ORIGINAL ARTICLE

PROGNOSTIC IMPACT OF TUMOR VOLUME IN PATIENTS WITH STAGE III–IVA HYPOPHARYNGEAL CANCER WITHOUT BULKY LYMPH NODES TREATED WITH DEFINITIVE CONCURRENT CHEMORADIOTHERAPY

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Abstract: *Background.* To investigate the prognostic value of volumetric analysis in patients with stage III–IVA hypopharyngeal cancer treated with concurrent chemoradiotherapy (CCRT).

Methods. Seventy-six stage III–IVA hypopharyngeal cancer patients without bulky lymph nodes were enrolled for a volumetric analysis. The pyriform sinus was the principal site of involvement in the 63 cases. All patients were allocated a course of CCRT. Tumor volume measurement was derived using separate calculations for the primary tumor volume (pGTV) and the nodal tumor volume (nGTV).

Results. The pGTV ranged from 3.8 to 152.4 mL (mean, 33.4 mL). The 3-year cause-specific survival (CSS) was 75% for those with a pGTV <30 mL and 20% when the pGTV was ≥30 mL ($p = .0001$). Furthermore, the 3-year primary tumor relapse-free survival (PRFS) was 72% for those with a pGTV <30 mL and 23% when the pGTV were ≥30 mL ($p = .0001$). The 3-year PRFSs for <30 mL and ≥30 mL were 74% and 25% for stage III disease ($p = .01$) and 65% and 22% for stage IVA tumors ($p = .01$), respectively. Multivariate analyses of the CSS revealed a single prognostic factor, namely pGTV <30 mL versus ≥30 mL ($p = .0001$, hazard ratio 2.84). Multivariate analyses of the PRFS gave a similar finding, with a pGTV ≥30 mL ($p = .0001$, hazard ratio 2.55) being significant.

Conclusion. A patient's pGTV is a strong outcome predictor for hypopharyngeal cancer treatment using CCRT. Therefore, a selected group of patients, mainly those with tumor volumes <30 mL should be considered for laryngeal preservation. *Head Neck* **31:** 709–716, 2009

Keywords: hypopharyngeal cancer; chemoradiotherapy; tumor volume; prognostic factor

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Radiotherapy (RT) or concurrent chemoradiotherapy (CCRT) allows preservation of laryngeal function among patients with hypopharyngeal cancer. Traditionally, patients with stage I and II hypopharyngeal cancer can be treated using a laryngeal preservation scheme. In contrast, stage III or IV lesions are considered to be unfavorable for laryngeal preservation scheme, and there is considerable controversy regarding

their optimum treatment method.[1–4] Total laryngectomy, combined with neck lymph node dissection, is often recommended in these patients. Curative RT or CCRT with surgical salvage in reserve is also an accepted protocol. Overall, the results of salvage surgery following laryngeal preservation scheme failure have been unsatisfactory.[1–3] A significant number of RT failures may not be salvaged with surgery either because of late diagnosis or the patient's refusal to undergo subsequent surgery. Nevertheless, among patients who are anatomically unsuitable or medically unfit for surgery, laryngeal preservation scheme is always suggested. For the optimization of treatment outcomes among patients treated using laryngeal preservation scheme, there is a need for better selection among patients with advanced tumors; in this way a more informed treatment choice can be made available.

Some concerns have been raised about the weakness of the TNM-classification for head and neck cancer.[5–7] Current methods to define tumor volume are usually not precisely quantitative.[6,7] The adverse effect of increasing tumor burden on local control using RT is an important concept. Thus, outcome variations among studies may be partly influenced by unaccounted for differences in the tumor volume. Pretreatment CT with volumetric analysis has been shown to be an effective predictor of local control in laryngeal tumors or other head and neck tumors treated with RT in some studies.[6–11] However, most reports investigating volumetric analysis for hypopharyngeal cancer included either a variety of head and neck tumors or all T classifications.[7,12–14] It is doubtful that hypopharyngeal cancer volumetric data can be reproducible from a study that involves the pooling of heterogeneous head and neck cancers. Also, it is questionable whether it is possible to achieve a conclusive result if the volumetric data calculation consists of a summation of the primary tumor volume (pGTV) and the nodal tumor volume (nGTV) because planned neck dissection may be a part of the routine care for bulky nodal disease. Furthermore, the clinical implication of a volumetric study is limited if the enrolled subjects only include those with early-stage disease since patients with stage I–II hypopharyngeal cancer are always treated with laryngeal preservation scheme. Thus, in the era of CCRT for advanced head and neck cancer, it has become imperative to conduct a volumetric study that includes a patient cohort with advanced-stage cancers that are treated with CCRT; this will allow the optimization of the selection criteria for laryngeal preservation scheme.

The aim of this study was to determine the prognostic value, following laryngeal preservation scheme, of volumetric analysis and other tumor or treatment-related parameters for the prediction of survival and local control in patients with stage III–IVA hypopharyngeal cancer. The result of this study should help to determine more appropriate selection criteria for these patients.

PATIENTS AND METHODS

Patients. From January 2000 through June 2006, 76 patients with stage III–IVA squamous cell carcinoma of the hypopharynx, who had been treated with laryngeal preservation scheme at the China Medical University Hospital, were enrolled in this retrospective analysis after institutional review board approval. The enrollment criteria were as follows:

1. Patients had completed their allocated CCRT treatment and had been followed up for a minimum of 1 year or until death.
2. Patients had been staged after a comprehensive physical examination, laryngoscopy, tumor biopsy, chest radiography, a CT scan of the neck, abdominal ultrasonography, and a bone scan.
3. Patients showed no evidence of bulky lymph nodes on a CT scan. A bulky node was defined as the presence of at least 1 enlarged lymph node with a maximal dimension of more than 3 cm on the CT scan of the neck. In addition, enrolled patients should have shown a clear demarcation between primary and nodal tumors.

Tumors of stage IVB disease are technically unresectable. Treatment of these patients is considered to be palliative, and therefore they were excluded from this analysis. In addition, patients with bulky nodes were always recommended for treatment with combined modality and they were also excluded because in this study there was no intended combined surgery following CCRT. The sites of tumor involvement were mainly based on the laryngoscopy and

Table 1. Patient characteristics (total, 76 patients).

Characteristic	Value
Age, y	36–79 (median, 57)
Sex	male 74, female 2
Pathology	
W-D/M-D squamous cell carcinoma	51
P-D squamous cell carcinoma	25
Stage	III 31, IVA 45
Performance status	
ECOG 0-1/2	66/10
Tracheostomy	
Negative/positive	58/18
Dysphagia score	
Grade 0-1/2-3	56/20
Primary tumor volume	3.5–152.4 mL (median 23.6; mean 33.4)
Special sites of tumor involvement	
Posterior pharyngeal wall	20
Larynx	18
Base of tongue and oropharynx	17
Radiation dose, Gy	68.4–73.8 (median, 70.2)
Radiation technique	
IMRT/Conventional RT	46/30
Treatment duration, days	42–87 (median, 58)
Concurrent chemotherapy	
Cisplatin (80–100 mg/m^2, D1, 22, 43)	57
3 Courses	37
2 Courses	17
1 Course	3
Cisplatin (70–100 mg/m^2, D1) + 5-FU (600–1,000 mg/m^2, D1 to 5)	19
2 Courses	14
1 Course	5
Median follow-up, mo	13–95 (median, 37)

imaging findings and all of the involved sites were recorded. The pyriform sinus was the principal site of involvement among the 63 cases. The patient characteristics and TNM-classification distribution are listed in Tables 1 and 2.

Treatment. The RT was performed using conventional RT for 30 patients, or using a sequential intensity-modulated radiotherapy (IMRT) technique for 46 patients. All patients received 1.8 Gy daily up to a total dose of between 68.4 and 73.8 Gy (median, 70.2 Gy). For patients treated using the conventional technique, they were initially treated with bilateral opposing fields and 1 anterior low-neck field to include the skull base and whole neck lymphatic drainage at 46.8 Gy. Primary tumors were further boosted to 70.2 Gy. Bilateral neck lymphatics were boosted with electron beams to a total dose of 70.2 Gy for N1-2 disease, and 54.0 to 59.4 Gy for N0 disease. For patients treated using IMRT, the clinical target volume (CTV) modeled regions were considered to be 2 regions with different risk. CTV1 encompassed the primary tumor, metastatic lymph nodes, and the regions adjacent to the gross tumor. CTV2 consisted of the ipsilateral or contralateral N0 regions at the risk of harboring microscopic tumors. The dose delivered to CTV1/CTV2 during the first course was 54 Gy (1.8 Gy $\times$ 30 Fr) and the CTV1 was boosted a further 16.2 Gy (1.8 Gy $\times$ 9 Fr) during the second course. Thus, the cumulative doses to CTV1/CTV2 were 70.2 Gy/54 Gy, respectively. The RT duration for all patients ranged from 42 to 89 days (median, 61 days).

All patients had concurrent chemotherapy. Before December 2003, 19 patients (25%) received 2 courses of chemotherapy that combined cisplatin (70–100 mg/m^2, on day 1) and 5-FU (600–1000 mg/m^2, on days 1 to 5). After December 2003, 57 patients (75%) received cisplatin (80–100 mg/m^2, on days 1, 22, 43) in terms of the schedule described in Intergroup study.[15] Details of the actual received treatment cycles are outlined in Table 1.

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 pathological when their smallest axis diameter was >1 cm.[16] The CT images from the PACS (picture archiving and communication system) were then transferred to a commercial planning system (Eclipse Version 7.1). Radiation oncologists then delineated the gross tumor volume of the primary (pGTV) and the metastatic lymph nodes (nGTV). The volumes of all tumors were measured by outlining the lesion on each image if it was visible. No attempts were done to differentiate the tumors from any related edema. The tumor volumes were contoured and the volumes calculated using the same planning system.

Table 2. Distribution of TMN stage.

	No. by T classification			
N classification	T2	T3	T4	Total
N0	0	22	10	32
N1	5	4	8	17
N2	3	8	16	27
Total	8	34	34	76

Generally, 2 different radiation oncologists carried out the contouring of the tumors for each patient. When the calculated values for any volume varied by $\leq$10%, an average of the 2 readings was used as the measured volume. When the variation exceeded 10%, another contouring and measurement was carried out to correct any bias.

Follow-Up. After the completion of the 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 the patients who were still alive at the time of this study, the follow-up period ranged from 13 to 95 months (median, 37 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 following initial complete remission, salvage surgery was suggested when this was technically feasible and the patient's condition allowed it.

Statistical Analysis. Cause-specific survival (CSS), primary tumor relapse-free survival (PRFS), and nodal relapse-free survival (NRFS) were calculated using the Kaplan-Meier method. Salvage of any recurrences was not taken into account when evaluating the PRFS. Statistical significance was determined as $p < .05$, 2-tailed. Significance levels between the curves were calculated using the log-rank test. Multivariate analyses were performed using the Cox's proportional hazards model.

RESULTS

At the time of analysis, 31 patients were alive without known recurrent disease and 8 patients had locoregional recurrence (7 at the primary tumor; 1 in a neck node) but were still alive after salvage or palliative treatment. Twenty-five patients had died of locoregional recurrence alone, while 3 patients had died of distant metastasis and 6 patients had died due to both locoregional recurrence and distant metastasis. Finally, 3 patients had died due to metachronous esophageal or lung cancer. Among the 39 patients with locoregional failure, 30 had developed primary tumor relapse, 3 were noted to have isolated neck lymph node recurrence, and 6 had both primary tumor relapse and neck lymph node recurrence. Because of the severity of the postirradiation fibrosis and the lack of a suitable timetable for salvage surgery, only 7 of these patients received salvage laryngectomy successfully after recurrence. The 3-year CSS for all patients were 51%. The 3-year PRFS rate for all patients was 48% and this could be split into 61% for stage III disease, and 35% for stage IVA disease ($p = .003$). The 3-year PRFS rate was 74% for patients with T2 disease, 59% for patients with T3 disease, and 34% for patients with T4 disease ($p = .01$), as depicted in Figure 1. The 3-year NRFS rate was 100% for patients with N0 disease, 91% for patients with N1 disease, and 67% for patients with N2 disease ($p = .001$).

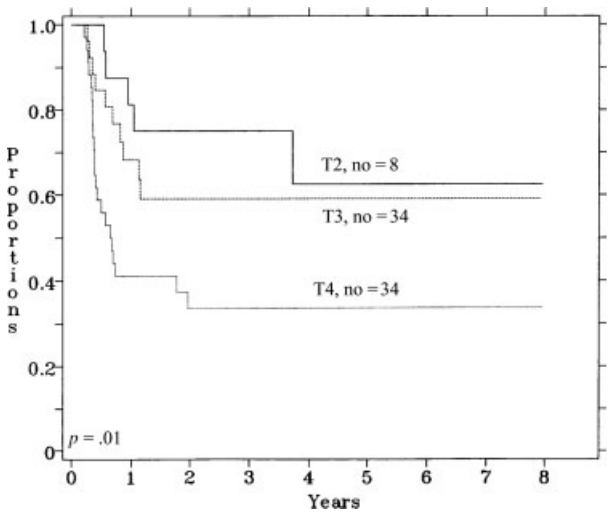

FIGURE 1. Primary tumor relapse-free survival curves according to T classification.

The pGTVs ranged from 3.8 to 152.4 mL (mean, 33.4 mL; median, 23.6 mL) and the distribution of the tumor volumes with respect to clinical staging and TNM classification is shown in Table 3. A significant correlation was found between the tumor volume stratified into volume classes and primary tumor control, which is shown in Figure 2. The 3-year CSS was 75% for those with a pGTV of less than 30 mL and 20% when the pGTV was $\geq$30 mL ($p = .0001$). Similarly, the 3-year PRFS was 72% for those with a pGTV of less than 30 mL and 23% when the pGTV was $\geq$30 mL ($p = .0001$). When subgroup analysis was carried out (Figures 3 and 4), the 3-year PRFS for $<$30 mL and $\geq$30 mL

Table 3. Primary tumor volume versus T classification and clinical stage.

	Patient no.	Mean tumor volume, mL	No. of pGTV <20 mL	No. of pGTV <30 mL	No. of pGTV <40 mL
T classification					
T2	8	9.4 (3.8–25.3)	6	8	8
T3	34	22.2 (3.8–131.2)	18	22	23
T4	34	55.4 (9.3–152.4)	8	9	13
Stage					
III	31	14.2 (3.8–44.6)	19	22	25
IVA	45	51.8 (5.7–152.4)	13	17	19

Abbreviation: pGTV, primary tumor volume.

were 74% and 25%, respectively for stage III tumors ($p = .01$) and 65% and 22%, respectively, for stage IVA tumors ($p = .01$). The impact of the tumors and the treatment related parameters on the CSS and PRFS was analyzed by univariate and multivariate analysis and the results are presented in Tables 4 and 5.

Multivariate analysis of the CSS results revealed 1 significant prognostic factor: pGTV <30 mL versus ≥30 mL ($p = .0001$, hazard ratio 2.84, 95% CI 1.34–8.52). Multivariate analysis of PRFS results showed a similar finding, with pGTV ≥30 mL ($p = .0001$, hazard ratio 2.55, 95% CI 1.21–7.29). The results were not significant when the cut-off tumor volume was adjusted to either 20 or 40 mL.

When a subgroup multivariate analysis of the 46 patients treated with sequential IMRT was carried out, the prognostic factors for CSS and PRFS were still the same as for the whole series. Furthermore, the outcomes of the 30 patients treated by the conventional technique, when stratified by stage or pGTV, showed no significant difference when compared to the IMRT outcomes.

For the 44 patients with N1 or N2 disease, the nGTV ranged from 1.6 to 75.1 mL (mean,

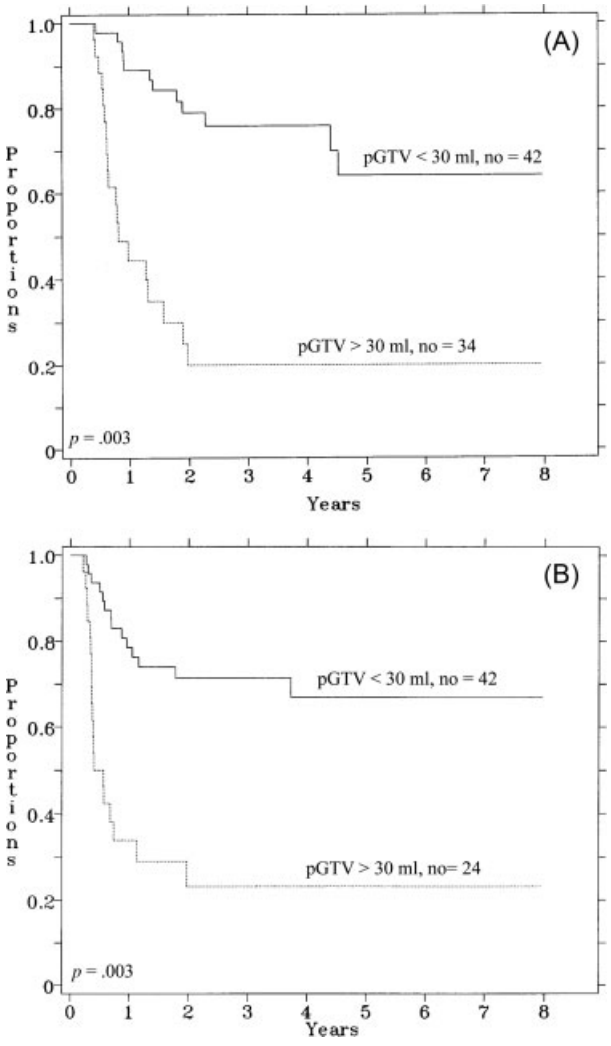

FIGURE 2. (**A**) Cause-specific survival curves according to pGTV. (**B**) Primary tumor relapse-free survival curves according to pGTV.

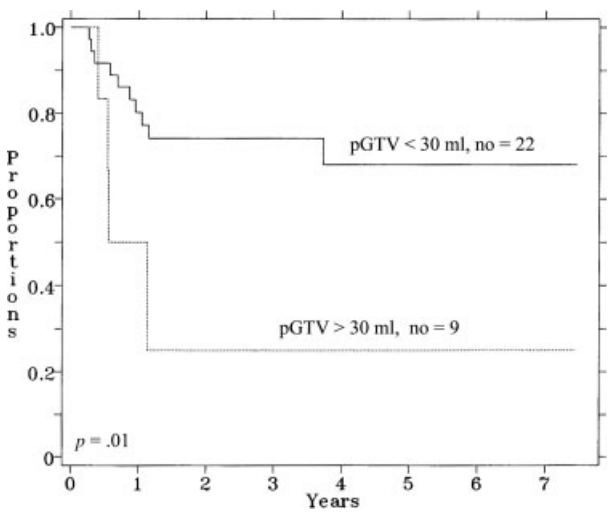

FIGURE 3. Primary tumor relapse-free survival curves for stage III patients according to pGTV.

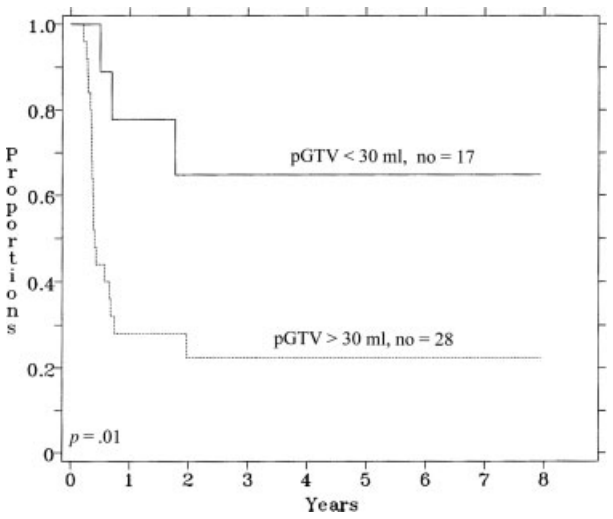

FIGURE 4. Primary tumor relapse-free survival curves for stage IVA patients according to pGTV.

24.8 mL; median, 16.2 mL). Univariate analysis showed nGTV ≥30 mL ($p = .07$) and the occurrence of a primary tumor relapse ($p = .05$) had a marginal impact on nodal recurrence, but there was no statistical difference when different cut-off values for the nodal volume were used.

Table 4. Univariate analysis of cause-specific survival and primary tumor relapse-free survival.

Factors	Cause-specific survival *p* value	Primary tumor relapse-free survival *p* value
T classification		
T2 vs T3 vs T4	.01	.01
T2-3 vs T4	.03	.01
N stage		
N0 vs N1-2	.06	.18
Stage		
III vs IVA	.003	.002
Primary tumor volume		
(<20 vs ≥20 mL)	.0001	.001
(<30 vs ≥30 mL)	.0001	.0001
(<40 vs ≥40 mL)	.0001	.0002
Posterior pharyngeal wall involvement	.44	.57
Oropharynx involvement	.82	.83
Larynx involvement	.18	.13
Age (<50 vs ≥50 years)	.31	.52
Performance (ECOG 0-1 vs 2-3)	.19	.11
Tracheostomy	.21	.19
Dysphagia (Grade 0-1 vs 2-3)	.12	.07
Treatment duration (<60 vs ≥60 days)	.54	.71
Treatment technique (IMRT vs conventional RT)	.24	.31
Chemotherapy scheme (cisplatin vs cisplatin + 5-Fu)	.87	.66

Table 5. Multivariate analysis of cause-specific survival and primary tumor relapse-free survival.

Factors	Cause-specific survival *p* value	Primary tumor relapse-free survival *p* value
T classification		
T2 vs T3 vs T4	.65	.87
T2-3 vs T4	.76	.96
N stage		
N0 vs N1-2	.42	.33
Stage		
III vs IVA	.12	.19
Primary tumor volume		
(<20 vs ≥20 mL)	.59	.92
(<30 vs ≥30 mL)	.0001	.0001
(<40 vs ≥40 mL)	.95	.79
Posterior pharyngeal wall involvement	.16	.70
Oropharynx involvement	.69	.14
Larynx involvement	.09	.54
Age (<50 vs ≥50 years)	.60	.81
Performance (ECOG 0-1 vs 2-3)	.87	.78
Tracheostomy	.78	.89
Dysphagia (Grade 0-1 vs 2-3)	.54	.63
Treatment duration (<60 vs ≥60 days)	.88	.79
Treatment technique (IMRT vs conventional RT)	.74	.66
Chemotherapy scheme (cisplatin vs cisplatin + 5-Fu)	.82	.79

DISCUSSION

At many institutions, decisions about the treatment strategy for a patient with stage III–IVA hypopharyngeal cancer are complex and include tumor location, patient condition, and individual preference. In 2008, the National Comprehensive Cancer Network guidelines for hypopharyngeal cancer reported that CCRT with or without salvage surgery might be the treatment of choice for those with T2-T4a with or without neck nodes. However, many physicians are still concerned about patient selection criteria when considering CCRT for laryngeal preservation scheme.

The clinical criteria used for classifying a tumor to a particular T classification for hypopharyngeal

Table 6. Results of volumetric studies with hypopharyngeal cancer in radiotherapy series.

First author	Primary	Patients	Stage	Treatment	Cut-off value, mL	End point/outcome	
						Below	Above
Pameijer[12]	Pyriform sinus	23	T1-T2	RT	6.5 (pGTV)	2-year local control	
						90%	25%
Plataniotis[13]	OC/OPC/HPC/LC	101	III-IV	RT ± CT	22.8 (tGTV)	Median survival	
						45.3 months	12.3 months
Grabenbauer[14]	OC/OPC/HPC/LC	87	III-IV	RT ± CT	110 (tGTV)	3-year locoregional control (RT + CT arm)	
						67%	23%
Studer[7]	OC/OPC/HPC/NPC	172	T1-T4	RT ± CT	15/70 (pGTV)	Local failure rate	
						<15 mL: 5.5%; 15–70 mL: 20%	>70 mL: 48%
Present study	HPC	76	III-IVA	RT + CT	30 (pGTV)	3-year primary relapse-free survival	
						72%	23%

Abbreviations: RT, radiotherapy; pGTV, primary tumor volume; OC, oral cancer; OPC, oropharyngeal cancer; HPC, hypopharyngeal cancer, LC, laryngeal cancer; CT, chemotherapy; tGTV: total tumor volume; NPC, nasopharyngeal cancer.

cancer are dependent on both the site involved and the tumor diameter, and therefore it is not surprising that the tumor volumes and T classifications are correlated to some extent. The presence of submucosal tumor extension or invisible deep tumor extension with advanced tumors can result in the involved sites and visible tumor diameters affecting the estimation of tumor volume and causing inaccuracy. Furthermore, advanced T classifications do not always well represent huge tumors volumes due to the irregularity of the tumor shape. These factors can explain why there are large overlaps in tumor volume between the different T classifications.

The fact that tumor volume can be a predictive factor is not novel issue. Treatment results might be optimized if volumetric data were used to supplement the clinical stage. For example, despite the survival curves for hypopharyngeal cancer patients in stage III being higher than in stage IVA, local recurrence occurred in nearly half of the stage III cases in our study, which is similar to other series.[1–4] These reports show that an indiscriminate application of laryngeal preservation scheme for those with stage III disease is questionable. In addition, the review of the National Cancer Data Base demonstrated that there was decreased survival among patients with laryngeal cancer in the mid-1990s that might be related to the use of less aggressive surgery during this period; among these changes, the most dramatic was an increase in CCRT.[17]

However, the clinical implication of volumetric data would seem to be limited if the studied group includes heterogeneous tumor sites or clinical stages. In this study, we calculated the pGTVs and the nGTVs rather than summation of both volumes. Thus, the prognostic impact of the 2 tumors volumes could be directly assessed during the investigation of the effects of CCRT on primary tumors and nodal disease. Furthermore, our results also provide a sound dataset for the selection of laryngeal preservation scheme in advanced hypopharyngeal cancer patients even if planned neck dissection is a part of routine care for bulky nodal disease. From our results, T2-T4 hypopharyngeal cancer patients with a pGTV of less than 30 mL formed a favorable group, and definitive CCRT with laryngeal preservation scheme may be suitable for these patients. In published volumetric studies investigating the outcome of stage III–IV head and neck cancer patients, Plataniotis et al[13] reported a cut-off value for total tumor volume of 22.8 mL as an independent prognostic factor. In contrast, Grabenbauer et al[14] showed a survival difference when using a total tumor volume of 110 mL as the cut-off value. On the other hand, Studer et al[7] suggested 2 cut-off values for the pGTV (15, 70 mL), which were able to differentiate the outcome in 172 head and neck cancers excluding the larynx. These substantial variations in cut-off value might be due to either the addition of nodal volumes, or the pooling of heterogeneous tumors sites. Table 6 summarized the results of the various volumetric studies investigating RT outcome for hypopharyngeal cancer that have been published to date.

Our results also showed that most failures were due to primary recurrence rather than neck lymph node failure. Of the 39 patients

with locoregional failure, only 9 (23.1%) developed nodal recurrence. The rarity of neck relapse might be attributable to the exclusion of bulky nodal disease in our patient cohort. For the 9 patients with nodal failure, they could be categorized as having either primary recurrence or bulky nodal disease. Nodal status was not found to be an independent predictor of survival or primary failure by the multivariate analysis. Nonetheless, given that planned neck dissection is a part of treatment, the clinical implications of the nodal volume could have been obscured.

However, 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,[10] 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. The volume data reported here can be used for 2 purposes. First, it is able to offer a more accurate informed consent process when the value of surgery and laryngeal preservation scheme for local control is being discussed. In addition, it is able to help determine the patients with large tumor volumes who should receive more aggressive combined modality treatment or an escalation of the irradiation dose.

In summary, pretreatment CT-based pGTV measurements are a strong predictor of survival and local control for stage III–IVA hypopharyngeal cancer when the patients are treated using definitive CCRT. For those with tumor volumes <30 mL, this approach should be considered for laryngeal preservation scheme. Some effort should be made to incorporate a combined modality approach into the treatment of patients with large tumor volumes.

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