

Decreased Local Control Following Radiation Therapy Alone in Early-Stage Glottic Carcinoma with Anterior Commissure Extension*

Abderrahim Zouhair¹, David Azria¹, Philippe Coucke¹, Oscar Matzinger¹, Luc Bron², Raphael Moeckli³, Huu-Phuoc Do³, René-Olivier Mirimanoff¹, Mahmut Ozsahin¹

Purpose: To assess the patterns of failure in the treatment of early-stage squamous cell carcinoma of the glottic larynx.

Patients and Methods: Between 1983–2000, 122 consecutive patients treated for early laryngeal cancer (UICC T1N0 and T2N0) by radical radiation therapy (RT) were retrospectively studied. Male-to-female ratio was 106 : 16, and median age 62 years (35–92 years). There were 68 patients with T1a, 18 with T1b, and 36 with T2 tumors. Diagnosis was made by biopsy in 104 patients, and by laser vaporization or stripping in 18. Treatment planning consisted of three-dimensional (3-D) conformal RT in 49 (40%) patients including nine patients irradiated using arytenoid protection. A median dose of 70 Gy (60–74 Gy) was given (2 Gy/fraction) over a median period of 46 days (21–79 days). Median follow-up period was 85 months.

Results: The 5-year overall, cancer-specific, and disease-free survival amounted to 80%, 94%, and 70%, respectively. 5-year local control was 83%. Median time to local recurrence in 19 patients was 13 months (5–58 months). Salvage treatment consisted of surgery in 17 patients (one patient refused salvage and one was inoperable; total laryngectomy in eleven, and partial laryngectomy or cordectomy in six patients). Six patients died because of laryngeal cancer. Univariate analyses revealed that prognostic factors negatively influencing local control were anterior commissure extension, arytenoid protection, and total RT dose < 66 Gy. Among the factors analyzed, multivariate analysis (Cox model) demonstrated that anterior commissure extension, arytenoid protection, and male gender were the worst independent prognostic factors in terms of local control.

Conclusion: For early-stage laryngeal cancer, outcome after RT is excellent. In case of anterior commissure extension, surgery or higher RT doses are warranted. Because of a high relapse risk, arytenoid protection should not be attempted.

Key Words: Glottic cancer · Radiotherapy · Surgery · Anterior commissure · Local relapse

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Verminderte lokale Kontrolle nach alleiniger Strahlentherapie bei Glottiskarzinom im Frühstadium mit Ausbreitung zur vorderen Kommissur

Ziel: Ergründung der Versagensmechanismen bei der Therapie des Larynxkarzinoms im Frühstadium.

Patienten und Methodik: Zwischen 1983 und 2000 wurden 122 konsekutive Patienten, die wegen eines Larynxkarzinoms (UICC T1N0 und T2N0) eine Strahlentherapie erhielten, retrospektiv untersucht. Das Verhältnis von Frauen zu Männern betrug 106 : 16, das mittlere Alter lag bei 62 Jahren. Es handelte sich um 68 Patienten mit T1a-, 18 mit T1b- und 36 mit T2-Tumoren. Die Diagnose wurde bei 104 Patienten mit Hilfe einer Biopsie und bei 18 Patienten mit Laservaporisation oder Stripping gestellt. Bei 49 Patienten (40%) bestand die Behandlungsplanung aus einer dreidimensionalen konformalen Strahlentherapie, einschließlich neun Patienten, die unter Arytänoidprotektion bestrahlt wurden. Die mittlere Dosis von 70 Gy (60–74 Gy) wurde über einen mittleren Zeitraum von 46 Tagen verabreicht. Die mittlere Nachbehandlungszeit erstreckte sich über 85 Monate.

Ergebnisse: Das 5-Jahres-Überleben betrug 80%. Das tumorspezifische 5-Jahres-Überleben lag bei 94%, und 70% der Patienten blieben während dieses Zeitraums erkrankungsfrei. 83% wiesen nach 5 Jahren kein Lokalrezidiv auf. Der mittlere Zeitraum bis zum Auftreten eines lokalen Rückfalls belief sich bei 19 Patienten auf 13 Monate (5–58 Monate). Die Rezidivbehandlung bestand bei 17 Patienten aus einem chirurgischen Eingriff (ein Patient lehnte die Rezidivbehandlung ab, ein anderer war inoperabel; totale Laryngektomie bei elf und partielle Laryngektomie bzw. Kordektomie bei sechs Patienten). Sechs Patienten starben an ihrem Larynxkarzinom. Eine einseitige Varianzanalyse zeigte, dass die Ausbreitung auf die vordere Kommissur, die Arytänoidprotektion

¹ Department of Radiation Oncology, and

² Department of Otorhinolaryngology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland,

³ Institute of Applied Radiophysics (IRA), Lausanne, Switzerland.

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oder eine Strahlendosis < 66 Gy die Prognose der Lokalrezidive verschlechterte. Eine Multivarianzanalyse (Cox-Modell) belegte, dass unter den berücksichtigten Faktoren die Ausbreitung auf die vordere Kommissur, die Protektion des Aryknorpels und männliches Geschlecht die schlechtesten unabhängigen Prognosefaktoren im Hinblick auf Lokalrezidive sind.

Schlussfolgerung: Beim Larynxkarzinom im Frühstadium erbringt die Strahlentherapie hervorragende Ergebnisse. Im Fall einer Ausbreitung auf die vordere Kommissur ist ein chirurgischer Eingriff oder eine höhere Strahlendosis erforderlich. Wegen des hohen Rezidivrisikos sollte keine Protektion des Aryknorpels vorgenommen werden.

Schlüsselwörter: Larynxkarzinom · Strahlentherapie · Chirurgie · Vordere Kommissur · Lokalrezidive

Introduction

Early glottic cancer is a highly curable disease using radiation therapy (RT) alone. It can be also treated with conservative surgery [8, 12, 47, 63]. The goal of treatment is to achieve the best local control with the least toxicity. Voice preservation is generally accepted to be better following RT alone compared with any surgical procedure, based on retrospective data [21, 43, 65].

The optimal treatment in case of anterior commissure infiltration in T1N0 or T2N0 tumors is a matter of debate. The anterior commissure is attached to the thyroid cartilage, and tumor involvement of the latter is considered to be a poor prognostic factor for outcome of RT. Therefore, partial laryngectomy is generally preferred in this particular subset of patients [7, 38]. However, there is also substantial amount of literature indicating a very good local control when using RT alone in cases of anterior commissure infiltration [42, 68].

In this retrospective single-center experience, we aimed at assessing the patterns of failure and prognostic factors, including anterior commissure extension and arytenoid protection in the treatment of early-stage squamous cell carcinoma of the glottic larynx.

Patients and Methods

Patients

122 patients with previously untreated T1N0 and T2N0 biopsy-proven squamous cell carcinoma of the glottic larynx, who were treated with RT alone at the Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, between 1983 and 2000, were included in this study.

All patients had previously untreated squamous cell carcinoma of the glottic larynx. The majority of the patients had well-differentiated tumors (n = 67; 55%). Male-to-female ratio was 106 : 16, and median age 62 years (range: 35–92 years). All patients underwent complete clinical examination and panendoscopy, and anterior commissure infiltration was always assessed, including the use of computed tomography (CT). When needed, magnetic resonance imaging (MRI) was also performed. Tumor staging was done according to the 1987 version of the UICC (International Union Against Cancer) classification criteria.

The treatment of choice at CHUV is RT alone for early-stage glottic cancer, and conservative surgery is indicated

when the patient refuses RT. No patient with impaired vocal cord mobility or with another synchronous malignant disease was included in this study (Table 1).

Radiation Therapy

RT and techniques are displayed in Table 2. All patients were treated using a planned, continuous course of RT with curative intent. A median dose of 70 Gy (range: 60–74 Gy) was given (2 Gy/fraction) over a median period of 46 days (range: 21–79 days). Most of the patients (n = 88) received 70 Gy in 7 weeks, 2 Gy/fraction. Recent patients (n = 15) received 70 Gy in 6 weeks using a slightly accelerated schedule starting with a concomitant boost every Friday from the beginning of treatment (Monday to Thursday 2 Gy/fraction/day; 2 × 2 Gy on Fridays). 19 patients received different hyperfractionated concomitant boost schedules according to two different local protocols. 65 patients were treated with a ⁶⁰Co unit, and 57 with linear accelerators, either with 6-MV photons (n = 21) or 10- to

Table 1. Patients' characteristics.

Tabelle 1. Patientencharakteristika.

Factor	Group	n	%
Sex	Male	106	87
	Female	16	13
Smoking	Yes	113	92
	No	9	8
Alcohol	Yes	93	76
	No	29	24
Dysphonia (months)	< 6	76	62
	6–12	31	26
	> 12	15	12
T-classification	1a	68	56
	1b	18	15
	2	36	29
Histological differentiation	Well	67	55
	Moderate	37	30
	Poor	18	15
Localization	Glottic (T1)	86	70
	Glottic-supraglottic	24	20
	Glottic-subglottic	10	8
	All 3 stages	2	2
Anterior commissure extension	Yes	61	50
	No	61	50

15-MeV electrons ($n = 36$). Treatment volume mainly included the glottic region, whether a CT simulation was performed or not. The typical borders for a T1 lesion would be the prevertebral fascia posteriorly, below the hyoid bone superiorly, below the cricoid cartilage inferiorly, and at the fall-off (1–2 cm) anteriorly. The dose was prescribed according to the ICRU criteria [33] after 1994 and to the midplane (85% isodose) before. T2N0 tumors were irradiated with ($n = 10$) or without ($n = 12$) elective nodal irradiation (subdigastric and midjugular nodes), depending on the physician's decision.

Adjuvant chemotherapy was not administered in this cohort of patients. The median follow-up period was 85 months (range: 12–178 months).

No patient was lost to follow-up. All patients were followed in a special head and neck consultation unit at CHUV. The follow-up visits were repeated every other month during the first 2 years, every 6 months until the 5th year, and once a year thereafter.

Statistical Analyses

Means were compared by Student's *t*-test. Proportions were compared using the χ^2 -test for values > 5 and Fisher's exact test for ≤ 5 . Local control, disease-free, cause-specific, and overall survival rates were calculated using the product-limit method [35]. Time to any event was measured from the date of pathologic diagnosis. The events were death (all causes of death included) for overall survival, larynx cancer-related mortality for cause-specific survival, death (including all causes of death) or any relapse for disease-free survival, local recurrence for local control (patients dying from any causes without local recurrence were censored), and metachronous second cancer for second cancer probability. Confidence intervals (CI) were calculated from standard errors. Differences between groups were assessed using the log-rank test [50]. Multivariate analyses were done using the Cox stepwise-regression analysis to determine the independent contribution of each prognostic factor [11].

Results

The 5-year overall survival was 80% (95% CI, 73–88). 5-year cancer-specific survival, disease-free survival, and local control were 94% (95% CI, 90–99), 70% (95% CI, 62–78), and 83% (95% CI, 76–90), respectively (Figure 1). A total of 35 patients died, and only six deaths were related to laryngeal cancer, while the others were due to secondary cancers or to intercurrent disease.

Median time to local recurrence in 19 patients was 13 months (range: 5–58 years). All recurrences were confirmed by biopsy. No single case of distant or nodal relapse was observed. Treatment plans of those 19 relapsing patients were reassessed. According to treatment energy, we observed ten relapses out of 65 patients (15%) treated with the cobalt unit, six out of 36 (17%) treated with electrons alone, and three out of 21 (14%) treated with 6-MV photons ($p > 0.05$). There was no

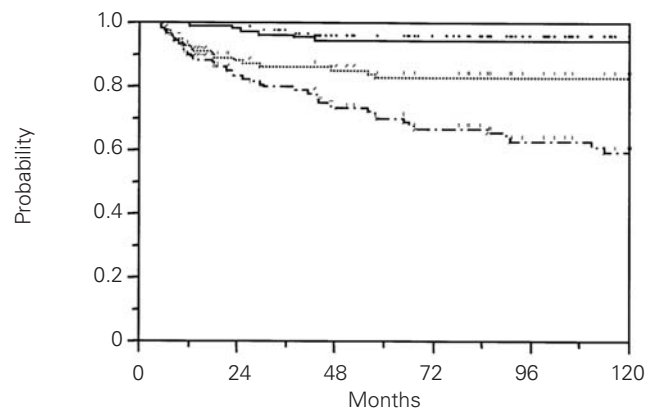
Table 2. Radiotherapy (RT) dose and technique.

Tabelle 2. Dosis der Strahlentherapie und Anwendungsweise.

Factor	Group	n	%
Immobilization method	Mask	53	43
	Tape	16	14
	No	53	43
Radiation portals	2 lateral	81	66
	2 lateral + 1 anterior	11	9
	1 anterior (electron beam)	30	25
3-D CT-assisted conformal RT	Yes	49	40
	No	73	60
Arytenoid protection	Yes	9	7
	No	113	93
Median total dose (Gy)		70	(60–74)
Median dose/fraction (Gy)		2	(1.66–2.50)
Median treatment duration (days)		46	(21–79)
Median interruption time (days)		1	(0–18)

geographic miss but we observed local relapse in four of the nine patients (44%) who had arytenoid shielding (all relapsing at the contralateral part of the larynx, which was not included in the planning treatment volume). All but three patients had anterior commissure extension. The details concerning local recurrences are given in Table 3.

Univariate analyses (Table 4) revealed that prognostic factors negatively influencing local control were anterior commissure extension (Figure 2), arytenoid protection, and total RT dose < 66 Gy. Among the factors analyzed, multivariate analysis (Cox model) demonstrated that anterior commissure



Patients at risk	0	24	48	72	96	120
CSS	122	108	85	69	51	33
LC	122	96	77	61	46	30
DFS	122	96	77	61	46	30

Figure 1. Cancer-specific survival (CSS; —), local control (LC;), and disease-free survival (DFS; - - -) in 122 patients with T1–T2N0 glottic cancer treated with radiation therapy alone.

Abbildung 1. Tumorspezifische Überlebensrate (CSS; —), lokale Kontrolle (LC;), und krankheitsfreie Überlebenszeit (DFS; - - -) bei 122 Patienten mit T1–T2N0-Glottistumoren, die nur mit Strahlentherapie behandelt wurden.

Table 3. Patterns of failure.

Tabelle 3. Versagensmuster.

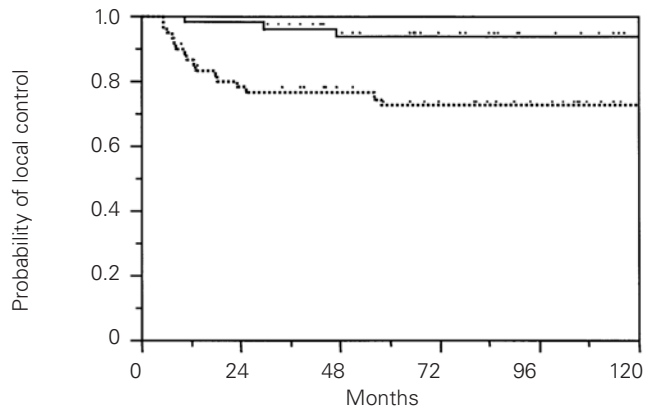
Site of failure	n	%
In field	15	79
In + out of field	3	16
Out of field	1	5

extension, arytenoid protection, and male gender were the worst independent prognostic factors in terms of local control (Table 5).

Salvage treatment consisted of surgery in 17 patients. One patient refused salvage treatment, and another one was judged to be inoperable. Total laryngectomy (TL) was realized in eleven patients, and partial laryngectomy (PL; n = 4) or cordectomy (n = 2) in six. Out of 17 patients who had a salvage treatment, four progressed again without ultimate control. The ultimate larynx preservation rate was, therefore, 88% (107 out of 122 patients: eleven salvage TL, progression after salvage PL in one and cordectomy in one, and two refusing salvage surgery). No reirradiation was proposed in this setting. Laryngeal cancer was considered a cause of death only in six out of 35 deaths. The 5-year local control rate, which was the same at 10 years, before and after salvage surgery amounted to 82% (95% CI, 75–89) and 94% (95% CI, 90–98), respectively (Figure 3).

According to the EORTC/RTOG Late Radiation Morbidity Scoring Scheme [49], there were six patients with grade 1 (mild arytenoid edema), four with grade 2 (moderate arytenoid edema), one with grade 3 (severe edema), and three with grade 4 (arytenoid necrosis) laryngeal complications. Three patients presented with grade 2 subcutaneous tissue fibrosis as well.

We observed 14 patients developing a second cancer during a median period of 49 months (range: 3–144 months). The 5- and 10-year metachronous second cancer incidence was 11% (95% CI, 5–18) and 15% (95% CI, 7–21), respectively. Five patients developed non-small-cell lung cancer, four metachronous head and neck tumors including one patient with vocal cord sarcoma, two esophageal cancer, two prostate cancer, and one patient non-Hodgkin's lymphoma of the nasopharynx. Salvage treatment for those patients consisted of surgery in five, curative RT in four, chemotherapy in one, and palliative treatment in four patients.



Patients at risk with or without anterior commissure extension

No	61	50	38	28	20	13
Yes	61	47	40	33	27	17

Figure 2. Local control with (.....) or without (—) anterior commissure infiltration in 122 patients with T1–T2N0 glottic cancer treated with radiation therapy alone.

Abbildung 2. Lokale Kontrolle, mit (.....) oder ohne (—) Infiltration der vorderen Kommissur bei 122 Patienten mit T1–T2N0-Glottistumoren, die nur mit Strahlentherapie behandelt wurden.

Table 4. Univariate analyses (log-rank test). RT: radiotherapy.

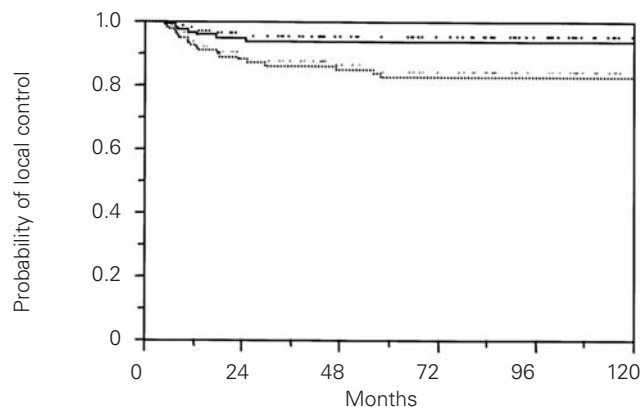
Tabelle 4. Univariate Analyse (Log-Rank-Test). RT: Strahlentherapie.

	n	Number of local relapses	5-year local control (%) before salvage surgery	p-value
All patients	122	19	83	
Gender				0.07
Female	16	0	100	
Male	106	19	80	
Dysphonia (months)				0.46
≥ 6	67	12	80	
< 6	55	7	86	
Anterior commissure extension				0.002
Yes	61	16	73	
No	61	3	94	
Arytenoid protection				0.008
Yes	9	4	56	
No	113	15	85	
Stage				0.36
T1a	68	9	85	
T1b	18	2	86	
T2	36	8	77	
Total dose (Gy)				0.05
≥ 66	106	14	86	
< 66	16	5	35	
Technique				0.28
2 lateral	81	13	82	
2 lateral + 1 anterior	11	0	100	
1 anterior	30	6	78	
Immobilization method				0.68
Mask	53	6	87	
Tape	16	3	79	
No	53	10	80	
3-D conformal RT				0.55
No	73	13	81	
Yes	49	6	86	
Interruption time (days)				0.50
Yes	48	6	83	
No	74	13	82	

Table 5. Multivariate analyses (Cox model).

Tabelle 5. Multivariananalyse (Cox-Modell).

Variable	Relative risk	p-value
Sex (male vs. female)	0.0008	0.004
Arytenoid protection (no vs. yes)	0.45	0.02
Anterior commissure extension (no vs. yes)	0.42	0.001



Patients at risk according to salvage surgery

After	122	104	85	69	51	33
Before	122	96	77	61	46	30

Figure 3. Local control before (.....) or after (—) salvage surgery in 122 patients with T1-T2N0 glottic cancer treated with radiation therapy alone.

Abbildung 3. Lokale Kontrolle vor (.....) und nach (—) „Salvage“-Chirurgie bei 122 Patienten mit T1-T2N0-Glottistumoren, die nur mit Strahlentherapie behandelt wurden.

Discussion

RT is widely used as a primary modality in the treatment of early glottic cancer [20, 24, 34, 54, 62]. Both RT and conservative surgery, i.e., cordectomy, laser microsurgery or partial laryngectomy, seem to be equally effective modalities in terms of local control and survival [55, 57] although not confirmed by any randomized comparison. However, voice quality is reported to be better after RT [5, 23, 25, 32, 45, 57]. This superiority is generally observed by the patient her- or himself, by the family, and/or by the physician. However, when assessed by acoustic analysis and speech aerodynamic studies, the quality of the voice does not return to normal following irradiation [2]. This is probably due to the tumor itself, or because RT produces a geometric asymmetry and, henceforth, a

loss of elasticity of the vocal folds. Some authors incriminate the use of continuing smoking [36] or the field size [64]. In our multidisciplinary tumor board, we explain the advantages and disadvantages of the various treatment modalities to the patients, who ultimately decide for themselves.

Numerous reports regarding the treatment of early glottic cancer have evaluated a number of prognostic factors, i.e., tumor volume and stage [20, 28, 37], tumor kinetics including p53 status [3, 13, 48], histological differentiation, intrinsic radiosensitivity [28], smoking habits and hypoxia [9], pretreatment hemoglobin level [14, 59, 69], dose per fraction [70], total dose [62], overall treatment time [4, 10, 18, 27, 52, 53, 58], field size [64], beam energy [16, 19], radiation technique [61], and anterior commissure involvement [41, 51]. These factors were not always reported to have a prognostic influence by all authors [17, 30, 46, 66, 67].

The majority of glottic cancers arises in the anterior part of the vocal cords, with relatively frequent involvement of the anterior commissure [44] (Table 6). Some authors [16, 61] advocate that relapses in this region are due to an underdosage in relation to the energy (cobalt vs. 6-MV photons), but even in earlier series, where only cobalt units were used, a worse local control was reported in such cases as well. In the present series, we did not observe any significant difference in terms of local relapses according to the treatment energy (cobalt vs. 6-MV photons vs. 10- to 15-MeV electrons). Anatomically, the anterior commissure is attached directly to the thyroid cartilage, which lacks a protective perichondrial lining as a potential tumor barrier [44]. This barrier is a relatively weak area concerning tumor dissemination [60] where the Broyles' ligament penetrates into the thyroid cartilage. The latter is also useful in defining the tumor's extent. Some investigators reported this to be associated with decreased local control following RT [29, 60, 71], while others did not [5, 16, 42]. In the present series, anterior commissure extension was found to be an independent prognostic factor in terms of local control, since we observed 16 relapses out of 61 patients with anterior

Table 6. Selected series of glottic cancer reporting anterior commissure infiltration (ACI).

Tabelle 6. Ausgewählte Studien zu Glottistumoren mit Infiltration der vorderen Kommissur.

Author	Number	Patients with ACI n (%)	Stage	Local control ^a at 5 years (%)		
				All	Without ACI	With ACI
Bron et al. [8]	81	43 (53)	T1-2	77	90	66
Mendenhall et al. [42]	519	328 (63)	T1-2	89	(No difference)	
Johansen et al. [34]	707	23 (3)	T1a	85	?	68
Grégoire et al. [23]	106	13 (12)	T1	91	(No difference)	
Marshak et al. [41]	207	60 (20)	T1-2	88	91	70
Le et al. [39]	398	174 (44)	T1	85	88	80
			T2	70	81	65
Present series	122	61 (50)	T1-2	83	85	56

^a local control without salvage surgery

commissure extension, compared to three out of 61 without ($p < 0.01$).

T-classification is a well-known prognostic factor in glottic cancer, and in all series, T1 tumors do better than T2 in terms of local control: at 5 years it ranges between 80–95% for T1, and 60–80% for T2 [28]. In the present series, the 5-year local control was 85%, 86%, and 77% for T1a, T1b, and T2 tumors, respectively. In order to ameliorate the local control in T2 tumors, either altered fractionation [22, 26, 31] or increased total dose [62] was proposed. In a study by Le et al. [39], local control was reported to be influenced by increasing the total dose only in T2 and not in T1 tumors. In the present study, total dose (≥ 66 Gy vs. < 66 Gy) was found to be a significant factor in terms of local control in uni- but not in multivariate analysis. A prospective phase III RTOG 95-12 study comparing hyper- to conventional fractionation in T2 tumors is currently under way.

Gender was reported by some to have an impact on local control, while others did not find it to be a significant factor [70, 56] whether in glottic cancer or in other tumors of the head and neck region. There is no clear-cut explanation for this finding [42].

Arytenoid protection is a potentially attractive technique to preserve the quality of the voice by decreasing the risk of laryngeal edema in the contralateral arytenoids, but only few data in the literature are concerning this particular point [1, 6, 15, 40]. In a series from Geneva, Allal et al. [1] retrospectively compared 40 patients using arytenoid protection to their historical control, and could not find any differences in terms of toxicity or local control. In our series, only nine patients (7%) with T1 tumors not involving the posterior cord were treated with arytenoid protection technique. We observed four local relapses out of nine patients treated with arytenoid protection compared to seven out of 77 patients with T1 tumors ($p < 0.01$). There were no geographic misses in the planning treatment volumes of the arytenoid protection cases.

Conclusion

This study was a retrospective analysis performed in 122 consecutive patients with early glottic cancer treated with definitive RT, of which the major goal was to assess the importance of anterior commissure involvement as an independent prognostic factor. Both uni- and multivariate analyses revealed that anterior commissure involvement and arytenoid protection were associated with worse prognostic factors in terms of local control.

In spite of this, we can conclude that, for early-stage glottic cancer, RT alone gives an excellent outcome. In case of anterior commissure extension, surgery, more aggressive irradiation including the use of altered fractionation, intensity-modulated RT, or innovative approaches such as concomitant radiochemotherapy should be explored. Because of a high relapse risk, arytenoid protection should not be attempted.

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Address for Correspondence

Mahmut Ozsahin, MD, PhD
 Department of Radiation Oncology
 Centre Hospitalier Universitaire Vaudois (CHUV)
 Bugnon 46
 1011 Lausanne
 Switzerland
 Phone (+41/21) 3144-604, Fax -601
 e-mail: esat-mahmut.ozsahin@chuv.hospvd.ch