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CLINICAL IMPLICATIONS OF THE TUMOR VOLUME REDUCTION RATE IN HEAD-AND-NECK CANCER DURING DEFINITIVE INTENSITY-MODULATED RADIOTHERAPY FOR ORGAN PRESERVATION

Shih-Neng Yang, M.D.,*¶ Chih-Ying Liao, M.D.,* Shang-Wen Chen, M.D.,*‡§ Ji-An Liang, M.D.,*‡ Ming-Hsui Tsai, M.D.,†‡ Chun-Hung Hua, M.D.,† and Fang-Jen Lin, M.D., Ph.D.*

Departments of *Radiation Oncology, †Otorhinolarygology, and ¶Biomedical Imaging and Radiological Science, and ‡School of Medicine, China Medical University, Taichung, and §School of Medicine, Taipei Medical University, Taipei, Taiwan

Purpose: To investigate the prognostic value of the volume reduction rate (VRR) in patients with head-and-neck cancer treated with intensity-modulated radiotherapy (IMRT).

Methods and Materials: Seventy-six patients with oropharyngeal cancer (OPC) and another 76 with hypopharyngeal cancer (HPC) were enrolled in volumetric analysis. All patients received allocated radiotherapy courses. Adaptive computed tomography was done 4 to 5 weeks after the start of IMRT. Primary tumor volume measurement was derived using separate images for the pretreatment gross tumor volume (pGTV) and the interval gross tumor volume.

Results: In the OPC group, the pGTV ranged from 6.6 to 242.6 mL (mean, 49.9 mL), whereas the value of the VRR ranged from 0.014 to 0.74 (mean, 0.43). In HPC patients, the pGTV ranged from 4.1 to 152.4 mL (mean, 35.6 mL), whereas the VRR ranged from −1.15 to 0.79 (mean, 0.33). Multivariate analysis of the primary tumor relapse-free survival for OPC revealed three prognostic factors: T4 tumor ($p = 0.0001$, hazard ratio 7.38), pGTV ≥20 mL ($p = 0.01$, hazard ratio 10.61), and VRR <0.5 ($p = 0.001$, hazard ratio 6.49). Multivariate analysis of the primary tumor relapse-free survival for HPC showed two prognostic factors: pGTV ≥30 mL ($p = 0.001$, hazard ratio 2.87) and VRR <0.5 ($p = 0.03$, hazard ratio 2.25).

Conclusion: The VRR is an outcome predictor for local control in OPC and HPC patients treated with IMRT. Those with large tumor volumes or a VRR <0.5 should be considered for a salvage operation or a dose-escalation scheme.

Head-and-neck cancer, Radiotherapy, Tumor volume, Volume reduction rate, Prognostic factor.

INTRODUCTION

The adverse effects of increasing tumor burden on local control using radiotherapy (RT) are important. Thus, outcome variations among studies may be partly influenced by unaccounted differences in the tumor volume. Some concerns have been raised about the weakness of the TNM classification for head-and-neck cancer (1–3). Current methods to define tumor volume are usually not precisely quantitative (2, 3). Pretreatment computed tomography (CT) with volumetric analysis has been shown to be an effective predictor of local control in many head-and-neck tumors treated with RT (2–10). However, most reports investigating volumetric analysis have not evaluated the clinical implications of the volume reduction rate (VRR) during RT.

Several methods for assessing tumor response during irradiation have been applied; the most easily used is the value of the VRR. In clinical practice, this value can be obtained when adaptive radiation planning has been arranged. From the radiobiologic point of view, VRR during irradiation might relate to many factors, such as intrinsic radiosensitivity, tumor kinetics, capacity for tumor repopulation, and proportion of normal tissue in the tumor. When assessing local control by RT, using a single biologic model to represent the final treatment outcome might be problematic. Despite recent advances in the response to RT in head-and-neck cancer, implementation of individualized therapy is limited by a lack of comprehensive knowledge about individual response to a given RT until treatment has been completed. If the prognostic value of the VRR for a certain tumor can be understood, radiation oncologists might be able to assess the feasibility of salvage surgery, or conduct a dose escalation scheme earlier for those who have great probability of local failure.

Reprint requests to: Shang-Wen Chen, M.D., Department of Radiation Therapy and Oncology, China Medical University Hospital, No. 2 Yuh-Der Road, Taichung, Taiwan 404. Tel: (+886) 4-22052121-2411; Fax: (+886) 4-22052121-2499; E-mail: vincent1680616@yahoo.com.tw

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Table 1. Patient characteristics in oropharyngeal cancer group (total, 76 patients)

Characteristic	Value
Age	38–77 (median, 49)
Sex	M 75, F 1
Pathology	
W-D/M-D squamous cell carcinoma	34
P-D squamous cell carcinoma/other	42
Stage	II 7, III 21, IVA 37, IVB 11
Performance status	
ECOG 0–1/2	66/10
Tracheostomy	
Negative/positive	72/4
Dysphagia score	
Grade 0–1/2–3	62/14
Radiation dose (Gy)	69.7–79.4 (median, 70.2)
Treatment duration (days)	48–114 (median, 57)
Concurrent chemotherapy	
Yes	63
No	13
Follow-up (mo)	6–75 (median, 37)

Abbreviation: W-D = well-differentiated; M-D = moderately-differentiated; P-D = poorly differentiated; ECOG = Eastern Cooperative Oncology Group.

Table 2. Patient characteristics in hypopharyngeal cancer (total, 76 patients)

Characteristic	Value
Age	36–79 (median, 58)
Sex	M 74, F 2
Pathology	
W-D/M-D squamous cell carcinoma	51
P-D squamous cell carcinoma	25
Stage	II 15, III 19, IVA 35, IVB 7
Performance status	
ECOG 0–1/2	66/10
Tracheostomy	
Negative/positive	58/18
Dysphagia score	
Grade 0–1/2–3	56/20
Radiation dose (Gy)	68.4–73.8 (median, 70.2)
Treatment duration (days)	42–87 (median, 58)
Concurrent chemotherapy	
Yes	56
No	20
Follow-up (mo)	8–65 (median, 35)

Abbreviation: W-D = well-differentiated; M-D = moderately-differentiated; P-D = poorly differentiated; ECOG = Eastern Cooperative Oncology Group.

Tumor volume reduction during RT treatment is of great value for lung tumors (11). In neoadjuvant concurrent chemoradiotherapy (CCRT) for advanced rectal cancer, Kim *et al.* (12) reported a significant difference in tumor volume and VRR between patients with or without downstaging. Another study showed that a marked reduction in tumor volume did not correlate with histopathologic downstaging or a good tumor regression grade (13). Despite the contradictory results in rectal cancer, the value of VRR is more important in definitive RT or CCRT for head-and-neck cancer because surgical resection is not always planned after treatment. Also, the correlation between the objective tumor volumetric analysis before/during RT/CCRT and the final outcome in head-and-neck cancer has rarely been reported. To optimize the treatment results, it has become imperative not only to analyze the pretreatment tumor volume but also to investigate the prognostic value of VRR during RT. To test the prognostic value of VRR in head-and-neck cancer during RT, we conducted this volumetric analysis in patients with T2 to T4 oropharyngeal cancer (OPC) and hypopharyngeal cancer (HPC) after an organ preservation scheme. The volumetric data during RT were derived from the adaptive CT image, which was done 4 to 5 weeks after the start of irradiation. The results of this study can clarify the role of VRR when determining more appropriate patient selection criteria for salvage treatment or a dose escalation scheme.

METHODS AND MATERIALS

Patients

From January 2003 through June 2008, 76 patients with OPC and another 76 with HPC with histologic proof of squamous cell carcinoma, who had been treated with an organ preservation scheme at China Medical University Hospital, were included in this retrospective analysis after institutional review board approval.

The inclusion criteria were as follows:

1. Patients had completed their allocated RT or CCRT treatment and had been followed up for a minimum of 6 months or until death.
2. Tumors had been staged after a comprehensive physical examination, laryngoscopy, tumor biopsy, chest radiography, CT scan of the neck, abdominal ultrasonography, and bone scan.
3. Primary tumors were categorized to be American Joint Committee on Cancer Stage T2 to T4, and there was a clear demarcation between primary and nodal tumors.
4. Patients received a planned adaptive CT image 4 to 5 weeks after the start of radiotherapy for evaluation of body contouring change.

The characteristics of the OPC and HPC patients are given in Tables 1 and 2.

Treatment

Radiotherapy was performed using a sequential intensity-modulated radiotherapy (IMRT) technique. All patients received 1.8 Gy daily up to a total dose of between 68.4 and 73.8 Gy (median, 70.2 Gy). The clinical target volume (CTV) modeled regions were considered to be two regions with different risks: CTV1 encompassed the primary tumor, metastatic lymph nodes, and the regions adjacent to the gross tumor, and CTV2 consisted of the ipsilateral or contralateral N0 regions at risk of harboring microscopic tumors. The dose delivered to CTV1/CTV2 during the first course was 50.4 to 54 Gy with a further boost of 16.2 to 21.6 Gy to the CTV1 during the second course. Thus, the median cumulative doses to the CTV1 and CTV2 were 70.2 Gy and 54.0 Gy, respectively. The median RT duration was 57 days for the OPC group and 58 days for the HPC group. Sixty-three OPC patients and 56 HPC patients had concurrent chemotherapy. The regimen consisted of cisplatin (80–100 mg/m^2 on Days 1, 22, 43).

Tumor volume delineation

Each patient underwent a pretreatment contrast-enhanced CT of the neck with 3-mm-thick contiguous sections. Neck lymph nodes were considered pathologic when their smallest axis diameter was >1 cm. The CT images from the picture archiving and communication system were then transferred to a commercial planning system (Eclipse Version 8.1, Varian Medical system Inc, CA, USA). Radiation oncologists then delineated the pretreatment gross tumor volume (pGTV) and the metastatic lymph node volume. The volumes of all tumors were measured by outlining the lesion on each image if it was visible. No attempts were made to differentiate the tumors from any related edema. The tumor volumes were contoured and the volumes calculated using the same planning system. To reduce interobserver variations, at least two different radiation oncologists carried out the contouring of the tumors for each patient. When the calculated values for any volume varied by less than 10%, an average of the readings was used as the measured volume. When the variation exceeded 10%, contouring and measurement were repeated by the third radiation oncologist to correct any bias. This procedure was addressed in our previous report (14). More than 20 % of volume difference was defined as a major variation, whereas more than 10 % but less than 20 % volume difference was a minor variation. The examples of contouring for both tumors are illustrated in Figs. 1 and 2.

Definition of volume reduction rate

Planned adaptive CT imaging was done in the fourth to fifth weeks (median, 29 days; range, 22–36) after the start of radiotherapy. This time point was chosen as a balance between allowing a dose adequate to produce a visible response and allowing for the possibility of adapting the radiation plan on the basis of this new information. By the same method, radiation oncologists then delineated the interval gross tumor volume (iGTV) of the primary tumor.

The VRR was calculated by the following equation:

$$\mathrm{VRR} = [(\mathrm{pGTV}) - (\mathrm{iGTV})/(\mathrm{pGTV})]$$

The definition of gross tumor volume for the second course of RT was based on the initial image, whereas the interval volume change was recorded for the study. The adaptive imaging was selected for the second course of RT planning in 49 patients of the OPC group and 41 patients of the HPC group. They were observed to have substantial changes in body contour.

Follow-up

After completion of treatment, all patients were followed up every 1 to 2 months over the first 2 years, and then every 3 to 4 months thereafter. A physical examination and laryngoscopy were performed during each follow-up examination, and a CT scan of the neck was done every 4 to 6 months over the first 2 years. For patients who were still alive at the time of this study, the follow-up period for all patients ranged from 6 to 75 months (median, 36 months). The definition of local failure was based on the laryngoscopy results, a CT scan of the neck, or both. When the patient had a persistent tumor or locoregional recurrence after initial complete remission, salvage surgery was suggested when this was technically feasible and the patient's condition allowed it.

Statistical analysis

The endpoint of the study was primary tumor relapse-free survival (PRFS) and was calculated using the Kaplan-Meier method. Salvage of any recurrence was not taken into account in evaluating the PRFS. Multivariate analysis was performed using Cox's proportional hazards model. Student's *t* test was used to assess the statistical significance of volumetric parameters between primary relapse and primary relapse-free groups. A p value of less than 0.05 was considered statistically significant. All calculations were performed with SPSS 13.0 for Windows (SPSS Inc, Chicago, IL, USA).

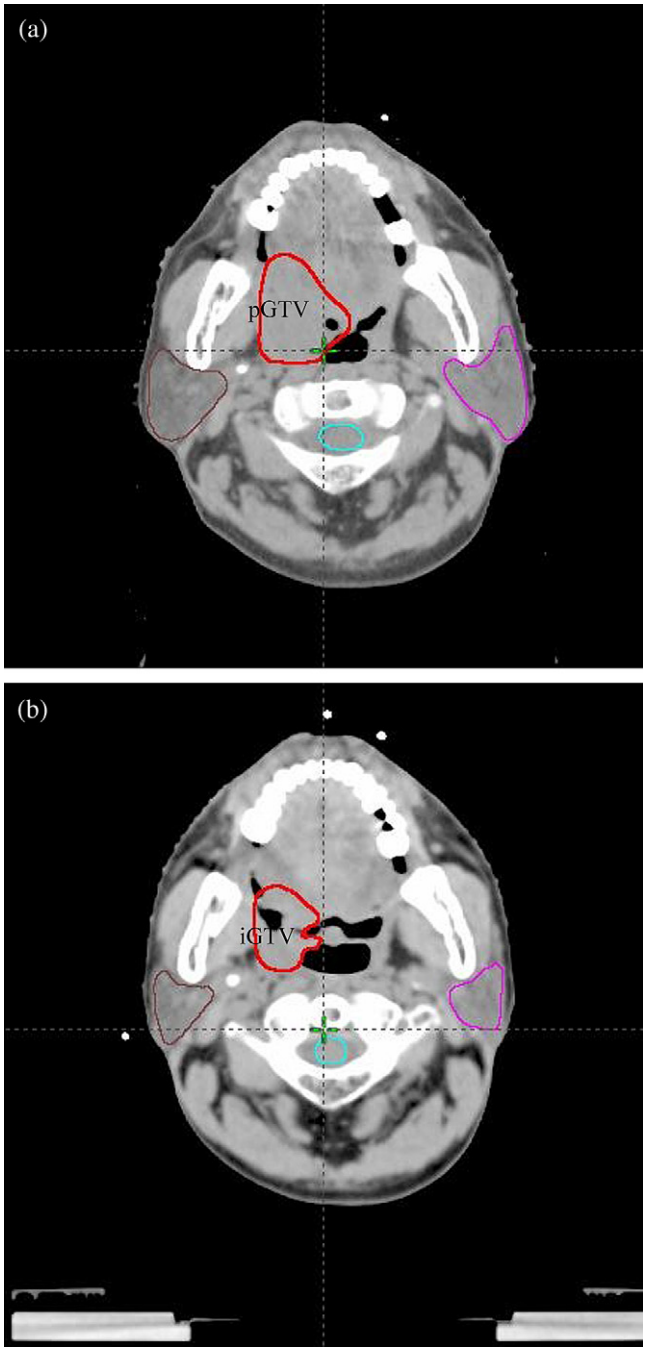

Fig. 1. Example of contouring in an oropharyngeal cancer patient (American Joint Committee on Cancer stage T4aN0M0). (a) Computed tomography image for pretreatment gross tumor volume (pGTV). (b) Similar slice of computed tomography image for interval gross tumor volume (iGTV).

RESULTS

Table 3 summarizes the outcome of patients in the two cancer groups. In brief, 33 patients developed recurrences at the

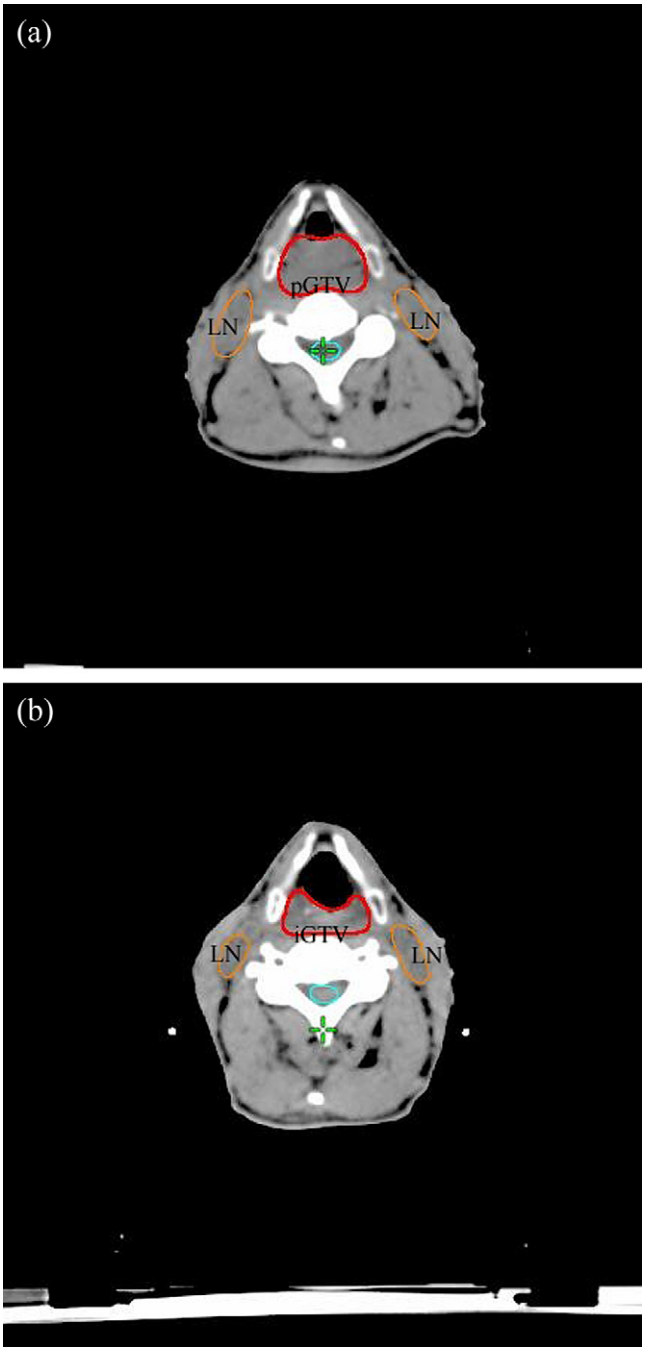

Fig. 2. Example of contouring in a hypopharyngeal cancer patient (American Joint Committee on Cancer stage T3N2M0). (a) Computed tomography image for pretreatment gross tumor volume (pGTV). (b) Similar slice of computed tomography image for interval gross tumor volume (iGTV). After 43.2 Gy of irradiation, substantial muscle wasting was observed in this patient.

primary site in the OPC group, in which the 3-year PRFS rate was 88% for patients with T2 disease, 68% for patients with T3 disease, and 24% for patients with T4 disease ($p = 0.000$). Thirty-eight patients were found to have primary failure in the HPC group, in which the 3-year PRFS rate was 65% for patients with T2 disease, 56% for patients with T3 disease, and 29% for patients with T4 disease ($p = 0.03$).

Table 3. Patient outcomes in two series of cancer

Outcome	OPC group (76)	HPC group (76)
Alive without evidence of recurrence	29	24
Alive with evidence of recurrence	8	8
Primary relapse	5	7
Neck LN relapse	0	1
Primary + neck LN relapse	3	0
Died of cancer		
Locoregional relapse	21	24
Distant metastasis	4	4
Both	4	7
Died of complication without evidence of recurrent cancer	3	2
Died of metachronous or synchronous second cancer without evidence of recurrent disease	7	7

Abbreviations: LN = lymph node; OPC = oropharyngeal cancer; HPC = hypopharyngeal cancer.

In the OPC group, the pGTV ranged from 6.6 to 242.5 mL (mean, 49.9 mL; median, 28.2 mL), whereas the iGTV ranged from 3.2 to 117.5 mL (mean, 26.3 mL; median, 17.8 mL). The value of the VRR ranged from 0.014 to 0.73 (mean, 0.43; median, 0.42). In the HPC group, the pGTV ranged from 4.1 to 152.4 mL (mean, 35.6 mL; median, 19.0 mL), whereas the iGTV ranged from 1.2 to 125.4 mL (mean, 22.7 mL; median, 12.3 mL). The value of the VRR ranged from −1.15 to 0.79 (mean, 0.33; median, 0.40). The ratio of the major and minor variation in the whole series was 6.5 % and 20.3 % for the pGTVs, and 12.5 % and 29.6 % for the iGTVs, respectively.

The distribution of the tumor volumes and VRR with respect to T classification in the two cancer groups is shown in Table 4. The correlation of volumetric parameters between primary failure and primary relapse-free groups is given in Table 5. In the OPC group, tumor volume changes, according to primary relapse, were as follows: the mean pGTV in relapse-free patients was 41.6 mL (range, 6.6–128.9 mL) and, in patients who had primary relapse, 62.2 mL (range, 17.3–242.5 mL) ($p = 0.08$). The mean iGTV in relapse-free patients was 18.4 mL (range, 3.2–65.7 mL) and, in patients who had primary relapse, 38.8 mL (range, 13.5–117.5 mL) ($p = 0.0003$). The mean VRR in relapse-free patients was 0.48 (range, 0.019–0.73) and, in patients with relapse, 0.35 (range, 0.014-0.55) ($p = 0.002$). In the HPC group, the mean pGTV in relapse-free patients was 28.9 mL (range, 4.1–152.4 mL) and, in patients who had primary relapse, 42.3 mL (range, 4.7–135.8 mL) ($p = 0.06$). The mean iGTV in relapse-free patients was 16.7 mL (range, 1.2–99.4 mL) and, in patients who had primary relapse, 28.6 mL (range, 2.7–116.7 mL) ($p = 0.06$). The mean VRR in relapse-free patients was 0.41 (range, 0.09–0.77) and, in patients with relapse, 0.27 (range, -1.15-0.79) ($p = 0.03$).

The impact of the tumors and the treatment-related parameters on the PRFS was analyzed by univariate and multivariate analysis, and the results are presented in Table 6. Multivariate analysis of the PRFS in OPC patients revealed

Table 4. Primary tumor volume and volume reduction rate vs. T classification

	Classification No.	Mean pGTV(mL)	Mean iGTV(mL)	Mean VRR	No. of VRR >0.6	>0.5	>0.4	>0.3
OPC group	76	49.9 (6.6–242.5)	26.3 (3.2–117.5)	0.43 (0.014–0.73)	15	31	42	56
T2	27	17.0 (6.6–50.0)	10.15 (3.2–23.3)	0.39 (0.054–0.65)	1	8	12	19
T3	24	42.0 (7.0–108.8)	23.4 (3.7–46.9)	0.42 (0.014–0.73)	3	10	14	19
T4	25	90.9 (15.7–242.5)	45.3 (4.2–117.5)	0.47 (0.017–0.72)	11	13	16	18
HPC group	76	35.6 (4.1–152.4)	22.7 (1.2–129.4)	0.33 (−1.15–0.79)	12	23	34	44
T2	18	11.1 (4.1–20.2)	7.5 (1.2–19.2)	0.32 (0.05–0.71)	1	4	6	7
T3	25	17.8 (4.7–40.9)	11.7 (3.0–33.1)	0.29 (−1.15–0.75)	3	7	9	14
T4	33	52.4 (12.9–152.4)	39.3 (3.8–129.4)	0.38 (−0.58–0.79)	8	12	19	23

Abbreviations: pGTV = pretreatment gross tumor volume; iGTV = interval gross tumor volume; VRR = volume reduction rate; OPC = oropharyngeal cancer; HPC = hypopharyngeal cancer.

three prognostic factors: T2–3 vs. T4 tumor ($p = 0.0001$, hazard ratio 7.38, 95% CI 2.94–18.49), pGTV <20 mL vs. ≧20 mL ($p = 0.0001$, hazard ratio 10.61, 95% CI 1.73–98.18), and VRR >0.5 vs. VRR ≦0.5 ($p = 0.001$, hazard ratio 6.49, 95% CI 2.37–17.54). Multivariate analysis of the PRFS results showed two prognostic factors: pGTV ≧30 mL ($p = 0.001$, hazard ratio 2.87, 95% CI 1.12–6.29) and VRR <0.5 ($p = 0.03$, hazard ratio 2.25, 95% CI 1.03–8.57). The results were not significant when the cutoff tumor volume or VRR was adjusted to other cutoff values. The sensitivity, specificity, and predictive values for the different cutoff values of the VRRs are shown in Table 7.

Figures 3 and 4 depict the correlation of the PRFS curves with the pGTV and VRR. In the OPC group, the 3-year PRFS for pGTV <20 mL + VRR >0.5, pGTV <20 mL + VRR ≦0.5, pGTV ≧20 mL + VRR >0.5, and pGTV ≧20 mL + VRR ≦0.5 were 90%, 57%, 69% , and 0%, respectively ($p = 0.000$). Similarly, in the HPC group, the 3-year PRFS for pGTV <30 mL + VRR >0.5, pGTV <30 mL + VRR ≦0.5, pGTV ≧30 mL + VRR >0.5, and pGTV ≧30 mL + VRR ≦0.5 were 81%, 52%, 30% , and 18%, respectively ($p = 0.01$).

Correlation between the pGTV and VRR was also performed. When the pGTV in the HPC group was stratified into <30-mL and ≧30-mL groups, the mean VRR was 0.31 (standard deviation [SD] = 0.30) for small tumors and 0.39 (SD = 0.28) for large tumors ($p = 0.24$). If the pGTV in the OPC group was stratified into <20-mL and ≧20-mL groups, the respective mean VRR values were 0.42 (SD = 0.18) and 0.43 (SD = 0.18), respectively ($p = 0.70$).

DISCUSSION

The fact that pretreatment tumor volume can be a predictive factor is not novel. Treatment results might be optimized if volumetric data were used to supplement the clinical stage. Because of variation in the radiosensitivity between tumors of different origins, the clinical implication of volumetric data seems to be limited if the studied group includes heterogeneous tumor sites. In this study, higher local failures were observed than in other IMRT reports (15–18). There are three possible explanations for the higher local failures in our series. First, patients with small tumor burden (*i.e.,* American Joint Committee on Cancer Stage T1 tumor) were not included in our studied cohort. Second, the median overall treatment duration was relatively longer because more fraction numbers were used in the sequential IMRT compared with that in the simultaneous integrated-boost IMRT (15–17). Finally, the inferior RT/CCRT outcome might be attributed to the lower prevalence of human papillomavirus (HPV)–related OPC in Asia (19–20). Nonetheless, our results provide a sound dataset for the selection of an organ preservation scheme in OPC and HPC patients even if planned neck dissection is a part of routine care for bulky nodal disease. From our results, T2–T4 OPC patients with a pGTV less than 20 mL and T2–T4

Table 5. Correlation between tumor volume parameters and primary tumor relapse

OPC group	Primary tumor relapse (−) ($n = 43$)	Primary tumor relapse (+) ($n = 33$)	p
Mean pGTV (mL) ±SD	41.6 ± 36.0	62.2 ± 53.4	0.08
Mean iGTV (mL) ±SD	18.38 ± 14.9	38.8 ± 25.5	0.0003*
Mean VRR (%) ±SD	0.48 ± 0.18	0.35 ± 0.19	0.002*
HPC group	**Primary tumor relapse (−) ($n = 38$)**	**Primary tumor relapse (+) ($n = 38$)**	**p**
Mean pGTV (mL) ±SD	28.9 ± 23.4	42.3 ± 33.5	0.06
Mean iGTV (mL) ±SD	16.7 ± 12.8	28.6 ± 18.0	0.06
Mean VRR (%) ±SD	0.41 ± 0.190	27 ± 0.150	.03*

Abbreviations: OPC = oropharyngeal cancer; HPC = hypopharyngeal cancer; pGTV = pretreatment gross tumor volume; iGTV = interval gross tumor volume; VRR = volume reduction rate; SD = standard deviation.

* Statistical significance.

Table 6. Univariate and multivariate analysis of the primary tumor relapse-free survival

Cancer type / Variables	OPC		HPC	
	Univariate *p*	Multivariate *p*	Univariate *p*	Multivariate *p*
T classification				
T2–3 vs. T4	0.000	0.000*	0.01	0.33
N stage				
N0 vs. N1–2	0.40	0.34	0.18	0.78
Primary tumor volume				
(<10 vs. ≧10 mL)	—	—	0.13	0.35
(<15 vs. ≧15 mL)	0.006	0.56	0.01	0.23
(<20 vs. ≧20 mL)	0.000	0.01*	0.002	0.29
(<25 vs. ≧25 mL)	—	—	0.002	0.27
(<30 vs. ≧30 mL)	0.001	0.67	0.001	0.001*
(<40 vs. ≧40 mL)	0.005	0.67	0002	0.79
Volume reduction rate				
(≦0.3 vs >0.3)	0.03	0.97	0.22	0.87
(≦0.4 vs >0.4)	0.04	0.52	0.10	0.96
(≦0.5 vs. >0.5)	0.01	0.001*	0.03	0.03*
(≦0.6 vs. >0.6)	0.31	0.45	0.09	0.76
Performance				
(ECOG 0–1 vs. 2–3)	0.001	0.65	0.07	0.63
Tracheostomy				
(negative vs. positive)	0.16	0.55	0.19	0.89
Dysphagia (Grade 0–1 vs. 2–3)	0.02	0.80	0.07	0.63
Treatment duration				
(< 60 vs. ≧60 days)	0.57	1.0	0.71	0.66
Concurrent chemotherapy				
(positive vs. negative)	0.25	0.62	0.16	0.38

Abbreviations: OPC = oropharyngeal cancer; HPC = hypopharyngeal cancer; ECOG = Eastern Cooperative Oncology Group.
* Statistical significance.

HPC patients with a pGTV less than 30 mL were favorable groups. Definitive CCRT or RT with an organ preservation scheme may be suitable for these patients.

Variable degrees of tumor volume regression and changes in body contour during irradiation are frequently observed. Repeated CT imaging and replanning during the course of IMRT for some head-and-neck cancer patients is essential to ensure adequate doses to target volumes and safe doses to normal tissues (21). The use of deformable image registration techniques and daily kilovoltage or megavoltage CT imaging have made it possible to adapt daily tumor or normal tissue dose–volume histograms. Nonetheless, a question remains concerning whether tumor regression itself is actually an important prognostic factor affecting the local control rate. Another issue that has occasionally been raised is how or when to conduct adaptive planning when a remarkable regression of the tumor has been observed. Before these questions are answered, it is important to investigate the clinical implications of the tumor volume regression rate during irradiation. Traditionally, direct measurement of the maximal tumor diameter was an easily used method to define a clinical response after definitive treatment. However, the weakness of T classification and of one- or two-dimensional measurement of the tumor area on a cross-sectional image has been previously addressed (1–3, 14).

Most tumor volume changes occur after the second week of treatment (22, 23). This means that the appropriate time for either adaptive interventions or assessment of tumor regression might be more than 2 weeks after the beginning of irradiation. If adaptive planning is done in the late phase

Table 7. Predictive value of volume reduction rate for primary relapse

Cancer type / Predictive value	OPC		HPC	
	Sensitivity/specificity	PPV/NPV	Sensitivity/specificity	PPV/NPV
Volume reduction rate				
(≦0.3 vs. >0.3)	0.43/0.83	0.60/0.71	0.50/0.66	0.59/0.57
(≦0.4 vs. >0.4)	0.57/0.63	0.47/0.71	0.63/0.52	0.57/0.58
(≦0.5 vs. >0.5)	0.79/0.52	0.49/0.81	0.82/0.42	0.59/0.70
(≦0.6 vs. >0.6)	0.89/0.25	0.41/0.80	0.89/0.21	0.53/0.67

Abbreviations: OPC = oropharyngeal cancer; HPC = hypopharyngeal cancer; PPV = positive predictive value; NPV = negative predictive value.
True positive is defined as the cases of primary failures when the volume reduction rate is equal or less than the values in the table.

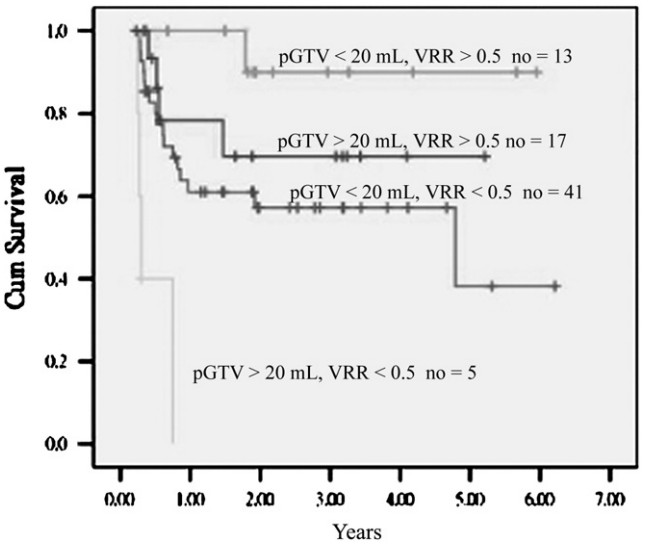

Fig. 3. Primary tumor relapse-free survival curves according to pretreatment gross tumor volume (pGTV) and volume reduction rate (VRR) in oropharyngeal cancer patients.

of an irradiation course, its advantages might be restricted because of the limited response time. In this study, the VRR values were obtained uniformly 4 to 5 weeks after the start of RT. The results showed that VRR values over 0.5 and pretreatment tumor volumes were two factors associated with local control of the primary tumor in OPC and HPC. Although several published IMRT reports of pretreatment tumor volumes in head-and-neck cancer, we were unable to find any available information of the VRR values during irradiation for direct comparison. The volume data reported here can be used in three ways. First, this method offers a more accurate informed consent process when the value of surgery and an organ preservation scheme

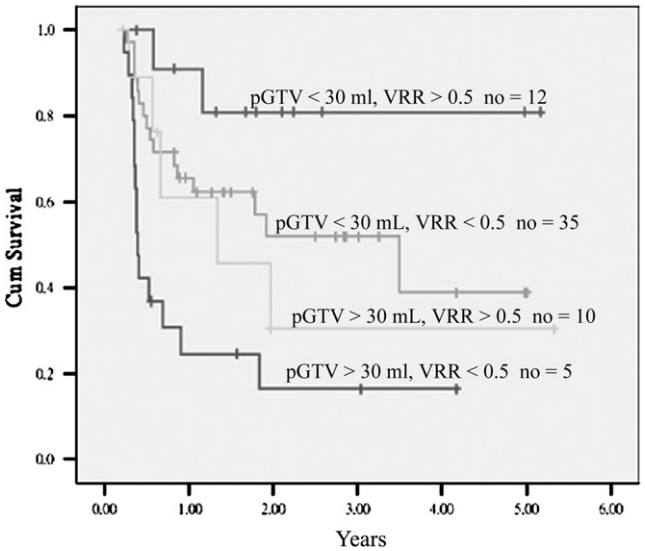

Fig. 4. Primary tumor relapse-free survival curves according to pretreatment gross tumor volume (pGTV) and volume reduction rate (VRR) in hypopharyngeal cancer patients.

for local control is being discussed. In addition, it can help determine patients with large tumor volumes or smaller VRRs who should receive more aggressive combined modality treatment or an escalation of the irradiation dose. Finally, the mean VRR in the OPC group was greater than that in the HPC group. It can be speculated that the HPV is associated with some oropharyngeal tumors, and better radiosensitivity could be achieved after 4 to 5 weeks of irradiation. It would be interesting to investigate the correlation between HPV-related OPCs and their VRRs.

A valid criticism has been raised concerning the knowledge and technique required to measure tumor volumes. The specific issue is the inclusion of adjacent tumor-related edema in the measured volume, which may be a source of potential error. As reported by Mancuso *et al*. (4) the elimination of this specific variable made the reproducibility of the measured volume possible in this study. In addition, more sophisticated volumetric data acquisition using a thin-slice thickness approach will be required for more precise quantification of tumor volumes.

There is a question concerning whether tumors with a larger pGTV can achieve a larger volume reduction than those with a smaller pGTV, as reported by Kupelian *et al*. (24). This might be attributed to the fact that RT-induced peritumoral edema was always taken into account in the calculated iGTV, which could exaggerate the iGTV values for the smaller pGTV group. From our data, there seemed to be a trend toward a smaller VRR for smaller tumors. However, great variation existed without statistical significance.

Despite the limitations, such as the small sample size, the lack of a uniform combination of chemotherapeutic agents, and interobserver variability, this study provides a novel volumetric marker for head-and-neck cancer. Of course, actual oncologic outcomes do not depend simply on volumetric factors alone. The VRR value itself might represent a combination outcome of several biologic parameters. Based on our data, we recommend using VRR during adaptive imaging as a parameter for assessing local control in some head-and-neck cancers. For the best treatment modification in simultaneous integrated boost technique, adaptive image at 4 to 5 weeks might be somewhat late. By contrast, all our studied patients were treated with a sequential IMRT technique (total, 35–39 fractions), and any image modification before the end of the first course of IMRT was feasible when conducting an adaptive planning. In other words, daily fraction size could be increased in the second course of IMRT if a dose-escalation scheme needs to be done without prolongation of treatment time. Nonetheless, the best timing of adaptive planning might be earlier and need further investigation for optimizing a dose-escalating scheme.

Recently, two studies reported the results of the role of fluorodeoxyglucose positron emission tomography (PET) during a course of RT (25, 26). Despite the concept that fluorodeoxyglucose PET would be uninterpretable until several months after RT, this imaging modality was successfully used to assess the interval response (changes

of maximum fluorodeoxyglucose activity) to RT, and the interval response was found to correlate with the short-term RT response. Also, such an approach might be considered for dose-escalation strategies. Thus, this is a subject of future trials to investigate the impact of VRR based on PET/CT on the final outcome in many head-and-neck cancers.

In summary, the pretreatment tumor volume and VRR are two outcome predictors for local control in OPC and HPC patients treated with IMRT. Therefore, OPC patients with T4 tumor or a pGTV >20 mL, HPC patients with a pGTV >30 mL, and those with VRR values less than 0.5 should be considered for a salvage operation or a dose-escalation scheme.

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