TUMOR VOLUME AS PROGNOSTIC FACTOR IN CHEMORADIATION FOR ADVANCED HEAD AND NECK CANCER

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Abstract: *Background.* Tumor volume is an important predictor of outcome in radiotherapy alone. Its significance in concomitant chemoradiation (CCRT) is much less clear. We analyzed the prognostic value of primary tumor volume for advanced head and neck squamous cell carcinoma (HNSCC) treated with CCRT.

Methods. Three hundred sixty patients treated with definitive CCRT for advanced HNSCC were selected. The pretreatment MRI or CT scan was used to calculate the primary tumor volume. Median follow-up was 19.8 months.

Results. The average primary tumor volume was 37.0 cm^3 (range, 2.1–182.7 cm^3; median, 28.7 cm^3). Multivariate analysis showed a significant effect of tumor volume on local control. The hazard ratio for a local recurrence increased by 14% per 10 cm^3 volume increase (95% CI, 8% to 21%). There was no significant independent effect of T and N status on local control.

Conclusion. For advanced HNSCC, tumor volume is more powerful for predicting outcome after CCRT than TNM status.
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Keywords: head and neck cancer; radiotherapy; chemoradiation; tumor volume; prognostic factor

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Worldwide, head and neck squamous cell carcinoma (HNSCC) is a considerable cause of morbidity and mortality. The majority of patients with head and neck cancer present with locally advanced, unresectable disease.[1]

Today, the role of concomitant chemoradiation (CCRT) is well established and CCRT has become an important and standard part in the treatment of locally advanced head and neck cancer, although increased incidences of acute and late toxicity are reported.[2–6] To optimize cancer control and functional outcome, it is essential to select the appropriate patients for CCRT. Patients that are unlikely to benefit from this treatment should be considered for alternative treatment options, sparing them unnecessary toxicity. However, powerful predictors for outcome in CCRT are scarce since staging beyond T2 status is mainly based upon surgical criteria rather than predictors of radiation or chemotherapy response.[7] On several occasions, conventional TNM information failed to predict response, especially in nonsurgical therapy.[8–10]

Increased tumor volume adversely affects the local control rate for patients treated with radiotherapy.[11–13] Many investigators have demonstrated a significant impact of primary tumor volume on treatment outcome in HNSCC after radiotherapy alone.[8,9,14–16] However,

the role of tumor volume as a prognostic factor in CCRT is much less clear. The purpose of the present study was to analyze and confirm primary tumor volume as a prognostic factor in a large multi-institutional series of patients treated with various CCRT regimens for advanced HNSCC.

MATERIALS AND METHODS

Patients. All patients treated with definitive CCRT at our institute and 5 participating centers for newly diagnosed, advanced HNSCC were reviewed. Only tumors of the oral cavity, oropharynx, and hypopharynx were selected. Tumor stage was limited to stage III and IV (M0) disease according to the Union Internationale Contre le Cancer (UICC) TNM criteria.[7] The reason for CCRT was either functionally or anatomically unresectable disease. All patients were treated with curative intent.

In the period between 1997 and 2006, a total of 471 patients fulfilled the criteria. A pretreatment MRI or CT scan that could be used for tumor volume assessment was available in 363 cases. Two patients were excluded because of insufficient or missing clinical and/or follow-up data, leaving a total of 361 patients available for analysis. The mean age at diagnosis was 56.4 years (range, 24.8–85.2 years). Other patient-related factors that were collected included sex, pretreatment hemoglobin level, pretreatment weight loss, performance score according to World Health Organization criteria and American Society of Anesthesiologists score (Table 1).[17] The median follow-up for all patients was 19.8 months (mean, 26.9 months).

Table 1. Patient and tumor characteristics.

Characteristic	No. (%)
Sex	
Male	261 (72.3)
Female	100 (27.7)
WHO score	
0	126 (34.9)
1	100 (27.7)
2	10 (2.8)
Missing	125 (34.6)
ASA score	
1	71 (19.7)
2	112 (31.0)
3	18 (5.0)
Missing	160 (44.3)
Weight loss	
<10%	180 (49.9)
>10%	132 (36.6)
Missing	49 (13.6)
Primary tumor site	
Oral cavity	81 (22.4)
Oropharynx	225 (62.3)
Hypopharynx	55 (15.2)
T status	
T2	14 (3.9)
T3	111 (30.7)
T4	236 (65.4)
N status	
N0	72 (19.9)
N1	49 (13.6)
N2	209 (57.9)
N3	31 (8.6)

Abbreviations: WHO, World Health Organization; ASA, American Society of Anesthesiologists.

Treatment. Treatment consisted of cisplatin-based chemotherapy and concomitant external beam radiotherapy. All patients were included in prospective phase II and III trials, with different CCRT regimens. Trial #1 ($n = 72$) was a phase II trial studying the effect and feasibility of high-dose superselective intra-arterial cisplatin and concomitant radiation (RADPLAT protocol).[18] Patients received 4 courses of intra-arterial infusion cisplatin (150 mg/m^2) and simultaneous IV sodium thiosulfate on days 2, 9, 16, and 23 concomitant with delivery of external beam radiotherapy. The total radiotherapy dose was 70 Gy, in 2-Gy fractions per day over a period of 7 weeks.[19] Trial #2 ($n = 189$) was a multicenter randomized phase III trial, comparing the intra-arterial regimen described above to (standard) IV cisplatin chemoradiation (100 mg/m^2) on days 1, 22, and 43 concomitantly with the same radiotherapy regimen.[20] Trial #3 ($n = 44$) was a phase II trial evaluating a regimen of daily low-dose cisplatin. Patients received IV cisplatin (6 mg/m^2) on every treatment day for a maximum of 20 days, concomitant with either standard radiotherapy (70 Gy/35 fractions/7 weeks) or accelerated radiotherapy with the same total dose and fractionation, but delivered in 6 weeks, 6 fractions per week (DAHANCA schedule).[21,22] The remainder of the patients ($n = 56$) were treated in a phase II trial with a CCRT regimen consisting of 5 to 6 weekly courses of IV cisplatin (40 mg/m^2) and concomitant accelerated radiotherapy. The total radiotherapy dose in this regimen was 68 Gy with 2-Gy fractions per day. By delivering 2 fractions daily during the last 1.5 weeks of treatment, the total treatment time was shortened to 5.5 weeks.

All patients were treated with a standard 3-field technique (2 opposing lateral fields for the upper neck region, with an adjacent supraclavicular field for the lower neck) or by CT-planning using a 3-dimensional (3D) conformal or intensity modulated radiotherapy technique depending on resources. Patients were followed once or twice weekly during treatment for adverse effects and/or complications. Six to 8 weeks after the end of treatment, the results were evaluated by radiologic investigations (MRI or CT scan, or ultrasound) and/or examination with the patient under general anesthesia. Follow-up visits were planned every 2 to 3 months in the first year after treatment, every 3 to 4 months in the second year, and less frequently thereafter.

Tumor Volume Assessment. The pretreatment MRI or CT scan was used for primary tumor volume assessment. Hard-copy scans were first digitized and

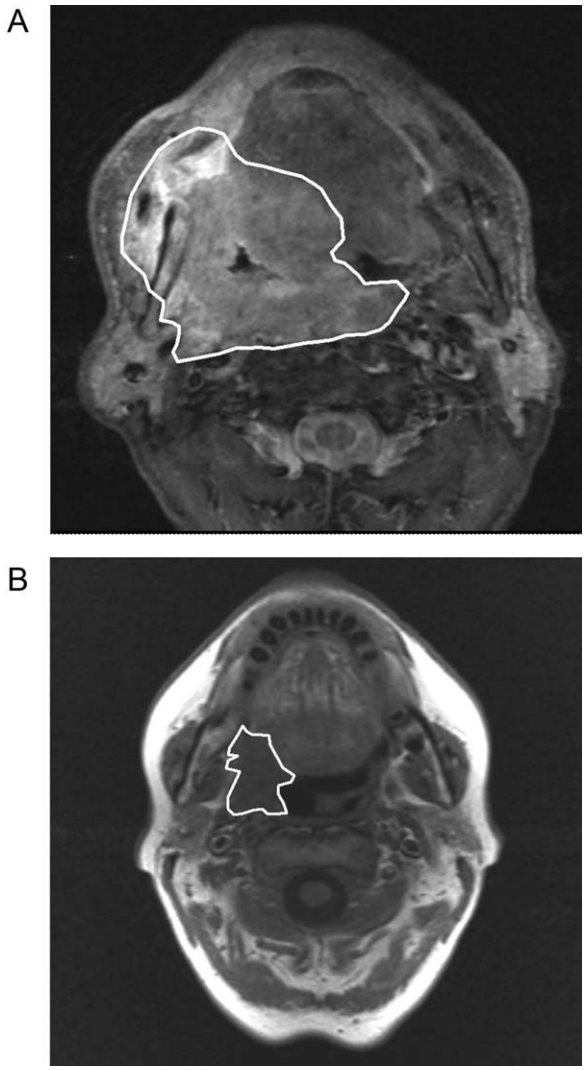

FIGURE 1. Two patients with oropharyngeal carcinoma and the same T and N status (T4N2), but very different primary tumor volumes: 86.3 cm^3 (**A**) and 11.8 cm^3 (**B**).

transferred to a PC workstation. Digital scans were directly transferred. For 3D computation of the tumor volume, all visible primary tumor tissue was manually delineated on every MRI or CT slice using delineation tools and software developed at our institute (Figure 1). Pathological lymph nodes were not included. The delineations were performed by a head and neck radiologist (F.A.P.) and 3 radiation oncologists (J.L.K., F.J.H., C.R.R.), all were blinded to the patients' treatment outcome. To test for interobserver variability, 50 patients were independently delineated by all 4 observers (F.A.P., J.L.K., F.J.H., C.R.R.).

Statistical Analysis. Local control and survival data were calculated from the start of treatment using the Kaplan–Meier method. Cox regression with follow-up as time scale was used to calculate hazard ratios (HRs) according to tumor volume and other potentially confounding variables. Continuous variables were appropriately categorized and trend tests were based on the significance of the slope for the continuous variable. Confounding was controlled by adjusting for all variables for which at least 1 category had a univariate HR exceeding 2.0 or significant at $p < .05$. In order to evaluate whether the effect of tumor volume was homogeneous across subgroups of other variables, we estimated separate volume effects for each category of a potential effect modifier while adjusting for its main effect, and compared the goodness of fit with the null model which includes 1 overall treatment effect via likelihood ratio methods.

RESULTS

Delineation Accuracy. For the 50 patients delineated by multiple observers, the mean difference in delineated primary tumor volume was 7.6% (range, 0.15% to 20.9%). This difference was constant across different tumor volumes. The Pearson correlation coefficient was 0.99, which implies good agreement between the observers.

Tumor Volume. A total of 361 primary tumors were delineated on the pretreatment MRI ($n = 275$) or CT ($n = 86$) scan. The distribution of the tumor volumes is shown in Figure 2. One patient had an extremely large tumor volume (393.8 cm^3). Leaving this patient out did not substantially change the results of any of the analyses (data not shown), so we decided to exclude this patient. All further results are based on the remaining 360 patients. The tumor volume ranged from 2.1 cm^3 to 182.7 cm^3. The mean and median tumor volumes were 37.0 cm^3 and 28.7 cm^3,

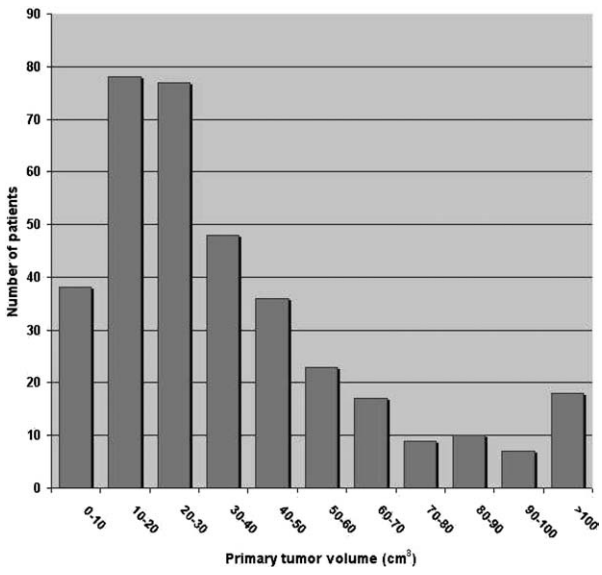

FIGURE 2. Distribution of the primary tumor volume (cm^3).

Table 2. Mean tumor volume, local control and overall survival stratified by T status, N status and primary tumor site.

	No. of patients	Mean primary tumor volume, cm^3	5-year local control, %	5-year overall survival, %
Total group	360	37.0	67.3	38.4
T status				
T2	14	16.3	78.6	24.2
T3	111	22.6	75.7	45.0
T4	235	45.0	62.7	35.6
N status				
N0	71	27.9	66.2	56.1
N1	49	30.9	69.4	30.8
N2	209	40.7	68.2	38.3
N3	31	42.1	62.4	13.7
Primary tumor site				
Oral cavity	80	39.4	50.3	28.6
Oropharynx	225	37.1	72.1	41.2
Hypopharynx	55	33.0	72.1	46.8

respectively. Table 2 shows the mean tumor volumes stratified by T status, N status, and primary tumor site. The highest volumes of disease were found in patients with T4 tumors (45.0 cm^3), N3 tumors (42.1 cm^3), and primary tumors of the oral cavity (39.4 cm^3).

Local Control. A total of 104 local recurrences were observed, and the mean time to local failure was 22.3 months (median, 14.5 months). The overall 5-year local control rate was 67.3%. T4 tumors, N3 tumors, and primary tumors of the oral cavity had the lowest 5-year local control rates, 62.7%, 62.4%, and 50.3%, respectively (Table 2). Patients without a complete remission ($n = 56$) were considered to have immediate failures for local recurrence. They had a higher tumor volume compared with those who reached complete remission (mean, 51.9 vs 33.8 cm^3; $p = .0001$). Cox regression analysis showed that there was a significant effect of tumor volume on local control (Table 3). There was no evidence of heterogeneity of the effect across subgroups defined by center, treatment, sex, age at diagnosis, primary tumor site, T status, N status, World Health Organization score, American Society of Anesthesiologists score, hemoglobin level, weight loss, or volume delineated on CT or MRI (data not shown). The HR for a local recurrence increased by 14% (95% CI, 8–21) per 10 cm^3 volume increase. There was no significant independent effect of T or N status on local control.

Survival. At the time of evaluation, 188 patients (52%) had died. The mean survival time was 26.9 months (median, 19.8 months). The 5-year disease-free and overall survival rates for the total group were 30.9% and 38.4%, respectively. Patients with T2 tumors, N3 tumors, and primary tumors of the oral cavity had the lowest overall survival rates, 24.2%, 13.7%, and 28.6%, respectively (Table 2). There was a significant effect of tumor volume on overall survival (Table 3). There was no evidence of heterogeneity of the effect across categories of other variables (see list above). The HR for overall survival increased by 14% (95% CI, 9–19) per 10 cm^3 volume increase. For T

Table 3. Results of the univariate and multivariate analysis for local control and overall survival.

				Univariate analysis		Multivariate analysis	
	Variable		No. of events	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Local control*	Tumor volume, cm^3	≤20	24	1.0 (ref)	<.001	1.0 (ref)	<.001
		21–40	34	1.4 (0.9–2.4)		1.2 (0.7–2.1)	
		41–60	18	1.7 (0.9–3.2)		1.4 (0.7–2.6)	
		>60	28	3.0 (1.7–5.2)		2.8 (1.5–5.2)	
	T status	T2	3	0.6 (0.2–1.9)	.0268	0.7 (0.2–2.3)	.292
		T3	23	0.6 (0.4–0.9)		0.8 (0.5–1.3)	
		T4	78	1.0 (ref)		1.0 (ref)	
	N status	N0	20	0.9 (0.6–1.5)	.481	–	–
		N1	13	0.9 (0.5–1.7)			
		N2	61	1.0 (ref)			
		N3	10	1.3 (0.6–2.5)			
Overall survival†	Tumor volume, cm^3	≤ 20	44	1.0 (ref)	<.001	1.0 (ref)	<.001
		21–40	59	1.3 (0.9–1.9)		1.2 (0.8–1.8)	
		41–60	36	1.8 (1.1–2.7)		1.5 (0.9–2.4)	
		>60	47	3.0 (2.0–4.5)		2.8 (1.8–4.3)	
	T status	T2	6	0.8 (0.4–1.9)	.0352	1.1 (0.5–2.4)	>.5
		T3	43	0.7 (0.5–0.9)		0.9 (0.6–1.3)	
		T4	139	1.0 (ref)		1.0 (ref)	
	N status	N0	28	0.7 (0.4–1.0)	.0017	0.7 (0.5–1.1)	.0133
		N1	28	1.2 (0.8–1.8)		1.3 (0.8–1.9)	
		N2	106	1.0 (ref)		1.0 (ref)	
		N3	25	2.2 (1.4–3.4)		2.5 (1.6–3.9)	

Abbreviations: HR, hazard ratio; CI, confidence interval; ref, reference.
**Multivariate model included tumor volume, T status, age at diagnosis, tumor site, and treatment.*
†Multivariate model included tumor volume, T status, N status, age at diagnosis, and tumor site.

and N status, only N status was a significant, independent factor for overall survival (Table 3). The effect of tumor volume on disease-free survival was significant as well. The HR for disease-free survival increased by 13% (95% CI, 8–18) per 10 cm^3 volume increase.

Distant Metastases. Distant metastases occurred in 56 patients as first event. The mean time to metastases was 22.3 months (median, 14.5 months). There was a significant effect of tumor volume and N status on metastases. The HR for distant metastases increased by 14% (95% CI, 5–24) per 10 cm^3 volume increase.

DISCUSSION

In our study, primary tumor volume was a powerful factor predicting treatment outcome in a large group of patients with advanced HNSCC treated with definitive CCRT. Despite our positive findings, we acknowledge some weaknesses in our research. Although most patients were treated on prospective trials, the volume comparison was done retrospectively which may preclude direct application of these findings to current practice. However, all patients in our study were treated with 4 different regimens of concomitant chemoradiation so they were a group with relatively homogenous treatment. There were no major differences in survival by treatment except for a significantly poorer local control (but not overall survival) among the 56 patients treated in the phase II trial (data not shown). Including treatment in the multivariate model for local control did not change the effect of tumor volume. It is less likely, therefore, that the observed volume effect is actually due to chance. The multivariate model for overall survival did not include treatment because none of the HRs for treatment was significantly different from 1.0 or exceeded 2.0 (according to our rule for inclusion of potential confounders in multivariate analyses). Finally, although patients with primary tumors of the oral cavity had a worse prognosis compared with other patients, the primary tumor site was included in the multivariate model for both local control and overall survival and did not change the effect of tumor volume.

The importance of tumor volume as prognostic factor has already been recognized previously for cancer at other sites, including cervix and lung.[23,24] The probability of tumor control is adversely affected by increasing tumor volume and several human and animal studies have shown that higher radiotherapy doses are needed to cure larger tumors. The simplest explanation for this fact is that a higher radiotherapy dose is needed to sterilize a higher number of clonogenic (stem) cells in larger tumors. Tumor control is related to the probability that no potential stem cells remain that are capable of causing tumor regrowth. Some authors have reported that the number of potential stem cells increases linearly with tumor volume.[11,13] Others found a less pronounced effect than would be expected from a simple proportionality and concluded that additional volume-related factors, such as clonogenic fraction, hypoxia, clonal radioresistance, and intercellular communication, may play a role as well.[12]

Several studies have been published on tumor volume as a prognostic factor in HNSCC, but only a few have investigated the role of primary tumor volume in CCRT.[9,10,25–27] Concomitant treatment regimens are frequently associated with a high degree of toxicity and imply a heavy burden on the patient. The improved clinical outcome with CCRT thus comes at the cost of considerable treatment-induced morbidity. The goal of using tumor volume as an outcome predictor is to identify patients who are unlikely to benefit from CCRT. These patients can be spared the intensive, toxic CCRT treatment regimens or can be considered for alternative treatment options, like (induction) chemotherapy, altered fractionation radiotherapy, or the combination of radiotherapy with other drugs like antibodies against the epidermal growth factor receptor or hypoxic cell radiosensitizers.[28–30] This will also help stratifying patients for clinical trials and prevent confounding of the analysis of treatment outcome by their presence. For the group of patients for whom a favorable response is predicted, strategies can be developed to decrease toxicity and side effects.

HNSCC is a heterogeneous disease with different presentation of equivalent disease stages. Therefore, stratification of HNSCC for outcome prediction has been a big challenge in the past. Despite this, TNM stage has been the main prognostic factor for treatment outcome in past years. The limitation of staging systems is that they generalize and categorize tumors with different volumes into the same stage (Figure 1). As nonsurgical, organ-preserving therapeutic approaches like CCRT are gaining acceptance and becoming a standard of care for many tumor types, more tailored pretreatment tumor evaluation is necessary. Attempts have been made to identify other radiologic and clinical factors that may be used as prognostic factors, but there is considerable uncertainty regarding their accuracy and few have been tested in predicting response to CCRT. Research is underway to identify genetic and molecular markers to develop predictive assays.[31,32] Other approaches include response to induction chemotherapy, human papillomavirus infection, measurement of cisplatin-DNA adduct formation, and hypoxia.[33–36] The clinical value of the new developments remain to be established and, to date, reliable methods of identifying patients who are likely to respond to primary CCRT have not been determined.

Imaging techniques have progressed significantly in past years and precise, accurate measurement of the actual tumor volume is easy to obtain. Many

authors have used diagnostic CT or MRI scans for tumor volume assessment.[9,14–16,25–27,37–39] Tumor volumes outlined on MRI have been reported to be equal to or smaller than volumes outlined on CT.[40,41] In our study, MRI scans were preferred for tumor delineation and only good quality, contrast-enhanced high-resolution CT scans were accepted. Our results did not differ by the imaging technique used for delineation. Another issue is intraobserver and interobserver variability. Studies on this subject have reported inconsistent results.[42,43] In our study, the interobserver differences in the volumes of the 50 multiple delineated patients were relatively small (mean, 7.6%) and constant across the range of volumes.

In 1 of our earlier reports by van den Broek et al,[10] based on a substantially smaller study, a nomogram that included primary tumor volume and other patient, tumor, and treatment characteristics was proposed for pretreatment selection of patients for intra-arterial CCRT. The current study included different CCRT regimens of which we decided to use only primary tumor volume for outcome prediction. Previous publications that used primary tumor volume as a prognostic factor in CCRT demonstrate great diversity of mean volumes and cut-off values.[9,25–27] These numbers are even more difficult to compare because volume and outcome parameters are not reported similarly. The method by which the tumor volume has been determined in these studies was comparable, although not exactly the same. However, even basic tumor volume measurement can be of prognostic value.[13] In a series of 64 patients with advanced head and neck cancer treated with targeted intra-arterial CCRT, Doweck et al[25] found primary tumor volume to be the only significant parameter related to local failure and survival with a cut-off tumor volume of 19.6 cm^3. In an analysis of CCRT for advanced hypopharyngeal cancer, Tsou et al[27] found the greatest risk for local failure among patients with primary tumor volumes >19.0 cm^3. Studer et al[9] used cut-off values of 15 and 70 cm^3 to define different prognostic subgroups in 172 patients with head and neck cancer. This method proved to be superior to the TNM stage in predicting outcome. In a recent publication from Chen et al[26] the prognostic value of tumor volume was investigated in 76 patients with advanced hypopharyngeal cancer treated with CCRT. They reported a strong correlation between primary tumor volume and outcome with a cut-off tumor volume of 30 cm^3.

To our knowledge, this current study represents the largest series reported so far on primary tumor volume and the outcome after CCRT. Therefore, we think that pretreatment tumor volume should be taken into account when making treatment decisions. How to implement these results into daily clinical practice is beyond the scope of this report but is clearly the next question that needs to be addressed. Based on our observation and without a formal evaluation, we propose to incorporate tumor volume in the TNM system for advanced tumors (T3–T4 status) and choose a cut-off volume of 30 cm^3. This volume is close to the median tumor volume of 28.7 cm^3 we found and also close to the cut-off volume of 29.7 cm^3 Doweck et al[25] found in their subgroup of patients with oropharyngeal cancer, which constitutes more than 60% of our patients. Furthermore, this cut-off volume was also found in the analysis by Chen et al.[26] The 5-year local control rate for patients with a T3 tumor and a volume $\leq$30 cm^3 ($n = 86$) is 81.8%. These tumors can be reclassified as T3a tumors. Larger (>30 cm^3) T3 tumors, with a worse prognosis, can be reclassified as T3b. The 5-year local control rate for these patients ($n = 25$) is 55.1%. In the same way, a separation into T4a ($n = 95$) and T4b ($n = 140$) can be made, with 5-year local control rates of 74.9% (T4a) and 53.5% (T4b). Figure 3 shows the Kaplan–Meier curves for local control for T3 and T4 tumors using 30 cm^3 as cut-off volume. The differences in outcome are significant (log-rank, $p = .002$ and $p = .004$, respectively). In this way, volume

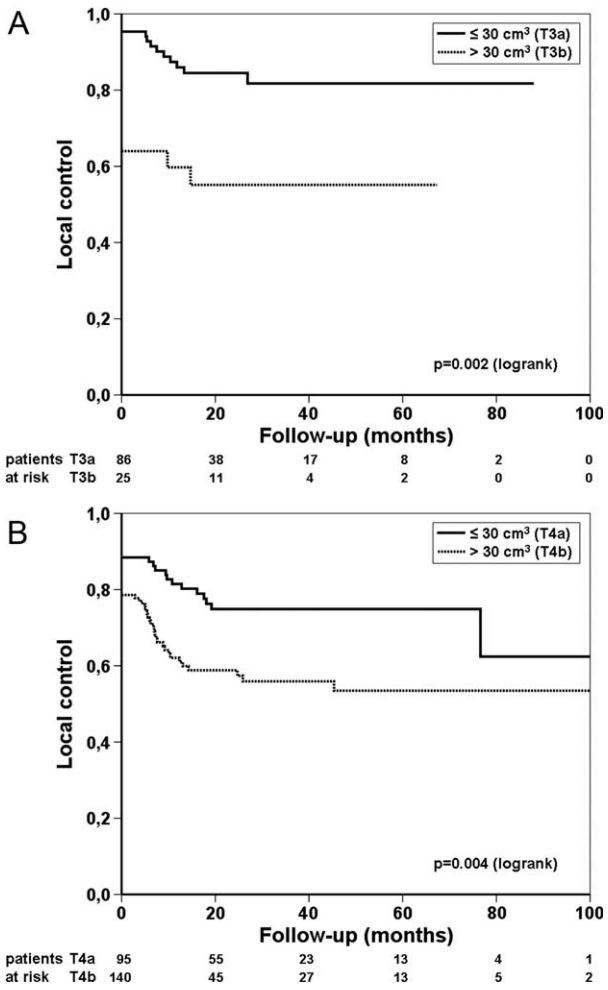

FIGURE 3. Kaplan–Meier plots of local control using 30 cm^3 as cut-off volume for T3 tumors (**A**) and T4 tumors (**B**).

measurement can serve as a tool for individualizing treatment. Prospective trials using volume measurements are needed to validate this approach.

CONCLUSION

Primary tumor volume is an important prognostic factor and a predictor for disease control and survival in patients with advanced HNSCC treated with CCRT. For advanced tumors, conventional TNM staging is an insufficient prognostic indicator of outcome after new multimodal treatment strategies. These findings can be used in pretreatment patient selection, thereby improving treatment results and avoiding unnecessary toxicity.

REFERENCES

1. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. N Engl J Med 1993;328:184–194.
2. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21: 92–98.
3. Allal AS, Bieri S, Miralbell R, et al. Combined concomitant boost radiotherapy and chemotherapy in stage III–IV head and neck carcinomas: a comparison of toxicity and treatment results with those observed after radiotherapy alone. Ann Oncol 1997;8:681–684.
4. Denis F, Garaud P, Bardet E, et al. Final results of the 94–01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69–76.
5. Eisbruch A, Lyden T, Bradford CR, et al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2002;53:23–28.
6. El Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta-analysis of prospective and randomized trials. J Clin Oncol 1996;14:838–847.
7. Sobin LH, Wittekind Ch. UICC TNM classification of malignant tumours. 6th ed. New York: Wiley-Liss Press, 2002.
8. Johnson CR, Khandelwal SR, Schmidt-Ullrich RK, Ravalese J III, Wazer DE. The influence of quantitative tumor volume measurements on local control in advanced head and neck cancer using concomitant boost accelerated superfractionated irradiation. Int J Radiat Oncol Biol Phys 1995;32:635–641.
9. Studer G, Lütolf UM, El-Bassiouni M, Rousson V, Glanzmann C. Volumetric staging (VS) is superior to TNM and AJCC staging in predicting outcome of head and neck cancer treated with IMRT. Acta Oncol 2007;46:386–394.
10. van den Broek GB, Rasch CR, Pameijer FA, et al. Pretreatment probability model for predicting outcome after intraarterial chemoradiation for advanced head and neck carcinoma. Cancer 2004;101:1809–1817.
11. Brenner DJ. Dose, volume, and tumor-control predictions in radiotherapy. Int J Radiat Oncol Biol Phys 1993;26:171–179.
12. Bentzen SM, Thames HD. Tumor volume and local control probability: clinical data and radiobiological interpretations. Int J Radiat Oncol Biol Phys 1996;36:247–251.
13. Dubben HH, Thames HD, Beck-Bornholdt HP. Tumor volume: a basic and specific response predictor in radiotherapy. Radiother Oncol 1998;47:167–174.
14. Hermans R, Op de beeck K, Van den Bogaert W, et al. The relation of CT-determined tumor parameters and local and regional outcome of tonsillar cancer after definitive radiation treatment. Int J Radiat Oncol Biol Phys 2001;50:37–45.
15. Kraas JR, Underhill TE, D'Agostino RB Jr, Williams DW III, Cox JA, Greven KM. Quantitative analysis from CT is prognostic for local control of supraglottic carcinoma. Head Neck 2001;23: 1031–1036.
16. Pameijer FA, Mancuso AA, Mendenhall WM, et al. Evaluation of pretreatment computed tomography as a predictor of local control in T1/T2 pyriform sinus carcinoma treated with definitive radiotherapy. Head Neck 1998;20:159–168.
17. Wolters U, Wolf T, Stützer H, Schröder T. ASA classification and perioperative variables as predictors of postoperative outcome. Br J Anaesth 1996;77:217–222.
18. Robbins KT, Storniolo AM, Kerber C, Seagren S, Berson A, Howell SB. Rapid superselective high-dose cisplatin infusion for advanced head and neck malignancies. Head Neck 1992;14:364–371.
19. Balm AJ, Rasch CR, Schornagel JH, et al. High-dose superselective intra-arterial cisplatin and concomitant radiation (RADPLAT) for advanced head and neck cancer. Head Neck 2004;26: 485–493.
20. Rasch CRN, Salverda GJ, Schornagel JH, et al. Plenary 2: intraarterial versus intravenous chemoradiation for advanced head and neck cancer, early results of a multi-institutional trial. Int J Radiat Oncol Biol Phys 2006;66(3 Suppl):S1–2.
21. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 2003;362:933–940.
22. Hoebers FJ, Heemsbergen W, Balm AJ, van Zanten M, Schornagel JH, Rasch CR. Concurrent chemoradiation with daily low dose cisplatin for advanced stage head and neck carcinoma. Radiother Oncol 2007;85:42–47.
23. Narayan K, Fisher R, Bernshaw D. Significance of tumor volume and corpus uteri invasion in cervical cancer patients treated by radiotherapy. Int J Gynecol Cancer 2006;16:623–630.
24. Basaki K, Abe Y, Aoki M, Kondo H, Hatayama Y, Nakaji S. Prognostic factors for survival in stage III non-small-cell lung cancer treated with definitive radiation therapy: impact of tumor volume. Int J Radiat Oncol Biol Phys 2006;64:449–454.
25. Doweck I, Denys D, Robbins KT. Tumor volume predicts outcome for advanced head and neck cancer treated with targeted chemoradiotherapy. Laryngoscope 2002;112:1742–1749.
26. Chen SW, Yang SN, Liang JA, Lin FJ, Tsai MH. Prognostic impact of tumor volume in patients with stage III–IVA hypopharyngeal cancer without bulky lymph nodes treated with definitive concurrent chemoradiotherapy. Head Neck 2009;31:709–716.
27. Tsou YA, Hua JH, Lin MH, Tsai MH. Analysis of prognostic factors of chemoradiation therapy for advanced hypopharyngeal cancer—does tumor volume correlate with central necrosis and tumor pathology? ORL J Otorhinolaryngol Relat Spec 2006;68: 206–212.
28. Overgaard J, Hansen HS, Overgaard M, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5–85. Radiother Oncol 1998;46: 135–146.
29. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–578.
30. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705–1715.
31. Buffa FM, Bentzen SM, Daley FM, et al. Molecular marker profiles predict locoregional control of head and neck squamous cell carcinoma in a randomized trial of continuous hyperfractionated accelerated radiotherapy. Clin Cancer Res 2004;10:3745–3754.
32. Salesiotis AN, Cullen KJ. Molecular markers predictive of response and prognosis in the patient with advanced squamous cell carcinoma of the head and neck: evolution of a model beyond TNM staging. Curr Opin Oncol 2000;12:229–239.
33. Urba S, Wolf G, Eisbruch A, et al. Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. J Clin Oncol 2006;24:593–598.
34. Weinberger PM, Yu Z, Haffty BG, et al. Molecular classification identifies a subset of human papillomavirus–associated oropharyngeal cancers with favorable prognosis. J Clin Oncol 2006;24: 736–747.
35. Hoebers FJ, Pluim D, Verheij M, et al. Prediction of treatment outcome by cisplatin-DNA adduct formation in patients with stage III/IV head and neck squamous cell carcinoma, treated by concurrent cisplatin-radiation (RADPLAT). Int J Cancer 2006; 119:750–756.

36. Hoogsteen IJ, Marres HA, Bussink J, van der Kogel AJ, Kaanders JH. Tumor microenvironment in head and neck squamous cell carcinomas: predictive value and clinical relevance of hypoxic markers. A review. Head Neck 2007;29:591–604.
37. Chufal KS, Rastogi M, Srivastava M, Pant MC, Bhatt ML, Srivastava K. Analysis of prognostic variables among patients with locally advanced head and neck cancer treated with late chemointensification protocol: impact of nodal density and total tumor volume. Jpn J Clin Oncol 2006;36:537–546.
38. Pameijer FA, Balm AJ, Hilgers FJ, Muller SH. Variability of tumor volumes in T3-staged head and neck tumors. Head Neck 1997;19:6–13.
39. Rudat V, Dietz A, Schramm O, et al. Prognostic impact of total tumor volume and hemoglobin concentration on the outcome of patients with advanced head and neck cancer after concomitant boost radiochemotherapy. Radiother Oncol 1999;53:119–125.
40. Rasch C, Keus R, Pameijer FA, et al. The potential impact of CT-MRI matching on tumor volume delineation in advanced head and neck cancer. Int J Radiat Oncol Biol Phys 1997;39: 841–848.
41. Daisne JF, Duprez T, Weynand B, et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology 2004;233:93–100.
42. Cooper JS, Mukherji SK, Toledano AY, et al. An evaluation of the variability of tumor-shape definition derived by experienced observers from CT images of supraglottic carcinomas (ACRIN protocol 6658). Int J Radiat Oncol Biol Phys 2007;67:972–975.
43. Preda L, Lovati E, Chiesa F, et al. Measurement by multidetector CT scan of the volume of hypopharyngeal and laryngeal tumours: accuracy and reproducibility. Eur Radiol 2007;17:2096–2102.