TLS

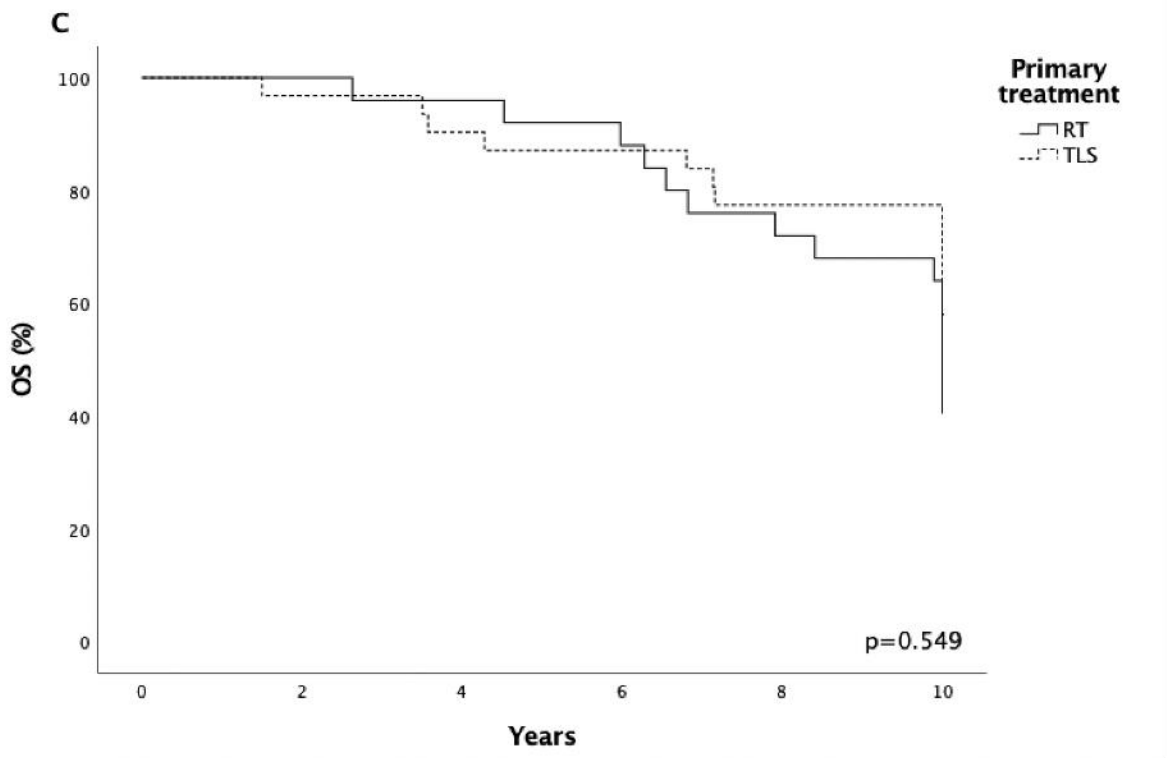


Figure 1. A) Five-year recurrence-free survival (RFS) according to primary treatment method in glottic T1a LSCC patients. B) Ten-year disease-specific survival (DSS) in glottic T1a LSCC. C) Ten-year overall survival (OS) in glottic T1a LSCC.