Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 4, pp. 1018–1026, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.01.021

CLINICAL INVESTIGATION **Head and Neck**

PROGNOSTIC IMPACT OF TUMOR VOLUMETRY IN PATIENTS WITH LOCALLY ADVANCED HEAD-AND-NECK CARCINOMA (NON-NASOPHARYNGEAL) TREATED BY RADIOTHERAPY ALONE OR COMBINED RADIOCHEMOTHERAPY IN A RANDOMIZED TRIAL

GEORGE A. PLATANIOTIS, M.D.,* MARIA-EKATERINI THEOFANOPOULOU, M.D.,* ANNA KALOGERA-FOUNTZILA, M.D.,† AFRODITI HARITANTI, M.D.,† ELISABETA CIULEANOU, M.D.,‡ NICOLAE GHILEZAN, M.D.,‡ NIKOLAOS ZAMBOGLOU, M.D.,§ ATHANASIOS DIMITRIADIS, M.D.,† IOANNIS SOFRONIADIS, M.D.,‖ AND GEORGE FOUNTZILAS, M.D.¶

*Department of Radiation Oncology, University of Thessalia, Thessalia, Greece; Departments of †Radiology, ‖Radiation Oncology, and ¶Medical Oncology, Aristotle University of Thessaloniki, Thessaloniki, Greece; ‡Department of Radiation Oncology, Cancer Institute Ion Ciricuta, Cluj, Romania; §Strahlenklinik, Staedtische Kliniken Offenbach, Offenbach, Germany

Purpose: Tumor volume (TV) is one of the main reported factors determining the outcome of treatment in head-and-neck carcinomas. In this study, the prognostic impact of TV was explored in the context of a randomized trial with the patients assigned to receive standard radiotherapy (RT) alone or RT plus platinum compounds (RT alone, RT plus cisplatin, or RT plus carboplatin).

Methods and Materials: The tumor outlines were traced and digitized on each pretreatment CT slice for each of the 101 patients studied. Taking into account the magnification factor of the scan and CT slice thickness, a computer with specifically designed software calculated the TV in cubic centimeters.

Results: The median overall survival for the whole group of patients was 21.6 months (95% confidence interval, 13.0–30.2) and the 3-year survival rate was 40%. The addition of platinum compounds to RT (Groups 2 and 3) significantly improved the survival rate (RT alone vs. RT plus cisplatin, hazard ratio 0.36, $p = 0.002$; RT alone vs. RT plus carboplatin, hazard ratio 0.53, $p = 0.029$). In univariate analysis, the most significant parameters for survival were treatment group, total gross tumor volume (TGTV), complete response, nodal GTV, primary GTV, and performance status. In multivariate analysis, treatment group, TGTV, gender, and primary site were independent prognostic factors for survival. A prognostic threshold of 22.8 cm^3 was detected for TGTV. Patients with a TGTV of <22.8 cm^3 were more likely to achieve a complete response and had a median survival of 45.3 months, and those with a TGTV >22.8 cm^3 had a median survival of 12.3 months (log–rank test, $p = 0.0102$).

Conclusion: The prognostic significance of the TGTV was confirmed and a cutoff value of 22.8 cm^3 derived. Our data indicated that locally advanced head-and-neck carcinomas should not be treated by standard (once-daily) RT alone. Tumor size and disease subsite should be taken into account in future randomized trials to increase their statistical power. **© 2004 Elsevier Inc.**

Head-and-neck cancer, Radiotherapy, Chemotherapy, Tumor volume, CT, Prognostic factors.

INTRODUCTION

Experimental and clinical data confirm that tumor volume (TV) is the main factor determining the outcome of treatment in head-and-neck carcinomas. The University of Florida College of Medicine group has repeatedly reported on the value of TV as a prognostic factor of radiotherapy (RT) in head-and-neck tumors (1–5). It has been argued that the TV should be incorporated in staging systems, because volume data may help to identify prognostic differences. In addition, the existence of a cutoff value for the TV could be a decision node in a therapeutic algorithm, facilitating the selection of an appropriate treatment modality: surgery or RT alone vs. surgery plus postoperative RT vs. concomitant radiochemotherapy, depending on the disease extent. Likewise, investigators at the University of Florida have adopted tumor volumetry and used the derived cutoff values in their daily clinical practice (2).

The reported threshold values lie in a relatively broad spectrum depending on the subsite of the disease in the

Reprint requests to: George A. Plataniotis, M.D., Department of Radiotherapy, University Hospital of Larissa, P.O. Box 1425, Mezourlo, Larissa 411 10, Greece. Tel: (+24)10-682-047; Fax: (+24) 10-670-117; E-mail: gplatan3@otenet.gr

Acknowledgments—We thank Mrs. Sonia Chalkidou (HeCOG office) for performing the statistical analysis, and D. Andreopoulos, M.D., Ph.D., Department of Radiotherapy, Bank of Cyprus Oncology Center, Nicosia, Cyprus, for providing the software we used for tumor volume measurement in this study.

Received Jul 15, 2003, and in revised form Jan 6, 2004. Accepted for publication Jan 7, 2004.

head-and-neck region; the disease extent; and the therapeutic modality used. Laryngeal tumors tend to have low TV cutoff values (2, 5–8).

Johnson *et al.* (9) reported on the influence of TV on the therapeutic outcome in patients with advanced head-and-neck carcinomas treated by RT. After incorporation of the variable "volume" into the final Cox model, variables such as T and N stage and age lost their significance with respect to the endpoint of local control. In terms of local control, they have estimated a cutoff TV value of 40 cm^3 (9).

Rudat *et al.* (10) and Grabenbauer *et al.* (11) also reported a statistically significant association between the total TV and survival in patients with advanced head-and-neck tumors treated by combined radiochemotherapy. They also derived a prognostic TV threshold of approximately 100 cm^3.

In a recent Greek-German collaborative study (12), the authors retrospectively analyzed 107 patients with squamous cell carcinomas of the head and neck treated by RT and concomitant platinum-based chemotherapy. The volumetric data analysis revealed that the pretherapeutic TV was prognostic and TNM classification and age were not. The initial TV was negatively associated with survival, with an increase in the relative risk of 6% per 10 cm^3 difference (relative risk, 1.006).

In the present study, we explored the prognostic significance of TV on the outcome of patients with locally advanced head-and-neck carcinomas.

METHODS AND MATERIALS

The study population consisted of patients treated in the context of a randomized clinical trial conducted by the Hellenic Cooperative Oncology Group (13). This randomized trial investigated the therapeutic impact of the addition of platinum compounds to standard RT in locally advanced (Stage III and IV) head-and-neck carcinomas.

All patients had to have biopsy-proven, previously untreated, Stage III or IV (M0), squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; measurable or assessable disease; no synchronous primary tumors; and age $\geq$18 years. In addition, patients had to have a performance status of $\leq$2 on the Eastern Cooperative Oncology Group scale, adequate bone marrow, hepatic, and renal function (creatinine clearance $>$60 mL/min); and a CT scan of the head-and-neck region within 2–3 weeks before treatment initiation. The cardiovascular, pulmonary, and nutritional status had to be adequate to tolerate all protocol treatment.

Between January 13, 1995 and July 27, 1999, 128 patients were entered into the study and were randomly allocated to one of three treatment groups: Group 1, standard RT monotherapy with a dose of 70 Gy (1.8–2 Gy/d, 5 d/wk); Group 2, the same RT regimen concomitantly with cisplatin, 100 mg/m^2 on Days 2, 22, and 42; and Group 3, the same RT regimen concomitantly with carboplatin area under the curve of 7 on Days 2, 22, and 42. Two patients with missing medical records were excluded, and 2 additional patients were considered noneligible, one with previous non-Hodgkin's lymphoma and one who had undergone total laryngectomy before study entry.

Of the 124 patients, 106 were men and 18 were women (age range, 31–78 years; median, 56 years). The site distribution of the primary tumor was the oral cavity in 17, oropharynx in 43, hypopharynx in 13, and larynx in 51. The distribution by T and N stage was T1 in 1, T2 in 6, T3 in 41, and T4 in 76 and N0 in 57, N1 in 15, and N2 in 52. Twenty-seven patients had Stage III and 97 Stage IV disease. The Protocol Review Committee of the Hellenic Cooperative Oncology Group and the institutional review boards at the participating institutions approved the protocol. All patients provided written informed consent before study entry. Blocked stratified randomization was performed centrally at the Hellenic Cooperative Oncology Group Data Office in Athens. Patients were stratified by center, clinical stage (III vs. IV), and primary site (larynx plus hypopharynx vs. oral cavity plus oropharynx).

The initial examination included history, clinical examination, complete endoscopy, complete blood count, complete biochemistry panel, electrocardiography, chest X-ray, bone scan, and liver echography. All patients were initially evaluated by an ear, nose, and throat surgeon, a medical oncologist, and a radiotherapist, and their disease was staged according to the 1997 American Joint Committee on Cancer staging classification. During follow-up, in the case of disease progression, appropriate treatment was offered to all patients.

Radiotherapy

Radiotherapy was delivered using a linear accelerator or ^{60}Co unit with a source-to-surface or source-to-isocenter distance of $\geq$80 cm. Simulation films and port films were required for each treatment field. Lateral opposing fields were used to treat the primary tumor and the regional lymph nodes in the upper neck, with a minimal 2–3-cm margin around the tumor and positive lymph nodes. An anterior supraclavicular field was used to treat the lower neck and supraclavicular region. A shrinking field technique was used. A total dose of 70 Gy was given using standard fractionation at 1.8–2-Gy/fraction/d, 5 d/wk. In lateral-opposing fields, the dose was specified at the midplane, and in the anterior field, the dose was calculated at a 3-cm depth. The clinically uninvolved areas received 50 Gy, and enlarged lymph nodes were irradiated with an additional 20-Gy boost. The primary treatment fields were reduced off the spinal cord at 45 Gy.

Response evaluation and follow-up

Patients were evaluated for response 10–12 weeks after RT completion. The assessment was based on the findings from clinical examinations, laryngoscopy, ultrasonography, and contrast-enhanced CT. A complete response (CR) was defined as the complete disappearance of all clinically evident disease. A partial response was defined as a decrease of

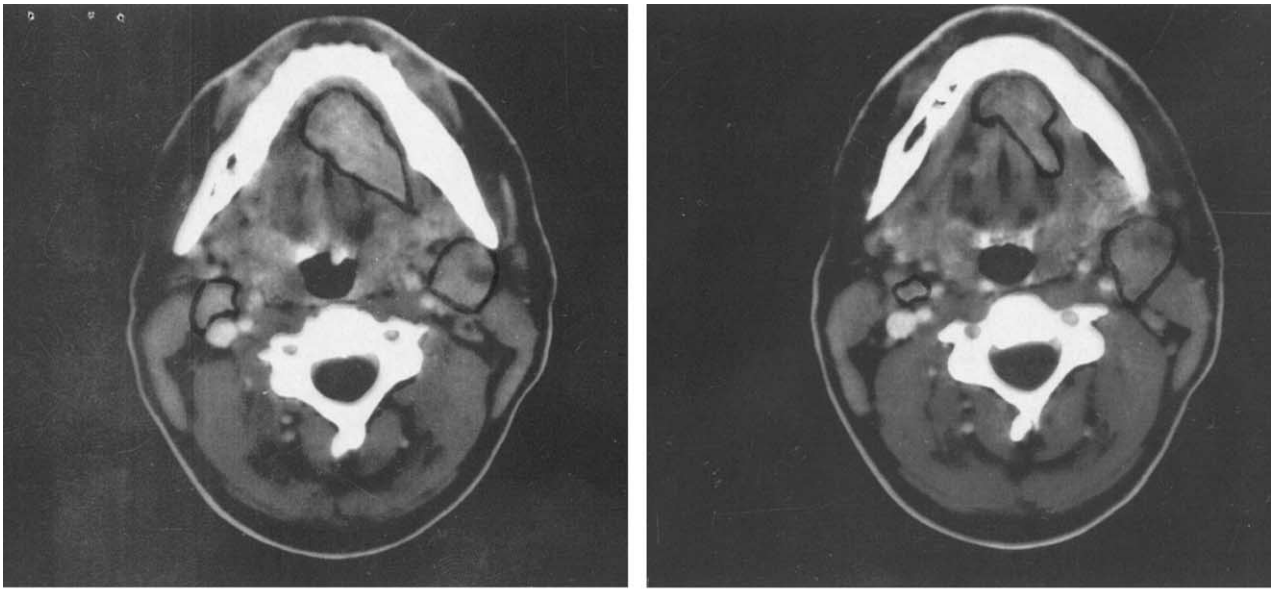

Fig. 1. (a,b) Computed tomography scans of 34-year-old male patient with carcinoma of floor of mouth, with nodal metastases at both sides of neck (Stage IV). Tumor volumes for this patient were PGTV 23.6, NGTV 19.6, and TGTV 43.2 cm^3. The patient belonged to Group 3 (RT plus carboplatin) and had a partial response to treatment. He died of locoregional disease progression 13.6 months after randomization.

>50% in the sum of the products of the largest perpendicular diameters of the measurable lesions. Stable disease was defined as an objective response without satisfying the criteria of partial response or an increase of <25% in the absence of new lesions. Progressive disease was defined as a >25% increase in the above measurements or the appearance of a new lesion. The Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer acute radiation morbidity scoring criteria were used to assess toxicity.

CT technique and evaluation

All imaging studies were performed with i.v. injection of contrast medium and during quiet breathing. A slice thickness of 5 mm was used in most cases.

The whole procedure of the CT review, tumor delineation, digitization of images, and tumor volumetry was coordinated by an experienced head-and-neck radiation oncologist (T.M.E.) who was aware of the clinical findings of the patients (clinical examination, staging) but unaware of the patients' outcome. The TVs were reviewed and outlined by two independent head-and-neck radiologists (K.F.A., H.A.) who were unaware of the patients' outcome. In the case of a >10% difference (arbitrarily defined) in any of the calculated TVs (primary gross TV [PGTV], nodal GTV [NGTV], total GTV [TGTV]), the CT scans were reviewed by the three observers and, if the difference remained, the average of the two values was taken (9 [9%] of 101 cases). In the case of a <10% difference in the calculated TVs, the final decision was left to the discretion of the radiation oncologist who evaluated the CT findings in combination with the clinical data on tumor extension (Fig. 1).

The criteria for tumor involvement were defined by consensus reached by the three above-mentioned authors and were abnormal contrast enhancement, soft tissue thickening, infiltration of fatty tissue, presence of a bulky mass, or a combination of these. Neck node involvement was diagnosed on the basis of the criteria recommended by Mancuso *et al.* (14) and Som (15): (*1*) a discrete mass >1 cm in diameter in the lymph node-bearing regions of the neck and not enhancing to the extent expected for vessels; (*2*) the presence of suspected necrosis of the nodal mass; or (*3*) grouping of three or more nodes, each 8–15 mm in diameter and contiguous. Nodal tumor was considered to invade the capsule when the nodal margin appeared irregular and/or in the case of thickening of the surrounding tissues. We did not differentiate tumor from peritumoral edema, because peritumoral edema may contain variable amounts of tumor cells. In this way, a component of the TV will represent edema, which will have an impact on the calculated TV. We have adopted the attitude of Nathu *et al.* (16) that this is the most consistent method to deal with this parameter, and we included peritumoral edema in the calculated TVs.

In 7 patients, it was not possible to distinguish between the primary tumor and metastatic lymph node metastases because of advanced and confluent disease on the CT scans. In these cases, only the TGTV was measured.

TV measurement

The tumor outlines were traced and digitized and were analyzed with a specifically designed computer software program. The digitized contours were extrapolated with a parabolic function to the contours of the next picture, taking into account the distance between them. Thus, knowing the

surface of the tumor, the volume could be estimated in cubic centimeters.

Statistical analysis

Overall survival (OS) was estimated from the initiation of treatment to the date of last follow-up or the patient's death. Time to progression was deemed as the time between the initiation of treatment and progression documented clinically and/or radiologically. Fisher's exact test (17) was used to compare the patient characteristics, response, and toxicity. The Kaplan-Meier method (18) was used to calculate the time to progression, median follow-up, and survival curves, and the log–rank test was used to compare the time to event distributions. Prognostic factor analyses were performed with logistic regression analysis and the Cox proportional hazards model (19). A backward selection procedure identified the subclass of significant variables among the following: treatment group (RT alone vs. RT plus cisplatin vs. RT plus carboplatin), age (>56 years vs. ≤56 years), gender (male vs. female), hemoglobin concentration (<12 g/dL vs. ≥12 g/dL), T stage (T1-T3 vs. T4), N stage (N0-N1 vs. N2), clinical stage (III vs. IV), primary site (oral cavity plus oropharynx vs. larynx plus hypopharynx), performance status (0 vs. 1-2), PGTV, NGTV, and TGTV as continuous and as binary variables (<22.8 cm^3 vs. ≥22.8 cm^3), and response (CR vs. all others). The statistically significant factors were kept in the model if the maximal likelihood ratio criterion had a p value <0.10. Bonferroni adjusted p values were used for multiple comparisons whenever appropriate. The prognostic threshold value for TGTV regarding the response to treatment was identified through logistic regression analysis and area under the receiver operative characteristic curve analysis. The radiologists' agreement on volume measurements was evaluated with the intraclass correlation coefficient of absolute agreement (20).

RESULTS

After the exclusion of 23 patients with CT scans of poor quality for volumetry, a total of 101 patients remained for the present analysis. The characteristics of those 101 patients are given in Table 1. Excluded patients were equally distributed among the three groups.

Response and survival

Forty-one patients (41%) responded completely to treatment. The distribution of CRs in the three treatment groups was 32%, 47%, and 39% for Groups 1, 2, and 3, respectively (p = 0.477). After a median follow-up of 60 months, 64 patients developed progressive disease: 55 locoregional, 4 distant, and 1 both; for 4 patients, the site was unknown. In 51 of the 55 patients with locoregional relapse observed within the first 3 years after treatment initiation, the median TGTV was 27 cm^3 (range, 1.3–153.3 cm^3), and for those without relapse, the median TGTV was 15.9 cm^3 (range, 1.3–72.6 cm^3; p = 0.017). The 3-year locoregional disease progression rate was 39.7% (Fig. 2).

Table 1. Selected patient and tumor characteristics

Characteristic	Group 1 (RT)	Group 2 (RT + DDP)	Group 3 (RT + Cb)
Patient (*n*)	34	34	33
Age (y)			
Median	57	56	54
Range	40–78	34–77	31–71
Gender (*n*)			
Men	30 (88)	31 (91)	25 (76)
Women	4 (12)	3 (9)	8 (24)
Performance status			
0	20 (59)	17 (50)	22 (67)
1	12 (35)	12 (35)	10 (30)
2	2 (6)	5 (15)	1 (3)
Primary site			
Larynx	16 (47)	14 (41)	13 (39)
Oral cavity	1 (3)	3 (9)	7 (21)
Oropharynx	12 (35)	13 (38)	10 (30)
Hypopharynx	5 (15)	4 (12)	3 (9)
T stage			
T1	0	1 (3)	0
T2	2 (6)	0	1 (3)
T3	14 (41)	6 (18)	12 (36)
T4	18 (53)	27 (79)	20 (61)
N stage			
N0	14 (41)	17 (50)	16 (48)
N1	6 (18)	3 (9)	2 (6)
N2a	1 (3)	7 (21)	10 (30)
N2b	7 (21)	4 (12)	4 (12)
N2c	6 (18)	3 (9)	1 (3)
Stage			
III	10 (29)	4 (12)	8 (24)
IV	24 (71)	30 (88)	25 (76)
NGTV (cm^3)	n = 31	n = 33	n = 30
Median	7.9	3.5	4.0
Range	0–108.5	0–78.6	0–48.5
PGTV (cm^3)	n = 31	n = 33	n = 30
Median	11.8	16.0	13.8
Range	1.3–102.6	1.2–87.0	1.8–54.0
TGTV (cm^3)	n = 34	n = 34	n = 33
Median	26.5	22.3	30.8
Range	1.3–122.8	3.5–153.3	1.8–62.6

Abbreviations: RT = radiotherapy; DDP = cisplatin; Cb = carboplatin; NGTV = nodal gross tumor volume; PGTV = primary GTV; TGTV = total GTV.

Values were rounded off; no statistically significant differences were found between groups.

The median OS time for the whole group of patients was 21.6 months (95% confidence interval [CI], 13.0–30.2), the 3-year survival rate was 40%, and the median time to progression was 11.4 months (95% CI, 3.0–19.7). The median OS for Groups 1, 2, and 3 was 12.3, 86.1, and 24.5 months, respectively (1 vs. 2, p = 0.0039; 1 vs. 3, p = 0.0058; 2 vs. 3, p = 0.9). The addition of cisplatin to RT (Group 2) or carboplatin (Group 3) significantly improved the survival rate (relative to RT alone). Survival curves for the whole group of patients and for the three treatment arms are shown in Fig. 3.

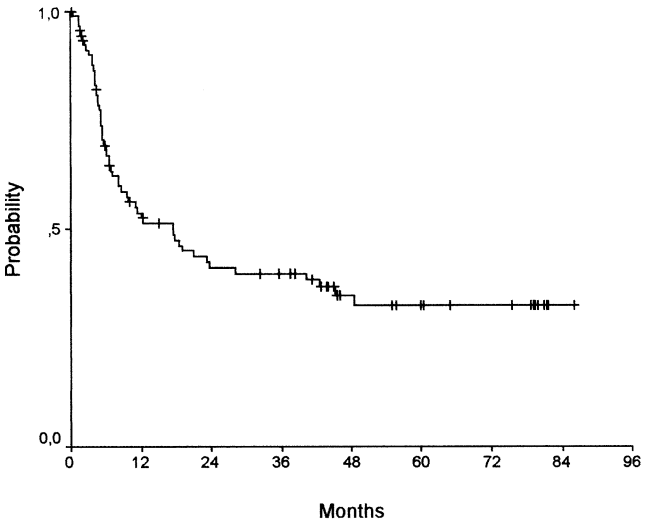

Fig. 2. Time to locoregional disease progression curve.

Volumes and correlations

For the whole group of patients, the median PGTV was 14.7 cm^3, median NGTV was 3.7 cm^3, and median TGTV was 25.8 cm^3.

A statistically significant correlation was observed between N volume and N stage (Spearman's rank correlation coefficient 0.734, $p < 0.001$) and between T volume and T stage (Spearman's rank correlation coefficient 0.352, $p < 0.001$). The mean volume differed significantly ($p = 0.036$) between T4 and T3 tumors (24.3 cm^3 [median, 17 cm^3; range, 1.17–102.6 cm^3] and 13.5 cm^3 [median, 9 cm^3; range, 1.3–54 cm^3], respectively).

The median and range of TVs according to the primary site are shown in Table 2. Multiple comparisons after Bonferroni corrections revealed that the median TGTV of hypopharyngeal tumors was significantly larger than the median of those from the oral cavity ($p = 0.034$) and larynx ($p = 0.004$). Statistically significant differences in NGTV were also observed between hypopharyngeal and oral cavity tumors ($p = 0.04$) and between hypopharyngeal and laryngeal tumors ($p = 0.013$). No statistically significant differences were observed for PGTV between the primary sites.

The intraclass correlation coefficient for absolute agreement for the two radiologists was 0.94 (95% CI, 0.89–0.96) for NGTV, 0.98 (95% CI, 0.97–0.99) for PGTV, and 0.98 (95% CI, 0.96–0.99) for TGTV, signifying a high level of agreement.

Prognostic factors

A prognostic threshold was detected in the TGTV regarding the response to treatment (22.8 cm^3). Patients with a TGTV of <22.8 cm^3 were more likely to achieve a CR and had a median survival of 45.3 months; those with a TGTV of >22.8 cm^3 had a median survival of 12.3 months (log–rank test, $p = 0.0102$; (Fig. 4). The number of patients in Groups 1, 2, and 3, with a TGTV >22.8 and <22.8 cm^3 was 20 and 14, 16 and 18, and 20 and 13, respectively.

The median values of the TVs according to survival status (alive vs. dead) at the end of follow-up were as follows: PGTV, 11.3 vs. 15.9 cm^3 ($p = 0.060$); NGTV 2 vs. 8.1 cm^3 ($p = 0.044$); and TGTV 15.3 vs. 28 cm^3 ($p = 0.006$, Mann-Whitney *U* test).

When exploring each factor separately, a statistically significant association with survival was found for treatment group (RT alone vs. RT plus cisplatin, hazard ratio [HR] 0.36, $p = 0.002$; RT alone vs. RT plus carboplatin, HR 0.53, $p = 0.029$), TGTV (HR 1.02, $p < 0.001$), CR (HR 0.16, $p < 0.001$), and NGTV (HR 1.02, $p = 0.002$), PGTV (HR 1.01, $p = 0.015$), TGTV as a binary variable (HR 1.9, $p = 0.012$), and performance status (HR 0.59, $p = 0.033$).

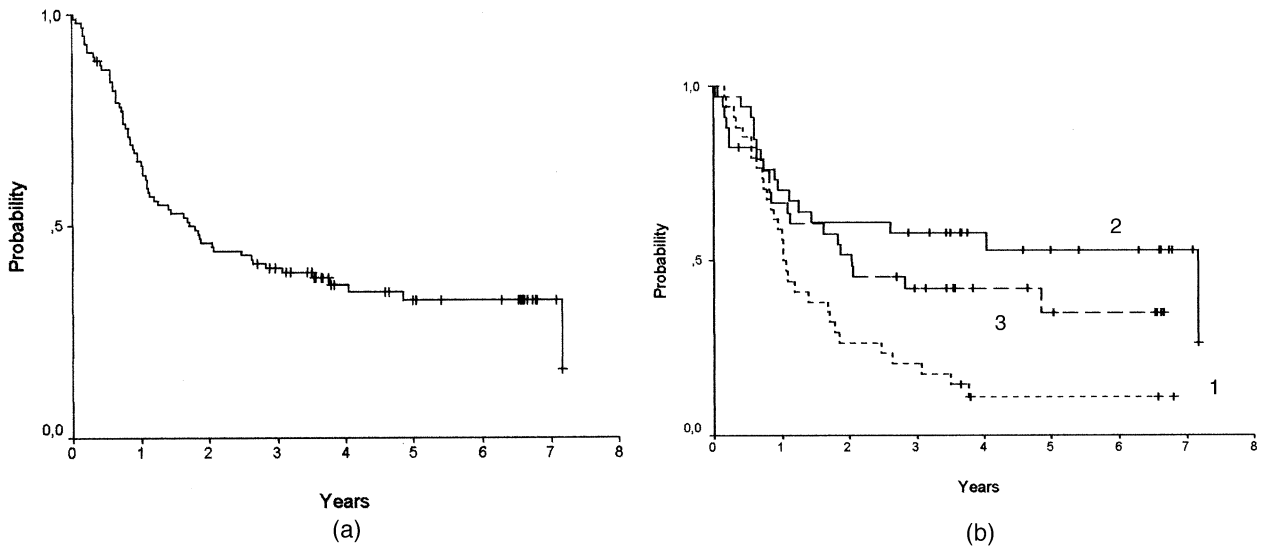

Fig. 3. (a) Survival curve for whole group of patients. (b) Survival curves for three treatment arms. Group 1, RT alone; Group 2, RT plus cisplatinum; and Group 3, RT plus carboplatin. The difference between Groups 1 and 2 ($p = 0.0039$) and between Groups 1 and 3 ($p = 0.0058$) was statistically significant, but between Groups 2 and 3 was not ($p = 0.9$).

Table 2. Calculated volumes for four subsites included in present study

	PGTV		NGTV		TGTV	
Subsite	Median	Range	Median	Range	Median	Range
Oral cavity	17	3–54	3.5	0–25	20.8	3–54
Oropharynx	13	1.2–102.6	11.3	0–58.3	27	6.2–145.3
Hypopharynx	22.6	5.8–74.7	13.4	0–108.6	49.3	5.8–153.3
Larynx	14.8	1.3–49.7	0	0–53.7	20	1.3–73.1

Abbreviations: PGTV = primary gross tumor volume; NGTV = nodal GTV (nodal metastases, including N0 cases); TGTV = total tumor volume (sum of primary disease and nodal metastases).

A backward selection procedure using the Cox model examined the influence and interrelationship for the following prognostic variables: T and N stage, PGTV, NGTV, TGTV (<22.8 vs. ≥ 22.8 cm^3), age, gender, primary site (oral cavity plus oropharynx vs. larynx plus hypopharynx), and treatment group. The final model is shown in Table 3. Treatment group, TGTV, gender, and primary site remained in the model.

Toxicity

The predominant acute toxicity was the mucosa reaction. Radiation Therapy Oncology Group Grade 3 mucosa reaction was observed in 27%, 31%, and 18% and Grade 4 in 0%, 0%, and 6% of the patients in Groups 1, 2, and 3, respectively. With the exception of nausea/vomiting, which was seen more frequently in patients in Groups 2 and 3 ($p = 0.021$), no statistically significant difference was observed among the three groups for nonhematologic toxicity. As expected, thrombocytopenia ($p = 0.003$) was more pronounced in the groups treated with combined chemoradiotherapy than in the group treated with RT alone. One patient died of sepsis.

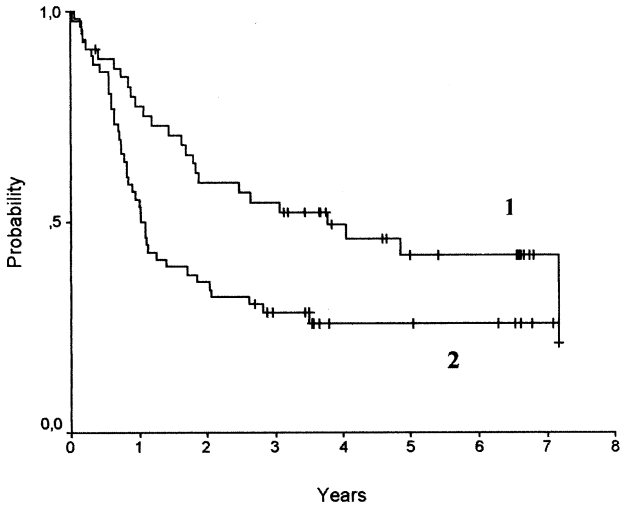

Fig. 4. Overall survival curves for patients with total gross tumor volume <22.8 cm^3 (1) and >22.8 cm^3 (2), ($p = 0.0102$).

DISCUSSION

The results of this study indicate that TV correlates with treatment outcomes for patients with locally advanced head-and-neck carcinomas treated by RT or RT plus chemotherapy. Patients with a TGTV greater than the estimated cutoff value of 22.8 cm^3 had a statistically significant worse OS rate. Furthermore, the multivariate analysis demonstrated that TGTV is an important prognostic factor, together with the addition of platinum analogs to standard RT, gender, and primary site.

Tumor volume as a predictive factor for RT is not new. A reasonable explanation for this association is the higher number of clonogenic tumor cells to be sterilized in larger tumors. Johnson *et al.* (9) radiobiologically analyzed the data from a clinical trial of 51 patients with advanced head-and-neck carcinomas treated by accelerated superfractionated RT. The authors assumed that TV and clonogen number (m) are related by the relationship $m = (\alpha)\ (TV^b)$, where α is a proportionality constant, and they estimated the volume exponent b to be 0.85 (95% CI 0.40–1.29), that is, very close to unity (21). This result proposes that the TV and clonogen number have almost a linear relationship. It becomes evident that larger tumors contain more clonogens and as a result need an increased radiation dose to be

Table 3. Independent prognostic factors for overall survival (using significance level 0.10)

Factor	HR	95% CI	*p*
Treatment group			
RT	1	—	—
RT + DDP	0.35	0.18–0.67	0.002
RT + Cb	0.42	0.22–0.78	0.006
Gender			
Male	1	—	—
Female	0.38	0.14–1.08	0.069
Primary site			
Oral cavity and oropharynx	1		
Hypopharynx and larynx	0.52	0.30–0.89	0.069
TGTV (cm^3)			
<22.835	1		
≥ 22.835	1.90	1.12–3.23	0.018

Abbreviations: HR = hazard ratio; CI = confidence interval; RT = radiotherapy; DPP = cisplatin; Cb = carboplatin; TGTV = total gross tumor volume.

controlled. In their trial (9), the median TGTV for (locally) controlled cases was 35 cm^3, and a rapid increase in the cumulative failure rate was observed above this threshold. In the final Cox model, TGTV, primary site, and gender were important independent variables, and T and N stage was not, unless the TGTV was removed from the model. One of the main conclusions of their study was that the TV should be incorporated into staging systems (9, 21).

Our results are consistent with prior reports of locally advanced head-and-neck carcinomas treated by radiochemotherapy. Grabenbauer *et al.* (11) have reported on the adverse impact of TV on patient outcome. They derived a prognostic cutoff value of TGTV of 110 cm^3 in a group of patients with advanced head-and-neck tumors treated by RT alone or concomitant radiochemotherapy. In their study, patients with laryngeal carcinomas were not included. The overall 3-year survival rate was 34%.

Very close to those of the previous study were the results reported by Rudat *et al.* (10) who treated a similar cohort of patients with radiochemotherapy (3-year OS rate of 35%). The pretreatment TGTV was significantly associated with survival ($p = 0.0008$), and the hemoglobin concentration was significantly associated with survival and locoregional control. A prognostic cutoff value of 112.3 cm^3 was defined for TGTV; only 13% of their patients had laryngeal carcinomas.

Volumetric analysis was also performed by Doweck *et al.* (22) in a similar group of patients treated by radiochemotherapy. These authors defined a prognostic threshold only for PGTV, equal to 19.6 cm^3. They did not demonstrate a statistically significant association between nodal volume and survival, although a trend toward a negative association was noted, a finding similar to ours. The authors explained this result by considering the primary tumor site, because hypopharyngeal and oropharyngeal cancers were associated with the largest nodal volume, compensated for by smallest nodal volumes of the oral cavity and glottic larynx. Moreover, in our material, 47 patients had Stage N0 and in 7 it was not possible to make a distinction between the primary tumor and metastatic lymph nodes. In these patients, the disease was not designated as either primary or nodal tumor (missing values) and was taken into account for the TGTV only. This probably introduced a favorable bias for the PGTV and NGTV (because some of the larger primary and/or nodal volumes were excluded from the primary and nodal volume analyses), but it was the only parameter we could think of that was representative of tumor bulk. Other groups have also applied the same method (9).

The impact of TV on the survival of patients with locally advanced head-and-neck carcinomas treated by platinum-based radiochemotherapy was also confirmed in the previously mentioned Greek-German collaborative study (12). The authors retrospectively analyzed 107 patients whose pretreatment CT scans were studied by the same volumetric technique as ours, and they concluded that the addition of chemotherapy to RT ($p = 0.017$) and the pretherapeutic TV ($p = 0.014$) were the only factors significantly associated with survival among all the initial patient characteristics assessed for prognostic value. The initial TV was negatively associated with survival, with an increase in relative risk of 6% per 10 cm^3 difference (relative risk 1.006).

In the first two of the above-mentioned studies (10, 12), the cutoff value was large (>100 cm^3) compared with our study (22.8 cm^3). In the third study (22), a similar value was used but only for the PGTV (19.6 cm^3). In these studies, either more intensive RT schedules or cisplatin was used, and one-third of our patients were treated by standard RT alone. This could probably explain the overestimation (i.e., lower cutoff value) of the impact on survival of TGTV in our material. The relatively high percentage of laryngeal tumors included in our study could probably have contributed to the lower estimated threshold (see below).

Head-and-neck primary tumors only centimeters apart can have very different radiosensitivities (e.g., base of tongue vs. oral tongue, tonsillar fossa vs. anterior tonsillar pillar). Also, they comprised a heterogeneous group of tumors, because it has been repeatedly reported that the threshold values of, for example, glottic tumors are much lower than those for other subsites (2, 5–8).

For supraglottic tumors treated by definitive RT, a threshold of 6 cm^3 has been estimated. Tumor control was achieved by Freeman *et al.* (1) in 83% of cases with volumes <6 cm^3 vs. 46% of those with volumes ≥ 6 cm^3. A recent update of that study confirmed these results (6). Similar findings have been reported by another group (7). A 6.5-cm^3 threshold has also been reported for T1-T2 pyriform sinus carcinomas (3).

For T3 glottic tumors treated by RT, the TV appears to be significant. Pameijer *et al.* (2) reported that for tumors measuring <3.5 cm^3, local control was achieved in 22 patients (85%), but for tumors ≥ 3.5 cm^3, local control was achieved in only 4 patients (25%; $p = 0.0002$). The higher threshold (6 cm^3) reported for supraglottic carcinomas could be attributed to biologic (different embryologic precursors) or anatomic factors. A glottic tumor is much more intimately related to laryngeal cartilage, causing occult cartilage invasion and resulting in decreased radiocurability (2). Lee *et al.* (8) studied 29 patients with T3 glottic carcinomas. They found that both the TV and involvement of specific sites within the larynx proved to be prognostic variables with an impact on local control. The results of volumetric studies in which a prognostic threshold was detected are shown in Table 4.

A marginal predictive value of the TV regarding locoregional control has been reported for tonsillar cancer treated by definitive RT (23). A possible explanation could be that squamous cell carcinoma of the oropharynx may be more radiosensitive than tumors in other sites, causing a less pronounced relationship between the TV and local control (16).

In general, Stage T3 head-and-neck tumors show a significant variability in TVs. Pameijer *et al.* (5), analyzing the clinical material of 42 patients with T3 head-and-neck tumors, reported that the TVs of Stage T3 larynx and hypopharynx carcinomas showed a highly significant variation ($p = 0.0001$). This could be because the TNM definitions of

Table 4. Results of volumetric studies reporting a prognostic threshold

Author	Primary	Patients (*n*)	Stage	Treatment	Threshold (cm^3)	Local control (%)		3-y survival (%)	
						Below threshold	Above threshold	Below threshold	Above threshold
Freeman *et al.* (1) and Mancuso *et al.* (6)	Supraglottic	63	T2-T3	RT	6	69 (5 y)		NR	
						89	52		
Pameijer *et al.* (2)	T3 glottic	42	T3	RT	3.5	85	25	NR	
Pameijer *et al.* (3)	Pyriform	23	T1-T2	RT	6.5	90	25 (2 y)	NR	
Johnson *et al.* (9)	All	51	III–IV	RT (accel/hyperfr)	35	92	34 (3 y)	NR	
Grabenbauer *et al.* (11)	Oral cavity, oropharynx, hypopharynx	87	III–IV	RT, RT + CHT	110	39 (3 y)		34 (all patients) 53 (RT) 69 (RT + CHT)	5 (RT) 22 RT + CHT)
Rudat *et al.* (10)	All except nasopharynx	68	III–IV	RT + CHT (Cb)	112	32 (3 y)		35 (all patients)	
								49	19
Doweck *et al.* (22)	All	64	III–IV	RT + CHT	19.6*	81 (5 y)		41.5	14
Kurek *et al.* (12)	All	107	III–IV	RT + CHT	NR				
Present study	All except nasopharynx	101	III–IV	RT, RT + DDP RT + Cb	22.8	39.7 (3 y)		54.7	28.5

Abbreviations: NR = not reported; CHT = chemotherapy; other abbreviations as in Table 1.
* Threshold for primary tumor only.

most T3 head-and-neck carcinomas are based on unidimensional extension or vocal cord fixation. In oropharyngeal carcinomas, such a striking difference was not observed within Stage T3, probably because of the dimensional definition of T stage in this subsite.

We derived a cutoff value between the values reported by other groups. This was an overestimation of the significance of the TGTV that could probably be attributed to the inferiority of standard fractionation RT alone (24) and the superiority of concomitant radiochemotherapy (25) and to the heterogeneity of head-and-neck carcinomas regarding their biologic behavior and natural history.

The review of the relevant studies and our results suggest that cutoff values taken from the literature should be interpreted and used for clinical decision making with caution, because they depend largely on the analyzed clinical material (patient characteristics, disease stage) on the applied treatment modality (Table 4), and on the method used for TV calculation (i.e., radiologic criteria of tumor extent, experience of radiologists, method of tumor delineation, computer software).

The interobserver variability in the TV calculation was low in the present study. This was probably a result of the initial consensus and the cooperation of the colleagues (in the case of a >10% difference) involved in tumor delineation and volumetry. Clinical practice has shown that discrepancies between independent observers are not infrequent. This was well documented for lung cancer in a study by Erasmus *et al.* (26).

Accurate target definition is highly desirable to achieve the benefits of improved treatment delivery by three-dimensional conformal and intensity-modulated RT. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) has shown promise for improving lung cancer volume delineation or detecting occult disease sites. In a study by Mah *et al.* (27), the information obtained by FDG-PET examination led to a reduction in the PTV in 24–70% of cases and to an increase in 30–76% of cases, depending on the planning physician. It also changed the treatment strategy (from radical to palliative) in 7 (23%) of 30 patients with non–small-cell lung carcinoma. For head-and-neck carcinomas, FDG-PET may be helpful in differentiating residual/recurrent disease from treatment-induced normal tissue changes when the findings of clinical examination and CT are equivocal. At present, TV delineation is based on clinical examination and CT images (28).

Although different studies have demonstrated an inverse correlation between TV and treatment outcome, failures in small tumors and cures in bulky tumors have been observed. This suggests that factors other than TV contribute to therapy response, including cellular repopulation, intrinsic radioresistance, and reoxygenation (9).

CONCLUSION

On the basis of the experience of the present study, we believe that advanced head-and-neck carcinomas should not be treated by standard (once-daily) RT alone. The addition of

platinum compounds to RT and/or the use of modified fractionation schedules must be studied in clinical trials in which patients should be stratified according to primary site and tumor size. As defined in ours and other studies, patients with tumors with a TGTV >20 cm^3 are the probable candidates for more intensive protocols.

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