



Prospective validation of an institutional treatment strategy for T1N0M0 glottic carcinoma

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ABSTRACT

Introduction: The aim of this study was to assess the validity of a treatment strategy for T1N0 glottic squamous cell carcinoma.

Methods: One hundred and seventeen patients were prospectively treated according to institutional guidelines, using 1) laser microsurgery (L) for exophytic tumor, limited to one vocal cord, without extension to the anterior commissure or the vocal process of the arytenoid cartilage, 2) radiotherapy (RT) for large or infiltrative tumor reaching the anterior commissure or the vocal process of the arytenoid cartilage, poor endoscopic exposure and cT1b or 3) partial laryngectomy (PL) for tumor infiltrating the anterior commissure. Ninety-five patients were treated with RT and 22 with surgery alone (S) [L:19; PL:3].

Results: The 5-year overall survival (OS) and disease-specific survival (DSS) were 81.5% and 97.1% (median follow-up: 73 months), respectively. There was no statistically significant difference in OS or DSS between patients treated with RT or S (logrank test: $p = 0.974$ and 0.978). The 5-year ultimate local control rate reached 98.3%. The local control rate with larynx preservation was 94.9% with no difference between RT (94.7%) and S (95.5%) (χ^2 : $p = 0.891$). Continued smoking after RT was significantly associated with a lower 5-year OS (77.9% versus 87%), [HR 3.458; $p = 0.043$ (95%CI 1.010–11.837)].

Conclusions: For patients with T1 glottic carcinoma, and based on our previous studies, these data prospectively confirm the oncologic validity of an institutional treatment strategy. Continued smoking after RT correlated with poor OS.

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Introduction

In laryngeal cancer, the glottic level is the most commonly invaded subsite [1–3]. Given that early cT1 glottic cancer is a highly curable disease, the main goal of treatment is cure with voice preservation and avoidance of severe complications [1–6].

Treatment options include radiation therapy (RT) and surgery (S), including transoral laser microsurgery (L) or partial laryngectomy (PL). Because prospective studies are lacking, there is currently no level I evidence to support either of these treatment modalities [2,4,7–10].

In 1998, we reported a retrospective analysis of 106 patients with cT1N0M0 glottic laryngeal carcinoma treated in our institution using all treatment modalities. Results suggested that, assuming proper selection of patients, RT and L yielded similar oncologic and functional outcomes whereas PL appeared to yield similar oncologic results but a worse quality of voice [11]. An additional economic analysis addressing cost considerations demonstrated that the selection of best practices favored RT and L, and restricted PL to highly selected cases [12].

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According to various retrospective studies and meta-analyses, functional and oncological outcome after RT and L are comparable [10]. However, no properly conducted randomized trial comparing RT with L exists. Given this and our previous experience, we defined institutional guidelines for the treatment of clinically staged cT1N0 glottic laryngeal carcinomas. The aim of the present study was to assess our institutional individualized treatment strategy on a series of patients treated according to these guidelines.

Patients and methods

Population

This study was approved by the Ethical Committee of St Luc University Hospital. One hundred and seventeen patients with clinically staged cT1N0 glottic squamous cell carcinoma (SCC) were prospectively treated between 1996 and 2016. There were 99 males and 18 females yielding a sex ratio of 5.5:1. The median age at the time of diagnosis was 65.5 years (range: 31–91 years). Among patients, 82.1% (96/117) were addicted to tobacco and 40.2% (47/117) were heavy drinkers. The median follow-up time was 73 months (range: 3–243 months) (Table 1).

Stage distribution and pathologic examination

All patients had a pre-treatment biopsy performed via direct endoscopy under general anesthesia as part of their initial work-up and were then clinically restaged according to the 2017 Union for International Cancer Control Tumor Nodes Metastases (UICC TNM) classification [13]. There were 72 patients with cT1a and 45 with cT1b. Pathologic diagnosis of invasive SCC was confirmed on biopsy in 103 patients. Fourteen patients with a diagnosis of carcinoma in situ on biopsy were included in the series because they were clinically considered to have a more infiltrative tumor based on endoscopic and CT assessment. One patient with two distinct tumors on each vocal cord was staged cT1b. Patients were clinically staged N0 after clinical examination. Computerized tomography

(CT) of the neck was performed in 91.5% (107/117) of the patients. Magnetic resonance imaging (MRI) of the neck was obtained for one patient and nine patients (7.7%) had no neck imaging. Chest imaging by X-ray and/or CT was performed in 96 patients (82.1%) and flexible gastroscopy in 67 patients (57.3%). Synchronous cancers were diagnosed in 6% (7/117) of the patients. Five of these had a second SCC in the head and neck, one was diagnosed with an adenocarcinoma of the esophagus, and one had a SCC of the skin.

Treatment options

All patients were treated with RT, L or PL. Treatment was selected according to the results of our previous studies which led to the development of institutional guidelines [11,12] briefly defined as:

L: Small exophytic tumor, located on one vocal cord, without extension to the anterior commissure or the vocal process of the arytenoid cartilage.

RT: Large or infiltrative tumor reaching the anterior commissure, poor endoscopic exposure, T1b PL: Tumor originating from the anterior commissure.

Patient characteristics per treatment modality are reported in Table 1.

Ninety-five patients were treated with RT. Eighty-five underwent RT alone and 10 had RT following L resection because of positive or borderline margins. Over the study period, the RT technique evolved. Prior to 2000, all patients were treated with parallel opposed fields on a 2D-fashion with 6 MeV X-Rays. From 2000 onwards, patients were treated with conformal RT and intensity-modulated RT (IMRT) was routinely introduced from 2006 on. The choice of the radiation dose was influenced by the tumor volume, more superficial tumors were typically treated with 60 Gy in 2 Gy fractions and more bulky tumors received a total dose of 64 Gy, 2 Gy fractions. The dose was prescribed on the median dose and at least 95% of the planning target volume (PTV) received 95% of the dose and at least 99% of the PTV received 90% of the dose. For anterior commissure tumors, a 5 mm bolus was typically added to improve dose homogeneity. All patients received conventional schedule of 5 fractions/week. The median overall treatment time was 44 days (range: 42–49 days). Patients treated with RT following L because of positive margins were finally included in the subgroup of patients treated with RT alone. Most of these patients had undergone superficial type I cordectomy according to the European Laryngological Society (ELS) classification [14,15] and this was mainly performed for diagnostic purposes. The median dose prescribed and the overall treatment time in RT following L patients were similar to patients treated with RT alone.

Nineteen patients were treated with L alone. Only type 2 and type 3 cordectomy were performed, avoiding more extended resections to optimally preserve voice function. Three patients (4%) were primarily treated with supracricoid PL. One of them was restaged as pT4a after surgery because of invasion through the thyroid cartilage observed in the resected specimen.

Study endpoints and statistical analysis

The endpoints of the study were 5-year overall survival (OS), 5-year disease-specific survival (DSS), 5-year disease-free survival (DFS), 5-year ultimate disease-free survival (UDFS), ultimate loco-regional control, and local control rate with larynx preservation. OS was defined as the time between the end of the first treatment and date of death or last contact date. DSS was calculated as the survival of patients from the end of treatment to the date of death from T1 glottic SCC, or any other head and neck SCC, or to the last follow-up date for patients still alive. According to the Food and

Table 1
Distribution of patient characteristics.

Characteristics n (patients)	RT 95	Laser 19	Par. Lar. 3	Total 117
Tumor stage				
T1a	54	18	0	72
T1b	41	1 ^a	3	45
Ant. Com. + (%)	43 (42.3)	–	3 (100)	46 (39.3)
Gender				
male/female	81/14	15/4	3/0	99/18
Age (average) years	64.6	64.4	70.6	64.7
Smoking before diagnosis				
Yes (%)	80 (84.2)	14 (73.7)	2 (66.6%)	96 (82.1)
No (%)	15 (15.8)	5 (26.3)	1 (33.3)	21 (17.9)
Stopped smoking after RT				
Yes(%)	53 (66.25).			
No (%)	22 (27.5)			
Unknown (%)	5 (6.25)			
Alcohol (%)	37 (38.9)	10 (45.5)	1 (33.3)	47 (40.2)
Mean follow-up (months)	73.3	92.9	30.0	75.0

Abbreviations: n: number of patients, RT: radiotherapy, Par. Lar.: partial laryngectomy, Ant. Com. +: anterior commissure involved.

^a One patient with two well distinct tumors on each vocal cord.

Drug Administration (FDA) guidelines, DFS was defined as the time from the end of the first treatment to the time of first recurrence, death from any cause or last contact date, whichever occurred first [16]. Patients who did not meet an event (death or recurrence) were censored at their last follow-up contact date. UDFS, the analysis of DFS in patients with recurrent disease, was defined as the time from the end of treatment for a first recurrence to the time of a new recurrence, death or last contact date, whichever occurred first. The local control rate with larynx preservation was defined as the rate of patients who ultimately were locally free of disease without total laryngectomy (TL). The χ^2 [2] test was used to test the null hypothesis that there was no difference in the number of patients controlled locally with larynx preservation between the two treatment groups. Actuarial survivals were assessed with Kaplan-Meier analysis [17]. The influence of treatment (RT versus S) was analyzed using the logrank test, and the Wald test for the Cox proportional hazard model was applied for the selected covariables of gender, age, cT1a vs cT1b, anterior commissure involvement and primary treatment modality [18]. For age as a continuous explanatory variable, the odds ratio corresponded to a unit increase in the risk factors. All statistical analyses were performed using SAS 9.4. A p-value < 0.05 was considered to be statistically significant.

Results

Survival

All results are reported at five years of follow-up. There was no

difference in OS between patients treated with RT or S (L or PL) (logrank test: $p = 0.974$). OS was 81.5% (Fig. 1); 81.1% in patients treated with RT and 83.3% in patients treated with S. A total of 25 patients died during follow-up. One patient died due to local recurrence, one patient died due to local and distant metastatic recurrence, one patient died from an uncontrolled lymph node neck metastasis with distant metastasis despite the tumor being locally controlled, and 22 patients died of a cause unrelated to glottic cancer. Similarly, there was no statistically significant difference in DSS between patients treated with RT versus S (logrank test: $p = 0.978$).

Overall, DSS was 97.1% (Fig. 2); 97.6% in patients treated with RT and 95.0% in patients treated with S. The DFS rate reached 66.0% (Fig. 3); 65.4% in patients treated with RT and 68.6% in patients treated with S. There was no statistically significant difference in DFS between patients treated with RT versus S (logrank test: $p = 0.783$). Overall, recurrences occurred in 24/117 patients (20.5%): 18 in the RT group and six in the S group. No recurrence was observed in the 10 patients who had RT following L. Local recurrences alone were observed in 18 patients and associated with regional recurrences in two of these. Isolated regional recurrences were reported in three patients, and one patient had a regional and distant metastasis. One patient, initially treated with L, experienced two episodes of local recurrence and was finally controlled, while another patient experienced an isolated neck recurrence followed by a local recurrence combined with distant metastasis. Among patients treated with RT, 15/95 (15.8%) had local or loco-regional recurrences, whereas there were 5/22 (22.7%) local and loco-regional recurrences in the S group (5/19 after L and 0/3 after PL).

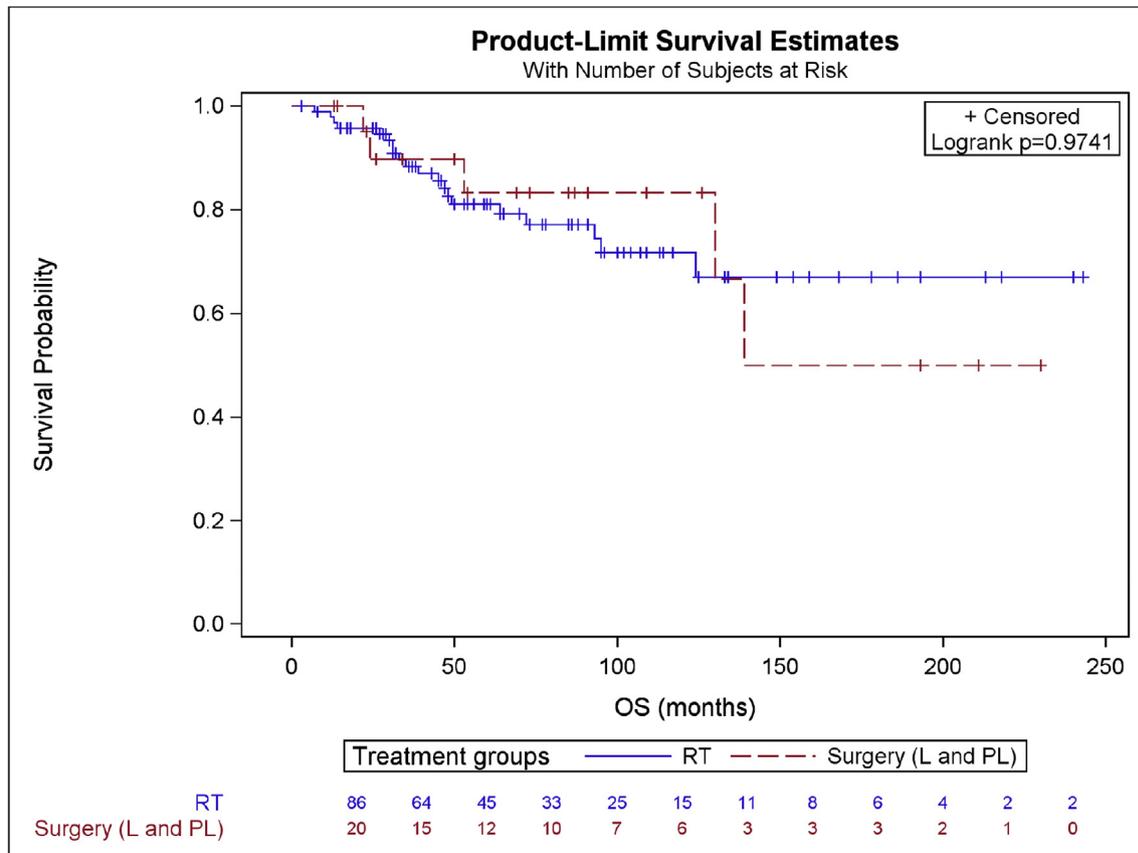


Fig. 1. Probability of overall survival (OS).
Abbreviations: RT: radiotherapy, L: laser, PL: partial laryngectomy

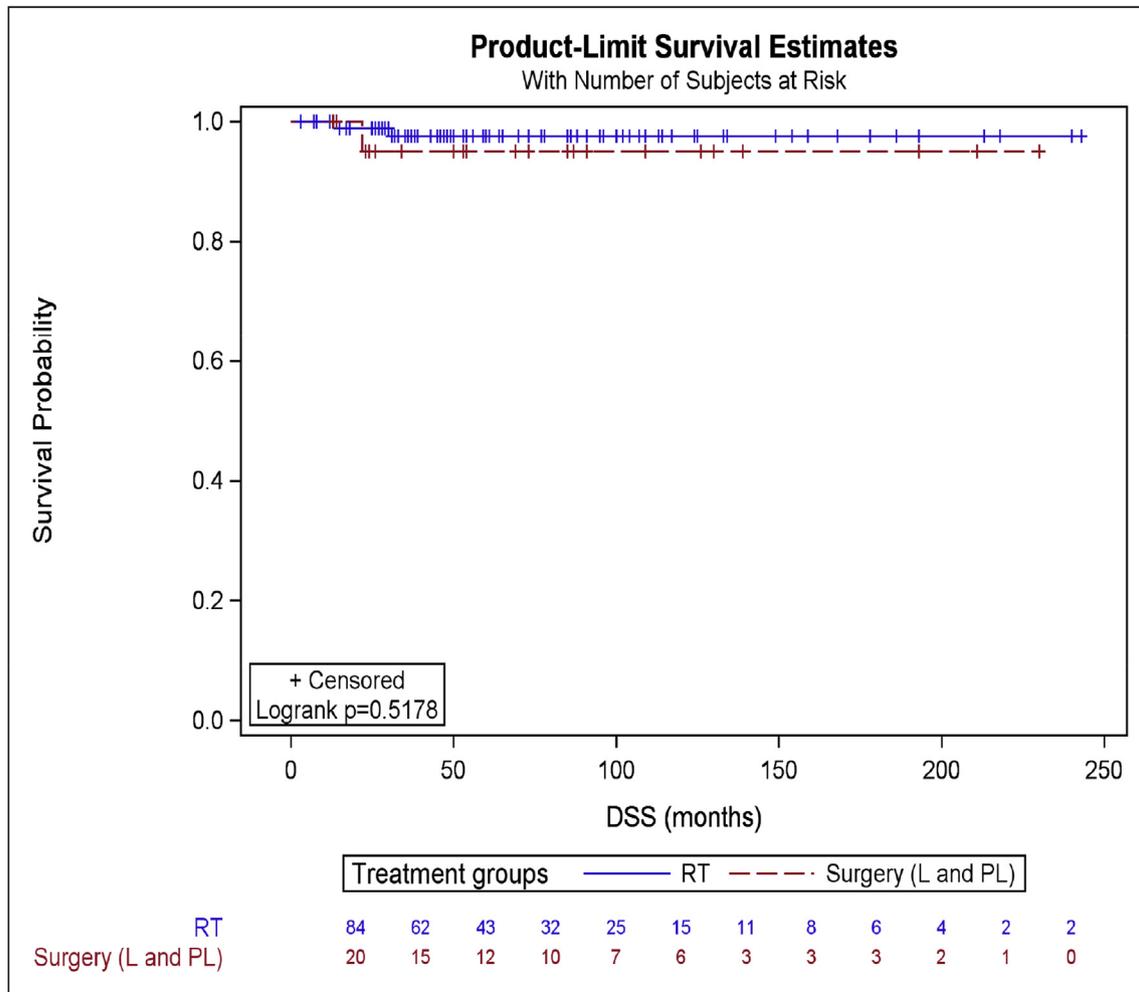


Fig. 2. Probability of disease-specific survival (DSS).
Abbreviations: RT: (radiotherapy), L: laser, PL: partial laryngectomy

Isolated neck recurrences were observed in one patient treated with PL and in two patients treated with RT. One patient treated with RT had concomitant regional and distant metastases. Local recurrences following RT were salvaged with L in four patients, PL in six patients and TL in five patients. Two patients with isolated neck recurrences were treated with neck dissection. One patient with regional and distant metastatic recurrence was treated with palliative care. Among the five recurrences following L, three patients were salvaged with RT, one patient was treated with chemoradiation (CRT) for a local and regional recurrence staged rT4N2b, and one patient had a second L resection. This last patient experienced a new recurrence 19 months after the second L and was finally treated with RT. At the time of last follow-up, all of these patients were free of recurrence. After PL, regional recurrence was reported in one patient salvaged with neck dissection. This patient developed a local regional recurrence with distant metastasis during follow-up and finally died from primary cancer.

The probability of DFS in recurring patients after salvage treatment (UDFS), reached 79.1% at five years. Again, there was no statistically significant difference in UDFS between patients treated with RT or S (logrank test: $p = 0.340$) (Fig. 4). Overall, including patients with no recurrence and patients with recurrence who had salvage treatment, the 5-year ultimate local control rate reached 98.3%: 100% after RT versus 90.9% after S (94.7% after L and 66.6% after PL).

Finally, the local control rate in patients free of total laryngectomy was 94.9% (CI 95%: 89.2–98.1); 94.7% (CI 95%: 88.1–98.3) in patients treated with RT, and 95.5% (CI 95%: 77.2–99.9) in patients treated with S (L and PL) (χ^2 [2] test: $p = 0.891$).

The results of the univariate analysis using the Cox proportional hazard model did not show any effect on OS for the analyzed variables of gender, age, cT1a vs. cT1b, anterior commissure involvement, or treatment modality [RT vs L + RT vs S (L and PL)] (Table 2). A similar analysis was not able to demonstrate any effect of the analyzed variables on DSS, DFS and UDFS (data not presented).

Last, we analyzed the impact of smoking in patients treated with RT. Smoking before RT was associated with a worse 5-year OS (78.6% versus 93.3%) and DFS (62% versus 80%) but the differences were not statistically significant, probably because of the imbalance between the numbers of smokers and non-smokers. Continued smoking after RT was significantly associated with a lower 5-year OS (77.9% versus 87%), [HR 3.458; $p = 0.043$ (95%CI 1.010–11.837)], but not with a lower DFS (64.3% versus 67.1%).

Incidence of second primary tumor

Over a maximum follow-up period of 243 months, 28 patients (23.9%) developed a second primary cancer. Twelve of these (42.8%) were related to smoking (eight lung cancer, three second head and neck SCC, and one synchronous lung and oropharynx SCC). At five

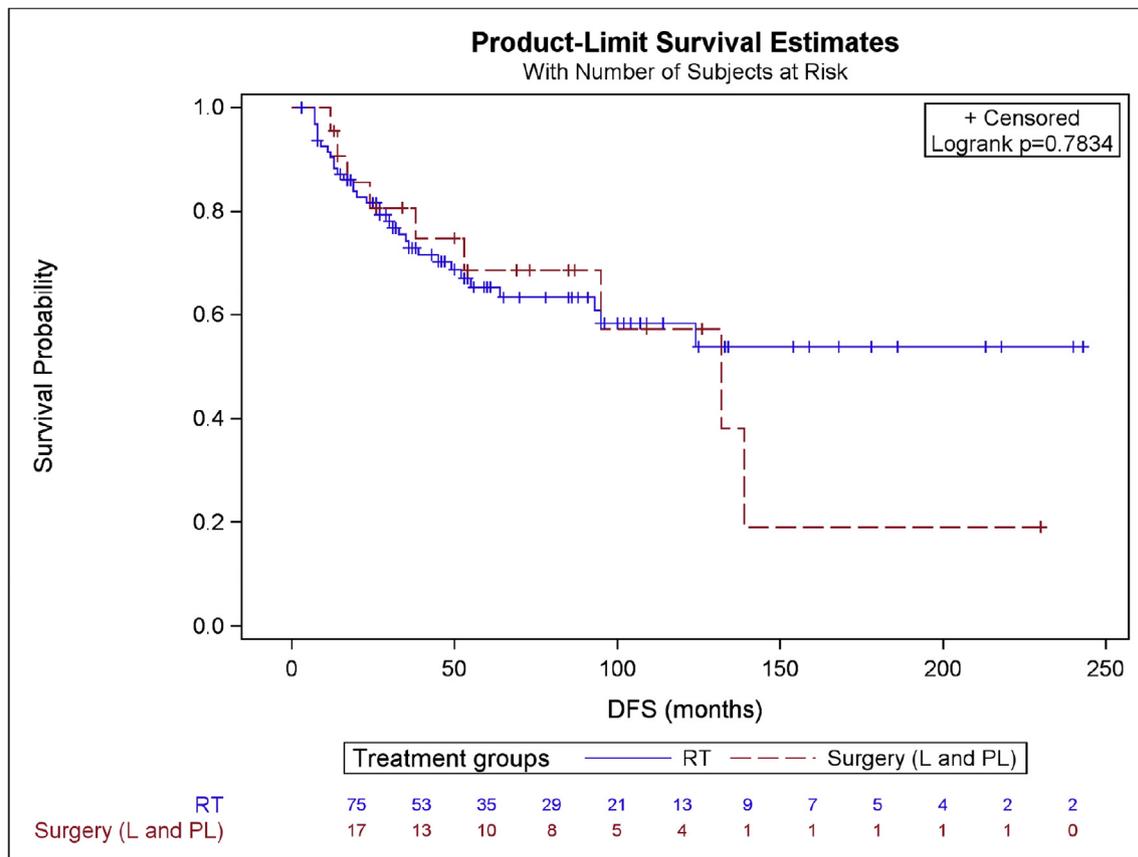


Fig. 3. Probability of disease-free survival (DFS).
Abbreviations: RT: (radiotherapy), L: laser, PL partial laryngectomy

years, the probability of developing a second primary tumor was estimated to be 13.7%.

Discussion

Individualized treatment strategy

Many publications analyze the outcomes of a retrospective series of patients treated with one or two treatment modalities, and then benchmark these against other reported series using the same modalities or other treatment procedures. In contrast, the aim of our study was to prospectively assess the validity of an individualized treatment strategy. To do this, we developed guidelines for the treatment of T1N0 glottic cancer based on the results of our reported studies [11,12]. For 20 years, patients were treated according to pre-established guidelines. Smaller tumors without extension to the anterior commissure or the vocal process were primarily treated by L, more extended tumors were treated by RT, and PL was only performed in a few patients with infiltrative tumors from the anterior commissure.

Oncologic results and larynx preservation

The 5-year OS and DSS rates of 81.5% and 97.1%, respectively, of the present series are comparable to those observed in our previously reported series (78% and 96%), which favorably challenges the question of physician preference to treatment selection [11]. In 2004, an exhaustive literature review reported 5-year survival rates after L, RT and PL of 79–84% for OS and 95–98% for DSS, comparable with the results of our present series [19]. Recent meta-

analyses reported similar results [1–3]. In our study, DSS was defined as the survival of patients who did not die from T1 glottic SCC or from a second head and neck SCC during follow-up. Only defining DSS as the survival of patients who did not die from a T1 glottic tumor would lead to the DSS reaching 100%, but the median survival would not be estimable due to too few events. The difference between OS and DSS highlights that most deaths are related to underlying disease within five years of treatment.

Survival rates are roughly comparable between the various treatment modalities, and minor differences are likely to reflect a selection bias rather than any differences in efficacy. Many studies generally report the results of one therapeutic modality used to treat a series of patients, with inherent biases due to their retrospective design and patient selection. In this series, and according to our institutional guidelines, the majority of T1b were treated with primary RT whereas, in the past, in our institution most of these more extended tumors were primarily treated with PL [11].

Five-year DFS reached 66.0%. This seemingly low rate of DFS is most likely due to the applied FDA definition which defines DFS as the time from end of treatment until recurrence of tumor or death from any cause. The 5-year UDFS reached 79.1%, highlighting that the great majority of recurrences were successfully salvaged. Local recurrences following L were treated with RT, CRT and second L, whereas local recurrences following RT were treated with voice-sparing surgery in two-thirds of the patients; one patient was treated palliatively because of distant metastasis concomitant to local recurrence. This policy of non-mutilating salvage treatment, when oncologically sound, allowed a local control rate with larynx preservation of 94.9% with no difference observed between RT or S.

The current literature reports local control rates for T1N0 after L

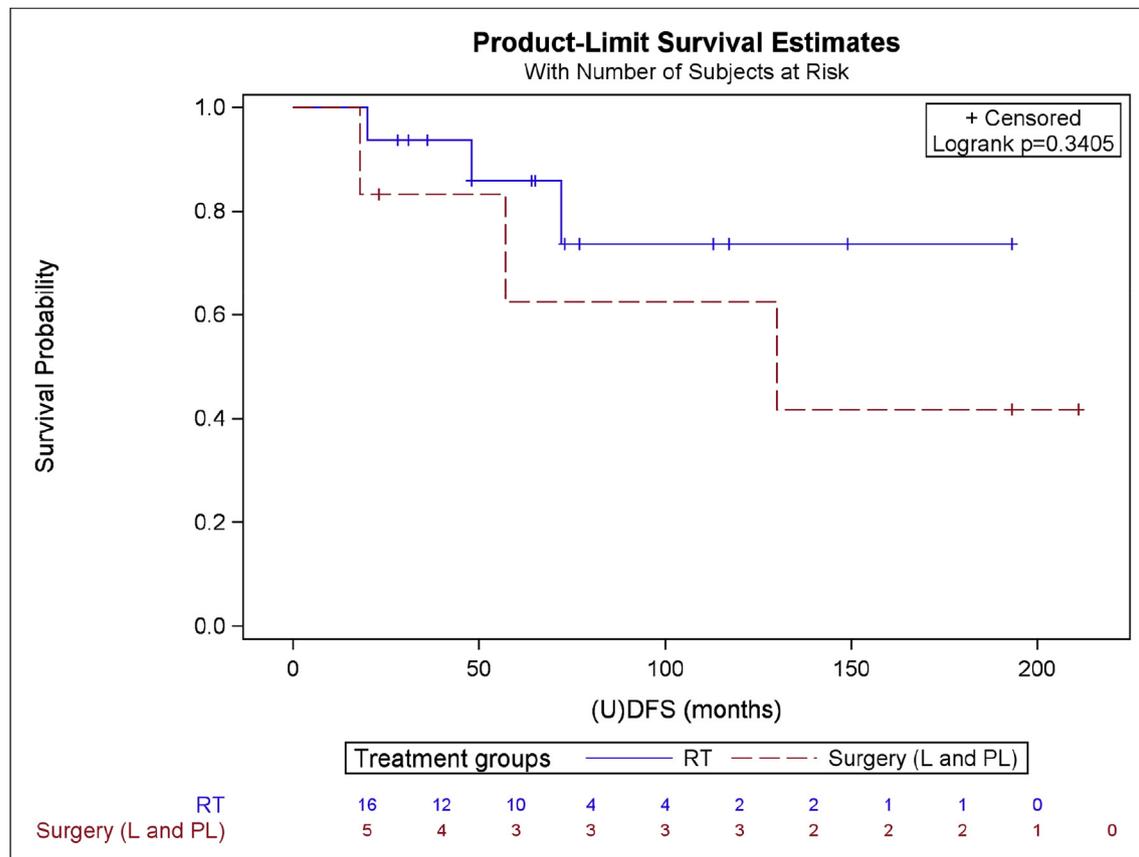


Fig. 4. Probability of ultimate disease-free survival (UDFS) of recurring patients (n = 24) after primary treatment. Abbreviations: RT: (radiotherapy), L: laser, PL: partial laryngectomy

Table 2
Univariate analysis on overall survival (OS) according to treatment (Cox proportional hazard model).

Characteristics	RT (n = 85)	L + RT (n = 10)	Surgery (L and PL) (n = 22)	Total (n = 117)
Survival				
Patients alive	67 (78.8%)	8 (80.0%)	17 (77.3%)	92 (78.6%)
Patients deceased	18 (21.2%)	2 (20.0%)	5 (22.7%)	25 (21.4%)
Kaplan Meier Estimate of Overall Survival (months)				
Median	NE	NE	139,00	NE
CI 95	(124.0 - NE)	(33.00 - NE)	(130.0 - NE)	(139.0 - NE)
Minimum	7.0	3.0	13.0	3.0
Maximum	243.0	213.0	230.0	243.0
Between groups comparison (logrank test)				0.979
HR (95%CI)				
Ant. Com. +				1.670 (0.550–5.075)
Age at diagnosis				1028 (0.990–1.068)
T1b				1031 (0.327–3.249)
Gender (male)				2552 (0.585–11.133)
Treatment: L + RT				1.172 (0.198–6.952)
Treatment: RT				1.012 (0.304–3.370)

Abbreviations RT: radiotherapy, L: laser, PL: partial laryngectomy, Ant. Com. +: anterior commissure involved.

Note: NE = Non-estimable due to insufficient events.

Note, Note: p-value from a log rank test. Hazard-ratios and corresponding Wald p-values from a Cox PH model.

Note, Note: References as follows: Ant. Com. +: No, T: T1a, Gender: female, Treatment: S (L and PL).

ranging from 80% to 90%. After salvage for recurrences, the ultimate local control rates with larynx preservation are reported to range from 90% to 95% [2,8,19]. Some studies suggest that laryngeal preservation is higher in the L group compared to the RT group [1,6], but others have shown no significant differences between both groups [20]. Our rate of total laryngectomy-free local control is comparable to reported studies in which L was the primary treatment [21–23]. In our series, all five patients requiring TL were

initially treated with RT, suggesting a better larynx preservation rate in patients treated with L. However, this information should not overlook the fact that patients treated with primary RT had more extended tumors than patients primarily treated with L. This deliberate choice could explain the lower larynx preservation rate in the group of patients treated with RT.

Overall, our 5-year ultimate local control rate of 98.3% is comparable with the figure reported in 1998 (97%) [11], and favorably

challenges the best results in the literature. Few studies report ultimate local control rates ranging from 90% to 95% [1,6,19]. After open PL, local control rates range from 90% to 95% for patients with cT1N0. After salvage for recurrences, ultimate local control rates exceed 95% [19]. After RT, 5-year local control rates vary from approximately 85%–94% in the setting of cT1N0 [6,19].

Investigators from the Netherlands reported that patients who continued to smoke after RT had significantly lower local control and OS rates compared with those who stopped smoking [24]. In our series, we also observed a lower OS, but not a lower DFS, in patients who continued to smoke after RT, suggesting that patients who continue to smoke are at a higher risk of death from other smoking-related diseases. These findings emphasize the importance of smoking cessation after treatment.

Higher local control rates have been reported with slightly accelerated radiotherapy [24,25]. In our series, we tended not to increase the dose per fraction to above 2 Gy to try to limit late reacting normal tissue toxicity and preserve the voice quality. We acknowledge that we do not have any data to indicate that other regimens did worse. Ultimate local control rates range from 90 to 95% [6,19]. Other studies have demonstrated ultimate local control of 93%–95% with a larynx preservation rate of 94%–100% reported in patients treated only with L, suggesting a bias in patient selection compared to our series which included all T1 glottic SCC regardless of treatment modality. Although some authors have advocated the use of L for the treatment of tumors involving the anterior commissure, poor functional results, as well as a lower local control rate [6,21–23], have been reported compared with RT [26].

Of note, most local recurrences following RT were treated with voice-sparing surgery, and all patients with local recurrence after L were salvaged by voice-sparing treatment modalities. As suggested by some studies, L is a suitable treatment option with good ultimate local control rates in selected early local recurrences [5,6].

Incidence of second primary tumors

The development of a second primary was not a rare event in this study population with the incidence reaching 13.7% at five years. This rate is comparable to the results of our previous study where the yearly incidence of a second primary reached 2.5% for the first five years [11]. Previous studies reported similar risk ranges of 12.3% [27]. During follow up, three patients developed neck lymph node metastases reported as a regional recurrence of the primary T1 glottic SCC despite the absence of concomitant local recurrence. While initial understaging was demonstrated in one patient treated with PL (who was finally staged as pT4a), understaging remains hypothetical in the other patients. However, because the occurrence of lymph node metastases is an uncommon event in early glottic cancer, the hypothesis of lymph node metastases from unknown primaries cannot be excluded. This information highlights the importance of good follow-up for these patients.

The present study included all patients with cT1N0 glottic SCC referred in our institution over a 20-year period who were prospectively treated with different treatment modalities according to an institutional individualized strategy based on oncologic control and voice quality. Our results show that this strategy is able to achieve optimal oncologic results. The results of this study have comparable oncologic outcomes compared to those in our previous retrospective study where the different treatment options reflected more so physician preference than institutional policy. We don't report data on voice outcomes, what could be considered as a weakness of the study. However, in our previous study, we have shown that, assuming appropriate patient selection, RT and L

yielded similar functional results [11]. Given that the main objective of the present study was to assess the oncologic validity of a treatment strategy for T1N0 glottic SCC, we mainly focused on survival and local control.

Conclusions

Our results prospectively demonstrate the suitability of an institutional approach towards the treatment of cT1N0 glottic SCC based on the reported results of our previous studies. Prioritizing voice quality and treatment costs is feasible without jeopardizing survival and loco-regional control. Smoking cessation after treatment is paramount.

Conflict of interest statement

There are no conflicts of interest to declare by any of the authors.

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