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Tumor Volume as a Prognostic Factor for Local Control and Overall Survival in Advanced Larynx Cancer

Adriana J. Timmermans, MD; Charlotte A. H. Lange, MD; Josien A. de Bois, RTT;
Erik van Werkhoven, MSc; Olga Hamming-Vrieze, MD; Frans J. M. Hilgers, MD, PhD;
Michiel W. M. van den Brekel, MD, PhD

Objectives/Hypothesis: Tumor volume has been postulated to be an important prognostic factor for oncological outcome after radiotherapy or chemoradiotherapy. This postulate was retrospectively investigated in a consecutively treated cohort of T3-T4 larynx cancer patients.

Study Design: Retrospective cohort study.

Methods: For 166 patients with T3-T4 larynx cancer (1999-2008), pretreatment computed tomography and magnetic resonance imaging scans were available for tumor volume delineation. Patients were treated with radiotherapy, chemoradiotherapy, or total laryngectomy with postoperative radiotherapy. Both a dedicated head and neck radiologist and the first author determined all tumor volumes. Statistical analysis was by Kaplan-Meier plots and Cox proportional hazard models.

Results: Patients with T3 larynx cancer had significantly smaller tumor volumes than patients with T4 larynx cancer (median = 8.1 cm³ and 15.8 cm³, respectively; $P < .0001$). In the group treated with total laryngectomy and postoperative radiotherapy, no association was found between tumor volume and local or locoregional control or overall survival. In the group treated with radiotherapy, a nonsignificant trend was observed between local control and tumor volume. In the chemoradiotherapy group, however, a significant impact of tumor volume was found on local control (hazard ratio = 1.07; 95% confidence interval = 1.01-1.13; $P = .028$).

Conclusions: Tumor volume was not significantly associated with local control, locoregional control, or overall survival in the surgically treated group. In the group treated with radiotherapy, there was no statistically significant association, but a trend was observed between local control and tumor volume. Only in patients treated with concurrent chemoradiotherapy was a significant impact of tumor volume on local control found.

Key Words: Head and neck cancer, larynx cancer, organ preservation, total laryngectomy, imaging, tumor volume, prognosis, outcome.

Level of Evidence: 4.

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INTRODUCTION

Advanced larynx cancer can be treated with radiotherapy (RT) alone, with RT with concurrent chemotherapy (CCRT), or with total laryngectomy (TL) with or without postoperative RT (PORT).¹⁻³ Decisions about treatment are based upon tumor staging according to the Union Internationale Contre le Cancer (Internation

tional Union Against Cancer; UICC) or the American Joint Committee on Cancer TNM classification,⁴ functionality of the larynx, the general condition of the patient, and patient as well as physicians preferences. At the Netherlands Cancer Institute, patients with T3 larynx cancer generally receive organ-preserving treatment (RT, or CCRT in the case of extensive nodal disease), and to patients with T4 larynx cancer TL + PORT is advised, a protocol based on the consensus protocol of the Dutch Head and Neck Society.⁵ To determine T and N classification, physicians rely on clinical examination, laryngoscopy, computed tomography (CT) or magnetic resonance imaging (MRI), ultrasound-guided fine-needle aspiration (cytology), and biopsy. The distinction between T3 and T4 is mainly based on thyroid cartilage destruction and extralaryngeal spread.⁴ Thus, T classification plays a major role in the treatment decision. However, some studies suggest that T classification is not sufficient to predict outcome, and several authors have identified tumor volume as a substitute/additional prognostic factor for local and locoregional control and for survival.⁶⁻⁹ Other authors, however, did not identify tumor volume as a useful prognostic factor in advanced larynx cancer.^{10,11}

From the Department of Head and Neck Oncology and Surgery, Netherlands Cancer Institute (A.J.T., F.J.M.H., M.W.M.V.D.B.), Department of Radiology (C.A.H.L.); Department of Radiation Oncology, Netherlands Cancer Institute (J.A.D.B., O.H.-V.); Biometrics Department, Netherlands Cancer Institute (E.V.W.); Institute of Phonetic Sciences/Amsterdam Center for Language and Communication, University of Amsterdam (F.J.M.H., M.W.M.V.D.B.); and Department of Oral and Maxillofacial Surgery, Academic Medical Center (M.W.M.V.D.B.) Amsterdam, the Netherlands

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Send correspondence to Michiel W. M. van den Brekel, MD, PhD, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands.
E-mail address: m.vd.brekel@nki.nl

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Recently, we published the results on 182 patients with T3 or T4 larynx cancer treated at the Netherlands Cancer Institute with TL + PORT, RT, or CCRT.¹² No difference in overall survival (OS) was found between T3 and T4 larynx cancers, or between the three treatment modalities applied. This was an unexpected finding because generally T3 tumors are considered to have a better prognosis than T4 disease, when corrected for nodal status. That the majority of T3 larynx cancers were treated with RT or CCRT and the majority of T4 with TL (\pm PORT) was a possible explanation for this finding.¹² In that study, all cases were uniformly restaged (based on the available radiology reports) according to the latest (seventh) UICC edition, because the classification has changed over time. However, tumor volume was not available for inclusion in that analysis. In view of the lack of discriminatory role for T classification for local control, locoregional control, and/or survival, the question arose whether tumor volume could play such a role in this patient cohort. Therefore, the aim of the present study was to measure tumor volume and to assess its prognostic value for local control, locoregional control, and OS.

MATERIALS AND METHODS

Patients

From a total of 635 larynx cancer patients treated at the Netherlands Cancer Institute between January 1999 and December 2008, 182 patients had biopsy-proven T3 or T4 larynx cancer and were treated with curative intent with RT, CCRT, or TL + PORT, as extensively described earlier.¹² Patient- and treatment-specific data collected included age, sex, American Society of Anesthesiologists score for comorbidity (ASA score), TNM classification,⁴ subsite, treatment, local and regional recurrences, distant metastases, and survival status. To achieve uniform staging in this cohort, because T3–T4 classification had undergone (mainly imaging-based) changes during the study period, tumors were restaged according to the seventh edition of the UICC TNM staging manual (2009) based on the available radiology reports. We will further refer to this restaged T classification as the original or “T_{org} classification.”¹²

Tumor Volume Assessment

Sixteen patients had to be excluded from tumor volume assessment because imaging was of insufficient quality for adequate volume measurements ($n = 9$) or imaging could not be traced (mostly performed in other hospitals; $n = 7$), leaving 166 patients for this assessment. In 151 patients, a diagnostic CT scan was used; in 10 patients, a diagnostic MRI scan was used. A treatment planning CT scan was used in five patients, because no diagnostic scan was available. Both hard-copy scans and digital scans were used. Hard-copy scans were first digitized and transferred to a delineation system, where three-dimensional (3D) volumes were (re)created. Digital scans were directly transferred. Tumors were manually delineated on the axial slices of the 3D volumes using delineation tools and software developed at our institute. Both a dedicated head and neck radiologist (C.A.H.L.) and the first author (A.J.T.) evaluated the scans and delineated all tumor volumes separately and in consensus. Tumor volumes were measured in cubic centimeters. All images were classified fol-

Characteristic	Total	Included	Excluded	<i>P</i>
Total	182	166	16	
Gender, No. (%)				.764*
Male	137	124 (74.7)	13 (81.2)	
Female	45	42 (25.3)	3 (18.8)	
Age at date of diagnosis, mean yr [SD]	182	61.9 [11.3]	65.1 [9.5]	.276†
T _{org} classification, No. (%)				.119*
T _{3org}	101	89 (53.6)	12 (75)	
T _{4org}	81	77 (46.4)	4 (25)	
N classification, No. (%)				1.00*
N0	99	90 (54.2)	9 (56.3)	
N+	83	76 (45.8)	7 (43.8)	
Subsite, No. (%)				.297‡
Supraglottis	104	93 (56.0)	11 (68.8)	
Glottis	31	27 (16.3)	4 (25.0)	
Subglottis	3	3 (1.8)	0	
Transglottis	44	43 (25.9)	1 (6.3)	

*Fisher exact test.

†Independent *t* test.

‡Pearson χ^2 .

SD = standard deviation; T_{org} = tumors were clinically staged according to the seventh edition of the International Union Against Cancer TNM staging manual (2009) based on the diagnostic workup including clinical examination, laryngoscopy, imaging reports, fine-needle aspiration, and biopsy.

lowing the UICC TNM staging manual (2009). We will further refer to this revision radiological T classification as “T_{radrev} classification.” However, because the T_{org} classification was based on clinical examination, laryngoscopy, and the original imaging report, and the T_{radrev} classification was based on revision of the imaging only, and also treatment decisions obviously were based on T_{org}; only the T_{org} classification was used in the multivariate analysis. Using the original T classification also makes comparison with earlier published results possible.¹² Pathological lymph nodes were not included in these volume measurements and revisions. Instead, the original medical records, imaging, and fine-needle aspiration were used to determine the presence (N+) or absence (N0) of pathological lymph nodes.

Outcome Measures

Outcome measures were local control, locoregional control, and OS. Local or locoregional control was defined as time from date of diagnosis until (histopathologic) confirmation of local or locoregional failure. To assess local control, the first local recurrence was recorded. To assess locoregional control, the first recurrence (local, regional, or locoregional) was recorded. In the case of residual disease, date of primary treatment was used as date of event. In the case of a second primary tumor in the head and neck area, TL for a dysfunctional larynx (or regional), or distant metastasis, date of diagnosis was used as moment of censoring. Other cases were censored at date of last follow-up or date the patient died. OS was defined as time from date of

TABLE II.
Patient and Tumor Characteristics Categorized per Treatment Group.

Characteristic	Total	TL ± PORT	RT	CCRT	<i>P</i> *
Total†	166	56	92	18	
Gender, No. (%)					
Male	124	48 (38.7)	66 (53.2)	10 (8.1)	.023‡
Female	42	8 (19.0)	26 (61.9)	8 (19.0)	
Age at date of diagnosis, mean yr [SD]	61.9 [11.3]	64.1 [11.9]	61.4 [11.5]	58.1 [6.4]	.111§
T _{org} classification, No. (%)					
T3 _{org}	89	5 (5.6)	74 (83.1)	10 (11.2)	.0001‡
T4 _{org}	77	51 (66.2)	18 (23.4)	8 (10.4)	
T _{radrev} classification, No. (%)					
T3 _{radrev}	90	8 (8.9)	68 (75.6)	14 (15.6)	.0001‡
T4 _{radrev} [#]	76	48 (63.2)	24 (31.6)	4 (5.3)	
N classification, No. (%)					
N0	91	31 (34.1)	57 (62.6)	3 (3.3)	.0001‡,
N+	75	25 (33.3)	35 (46.7)	15 (20.0)	
Subsite, No. (%)					
Supraglottis	93	18 (19.4)	58 (62.4)	17 (18.3)	.0001‡
Glottis	27	10 (37.0)	16 (59.3)	1 (3.7)	
Subglottis	3	2 (66.7)	1 (33.3)	0	
Transglottis	43	26 (60.5)	17 (39.5)	0	
Tumor volume, median cm ³ {IQR}	11.6 {5.7–21.3}	19.7 {11.8–30.8}	7.4 {4.3–12.4}	13.5 {5.7–25.2}	.0001¶

*Differences were calculated between the three treatment groups.

†Due to rounding, not all percentages total exactly 100%.

‡Pearson χ^2 .

§One-way analysis of variance.

#Only two patients were radiologically classified as having a T4b tumor, with tumor volumes of 10.7 and 49.8 cm³, respectively.

||Difference between TL and RT was not significant ($P = .491^{\dagger}$), whereas differences between CCRT versus RT and TL were significant (TL vs. CCRT, $P = .006^{\ddagger}$; RT vs. CCRT, $P = .001^{\ddagger}$).

¶Kruskal-Wallis.

CCRT = concomitant chemoradiation; IQR = interquartile range; PORT = postoperative radiotherapy; RT = radiotherapy; SD = standard deviation; TL = total laryngectomy; T_{org} = tumors were clinically staged according to the seventh edition of the International Union Against Cancer TNM staging manual (2009) based on the diagnostic workup including clinical examination, laryngoscopy, imaging, fine-needle aspiration, and biopsy; T_{radrev} = radiological T classification.

diagnosis until last follow-up or death. The last follow-up date was defined by the last visit to the outpatient clinic at our institute. The last follow-up date and survival status were updated on April 1, 2014.

Statistical Analysis

Descriptive statistics were performed. To find differences between groups the Pearson χ^2 , Fisher exact test, independent *t* test, one-way analysis of variance, Mann-Whitney *U* test, and Kruskal-Wallis test were used. The latter two tests were used in the case of nonparametric distribution of data. Univariate analysis was performed by Cox regression analysis to reveal factors associated with a higher likelihood of local failure, locoregional failure, and mortality. Furthermore, for multivariate analysis, Cox regression analysis was used and hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. We also tested for a possible interaction between primary treatment and tumor volume for local control. For local and locoregional control and OS, Kaplan-Meier curves were plotted. Maximally selected log-rank statistics were used to look for possible cut-points of volume as a prognostic factor. Variables with $P < .05$ were considered statistically significant. Analyses were performed with SPSS Statistics 21.0 (IBM, Armonk, NY) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients and Treatment

In total, 166 patients were included in this study. There were no significant differences between the included cohort and the 16 patients who had to be excluded from this tumor volume assessment study because of absence or insufficient quality of the imaging (Table I).

Patient and tumor characteristics of the remaining 166 patients are shown in Tables II and III. In the previous publication on this patient cohort, a more detailed description of the treatment characteristics can be found.¹² The mean age at diagnosis was 61.9 years (standard deviation [SD] = 11.3). The male to female ratio was 3:1. When compared to TL (mean age = 64.1 years, SD = 11.9), patients primarily treated with CCRT were significantly younger (mean age = 58.1 years, SD = 6.4; independent *t* test: $P < .008$). Eighty-nine patients were originally diagnosed with T3_{org} larynx cancer, whereas 77 patients were diagnosed with T4_{org} larynx cancer. After the current radiological revision, 14 patients (8.4%) were up-staged from T3 to T4 and 15 (9.0%) were down-staged from T4 to T3.

Of a total of 166 patients, primary TL with or without planned postoperative RT was employed in 56 (33.7%;

TABLE III.
Patient and Tumor Characteristics Categorized per T_{org} Classification.

Characteristic	Total	T3 _{org}	T4 _{org}	P*
Total	166	89	77	
Gender, No. (%)				
Male	124	61 (49.2)	63 (50.8)	.073 [†]
Female	42	28 (66.7)	14 (33.3)	
Age at date of diagnosis, mean yr [SD]	61.9 [11.3]	60.9 [11.3]	63.2 [11.2]	.195 [‡]
T _{radrev} classification, No. (%)				
T3 _{radrev}	90	75 (83.3)	15 (16.7)	.0001 [§]
T4 _{radrev} [#]	76	14 (18.4)	62 (81.6)	
N classification, No. (%)				
N0	91	49 (53.8)	42 (46.2)	1.000 [†]
N+	75	40 (53.3)	35 (46.7)	
Subsite, No. (%)				
Supraglottis	93	63 (67.7)	30 (32.3)	.0001 [§]
Glottis	27	12 (44.4)	15 (55.6)	
Subglottis	3	1 (33.3)	2 (66.7)	
Transglottis	43	13 (30.2)	30 (69.8)	
Tumor volume, median cm ³ {IQR}	11.6 {5.7–21.3}	8.1 {4.9–13.7}	15.8 {8.0–29.8}	.0001
Primary treatment, No. (%)				
TL ± PORT	56	5 (8.9)	51 (91.1)	.0001 [§]
RT	92	74 (80.4)	18 (19.6)	
CCRT	18	10 (55.6)	8 (44.4)	

*Differences were calculated between T subgroups.

[†]Fisher exact test.

[‡]Independent *t* test.

[§]Pearson χ^2 .

[#]Only two patients were radiologically classified as having a T4b tumor, with tumor volumes of 10.7 and 49.8 cm³, respectively.

^{||}Mann-Whitney *U* test.

CCRT = concomitant chemoradiation; IQR = interquartile range; PORT = postoperative radiotherapy; RT = radiotherapy; SD = standard deviation; TL = total laryngectomy; T_{org} = tumors were clinically staged according to the seventh edition of the International Union Against Cancer TNM staging manual (2009) based on the diagnostic workup including clinical examination, laryngoscopy, imaging, fine-needle aspiration, and biopsy; T_{radrev} = radiological T classification.

51 of 77 T4, five of 89 T3) patients. Primary single modality RT was given to 92 (55.4%; 18 of 77 T4, 74 of 89 T3) and CCRT to 18 (10.8%; eight of 77 T4, 10 of 89 T3) patients. Most patients with T4_{org} larynx cancer (51 of 77; 66.2%) underwent TL, whereas most patient with T3_{org} larynx cancer (74 of 89; 83.1%) underwent RT (for details see Table II).

Tumor Volume

Table IV shows tumor volumes per T and N classification, per subsite, and per primary treatment. Median tumor volume for the total study population was 11.6 cm³ (interquartile range [IQR] = 5.7–21.3). Median tumor volume for T3_{org} larynx cancer was 8.1 cm³ (IQR = 4.9–13.7) and for T4_{org} was 15.8 cm³ (IQR = 8.0–29.8; Mann-Whitney *U*: *P* < .0001). Median tumor volume for T3_{radrev} larynx cancer was 8.7 cm³ (IQR = 5.0–15.9) and for T4_{radrev} was 14.2 cm³ (IQR = 6.8–28.5; Mann-Whitney *U*: *P* = .001). Patients who were treated with TL ± PORT had significantly higher tumor volume (19.7 cm³; IQR = 11.8–30.8) when compared to RT (7.4 cm³; IQR = 4.3–12.4; Mann-Whitney *U*: *P* < .0001), but not when compared to CCRT (13.5 cm³; IQR = 5.7–25.2; Mann-Whitney *U*: *P* = .42).

Local Control and Locoregional Control and Tumor Volume

Median follow-up for all patients was 37 months (IQR = 13.8–74.0). Five-year local control for the total group was 77%; after TL ± PORT it was 88%, after RT it was 70%, and after CCRT it was 72%. Five-year locoregional control rates were 70% (overall), 84% (TL + PORT), 61% (RT), and 68% (CCRT). No associations between tumor volume and local and locoregional control (data not shown) were found with univariate and multivariate analysis (Table V). No significant cutoff point was found by a systematic search over the range of possible volumes. In the multivariate analysis, we found that primary treatment was associated with local control. When compared to TL ± PORT, patients undergoing RT have higher hazards to develop local recurrences (HR = 5.47; 95% CI = 1.61–18.60; *P* = .006). The interaction between primary treatment and tumor volume with local control as endpoint was tested and found to be significant (*P* = .036; Fig. 1). Subsequently, subgroup analyses were performed for the separate treatment groups. In univariate analysis, we found that patients treated with CCRT had an HR of 1.07 (95% CI = 1.01–1.13; *P* = .028) per 1-cm³ increase in tumor volume to develop a local recurrence. It should be noted

TABLE IV.
Tumor Volumes per T and N Classification, Subsite, and Primary Treatment.

Characteristic	Tumor Volume, Median cm ³ (IQR)	P
Total	11.6 (5.7–21.3)	N/A
T _{org} classification		
T3 _{org}	8.1 (4.9–13.7)	<.0001*
T4 _{org}	15.8 (8.0–29.8)	
R _{radrev} classification		
T3 _{radrev}	8.7 (5.0–15.9)	.001*
T4 _{radrev} [†]	14.2 (6.8–28.5)	
N classification [‡]		
N0	10.7 (4.7–17.0)	.35*
N+	13.0 (6.4–23.4)	
Subsite _{org}		
Supraglottis _{org}	12.0 (6.6–22.4)	.42 [§]
Glottis _{org}	5.4 (3.0–15.8)	
Subglottis _{org}	3.1 (2.1–16.1)	
Transglottis _{org}	11.8 (5.8–23.4)	
Primary treatment		
TL ± PORT	19.7 (11.8–30.8)	
RT	7.4 (4.3–12.4)	TL vs. RT: <.0001*
CCRT	13.5 (5.7–25.2)	TL vs. CCRT: .42*

*Mann-Whitney *U* test.

[†]Only two patients were radiologically classified as a T4b tumor, with tumor volumes of 10.7 and 49.8 cm³, respectively.

[‡]Referring to the primary tumor volumes specified per N subgroup.

[§]Kruskal-Wallis.

CCRT = concomitant chemoradiation; IQR = interquartile range; N/A = not applicable; PORT = postoperative radiotherapy; RT = radiotherapy; TL = total laryngectomy; T_{org} = tumors were clinically staged according to the seventh edition of the International Union Against Cancer TNM staging manual (2009) based on the diagnostic workup including clinical examination, laryngoscopy, imaging, fine-needle aspiration, and biopsy; T_{radrev} = radiological T classification.

that this was a small subgroup of 18 patients, of whom four developed a local recurrence. For the RT and TL groups, no significant association was found. In the group treated with RT, there was a nonsignificant trend of HR = 1.03 per cm³ (95% CI = 0.98-1.07; *P* = .24), whereas in the subgroup that had a TL + PORT a nonsignificant inverse trend was seen (HR = 0.97; 95% CI = 0.91-1.04; *P* = .39). Further subgroup analyses (T3/RT and T4/TL subgroups) did not reveal any associations between tumor volume and one of the outcome measures (data not shown).

OS and Tumor Volume

Five-year OS for T3_{org} and T4_{org} was similar: 49% and 46%, respectively (log-rank: *P* = .597). Five-year OS per T_{radrev} classification was also similar; for T3_{radrev} it was 49%, for T4_{radrev}^a it was 46%, and for T4_{radrev}^b it was 50% (log-rank: *P* = .754). Five-year OS analyzed per treatment also showed similar survival figures; after TL it was 51%, after RT it was 49%, and after CCRT it was 36% (log-rank: *P* = .586). With univariate and multivariate analysis, no association between tumor volume and OS was found (Table VI). Per treatment group (TL, RT,

CCRT) and in subgroup analyses (T3/RT and T4/TL), no prognostic value of tumor volume was found for OS (data not shown). In the multivariate analysis we found (again) that patients with higher ASA score and positive lymph nodes have higher hazards for mortality.

DISCUSSION

In this study, including 166 patients with T3–T4 larynx cancer treated with TL + PORT, RT, or CCRT, tumor volume was not significantly associated with local and locoregional control or OS, except for the CCRT group, wherein tumor volume was significantly associated with local control. Furthermore, T4 tumors were significantly larger than T3 lesions and tumor volumes (in part) were significantly different between the three treatment groups (TL > CCRT > RT).

In the literature studies are conflicting regarding these results. Recently, Janssens et al. prospectively investigated the impact of tumor volume on outcome in 270 patients with cT2–cT4 larynx cancer treated with accelerated RT with or without carbogen breathing and nicotinamide. These authors found no correlation between primary tumor volume and local control. They also reported the presence of a correlation between primary tumor volume and T classification.¹⁰ Bernstein et al. concluded that in 114 patients with advanced larynx or hypopharynx cancer treated by organ preservation strategies, tumor volume was not an independent prognostic factor for locoregional control. However, these authors did find that a higher tumor volume was an independent prognostic factor for disease-specific mortality.¹¹ Conversely, there are several studies that identified tumor volume as a prognostic factor for oncological outcome. Hoebbers et al. reported on 117 patients with cT3–cT4 larynx cancer treated with primary RT only and found that gross tumor volume was an independent prognostic factor for both OS (HR = 1.016; 95% CI = 1.006-1.026; *P* = .001) and local relapse-free survival (HR = 1.017; 95% CI = 1.007-1.027; *P* = .001), whereas cT and cN classification were not significant prognostic factors for OS.⁶ Also, Pameijer et al. found in 42 patients with T3 larynx cancer treated with RT alone that tumor volume significantly influenced local control.¹³ Knebjergs et al. found that in 361 patients treated with chemoradiation for advanced head and neck cancer, tumor volume was more powerful for predicting outcome after chemoradiation than the TNM classification. However, in that study no patients with larynx cancer were included.⁸ Finally, Yang et al. found that in 182 patients with larynx and hypopharynx cancer treated with either surgery or organ-preserving treatment, primary tumor volume had significant influence on OS in univariate analysis. Because of multicollinearity between total tumor volume (also including metastatic neck lymph nodes), primary tumor volume, and other variables, only total tumor volume was included in multivariate analysis, where total tumor volume at a cutoff value of 8.38 cm³ remained a significant predictor.⁹

It should be noted, however, that most studies focused on irradiated patients (with or without

TABLE V.
Univariate and Multivariate Analysis of Local Control in Patients With T3/T4 Larynx Cancer.

Characteristic	Patients, No.	Events, No.	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	P	HR (95% CI)	P
Primary treatment				.080		.024
TL ± PORT	56	5	Ref		Ref	
RT	92	22	3.01 (1.14–7.96)	.026	5.47 (1.61–18.60)	.006
CCRT	18	4	2.90 (0.78–10.79)	.113	3.13 (0.73–13.51)	.126
Age, per year	166	31	0.99 (0.96–1.02)	.413	1.00 (0.96–1.04)	.89
Sex				.638		.46
Male	124	25	Ref		Ref	
Female	42	6	0.81 (0.33–1.97)		0.70 (0.27–1.79)	
ASA				.744		.675
ASA 1	32	6	Ref		Ref	
ASA 2	80	18	1.36 (0.54–3.42)	.519	1.53 (0.57–4.12)	.400
ASA 3/ASA 4	47	7	1.05 (0.35–3.13)	.931	1.18 (0.38–3.63)	.776
T _{org} classification				.362		.395
T _{3org}	89	19	Ref		Ref	
T _{4org}	77	12	0.72 (0.35–1.47)		1.48 (0.60–3.63)	
T _{radrev} classification				.434		
T _{3radrev}	90	19	Ref		Ref	
T _{4radrev} and 4b	76	12	0.75 (0.36–1.55)	.434		
N classification				.361		.380
N0	91	16	Ref		Ref	
N+	75	15	1.39 (0.69–2.82)		1.44 (0.64–3.23)	
Tumor volume, per cm ³	166	31	1.00 (0.98–1.02)	.821	1.01 (0.98–1.03)	.548

HRs and P values were calculated using Cox regression.

ASA = American Society of Anesthesiologists score; CCRT = concomitant chemoradiation; CI = confidence interval; HR = hazard ratio; PORT = post-operative radiotherapy; Ref = reference; RT = radiotherapy; TL = total laryngectomy; T_{org} = tumors were clinically staged according to the seventh edition of the International Union Against Cancer TNM staging manual (2009) based on the diagnostic workup including clinical examination, laryngoscopy, imaging, fine-needle aspiration, and biopsy; T_{radrev} = radiological T classification.

chemotherapy) and that studies focusing on surgery are scarce.^{9,14} Gallo et al. studied 327 T3N0 larynx cancer patients treated with TL and reported that a tumor size of >2 cm resulted in a higher risk of tumor recurrence. However, these authors used (2D) tumor size instead of

(3D) tumor volume as an outcome measure.¹⁴ Lo et al. studied 55 patients with T2–T3 larynx cancer treated with either primary RT (n = 39) or primary TL (n = 16). The authors did not identify tumor volume as a predictor of locoregional control in the surgically treated patients.¹⁵

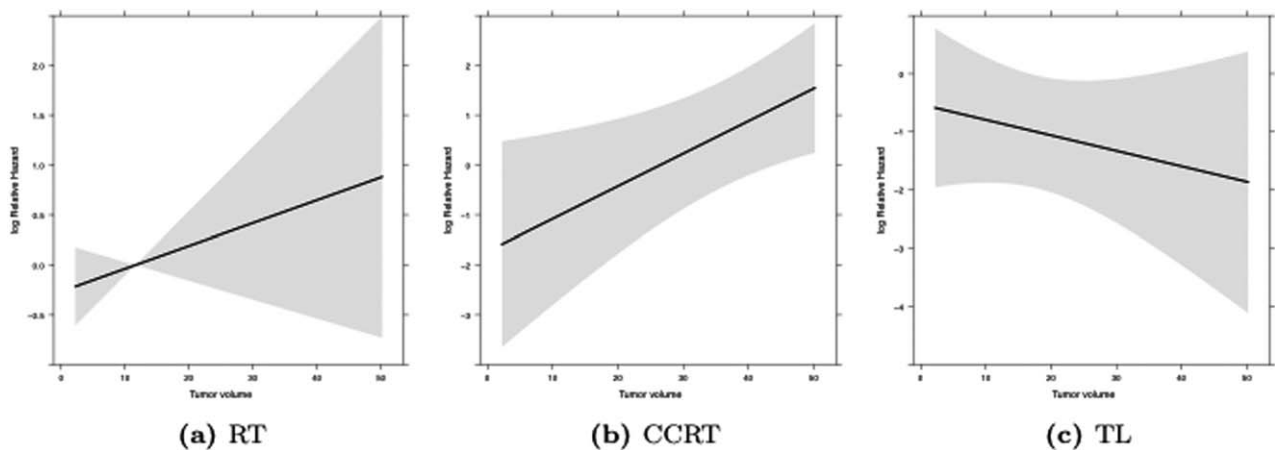


Fig. 1. Estimated log relative hazards (black lines) with 95% confidence intervals (shaded areas) for local control from a model with interactions between volume and primary treatment. CCRT = chemoradiotherapy; RT = radiotherapy; TL = total laryngectomy.

TABLE VI.
Univariate and Multivariate Analysis of Overall Survival in Patients With T3 or T4 Larynx Cancer.

Characteristic	Patients, No.	Events, No.	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	P	HR (95% CI)	P
Primary treatment				.65		.23
TL ± PORT	56	33	Ref		Ref	
RT	92	51	1.06 (0.68–1.65)	.79	1.67 (0.89–3.14)	.11
CCRT	18	13	1.35 (0.71–2.58)	.36	1.15 (0.53–2.51)	.73
Age, per year	166	97	1.03 (1.01–1.05)	.005	1.04 (1.01–1.06)	.003
Sex				.03		.057
Male	124	68	Ref		Ref	
Female	42	29	1.60 (1.04–2.48)		1.63 (0.99–2.68)	
ASA				.04		.041
ASA 1	32	12	Ref		Ref	
ASA 2	80	47	1.89 (1.00–3.57)	.05	2.11 (1.09–4.09)	.028
ASA 3/ASA 4	47	34	2.98 (1.54–5.76)	.001	2.40 (1.20–4.80)	.014
T _{org} classification				.63		.38
T _{3org}	89	50	Ref		Ref	
T _{4org}	77	47	1.10 (0.74–1.64)		1.28 (0.74–2.20)	
T _{radrev} classification				.20		
T _{3radrev}	90	47	Ref		Ref	
T _{4radrev} a and 4b	76	50	1.38 (0.94–2.01)	.099		
N classification				.002		.001
N0	91	46	Ref		Ref	
N+	75	51	1.86 (1.25–2.78)		2.27 (1.42–3.64)	
Tumor volume, per cm ³	166	97	1.002 (0.99–1.01)	.758	1.009 (1.00–1.02)	.18

HRs and P values were calculated using Cox regression.

ASA = American Society of Anesthesiologists score; CCRT = concomitant chemoradiation; CI = confidence interval; HR = hazard ratio; PORT = post-operative radiotherapy; Ref = reference; RT = radiotherapy; TL = total laryngectomy; T_{org} = tumors were clinically staged according to the seventh edition of the International Union Against Cancer TNM staging manual (2009) based on the diagnostic workup including clinical examination, laryngoscopy, imaging, fine-needle aspiration, and biopsy; T_{radrev} = radiological T classification.

The reason we did not find an influence of tumor volume on oncological outcome—except for the association with local control in the CCRT group—remains unclear, but it might not be surprising, considering our initial finding that there was also no difference in prognosis between (the smaller volume) T3 and (the larger volume) T4. It is thus probably due to a selection bias; patients with the higher tumor volumes were selected for TL (median volume T4 = 15.8 cm³; median volume TL = 19.7 cm³), leaving the smaller tumors for organ preservation treatment. This lack of the full range of tumor volumes thus might have obscured a possible significant volume effect in the RT-only group, although a trend was noted in this group as well (Fig. 1).

Tumor volume measurements are still time consuming despite the progress in digital/software evaluation tools, and are still not routinely used in everyday practice. In the future, this might become easier when automated volume measurement become available.¹⁶ Nevertheless, because T3–T4 classification is associated with tumor volume and there seems not to be a significant association between tumor volume and local control in the laryngectomy group, in these cases volume measurement is not indicated. If, conversely, CCRT is considered as a treatment modality, volume measurement

might help in decision making and patient counseling, as local control in larger tumors might be impaired.

The limitations of the present study are inherent to any retrospective analysis, where treatment selection biases are unavoidable and difficult to unravel from the patient charts. Furthermore, in this study only patients from one institution were analyzed. However, that our study comprises an unselected cohort of consecutively treated patients in any case means that there is no other selection bias than the one mentioned, as might not be the case in clinical trial cohorts.

CONCLUSION

In this retrospective cohort study including 166 patients with T3–T4 larynx cancer, tumor volume was not significantly associated with local control, locoregional control, or OS in the surgically treated group. In the group treated with RT, there was no statistically significant association, but a trend was observed between local control and tumor volume. Only in patients treated with CCRT was a significant impact of tumor volume on local control found.

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