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Importance of tumor volume in supraglottic and glottic laryngeal carcinoma

At present about 50% of laryngeal carcinoma patients are primarily treated with (chemo-)radiotherapy [1]. In our hospital, this number is even higher (≈70–80%; unpublished data). Knowledge of pretreatment factors, which are predictors of outcome, is important. It is commonly known that prognosis declines with more advanced tumor stage (T-stage) [2, 3, 4, 5, 6, 7]. Another important predictor in head and neck squamous cell carcinoma is tumor volume (TV). It is suggested that TV is even more important for outcome than T-stage [8, 9, 10, 11, 12, 13]. For example, in T3 glottic carcinoma local control was achieved in 85% of patients for tumors measuring <3.5 cm^3, whereas for tumors >3.5 cm^3 local control was achieved in only 25%.[14]. Mancuso et al. [15] found a local control of 89% vs. 52% with a TV threshold of <6 cm^3 vs. >6 cm^3 in supraglottic carcinoma. Within the AJCC and UICC staging system, volume is not taken into account. Since there is a large variation in volume within T-stages [10, 15, 16, 17], volume might have additional prognostic value besides T-stage in patients with laryngeal squamous cell carcinoma (SCC).

The aim of our study was to assess the prognostic value of TV compared to and in addition to T-stage in glottic and supraglottic laryngeal carcinoma on local control (LC), disease-free survival (DFS), and overall survival (OS).

Material and methods

Patients

Between 1996 and 2009, 689 patients were treated for laryngeal SCC at the radiation oncology department of our hospital. To improve group homogeneity, we included patients with supraglottic and glottic laryngeal SCC, who were primarily treated with accelerated radiotherapy according to the ASO schedule [18] or who were included in the ARCON study [19]. No chemotherapy was given. A diagnostic CT scan had to be available, on which the tumor had to be clearly visible without artifacts. Finally, 150 patients were eligible for this study.

Measurements

Volume

Visible tumor mass was delineated manually on the transversal slices of the contrast-enhanced diagnostic CT. In the majority of the CT scans, a single-slice technique was used. Most diagnostic CT scans had a slice thickness of 1.5–2 mm. Delineations were performed by the first author in consensus with an experienced radiation oncologist (CHJT). In difficult cases, an experienced head and neck radiologist (FAP) was consulted. Criteria for tumor involvement were abnormal contrast enhancement, soft tissue thickening, presence of a mass lesion, infiltration of fatty tissue, or a combination of these. Delineation was performed using 3D delineation software (developed in-house) [20].

T-stage

In a previous study, division of T-stage 2 in 2a and 2b based on the mobility of the vocal cord was suggested, i.e., in stage T2a the mobility of the vocal cord is normal and in T2b the mobility of the vocal cord is impaired [18]. Impaired vocal cord mobility led to a worse ultimate local control when treated with a conventional radiotherapy schedule. LC of stage T2a laryn-

Tab. 1 Characteristics of patients with laryngeal squamous cell carcinoma

n=150	n (%)	Event
Gender		
Male	128 (85)	41 (32%)
Female	22 (15)	7 (32%)
Location		
Glottic	73 (49)	19 (26%)
Supraglottic	77 (51)	29 (38%)
T-stage		
2a	39 (26)	8 (21%)
2b	43 (29)	13 (30%)
3	54 (36)	19 (35%)
4	14 (9)	8 (57%)
LLN		
–	112 (75)	26 (23%)
+	38 (25)	22 (58%)
	Mean	**Mean**
Age	63 years (range 40–86 years)	61 years
Volume	5.4 cc (0.2–26.2 cc)	7.3 cc

LLN + pathological lymph nodes present at diagnosis, *LLN* – no pathological lymph nodes present at diagnosis, ***Event*** local recurrence, regional recurrence or metastasis.

Tab. 2 Cox regression models on the association between tumor volume and T-stage on local control, disease-free survival, and overall survival in laryngeal cancer patients

	Local control					Disease-free survival					Overall survival				
	HR	p value	CI (95%)	C-statistic	SD	HR	p value	CI (95%)	C-statistic	SD	HR	p value	CI (95%)	C-statistic	SD
Model 1				0.61	0.10				0.68	0.08				0.57	0.08
Volume	1.06	0.050	1.00–1.12			1.09	0.000	1.04–1.13			1.07	<0.001	1.03–1.12		
Model 2				0.63	0.09				0.59	0.08				0.54	0.07
T-stage 1+2a		0.049					0.081					0.385			
2b	3.79	0.041	1.06–13.60			1.55	0.327	0.64–3.75			1.13	0.435	0.67–2.50		
3	3.50	0.050	1.00–12.30			1.85	0.145	0.81–4.23			1.05	0.884	0.56–1.97		
4	7.24	0.005	1.81–29.02			3.56	0.011	1.33–9.52			1.93	0.118	0.85–4.38		
Model 3															
Location	1.07	0.847	0.54–2.12			1.67	0.084	0.93–2.97			1.39	0.173	0.87–2.25		
Model 4				0.69	0.09				0.68	0.08				0.61	0.07
Volume	1.04	0.172	0.98–1.11			1.08	0.003	1.03–1.13			1.07	0.001	1.03–1.12		
T-stage 1+2a		0.107					0.490					0.541			
2b	4.04	0.032	1.12–14.55			1.67	0.253	0.69–4.04			1.41	0.305	0.73–2.72		
3	3.29	0.064	0.93–11.58			1.63	0.247	0.71–3.75			0.96	0.892	0.51–1.80		
4	5.60	0.020	1.31–23.89			2.22	0.139	0.77–6.41			1.35	0.492	0.57–3.19		
Model 5				0.69	0.09				0.68	0.08				0.61	0.07
Volume	1.04	0.288	0.97–1.12			1.06	0.035	1.00–1.12			1.07	0.006	1.02–1.13		
T-stage 1+2a		0.120					0.396					0.564			
2b	4.13	0.035	1.10–15.45			1.85	0.188	0.74–4.65			1.41	0.331	0.71–2.80		
3	3.34	0.065	0.93–12.05			1.77	0.191	0.75–4.15			0.96	0.891	0.50–1.84		
4	5.74	0.022	1.29–25.63			2.51	0.101	0.84–7.55			1.35	0.520	0.54–3.34		
Location	1.06	0.893	0.45–2.50			1.33	0.437	0.65–2.69			0.99	0.983	0.54–1.84		

HR hazard ratio, *CI* confidence interval, *SD* standard deviation.

geal carcinoma showed a comparable LC to stage T1 laryngeal SCC [21, 22].

Outcome

The primary endpoint in this study was disease-free survival (DFS). We chose DFS as our primary endpoint since we hypothesized that larger volume could lead to decreased local control but also metastasize earlier to regional and distant locations. Follow-up data were collected retrospectively by chart control. If patients were lost to follow-up in the radiation oncology department, follow-up data were retrieved from other hospitals, general practitioners or municipal databases, up until the time of analysis. For statistical analysis, DFS time was calculated as the number of months between the date of diagnosis and the date of death, local or regional recurrence, distant metastasis or censoring, whichever occurred first. Censoring occurred if the patient was still alive at the time of last contact.

Local control (LC) and overall survival (OS) were also included, as secondary outcomes.

Statistical analysis

Baseline characteristics are reported as means for continuous variables or as percentages for categorical or dichotomous variables stratified by patients who developed or did not develop an event. Outcome was assessed using Kaplan–Meier survival curves, and differences in DFS between glottic and supraglottic laryngeal carcinoma were evaluated using the log-rank test. We applied crude and multivariable Cox regression analysis to relate volume (continuous), T-stage, and the combination to 5-year DFS, OS, and LC. Prior to this, we examined the linearity assumption of the association between volume and outcome with restricted cubic spline functions. We assessed 5 Cox regression models: (1) a crude model with volume only, (2) with T-stage only, and (3) with location only, (4) a model combining volume and T-stage, and (5) model 4 plus location as covariate.

Prognostic performance of the models was examined by determination of the model's discrimination. Discriminative ability was determined with the C statistic, which is equivalent to the area under the ROC. The ROC area refers to the ability to discriminate between patients who do and do not develop an event during follow-up. The C statistic has a theoretical range between 0.5 and 1.0, but it typically ranges from 0.60–0.85 for prognostic models [23]. Analyses were performed using statistical software SPSS 20 (statistical package of social sciences IBM) and R 2.10 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Results

The follow-up time ranged from 1–156 months with a mean follow-up of 52 months. A summary of the patients' characteristics for 150 patients are provided in ◘ **Tab. 1**.

In 48 patients, 65 events were recorded (33 local recurrences, 10 regional recurrences, and 22 distant metastases). Supraglottic SCC showed more regional recurrences (p=0.06) and metastasis (p=0.03).

Primary tumor volume

The mean primary TV on the diagnostic CT scan was 5.4 cc (standard deviation [SD] 5.5, range 0.2–26.2 cc). The mean TV delineated on diagnostic CT scan for glottic laryngeal tumors (2.6 cc) was smaller than the TV of supraglottic tumors (8.0 cc; p<0.001). Mean TVs with or without an event were 7.3 and 4.4 cc, respectively (p=0.002).

The restricted cubic spline plot did not indicate a non-linear relationship between TV and 2-year DFS in supraglottic and glottic tumors or in laryngeal tumors as a whole. Therefore, we modeled volume as a linear variable in the Cox regression models.

In the crude analysis (◘ **Tab. 2**), a significant association between volume on diagnostic CT scan and disease-free survival (DFS) was found (p<0.001, HR 1.09, 95% confidence interval (CI) 1.04–1.13). In other words, with every cc increase in TV the risk of an event increases by 9%. There was also a significant association found between volume and OS (p<0.001, HR 1.07, CI 1.03–1.12). There was a borderline significant association between TV and local control (p=0.050, HR 1.06, 95% CI 0.10–1.12).

T-stage

The 5-year DFS and OS were 77 and 58% in T1+2a, 69 and 56% in T2b, 61 and 60% in T3 and 35 and 36% in T4 laryngeal SCC. In the crude analysis (◘ **Tab. 2**), there was a borderline significant association between T-stage and DFS (p=0.08) and none with OS (p=0.39). There was a more pronounced association between T-stage and LC (p=0.049; ◘ **Tab. 2**, ◘ **Fig. 1**).

Abstract · Zusammenfassung

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Importance of tumor volume in supraglottic and glottic laryngeal carcinoma

Abstract

Purpose. The aim of our study was to assess the prognostic value of tumor volume compared to and in addition to T-stage on local control (LC), disease-free survival (DFS), and overall survival (OS) in glottic and supraglottic laryngeal carcinoma patients.

Patients and methods. In 150 patients, we determined tumor volume on diagnostic CT scans. We applied crude and multivariable Cox regression analysis to relate volume (continuous), T-stage and the combination to 5-year DFS, OS, and LC. Before, we examined the linearity assumption of the association between volume and outcome with restricted cubic spline functions. Prognostic performance of the models was examined by determination of the model's discrimination. Discriminative ability was determined with the C statistic referring to the ability to discriminate between patients who do and do not develop an event during follow-up.

Results. A strong association between tumor volume and DFS and OS was found. The restricted cubic spline plot did not indicate a non-linear relationship between tumor volume and DFS and local control. Tumor volume demonstrated a better discriminative ability to predict DFS and OS compared to T-stage (0.68 and 0.57 vs. 0.59 and 0.54, respectively). For local control, T-stage showed a higher discriminative ability than tumor volume (0.63 vs. 0.61). The combined model increased discriminative power (0.69).

Conclusion. Volume seems to be more important than T-stage in prediction of DFS or OS in laryngeal squamous cell carcinoma patients. Perhaps prediction of DFS, OS, and LC could be improved by including tumor volume into the staging process.

Keywords

Laryngeal neoplasms · T-stage · Treatment outcome · Survival analysis · Neoplasm staging

Einfluss des Tumorvolumens beim glottischen und supraglottischen Larynxkarzinom

Zusammenfassung

Ziel. Ziel der Studie war es, die prognostischen Werte des Tumorvolumens und/oder des T-Stadiums hinsichtlich der Entwicklung eines Lokalrezidivs (LC), des krankheitsfreien Überlebens (DFS) und des Gesamtüberlebens (OS) für Patienten mit glottischen und supraglottischen Larynxkarzinomen vergleichend zu bewerten.

Patienten und Methodik. Das Volumen des primären Larynxkarzinoms wurde in 150 Patienten mittels Computertomographie bestimmt. Anschließend wurden die Zusammenhänge von Tumorvolumen, T-Stadium und die Kombination beider Kriterien mit dem DFS, OS und der Entwicklung eines Lokalrezidivs nach 5 Jahren mittels univariater und multivariater Cox-Regression analysiert. Die Annahme eines linearen Zusammenhangs zwischen Volumen und therapeutischem Ergebnis wurde mit Hilfe einer quadratischen Approximationsfunktion untersucht. Die Vorhersagekraft der Modelle für das Wiederauftreten von Tumorerkrankungen in der Nachsorgeperiode wurde durch die Auswertung der jeweiligen Grenzwertoptimierungskurve ermittelt.

Ergebnisse. Es wurde ein klarer Zusammenhang zwischen Tumorvolumen und DFS und OS gefunden. Allerdings ergab die Auswertung der quadratischen Approximation keine non-lineare Abhängigkeit des DFS und des LC vom Tumorvolumen. Der prognostische Wert der Untersuchung des Tumorvolumens bezüglich des DFS und OS erwies sich dabei derer des T-Stagings überlegen (jeweils 0,68 und 0,57 vs. 0,59 und 0,54). Bei der Entwicklung eines Lokalrezidivs resultierte für das T-Staging eine bessere Unterscheidung als für die Volumenbestimmung (0,63 vs. 0,61). Die Kombination beider Methoden ergab ebenfalls eine bessere Unterscheidungsfähigkeit (0,69).

Schlussfolgerung. Die Studie zeigt, dass die Voraussagekraft des primären Tumorvolumens bezüglich des DFS und OS bei Larynxkarzinomen derer des T-Stadiums überlegen ist. Eine Ergänzung des T-Staging mit der Untersuchung des Tumorvolumens könnte daher zu einer verbesserten Voraussage von DFS, OS und der Entwicklung eines Lokalrezidivs führen.

Schlüsselwörter

Larynxkarzinom · T-Stadium · Behandlungserfolg · Überlebensanalyse · Neoplasie-Staging

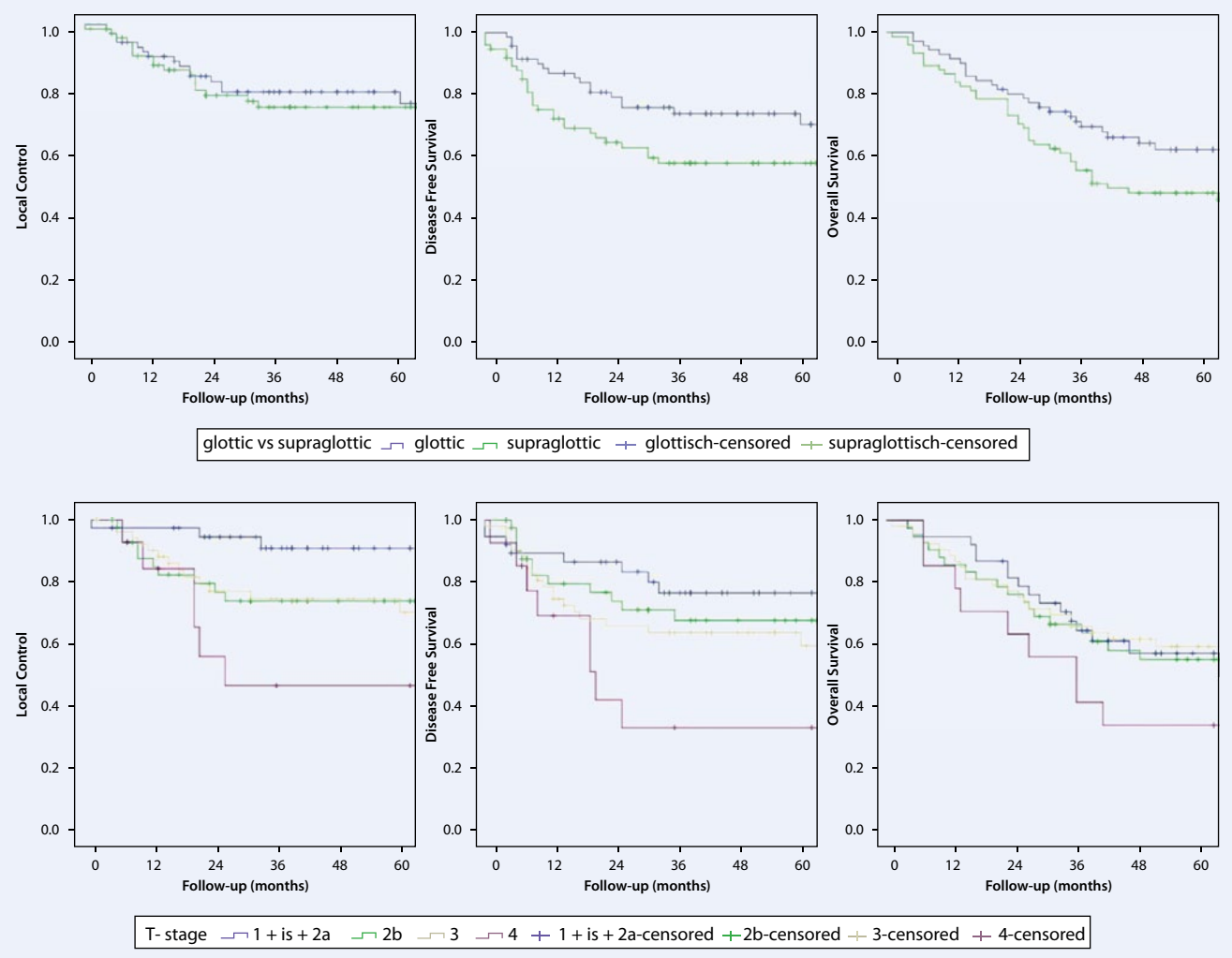

Fig. 1 ▲ Kaplan–Meier survival analysis on location and T-stage vs. local control, disease-free survival and overall survival

Location

We found a borderline significant association between location and DFS in the crude analysis (**Tab. 2**, **Fig. 1**). When combined in the Cox proportional regression analysis with T-stage, the association between location and DFS is significant (p=0.040). But combined with volume, with or without T-stage, there is no association between location and DFS (p=0.437 and p=0.855, respectively). There is no association between location and local control or OS.

Combination of T-stage and TV

When we combined TV and T-stage in the Cox proportional regression analysis, the significant association between TV and DFS or OS is maintained. Location of the tumor did not influence this association (**Tab. 2**).

Discriminative value of the models

The discriminative value (C statistic) of volume to predict the development of an event or death was 0.68 (SD 0.08) and 0.57 (SD 0.08), respectively, and of T-stage was 0.59 (SD 0.08) and 0.54 (SD 0.07), respectively. Adding T-stage to the model on DFS with TV did not increase the discriminative power of the model (0.68; SD 0.08). But adding T-stage to the model on OS did increase the discriminative power slightly (0.61; SD 0.07). We also performed C statistic analysis for local control. T-stage (0.63; SD 0.09) showed a better performance than diagnostic TV (0.61; SD 0.10) only. Combining volume and T-stage improved the performance (0.69; SD 0.09). Location was of no additive value to the models.

Discussion

Although T-stage is widely used, diagnostic TV seems to be a better predictor in case of DFS and OS, and is of additive value for LC in this study. Although volume and T-stage have been investigated with respect to outcome (in univariate and multivariate analysis; **Tab. 3**), the combination of the two as one predictor has never been investigated.

In this study, we compared the predictive value of T-stage and volume and their combination on outcome in patients with laryngeal SCC. TV appeared to have better discriminative ability to predict DFS and OS compared to T-stage. The combination of both predictors had a slightly

Tab. 3 Results in literature of association between volume and outcome

Reference	n	Location	Diagnostic modality	Volume (mean cm^3)	Treatment	Outcome	Results Univariate		Results Multivariate	
							Volume	T-stage	Volume	T-stage
Ljumanovic et al. 2007 [27]	118	Glottic	MRI	2.3	Radiotherapy	LC	s	s	ns	ns
Ljumanovic et al. 2004 [28]	84	Supraglottic	MRI	10.3	Radiotherapy	LC	s	ns	na	na
Murakami et al. 2000 [29]	68	Glottic	CT	Unknown	Radiotherapy	LC	s	s	ns	ns
Lo et al. 1998 [30] (abstract only)	55	Glottic and supraglottic	CT	4.5 (RTx) 11 (surgery)	Radiotherapy or surgery	LC	ns	na	ns	na
Freeman et al. 1990 [31] (abstract only)	31	Supraglottic	CT	Unknown	Radiotherapy	LC	s	na	s	na
Mancuso et al. [15]	63	Supraglottic	CT	Unknown	Radiotherapy	LC	s	na	s	ns
Pameijer et al. [14]	42	Glottic	CT	Unknown	Radiotherapy	LC	s	Only T3	s	Only T3
Van Bockel et al.	150	Glottic and supraglottic	CT	5.3	Radiotherapy	LC DFS OS	bs s s	s bs ns	ns s s	ns ns ns

s significant (p<0.05), *ns* non-significant, *bs* borderline significant, *na* not assessed.

better discriminative ability on OS. For local control, T-stage seems to have a better discriminative ability than TV, but combination of both predictors improved the discriminative ability of the model.

For oropharyngeal, oral and hypopharyngeal carcinoma, tumor diameter is included in T-staging. The question is why this is not the case for laryngeal carcinoma. Our data show that volume is just as important as, and of additive value to T-stage in prediction of outcome in laryngeal carcinoma. From a practical viewpoint, it would make sense to include TV on the diagnostic CT scan in the TNM classification.

Other studies used TV as a dichotomous variable. Only Pameijer et al. [14] also investigated TV as a continuous variable (**Tab. 3**). Since we could not find a non-linear relationship, like an S curve, between TV and outcome, we used TV as a continuous variable. Therefore, it could be difficult to determine a threshold for TV to implement in T-stage. Using our data to confirm the thresholds stated by the Mancuso group [14, 15], we did find significant associations with outcome. But we also found these significant associations when we chose higher or lower thresholds [14, 15]. Thus, further research on how to implement volume in T-stage is warranted.

In our study, location did not influence the association between TV/T-stage and local control, OS or DFS. Several studies suggest that supraglottic tumors have a worse prognosis than glottic tumors and that supraglottic location is an independent predictor of survival [24]. Also, in the Netherlands the 5-year survival is 85% for glottic tumors and 50% for supraglottic tumors (IKNL: Integral Cancer Centre the Netherlands). When analyzing the effect of location only on 5-year DFS, we did find a trend for a slightly worse prognosis for supraglottic tumors. This might not have influenced the association between volume/T-stage and outcome since supraglottic tumors were mainly larger in this study. When location is analyzed in the same model as volume, the borderline significance of location is lost without any influence on the HR of volume. This suggests that TV is a better predictor for 5-year DFS in laryngeal SCC patients. Furthermore, another reason why we did not find a large effect of location on outcome might be the fact that all patients were treated with accelerated radiotherapy schedules instead of conventional schedules. In our opinion, it is possible that accelerated radiotherapy counteracts possible differences in glottic and supraglottic laryngeal SCC.

This study had some limitations, which should be mentioned: Using TV in clinical staging could lead to some problems. First, delineation of the TV could be time consuming. However, the number of centers performing a planning CT scan as a diagnostic CT scan before radiotherapy is increasing. The delineation of the radiation oncologist could be used for this purpose.

Second, with every delineation, there is bias because of intra- and interobserver variability. Because of the relatively small volumes in laryngeal carcinoma, this could make it difficult to determine practical thresholds. In a study of Mukherji et al. [26], radiation oncologists and radiologists demonstrated a reliable and reproducible TV measurement in the supraglottic region, delineated on CT. However, the estimation of the tumor shape was imprecise. Variability decreases if the two readers are from the same profession [25, 26]. Therefore, we tried to diminish this variability by delineating each CT scan with at least two observers.

A strength of this study is that we included a relatively large homogenous

group of patients (n=150), with laryngeal SCC only, all treated with accelerated radiotherapy. TV was delineated on a single modality, i.e., CT scan. There are several other studies that investigated the influence of TV on outcome, but some used different locations of head and neck cancers, or used different modalities for delineation (MRI/CT). Others selected a more homogenous group, but had therefore the disadvantage of small patient numbers [8, 10, 12, 13, 14, 15, 16].

Conclusion

Volume seems to be more important than T-stage in the prediction of DFS and OS, and of additive value in predicting LC in laryngeal squamous cell carcinoma. Probably, prediction of DFS, OS, and LC in these patients could be improved if TV would be represented into the staging process.

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Compliance with ethical guidelines

Conflict of interest. L.W. van Bockel, E.M. Monninkhof, F.A. Pameijer, and C.H.J. Terhaard state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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