Reports of Practical Oncology and Radiotherapy 25 (2020) 860–866

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Surgery versus radiotherapy: Long term outcomes of T1 glottic cancer

Nelson Ferreira[a,*], Eduardo Netto[a,b], Leonor Fonseca[a], João Fonseca[a], Susana Esteves[c], Miguel Labareda[a], António Mota[a], Rute Pocinho[a], Miguel Magalhães[d], Filomena Santos[a]

[a] Instituto Português de Oncologia de Lisboa Francisco Gentil – EPE, Radiation Oncology, Lisboa, Portugal
[b] NOVA Medical School, Faculdade de Ciências Médicas, Lisboa, Portugal
[c] Instituto Português de Oncologia de Lisboa Francisco Gentil – EPE, Clinical Research Unit, Lisboa, Portugal
[d] Instituto Português de Oncologia de Lisboa Francisco Gentil – EPE, Otorhinolaryngology, Lisboa, Portugal

ARTICLE INFO

Article history:
Received 23 April 2019
Received in revised form 5 June 2020
Accepted 12 August 2020
Available online 19 August 2020

Keywords:
Glottic cancer
T1
Radiotherapy
Surgery
Larynx preservation
Outcome

ABSTRACT

Aim: The aim of this study was to compare the outcomes, patterns of failure and laryngeal preservation rates in patients with T1N0 glottic cancer treated with surgery or radiotherapy.
Materials/methods: Retrospective study of T1N0 glottic cancer patients treated in our institution between January 2007 and December 2017. Histologically proven squamous cell carcinoma patients, treated with upfront cordectomy/partial laryngectomy (S group) or radiotherapy (RT group) were included. Elective treatment of the neck was not permitted. Local failure (LF), disease-free survival (DFS), ultimate disease-free survival (UDFS), laryngectomy-free survival (LFS), disease-specific mortality (DSM) and overall survival (OS) were evaluated.
Results: Two hundred and one patients were eligible (172 S group, 29 RT group), with a median follow-up of 38.8 months. Overall, 33 (16%) patients had a recurrence, 30 (17%) in the S group and 3 (10%) in the RT group. Local failure was the predominant site of failure (28 S, 2 RT). Overall, of all those that were salvaged, 17 (8%) underwent total laryngectomy (15 S, 2 RT). There was no significant difference in the 5-year cumulative incidence of LF (20.8% S, 8.1% RT, $p = 0.138$), 5-y LFS (85.0% vs. 91.7%, $p = 0.809$), 5-y DFS (67.5% vs. 82.1%, $p = 0.343$), 5-y UDFS (82.5% vs. 90.3%, $p = 0.647$) and 5-y OS (84.5% vs. 90.3%, $p = 0.892$). Multivariate analysis showed no correlation between initial treatment and the analyzed outcomes.
Conclusion: Primary surgery or radiotherapy were similar first line options, since they do not differ in all outcomes. Patients' and physician's preferences must be considered when choosing first treatment.

1. Introduction

Worldwide, there are estimated 238,000 cases of laryngeal cancer and 106,000 deaths annually.[1] It is one of the most common malignancies of the head and neck and its incidence is increasing over time. Laryngeal cancer, even in locally advanced stages, has a relatively high cure rate if managed appropriately. Disease control is not the only consideration in the management of this disease, as voice preservation and avoidance of tracheal stoma are also important priorities. Therefore, it has become the paradigm for the concept of organ preservation in oncologic patient management.

Glottic cancer accounts for approximately two-thirds of all laryngeal cancers.[2] The management of early (T1-2) glottic carcinomas is controversial and is often determined by an anticipated functional outcome, general medical condition, patient's wishes, preferences and expertise of the attending physicians and tumor factors. It should be treated with the intent to preserve the larynx, generally with a single modality, either radiotherapy (RT) or transoral laser microsurgery (TLM), with 5-year cause-specific and overall survival (OS) rates of approximately 95% and 80%, respectively.[3] Local control (LC) rates are similar with both modalities, commonly exceeding 90% for T1 tumors, and ultimate control rates after salvage surgery for recurrences range from 90% to 95%.[4–8] Although some patients can be salvaged with larynx-preserving procedures after RT, total laryngectomy is necessary in more than one half of the cases.[9]

This study aims to compare larynx-preserving surgery (cordectomy or partial laryngectomy) and RT in cT1N0 glottic cancer patients treated at a single academic institution, by analyzing their outcomes regarding disease control, patterns of failure, survival outcomes and laryngeal preservation rates.

* Corresponding author at: Instituto Português de Oncologia de Lisboa, Rua Prof. Lima Basto, 1099-023 Lisboa, Portugal.
E-mail address: nelson2357@gmail.com (N. Ferreira).

https://doi.org/10.1016/j.rpor.2020.08.007
1507-1367/

2. Material and methods

2.1. Patients

Using a Regional Cancer Database, patients with early laryngeal cancer treated at a single academic tertiary referral center between the 1st January 2007 and 31st December 2017 were identified. Medical records of all patients were reviewed, and demographic, clinical, histopathological, treatment and follow-up data were collected.

The inclusion criteria for this study were: age ≥ 18 years, histologically proven squamous cell carcinoma restricted to the glottis, stage cT1N0 (according to the seventh edition of the American Joint Committee on Cancer), curatively treated with RT or surgery. Patients with synchronous second primary malignancies were excluded.

2.2. Treatments

Patients were primarily treated with surgery or glottic radiotherapy. Surgical patients were either submitted to TLM or open partial laryngectomy. In case of close (1 mm or less) or positive margins, re-resection or adjuvant RT was indicated. Two-dimensional radiotherapy was used until June 2008. Since then all patients were treated with 3D conformal radiotherapy techniques. Patients with elective treatment of the neck (irradiated or dissected) or with other prior treatment were excluded.

2.3. Outcomes and endpoints

Local, regional (neck) and distant failures were noted. Events considered in each time-to-event outcome were: recurrence at the primary site for local failure (LF) with death by any cause defined as a competing event; any recurrence or death from any cause for disease-free survival (DFS); death from any cause for overall survival (OS); death from laryngeal cancer for disease-specific mortality (DSM), with death unrelated to laryngeal cancer considered as a competing event; total laryngectomy or death from laryngeal cancer for laryngectomy-free survival (LFS). Incidence of total laryngectomy was also calculated, using death from any cause as a competing event. Date of surgery or first day of RT, as applicable, were the starting point for calculating time-to-event endpoints. Ultimate disease-free survival (UDFS) was defined as the time between the primary or salvage treatment, whichever is last, and any tumor recurrence or death from any cause.

2.4. Statistical analysis

Statistical analysis was undertaken using the R statistical software. LF, total laryngectomy and DSM were calculated as cumulative incidence functions using the competing risk analysis. The Kaplan Meier method was used for DFS, LFS, UDFS and OS. To assess prognostic values of different variables, the log rank test and Gray test were used for univariate analysis. We also conducted a multivariable analysis, using the proportional hazards Cox model and the Fine and Gray competing risks model, to assess the impact of the primary treatment on DFS, LF and LFS controlling for the confounding factors defined a priori age, T stage and smoking status. Detection of differences in the clinical-demographic variables between the surgical and RT groups was performed using the Fisher's exact test and the Wilcoxon rank sum test. All tests were two-sided and a p value < 0.05 was considered to be statistically significant.

3. Results

3.1. Patients and treatment characteristics

Patient and tumor characteristics are summarized in Table 1. A total of 205 patients met the inclusion criteria. Four patients had insufficient data or were lost to follow-up, leaving 201 total patients eligible for analysis, 172 in the surgery group and 29 in the RT group, with a median follow-up for living patients of 38.8 months (inter-quartile range 24.5–64.9). The vast majority were men (97%) with a median age of 64 years (range 41–84). Most were former or active smokers (88%) of a median of 45 pack-years (2–120), with the Eastern Cooperative Oncology Group Performance Status between 0 and 1 in 75%. T1a was the predominant T stage, occurring in 86% of patients, versus 14% for T1b. When comparing clinical and demographic variables between treatment groups, a statistically significant difference was detected for age and T stage. RT patients were older ($p = 0.0257$) and had a higher proportion of T1b tumors ($p = 0.0026$).

Surgery was the initial treatment in 172 patients, 135 cordectomies and 37 partial laryngectomies. For 27 of the operated patients, the margin status was not reported, and they were not measurable (due to fragmentation) in 12 cases. Of the remaining 133, 15 had positive margins, 16 close margins and 102 had negative margins. Overall, 17 patients had adjuvant glottic RT and 32 underwent a second resection (and obtained tumor-free margins) due to close or positive margins.

Twenty-nine patients were primarily treated with RT, the majority (81%) with 3D conformal techniques. The median dose was 63 Gy (range 63–70) in 2.25 Gy per fraction (range 2.0–2.25 Gy/fraction). Median overall treatment time was 43 days (range 37–50).

3.2. Patterns of failure and salvage therapies

The patterns of failure and salvage therapies are summarized in Table 2. Overall, 33 (16%) patients experienced a recurrence, 30 (17%) in the surgery group and 3 (10%) in the RT group. Curative salvage treatment was given to 94% of the patients that had failed. Ten patients had two or more relapses, all in the surgical group.

In the surgical group ($n = 172$), 28 patients had a local relapse, 22 of them isolated. Seven patients had regional failure, of whom two had local control. Only three patients eventually developed distant metastasis, all with local and/or regional failure. Median time to first recurrence was 23.5 months (range 1.4–88.4). Most of the local relapses were treated, at the first recurrence, with larynx-preserving surgery (13) with or without adjuvant treatment. Total laryngectomy was the first choice in 10 patients, definitive RT in 4 patients, and concurrent chemoradiotherapy in 1 patient. Overall, 15 patients (9%) were submitted to total laryngectomy in the course of the disease.

Of the 15 patients with positive margins, 6 received postoperative RT and are disease-free. The remaining 9 did not receive any adjuvant treatment, and 6 of them had local failure (1 also with regional and distant failure). Of the 16 patients with close margins, 10 had less than 1 mm margins, in 7 of these no further treatment was given and 2 of them relapsed locally. All 6 patients with 1 mm margins did not receive additional treatment and are disease-free. Only 1 of the 102 negative-margin patients received adjuvant RT (due to estimated 2 mm fragmented margin) and 10 of these 102 had local failure (8 isolated) and 1 isolated nodal failure. Ten of the 39 patients with combined unmeasurable or missing data margins, had local relapse.

Median time to recurrence was 27.6 months (range 5.6–60.9) in the RT cohort. Two patients had an isolated local relapse that was

Table 1
Patient and tumor characteristics.

Characteristic	Total $n = 201$ (%)	Surgery $n = 172$ (%)	Radiotherapy $n = 29$ (%)	p-value
Age (years)				
Median	64	63	71	0.0257
Range	41–84	41–84	47–83	
Gender				
Male	195 (97)	166 (97)	29 (100)	0.5961
Female	6 (3)	6 (3)	0	
PS ECOG at presentation				
0–1	150 (75)	135 (79)	15 (52)	0.4834
2–3	25 (12)	21 (12)	4 (14)	
Unreported	26 (13)	16 (9)	10 (34)	
Smoking history				
Yes	176 (88)	151 (88)	25 (86)	1.000
Median pack-years (range)	50 (2–120)	50 (2–120)	55 (15–120)	
No	17 (8)	15 (9)	2 (7)	
Unreported	8 (4)	6 (3)	2 (7)	
T stage				
T1a	172 (86)	153 (89)	19 (66)	0.0026
T1b	29 (14)	19 (11)	10 (34)	

Abbreviation: PS ECOG: Performance Status Eastern Cooperative Oncology Group.

Table 2
Patterns of failure and salvage treatments by treatment modality.

Parameter	Total $n = 201$ (%)	Surgery $n = 172$ (%)	Radiotherapy $n = 29$ (%)
Follow-up (years)			
Median	3.2	3.1	4.0
Range	(0.3–10.1)	(0.3–10.1)	(0.7–10.0)
Recurrences	33 (16)	30 (17)	3 (10)
Local	30 (15)	28 (16)	2 (7)
Regional	8 (4)	7 (4)	1 (3)
Regional (w/o local)	3 (1)	2 (1)	1 (3)
Distant	4 (2)	3 (2)	1 (3)
2 + recurrences	10 (5)	10 (6)	0
Time to 1st recurrence (months)			
Median	–	23.5	27.6
Range	–	(1.4–88.4)	(5.6–60.9)
Treatment of 1st recurrence			
RT alone	–	4	0
Cordectomy/Partial laryngectomy alone	–	11	0
CRT (definitive)	–	1	0
Total laryngectomy ± RT ± CT	–	10	2
Larynx-preserving surgery + RT ± CT	–	3	0
Palliative/None	–	1	1
Treatment of 2nd recurrence			
RT alone	–	0	0
Cordectomy/Partial laryngectomy alone	–	3	0
CRT (definitive)	–	0	0
Total laryngectomy ± RT ± CT	–	4	0
Larynx-preserving surgery ± RT ± CT	–	1	0
Palliative/None	–	2	0
Total laryngectomy	17 (8)	15 (9)	2 (7)
Deaths	29 (14)	24 (14)	5 (17)
Cancer related	7 (3)	6 (3)	1 (3)

Abbreviation: RT = Radiotherapy; CT = Chemotherapy.

successfully salvaged with total laryngectomy. One patient died after regional and distant relapse in the lungs and bone.

3.3. Outcomes

The overall 2- and 5-year cumulative incidence of LF was 8.4% and 18.8%, respectively, and for the cumulative incidence of total laryngectomy it was 3.1% and 13.8%. Overall, 93.6% and 84.0% achieved ultimate disease control at 2- and 5-year, respectively. The 2- and 5-year DSM was 1.6% and 3.9%. Other 2- and 5-year outcomes are summarized in Table 3.

There were more local failures in the surgically treated patients (2- and 5-year cumulative incidence of 9.1% and 20.8%, respectively) compared to the RT group (3.4% and 8.1%), but it was not statistically significant ($p = 0.138$).

Patients treated with upfront surgery also had lower 5-year LFS (85% vs. 91.7%), but again it was not statistically significant ($p = 0.773$). Nor was there any statistically significant difference

Table 3
The 2- and 5-year outcomes of patients with T1 glottic cancer treated with surgery or radiotherapy.

		Surgery (%)	RT (%)	Overall (%)	*p*-value
LF[a]	2y	9.1	3.4	8.4	0.138
	5y	20.8	8.1	18.8	
DFS	2y	88.5	92.2	88.9	0.343
	5y	67.5	82.1	70.0	
UDFS	2y	93.3	95.7	93.6	0.647
	5y	82.5	90.3	84.0	
LFS	2y	97.0	96.6	96.9	0.809
	5y	85.0	91.7	86.1	
DSM[a]	2y	1.8	0	1.6	0.890
	5y	4.6	0	3.9	
OS	2y	95.7	95.7	95.7	0.892
	5y	84.5	90.3	85.5	

[a] Cumulative incidence function.

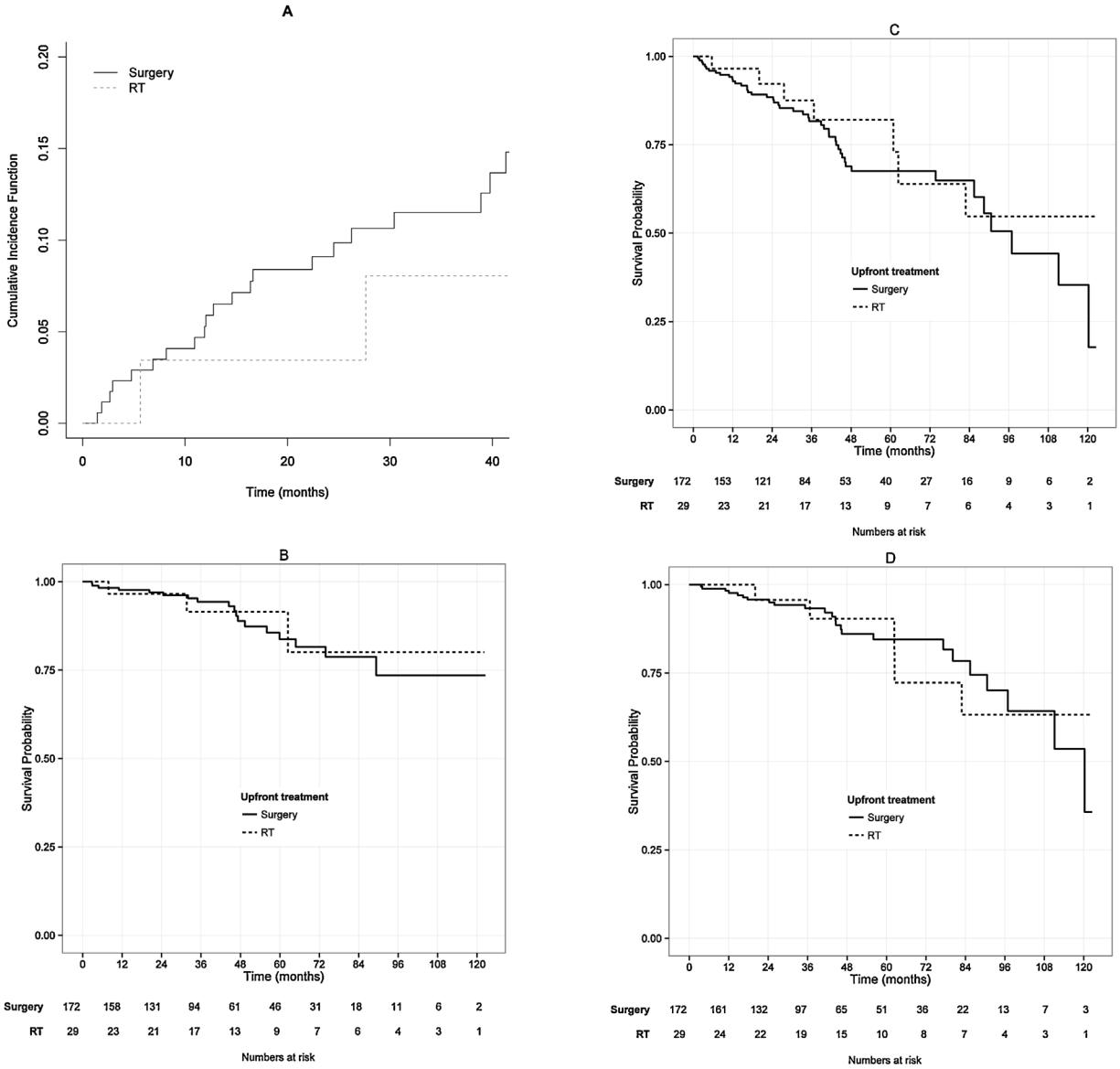

Fig. 1. Outcomes by upfront treatment: Cumulative incidence of local failure (a). Kaplan Meier estimates of Laryngectomy-free survival (b), disease-free survival (c) and overall survival (d).

Table 4
Multivariate analysis for local failure, disease-free survival and laryngectomy-free survival.

Variable	LF			DFS			LFS		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Primary treatment (S/RT)	0.53	0.13–2.25	0.39	0.86	0.38–1.95	0.98	0.97	0.28–3.40	0.96
Age (per additional year)	0.97	0.93–1.01	0.19	1.01	0.98–1.05	0.89	1.0	0.96–1.05	0.94
T stage (T1a/T1b)	0.41	0.08–1.71	0.3	0.22	0.05–0.93	0.14	1.04	0.21–5.2	0.96
Smoker or former Smoker/never smoker	0.33	0.09–1.09	0.11	0.48	0.20–1.16	0.97	2.35	0.24–23.34	0.47

Table 5
The 2- and 5-year outcomes of patients with T1 glottic cancer submitted exclusively to upfront surgery (i.e. no adjuvant RT) and TLM only.

		Upfront surgery only (%)	TLM only (%)
LF[a]	2y	9.4	8.6
	5y	22.6	20.0
	p value	0.138	0.135
DFS	2y	88.6	88.2
	5y	67.0	70.4
	p value	0.400	0.600
LFS	2y	96.7	97.6
	5y	83.0	84.6
	p value	0.740	0.690

[a] Cumulative incidence function.
p values of univariate analysis comparing these surgical subgroups to the RT group.

in 5y-DFS (67.5% vs. 82.1%, $p = 0.343$) and 5y-OS (84.5% vs. 90.3%, $p = 0.892$), between the surgery and RT group (Fig. 1).

On univariate analysis, only the T stage classification had an impact on DFS (but not LF or LFS), as T1b patients had higher DFS than T1a ($p = 0.021$). No other clinical variables showed a meaningful impact in LF, DFS LFS, as there was no correlation between age at diagnosis, T stage, smoking status and the above endpoints.

On multivariate analysis (Table 4), there was no association between the choice of the first treatment (surgery vs. RT) and LF (HR = 0.53, 95%CI: 0.13–2.25), DFS (HR = 0.86, 95%CI 0.38–1.95) or LFS (HR = 0.97, 95%CI: 0.28–3.40).

A couple of subset analysis was also performed. When comparing the group of patients submitted exclusively to upfront surgery (i.e. no adjuvant RT) versus the upfront RT group, both in univariate and multivariable analyses, although the risk of LF (HR = 0.53, 95%CI: 0.13–2.18, $p = 0.370$), the DFS (HR = 0.92, 95%CI: 0.40–2.11, $p = 0.843$) and LFS (HR = 0.98, 95%CI: 0.28–3.40, $p = 0.970$) seem to favor RT, we could not demonstrate a statistically significant result. The same trend was observed when comparing the patients that had undergone TLM only to the RT patients, considering LF (HR = 0.54, 95%CI: 0.13–2.25, p = 0.400), DFS (HR = 0.96, 95%CI: 0.41-2.27, p = 0.929) and LFS (HR = 0.94, 95%CI: 0.25–3.50, $p = 0.930$), but again with no statistically significant difference. More detailed results are provided in Table 5.

4. Discussion

An analysis of the five year outcomes of cT1N0 glottic cancer patients treated at our institution suggests that both surgery and radiotherapy, as initial treatments, provide similar outcomes. Regarding disease control, it is important to distinguish between local control and ultimate local control rates. While local control is linked to the first treatment efficacy, ultimate local control refers to the disease control after the last treatment, accounting for all the relapses and salvages the patient might undergo. Despite the comparable ultimate local control rates between the two modalities, upfront treatment with surgery can have its disadvantages. In our series, 10% of patients treated with surgery were submitted to adjuvant radiotherapy. They also had more local recurrences, as suggested by the 20.8% cumulative incidence at 5 years, compared to 8.1% for the RT group. None of the RT patients had two or more recurrences, as opposed to 10 (6%) in the surgery group. Similarly, Low et al.[10] noted that patients undergoing TLM more frequently needed a second resection for involved margins, and had more local recurrences requiring two or more procedures, despite its not having an impact on the 5-year ultimate local control and DFS, compared to RT. They did, however, detect a statistical difference in laryngectomy-free disease-specific survival favoring surgery, explained by the most common type of salvage treatment after each treatment modality. In our series all RT patients that failed locally were salvaged by total laryngectomy, as opposed to the predominant larynx-preserving options in the surgical recurring patients. Although we used a similar definition for LFS, both treatments resulted in similar LFS in our cohort. Furthermore, half of the 16 patients with either positive or less than 1 mm margins that had not received additional treatment, relapsed locally. In contrast, all 9 patients that had received adjuvant RT did not relapse. This emphasizes the importance of additional treatment in this population and might account for the higher cumulative incidence of local failure in the surgical group, as can the under-reporting of the margin status.

In contrast, Shelan et al.[11] reported a higher relapse-free survival with RT compared with surgery for stage I glottic cancer, even though the authors acknowledge possible selection bias in their institutional analysis. The same trend was demonstrated in a Korean study,[12] as RT was associated with better LC and DFS rates than cordectomy, in T1 glottic cancer patients. The RT patients did appear to perform better in every clinical endpoint in our series, but it was not statistically significant. Another recent retrospective analysis includes a study by De Santis et al.[13] that did not demonstrate a difference in 5-year DSS, DFS and LFS between the TLM and RT early glottic cancer patients treated in a Canadian center. Similar outcomes were also observed in T1 glottic carcinoma patients treated with either RT or KTP (potassium titanyl phosphate) TLM.[14]

As no proper randomized controlled trial exists, a number of meta-analysis and systematic reviews have recently been published to aid in decision-making. A 2016 meta-analysis[15] selected 11 comparative studies between TLM and RT for T1 glottic cancer, and higher OS and laryngeal preservation rates were associated with TLM, but the authors question the selection bias in some studies. A more extensive and recent meta-analysis also favored TLM in Tis/T1a glottis cancer patients, having better OS, DSS and lower incidence of total laryngectomy, albeit with no difference in LC.[16] Similarly, a recent Surveillance, Epidemiology and End Results (SEER) database analysis reported that surgery yielded better survival outcomes in early stage laryngeal cancer in patients who were ≤60 years old or had T1a or well-differentiated tumors.[17] On the other hand, the last Cochrane reviews showed that, despite the poor quality of the existing evidence, the two treatment modalities perform equally in terms of 5y-OS.[18]

As it appears that no detectable difference exists in disease control and survival, these outcomes might not be the primary focus when treating this population. The higher burden of procedures in the surgically treated patients can have an impact in the voice quality, swallowing outcomes and overall quality of life. The

anticipated voice quality after treatment is an important factor in selecting therapy for individual patients. RT might result in better voice quality using objective measures, at least for T1a tumors.[16,19] A randomized trial that compared RT with laser surgery in 60 men with stage I disease found that patients treated with RT reported less hoarseness-related inconvenience two years after treatment, with no differences in oncologic outcomes.[20] However, it is a complex assessment due to the multiple tools and endpoints used in the studies to evaluate voice quality, and lack of prospective data, but considering voice self-perception and its impact in life quality (Voice Handicap Index), results are similar with both modalities.[16,21,22]

Results concerning quality of life (QoL) have also been somewhat conflicting, as there are studies using the EORTC QoL questionnaires that favor RT,[23] others reporting higher QALYS (Quality Adjusted Life Years) for surgery,[24] and others showing no difference in overall QoL between the two treatment modalities.[25]

Ultimately, one has to look for cost-effectiveness of treatment, as an increasingly important aspect in decision-making. On this matter, the laser surgery alternative is clearly favored over RT in several studies.[24,26–28]

4.1. Limitations

The retrospective nature of this study is one of its limitations, and intrinsically related, the lack of toxicity data. The selection bias is always present in studies that compare surgery to RT, as older patients or with multiple comorbidities or who are unsuitable for general anesthesia could have been treated preferentially with RT. More related to this specific cancer patients is the fact that those who have inadequate endolaryngeal exposure, patients with tumor extending to anterior commissure or more extensively to both cords, are also less ideal candidates to surgery. The underreporting of the margin status and the imbalance in the groups, explained by our institutional policy, are also limitations. The small number of events in the RT group could have affected the observed results and makes it difficult to detect any statistically significant difference between the groups, if any exists. We also acknowledge that there have been technological advances in the past decade, both in surgery and in radiation oncology, although not within the scope of this manuscript, which may mandate further reassessment of outcomes in the future.

5. Conclusion

Patients with T1 glottic cancer treated with surgery or RT have similar control and survival outcomes in our group. Rigorous determination of the margin status is essential to guide further actions. In the absence of a high level of evidence from randomized controlled trials, the decision between the two modalities for the optimal treatment of T1 glottic cancer patients continues to be based on the patients' preferences, the institutions' expertise and policy, and tumor and patient related factors.

Compliance with ethical standards

This study complies with the national ethical guidelines, following the Data Protection National Committee requirements.

Conflicts of interest

None declared.

Funding

None declared.

References

1. Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study global burden. *JAMA Oncol*. 2017;3(4):524–548, http://dx.doi.org/10.1001/jamaoncol.2016.5688.
2. Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *Laryngoscope*. 2006;116(S111):1–13, http://dx.doi.org/10.1097/01.mlg.0000236095.97947.26.
3. Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1-T2 Glottic carcinomas. *Cancer*. 2004;100(9):1786–1792, http://dx.doi.org/10.1002/cncr.20181.
4. Al-Mamgani A, van Rooij PH, Woutersen DP, et al. Radiotherapy for T1-2N0 glottic cancer: a multivariate analysis of predictive factors for the long-term outcome in 1050 patients and a prospective assessment of quality of life and voice handicap index in a subset of 233 patients. *Clin Otolaryngol*. 2013;38(4):306–312, http://dx.doi.org/10.1111/coa.12139.
5. Chera BS, Amdur RJ, Morris CG, Kirwan JM, Mendenhall WM. T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010;78(2):461–466, http://dx.doi.org/10.1016/j.ijrobp.2009.08.066.
6. Khan MK, Koyfman SA, Hunter GK, Reddy CA, Saxton JP. Definitive radiotherapy for early (T1–T2) glottic squamous cell carcinoma: a 20 year Cleveland clinic experience. *Radiat Oncol*. 2012;7:193.
7. Canis M, Ihler F, Martin A, Matthias C, Steiner W. Transoral laser microsurgery for T1a glottic cancer: review of 404 cases. *Head Neck*. 2015;37(6):889–895, http://dx.doi.org/10.1002/hed.23688.
8. Cacicedo J, Casquero F, del Hoyo O, et al. Definitive radiotherapy for T1 glottic squamous cell carcinoma: a 15-year Cruces University Hospital experience. *Clin Transl Oncol*. 2013;15(11):925–931, http://dx.doi.org/10.1007/s12094-013-1025-1.
9. Smee RI, Williams JR, Broadley K, Bridger GP. Early glottic carcinoma treated by radiotherapy: defining a population for surgical salvage. *Laryngoscope*. 2013, http://dx.doi.org/10.1002/lary.23663.
10. Low TH, Yeh D, Zhang T, et al. Evaluating organ preservation outcome as treatment endpoint for T1aN0 glottic cancer. *Laryngoscope*. 2017;127(6):1322–1327, http://dx.doi.org/10.1002/lary.26317.
11. Shelan M, Anschuetz L, Schubert AD, et al. T1-2 glottic cancer treated with radiotherapy and/or surgery. *Strahlenther Onkol*. 2017;193(12):995–1004, http://dx.doi.org/10.1007/s00066-017-1139-4.
12. Chung SY, Keum KC. Radiotherapy versus cordectomy in the management of early glottic. *Cancer*. 2018;50(1):156–163.
13. De Santis RJ, Poon I, Lee J, Karam I, Enepekides DJ, Higgins KM. Comparison of survival between radiation therapy and trans-oral laser microsurgery for early glottic cancer patients: a retrospective cohort study. *J Otolaryngol – Head Neck Surg*. 2016;45(1):1–17, http://dx.doi.org/10.1186/s40463-016-0155-1.
14. Ahmed J, Ibrahim ASG, Freedman ML, Rosow DE. Oncologic outcomes of KTP laser surgery versus radiation for T1 glottic carcinoma. *Laryngoscope*. 2018;128(5):1052–1056, http://dx.doi.org/10.1002/lary.26853.
15. Mo HL, Li J, Yang X, et al. Transoral laser microsurgery versus radiotherapy for T1 glottic carcinoma: a systematic review and meta-analysis. *Lasers Med Sci*. 2017;32(2):461–467, http://dx.doi.org/10.1007/s10103-016-2103-8.
16. Guimarães AV, Dedivitis RA, Matos LL, Aires FT, Cernea CR. Comparison between transoral laser surgery and radiotherapy in the treatment of early glottic cancer: a systematic review and meta-analysis. *Sci Rep*. 2018;8(1):11900, http://dx.doi.org/10.1038/s41598-018-30218-x.
17. Zhan C, Yang X, Song X, Yan L. Radiotherapy vs surgery for T1-2N0M0 laryngeal squamous cell carcinoma: a population-based and propensity score matching study. *Cancer Med*. 2018;7(7):2837–2847, http://dx.doi.org/10.1002/cam4.1525.
18. Warner L, Chudasama J, Kelly CG, et al. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. *Cochrane Database Syst Rev*. 2014;(12):CD002027, http://dx.doi.org/10.1002/14651858.CD002027.pub2.
19. Huang G, Luo M, Zhang J, Liu H. The voice quality after laser surgery versus radiotherapy of T1a glottic carcinoma: systematic review and meta-analysis. *Onco Targets Ther*. 2017;10:2403–2410, http://dx.doi.org/10.2147/OTT.S137210.
20. Aaltonen L-M, Rautiainen N, Sellman J, et al. Voice quality after treatment of early vocal cord cancer: a randomized trial comparing laser surgery with radiation therapy. *Int J Radiat Oncol Biol Phys*. 2014;90(2):255–260, http://dx.doi.org/10.1016/j.ijrobp.2014.06.032.
21. Lombardo N, Aragona T, Alsayyad S, Pelaia G, Terracciano R, Savino R. Objective and self-evaluation voice analysis after transoral laser cordectomy and radiotherapy in T1a–T1b glottic cancer. *Lasers Med Sci*. 2018;33(1):141–147, http://dx.doi.org/10.1007/s10103-017-2361-0.
22. Greulich MT, Parker NP, Lee P, Merati AL, Misono S. Voice outcomes following radiation versus laser microsurgery for T1 glottic carcinoma. *Otolaryngol Neck Surg*. 2015;152(5):811–819, http://dx.doi.org/10.1177/0194599815577103.

23. Arias F, Arraras JI, Asin G, et al. Quality of life and voice assessment in patients with early-stage glottic cancer. *Head Neck*. 2015;37(3):340–346, http://dx.doi.org/10.1002/hed.23603.
24. Prettyjohns M, Winter S, Kerawala C, Paleri V. the NICE cancer of the upper aerodigestive tract guideline committee, Transoral laser microsurgery versus radiation therapy in the management of T1 and T2 laryngeal glottic carcinoma: which modality is cost-effective within the UK? *Clin Otolaryngol*. 2017;42(2):404–415, http://dx.doi.org/10.1111/coa.12807.
25. Loughran S, Calder N, MacGregor FB, Carding P, MacKenzie K. Quality of life and voice following endoscopic resection or radiotherapy for early glottic cancer. *Clin Otolaryngol*. 2005;30(1):42–47, http://dx.doi.org/10.1111/j.1365-2273.2004.00919.x.
26. Diaz-de-Cerio P, Preciado J, Santaolalla F, Sanchez-del-Rey A. Cost-minimisation and cost-effectiveness analysis comparing transoral CO2 laser cordectomy, laryngofissure cordectomy and radiotherapy for the treatment of T1-2, N0, M0 glottic carcinoma. *Eur Arch Oto-Rhino-Laryngol*. 2013;270(4):1181–1188, http://dx.doi.org/10.1007/s00405-012-2139-8.
27. Higgins KM. What treatment for early-stage glottic carcinoma among adult patients: CO2 endolaryngeal laser excision versus standard fractionated external beam radiation is superior in terms of cost utility? *Laryngoscope*. 2011;121(1):116–134, http://dx.doi.org/10.1002/lary.21226.
28. Phillips TJ, Sader C, Brown T, et al. Transoral laser microsurgery versus radiation therapy for early glottic cancer in Canada: cost analysis. *J Otolaryngol Head Neck Surg*. 2009;38(6):619–623.