Primary Tumor Volume of Nasopharyngeal Carcinoma: Significance for Recurrence and Survival

Sau-Tung Chu[1], Pi-Hsiung Wu[1], Yu-Yi Hou[1], Kuo-Ping Chang[1], Chao-Chuan Chi[1], Ching-Chih Lee[2,3]*

[1]Department of Otolaryngology, Kaohsiung Veterans General Hospital, Kaohsiung, [2]Community Medicine Research Center and Institute of Public Health, National Yang-Ming University, Taipei, and [3]Department of Otolaryngology, Buddhist Tzu Chi Dalin General Hospital, Chiayi, Taiwan, R.O.C.

Background: Primary tumor volume (PTV) is known to be a significant prognostic factor in malignant tumor. There have been several studies of nasopharyngeal carcinoma (NPC) relating tumor volume to treatment outcome. Our study was designed to evaluate the effect of PTV on treatment outcomes in NPC treated with radiotherapy (RT)/concurrent chemoradiotherapy (CCRT) or CCRT with adjuvant chemotherapy.

Methods: We retrospectively reviewed 100 cases with newly diagnosed NPC who were treated with RT/CCRT or CCRT with adjuvant chemotherapy from 2002 to 2006. Magnetic resonance imaging-derived PTV was calculated using the summation-of-area technique. Kaplan-Meier plots and the log-rank test were used to estimate tumor recurrence (locoregional, distant, or both) and overall survival. Cox proportional hazards regression analysis was used to assess the prognostic impact of PTV.

Results: The median PTV was 12.94 mL. PTV remained an independent prognostic factor for distant metastasis (hazard ratio [HR], 1.04; $p = 0.03$), for any relapse (HR, 1.04; $p = 0.02$), and for overall survival (HR, 1.09; $p < 0.001$) in multivariate analysis. In the large tumor volume group (PTV > 15 mL), patients' metastasis-free survival rates, with and without adjuvant chemotherapy, were 100% and 68.3%, respectively ($p = 0.002$). Their 3-year recurrence-free survival rates, with and without adjuvant chemotherapy, were 94.1% and 69.6%, respectively ($p = 0.006$). In the small tumor volume group (PTV ≤ 15 mL), this phenomenon was not observed.

Conclusion: PTV had a close relationship with survival rates and recurrence rates in patients with NPC. The large tumor volume group (PTV > 15 mL) was associated with more recurrence and poor survival rate, and it was suggested that these high-risk patients should benefit from CCRT followed by adjuvant chemotherapy. [*J Chin Med Assoc* 2008;71(9): 461–466]

Key Words: nasopharyngeal carcinoma, primary tumor volume, survival

Introduction

Nasopharyngeal carcinoma (NPC) is prevalent in Southern China and Taiwan. To optimize treatment strategies for cancer patients, accurately predicting prognosis and failure is crucial. Numerous staging systems for NPC have been used throughout the world. The most popular and widely used is the TNM staging system: the American Joint Committee of Cancer (AJCC) staging system. However, it has some limitations, and incorporation of additional prognostic factors might be helpful for further refinement of prognostic accuracy. It is now known that primary tumor volume (PTV) is a significant prognostic factor in the treatment of malignant tumor.[1–5] Several studies have confirmed the relationship between tumor volume and treatment outcome in NPC. Sze et al[6] reported that NPC patients with larger tumor volume had more locoregional recurrence. Chen et al[7] revealed that when PTV was separated into 4 categories, the corresponding survival curves were clearly separated and hazard ratios increased with increasing tumor volume.

*Correspondence to: Dr Ching-Chih Lee, Department of Otolaryngology, Buddhist Tzu Chi Dalin General Hospital, 2, Min-Sheng Road, Dalin, Chiayi 622, Taiwan, R.O.C.
E-mail: ml2406@hotmail.com • Received: February 15, 2008 • Accepted: August 11, 2008

Multivariate analysis revealed that tumor volume was a dominant covariate after adjusting for T stage, N stage, and disease stage.[6–8] Chua et al[8] reported that PTV represented an independent prognostic factor of local control and appeared to be predictive.

Nevertheless, the outcome of different treatment modalities according to different tumor size or prognostic factor has seldom been addressed.[9] In this study, we explored the failure patterns of NPC patients, according to PTV, who were treated in Kaohsiung Veterans General Hospital, and analyzed how the patterns of failure were affected by different treatment approaches.

Methods

From 2002 to 2006, 133 patients with newly diagnosed NPC were identified from the Department of Otolaryngology. Thirty-three patients were not eligible for analysis because of the presence of distant metastasis at the time of presentation, loss to follow-up or incomplete baseline magnetic resonance imaging (MRI) information. Patients were staged according to the 1997 AJCC stage classification.

Measurement of gross tumor volume of the primary and involved retropharyngeal nodes was based on the imaging system in our hospital. First, manual tracing was performed using a graphic user interface and area inside the outline was automatically labeled and calculated. The volume was calculated by multiplying the sum of all areas by the image reconstruction interval (summation of area technique). All images were evaluated by the first author (S.T.C.). A radiologist who specialized in head and neck cancer participated when the outline of the tumor margin was unclear.

A multidisciplinary team including head and neck surgeons and medical, radiation and nurse oncologists were responsible for patient management. A complete course of 3-dimensional conventional radiotherapy (RT) with a radiation dosage of 70–75 Gy was applied to all patients. Concurrent chemoradiotherapy (CCRT) was arranged for patients who had advanced T (T2–T4) classification or positive neck metastasis. These patients received 3 cycles of cisplatin (100 mg/m^2 injection on day 1 concomitantly with RT in weeks 1, 4 and 7). Subsequent adjuvant chemotherapy consisted of cisplatin 100 mg/m^2 injection on day 1 and 5-FU 1,000 mg/m^2 24-hour continuous infusion on day 1–5 for 3 courses after CCRT in patients with T2b–T4 or N2–3 stage, according to the regimen used in Intergroup study 0099.[10]

MRI was arranged for assessment of tumor response at 2 months after completion of treatment. On completion of treatment, patients would undergo biopsy if residual tumor was visible at 6 weeks after treatment. Patients with a complete response to treatment were followed-up regularly every 1 month in the first year, every 2 months in the second year, and every 3 months thereafter. Chest X-ray was taken yearly, whereas MRI, bone scan, and ultrasound of the abdomen were performed only when clinically indicated.

Statistical analysis was performed using SPSS statistical software (SPSS Inc., Chicago, IL, USA). For continuous variables, we used 2-sample *t* tests to examine the difference between the 2 groups. For categorical variables, Pearson's χ^2 test or Fisher's exact test were used to assess the associations between different treatment groups. Kaplan-Meier plots and the log-rank test were used to estimate tumor recurrence (locoregional, distant, or both) and overall survival. Cox proportional hazards regression analysis was used to assess the prognostic impact of PTV. Receiver operating characteristic (ROC) curve analysis was performed to select the most appropriate tumor size for clinical use.

Results

Forty-one patients (41%) received CCRT and 26 patients (26%) received CCRT with adjuvant chemotherapy. The median PTV of the whole series was 12.94 mL (range, 1.25–69 mL). With a median follow-up of 28.5 months (range, 6–64 months), 17 (16%) patients had relapse, 9 (8.5%) had locoregional recurrence, and 11 (10.3%) had distant metastasis. Six patients died. The 5-year overall survival was 93.7%, locoregional control survival was 90.9%, and distant metastasis-free survival was 87.5%. Table 1 shows the T stage distribution and PTV for each stage. Although the variation within the same T stage was wide, the median PTV increased in an orderly fashion with advancing T stage: T1 (n=21), 6.81 mL; T2 (n=20), 12.95 mL; T3 (n=36), 15.57 mL; and T4 (n=23),

Table 1. T stage of nasopharyngeal carcinoma patients and primary tumor volume (PTV)

	PTV (mL)	
	Median	Range
T1 (n=21)	6.81	2.99–15.34
T2 (n=20)	12.95	5.76–31.06
T3 (n=36)	15.57	7.21–34.35
T4 (n=23)	33.97	11.22–75.01

33.88 mL. Overlap of PTV was noted between each T stage. However, primary tumor classified as a more advanced T stage had a significantly larger PTV than those with an early T stage ($p<0.001$).

ROC analysis was applied to find the appropriate cut-off point of tumor size. The selected sensitivity and specificity for cut-off points of tumor size are presented in Table 2. Tumor size ≥15 mL was used to define positive cases; this resulted in the most appropriate sensitivity of 1.0 and specificity of 0.54 for overall survival, sensitivity of 0.73 and specificity of 0.54 for distant metastasis, and sensitivity of 0.56 and specificity of 0.53 for any recurrence. Fifteen mL was defined as the critical cut-off tumor volume, and 3-year overall survival in the large tumor volume group (>15 mL) and small tumor volume group (≤15 mL) were 77.9% and 100%, respectively ($p=0.002$; Figure 1). The 3-year metastasis-free survival was 81.6% in the large tumor volume group and 91.2% in the small tumor volume group ($p=0.08$; Figure 2). Although the large tumor volume group had more locoregional failure and recurrence, the differences were not statistically significant ($p=0.55$ and $p=0.3$, respectively).

PTV was a significant prognostic factor for distant metastasis (hazard ratio [HR], 1.05; $p=0.005$), any relapse (HR, 1.04; $p=0.006$), and overall survival (HR, 1.1; $p<0.001$) on univariate analysis. PTV remained an independent prognostic factor for distant metastasis (HR, 1.04; $p=0.03$), any relapse (HR, 1.04; $p=0.02$), and overall survival (HR, 1.09; $p<0.001$) when using T stage as a covariate (T1–2 *vs.* T3–4). The HRs for advanced T stage (T3–4) were not statistically significant for distant metastasis, any relapse and overall survival ($p=0.41$, 0.95 and 0.96, respectively).

Table 3 shows the general data and failure patterns of NPC patients treated with RT or CCRT alone *vs.* CCRT with adjuvant chemotherapy. Among patients with small tumor volume (PTV≤15 mL), there was no significant difference in total failure between different treatment modalities ($p=0.87$). The 3-year metastasis-free survival rate for this subset of patients with small tumor volume treated with RT or CCRT

Table 2. Validity of tumor size using death, distant metastasis or any recurrence as the standard

Cut-off point	Overall survival		Distant metastasis		Any recurrence	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
10 mL	1	0.31	0.91	0.32	1	0.32
15 mL	1	0.54	0.73	0.54	0.56	0.53
20 mL	1	0.78	0.55	0.77	0.38	0.76
30 mL	0.83	0.89	0.36	0.87	0.31	0.87
40 mL	0.67	0.99	0.18	0.96	0.19	0.98

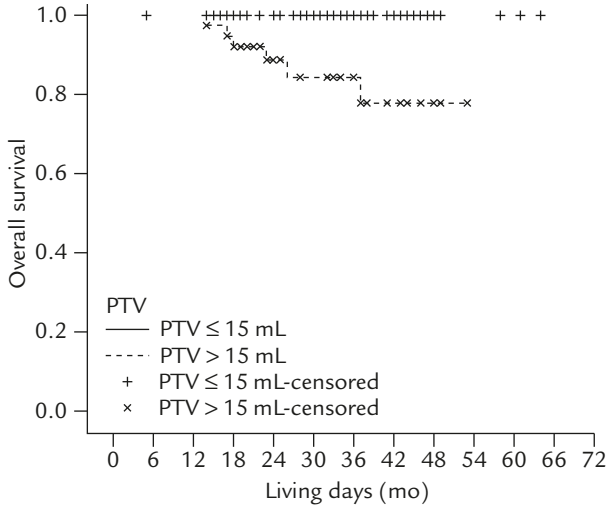

Figure 1. Effect of primary tumor volume (PTV) on overall survival of nasopharyngeal carcinoma patients.

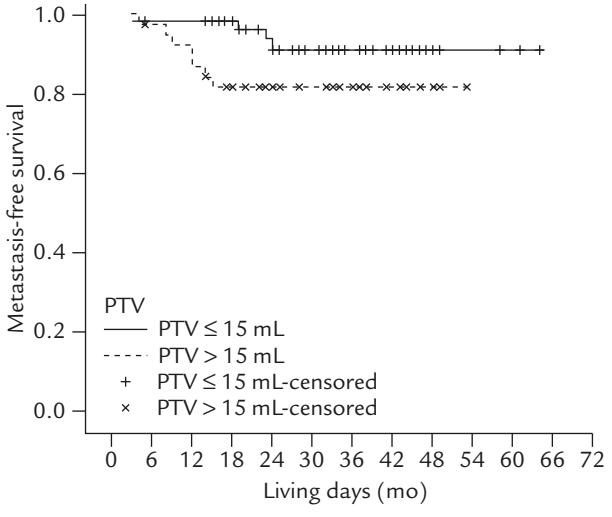

Figure 2. Effect of primary tumor volume (PTV) on metastasis-free survival rates of nasopharyngeal carcinoma patients.

Table 3. Failure patterns of patients treated with radiotherapy (RT)/concurrent chemoradiotherapy (CCRT) alone or CCRT with adjuvant chemotherapy (CT) according to different primary tumor volumes (PTV)

	PTV ≤ 15 mL			PTV > 15 mL		
	CCRT or RT (n = 41)	CCRT + CT (n = 8)	p*	CCRT or RT (n = 33)	CCRT + CT (n = 18)	p*
PTV, mL			0.96			0.06
Mean ± SD	9.38 ± 0.51	9.32 ± 1.15		24.93 ± 2.58	33.91 ± 3.56	
Range	2.99–14.78	6.89–14.07		15.04–75	16.48–67.8	
T stage, n			0.45			0.69
T1–T2	25	6		7	3	
T3–T4	16	2		26	15	
Failure patterns, n (%)						
LR	4 (9.8)	0 (0)		4 (12.1)	1 (5.6)	
DM	2 (4.9)	1 (12.5)		8 (24.2)	0 (0)	
LR + DM	0 (0)	0 (0)		3 (9.1)	0 (0)	
Total failure rate	6 (14.63)	1 (12.5)	0.87	9 (27.3)	1 (5.6)	0.06

**Peasons's χ^2 test or Fisher's exact test for categorical variables and 2-sample t test for continuous variables. SD = standard deviation; LR = locoregional recurrence; DM = distant metastasis.*

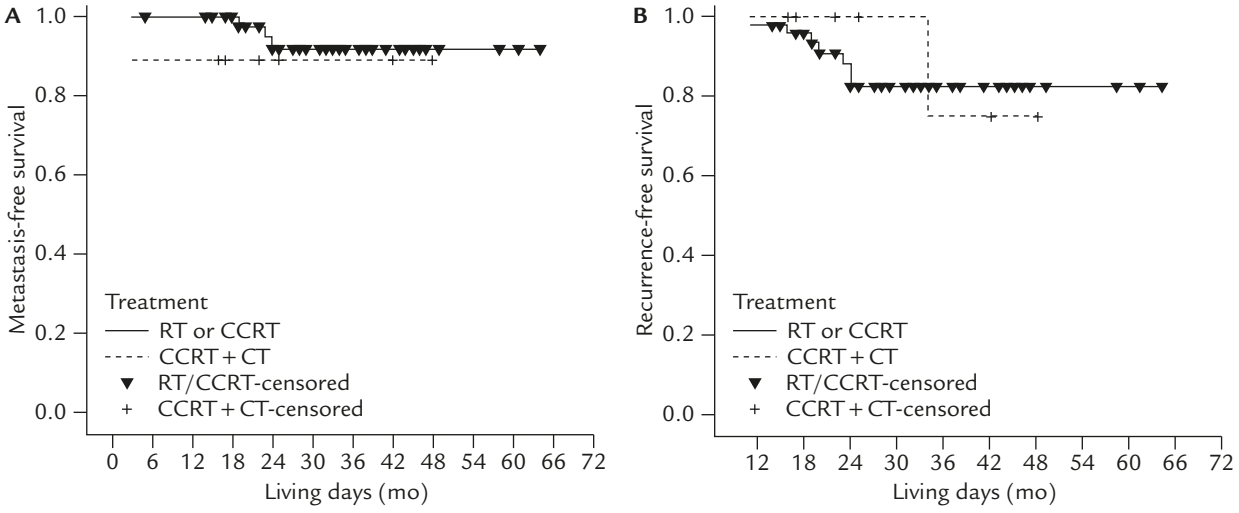

Figure 3. (A) Metastasis-free survival and (B) recurrence-free survival in nasopharyngeal carcinoma patients with small tumor volume treated with and without adjuvant chemotherapy.

alone was 91.8%; for those treated with CCRT followed by adjuvant chemotherapy, it was 88.9% (p = 0.44; Figure 3A). The 3-year recurrence-free survival rate for patients treated with RT or CCRT alone was 82.7%; for those treated with CCRT followed by adjuvant chemotherapy, it was 75% (p = 0.84; Figure 3B). The 3-year overall survival rate for patients treated with any treatment was 100%.

This retrospective analysis showed a significant reduction in recurrence (locoregional recurrence, distant metastasis) in the large tumor volume group (PTV > 15 mL) treated with CCRT with adjuvant chemotherapy compared with those treated with RT or CCRT alone. The total failure rate was reduced from 27.3% to 5.6% (p = 0.06). Within this subset, locoregional recurrence with adjuvant chemotherapy was reduced from 12.1% to 5.6% (p = 0.42), and distant metastasis from 24.2% to 0% (p = 0.02). The 3-year metastasis-free survival rate for this subset of patients with large tumor volume treated with RT or CCRT alone was 68.3%; for those treated with CCRT followed by adjuvant chemotherapy, it was 100% (p = 0.02; Figure 4A). The 3-year recurrence-free survival rate for patients treated with RT or CCRT alone was 69.6%; for those treated with CCRT followed by adjuvant chemotherapy, it was 94.1% (p = 0.06; Figure 4B). The 3-year overall survival rate for patients treated with RT or CCRT alone was 81.2%; for those treated

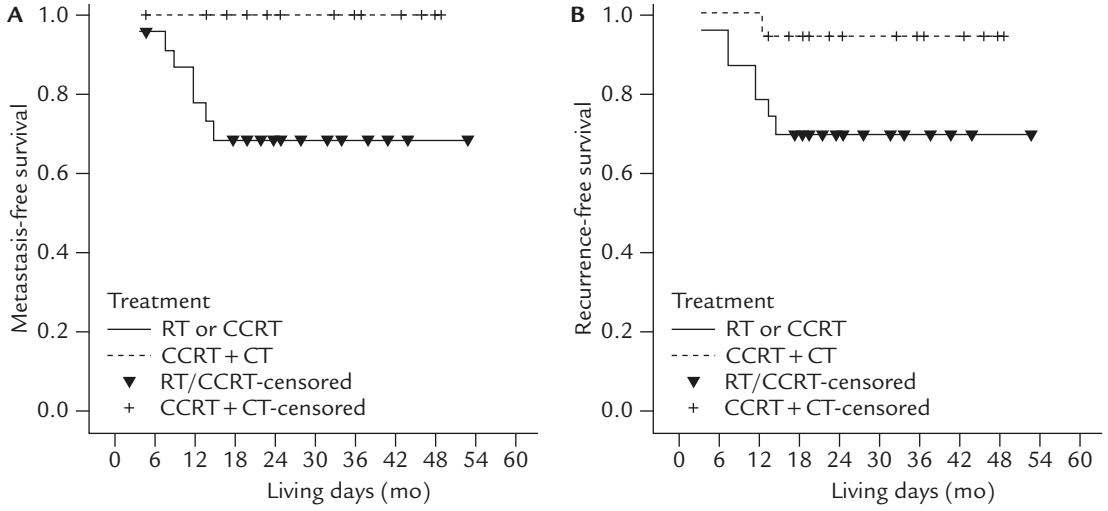

Figure 4. (A) Metastasis-free survival and (B) recurrence-free survival in nasopharyngeal carcinoma patients with large tumor volume treated with and without adjuvant chemotherapy.

with CCRT followed by adjuvant chemotherapy, it was 87.4% ($p=0.59$).

Discussion

PTV has a close relationship with survival rates of patients with NPC according to previous studies. Chua et al[8] revealed that PTV represented an independent prognostic factor of local control and appeared to be more predictive than Ho's T classification. Chen et al[7] reported that PTV was better at determining cumulative survival for patients with NPC than the AJCC staging system. Multivariate analysis revealed that tumor volume was a dominant covariate after adjusting for T stage, N stage and disease stage.[6–8]

In this study, we retrospectively analyzed the MR images of patients with newly diagnosed NPC. Manual tracing was performed using a graphic user interface and area inside the outline was automatically labeled and calculated. The volume was calculated by multiplying the sum of all areas by the image reconstruction interval (summation of the area technique). The mean percentage errors of volume calculations using the technique were within a range of 5–10% when compared with volume determined by water displacement and the reproducibility of volume measurement was even better than 5%.[11,12] Measurement of tumor volume has become simpler and no more time-consuming nor labor-intensive with the improvement of imaging software. MRI was chosen to evaluate the tumor contour of the NPC patients in this series. MRI is superior to computed tomography for depicting the gross extent of tumor infiltration, and positive correlation between tumor volume and T classification has been validated by previous studies.[13]

A statistically significant correlation between PTV and T stage was found in our study, with median PTV increasing in an orderly fashion from 6.81 mL for T1 to 33.97 mL for T4 (Table 1). Univariate analysis showed that PTV was a significant prognostic factor for distant metastasis (HR, 1.05; $p=0.005$), any relapse (HR, 1.04; $p=0.006$), and overall survival (HR, 1.1; $p<0.001$). PTV remained an independent prognostic factor for distant metastasis (HR, 1.04; $p=0.03$), any relapse (HR, 1.04; $p=0.02$), and overall survival (HR, 1.09; $p<0.001$) when using T stage as a covariate. However, the HRs for advanced T stage (T3–4) were not statistically significant for distant metastasis, any relapse and overall survival.

Our data also showed that a volume of 15 mL was a useful cut-off point to categorize patients into good and poor prognostic groups. NPC patients with PTV ≤ 15 mL had better 5-year overall survival rate and metastasis-free survival ($p=0.0045$ and 0.045, respectively).

In the Intergroup study, NPC patients with AJCC stage II–IVB were treated with CCRT and adjuvant chemotherapy.[10] Cheng et al[9] reported that stage II–III NPC with T2b and T3 disease conferred a greater risk of recurrence and is a group that would benefit from CCRT followed by adjuvant chemotherapy. The 5-year survival rate was expected to improve from 62.5% to 84.4% ($p=0.005$) in T2b or T3 disease. The improvement in survival rate with adjuvant chemotherapy was not observed in low-risk patients without parapharyngeal invasion or skull base involvement. In our study, dividing the patients into 2 groups according to the

critical volume of 15 mL was appropriate for analysis. Differences were not significant with a cut-off tumor volume of 10 mL or 20 mL. In the large tumor volume group (PTV > 15 mL), our data showed the potential benefits of adjuvant chemotherapy in addition to RT or CCRT. Using adjuvant chemotherapy, the 3-year metastasis-free survival increased from 68.3% to 100% ($p = 0.02$; Figure 4) and the 3-year recurrence-free survival increased from 69.6% to 94.1% ($p = 0.06$). The benefit of adjuvant chemotherapy was not observed in the small tumor volume group.

Wu et al[14] reported the important relationships among tumor volume, radiation dose, and local control. They suggested that escalation of radiation dose, such as by using conformal RT, was worth considering in patients with large tumor volume. Teo et al[15] reported that addition of a brachytherapy boost could significantly improve the 5-year local failure-free survival from 88% to 94% for stage T1–T2a treated by 2-dimensional RT. However, 6% of patients with the boost experienced chronic ulceration in the nasopharyngeal area compared with 0.3% of those without the boost. Cheng et al[9] reported that NPC patients with parapharyngeal invasion or skull base involvement had worse survival rate and these patients could benefit from CCRT followed by adjuvant chemotherapy. It would be of value if we could accurately identify the high-risk patients and tailor the radiation dose and adjuvant chemotherapy accordingly. PTV was a significant prognostic factor in NPC patients in univariate and multivariate analyses according to our study. Large tumor volume (PTV > 15 mL) treated with CCRT followed by adjuvant chemotherapy had less recurrence and distant metastasis.

In conclusion, the risk of recurrence in NPC patients with small tumor volume is low. NPC patients with large tumor volume (PTV > 15 mL) have more recurrence and poor survival rates. They would benefit from CCRT followed by adjuvant chemotherapy. In addition to the current AJCC staging system, measurement of PTV may be needed to predict prognosis of NPC and help to identify high-risk patients and adjust treatment strategy.

References

1. Chen SW, Yang SN, Liang JA, Tsai MH, Shiau AC, Lin FJ. Value of computed tomography–based tumor volume as a predictor of outcomes in hypopharyngeal cancer after treatment with definitive radiotherapy. *Laryngoscope* 2006;116:2012–7.
2. Johnson CR, Thames HD, Huang DT, Schmidt-Ullrich RK. The tumor volume and clonogen number relationship: tumor control predictions based upon tumor volume estimates derived from computed tomography. *Int J Radiat Oncol Biol Phys* 1995;33:281–7.
3. Mayr NA, Magnotta VA, Ehrhardt JC, Wheeler JA, Sorosky JI, Wen BC, Davis CS, et al. Usefulness of tumor volumetry by magnetic resonance imaging in assessing response to radiation therapy in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1996;35:915–24.
4. Mukherji SK, Schmalfuss IM, Castelijns J, Mancuso AA. Clinical applications of tumor volume measurements for predicting outcome in patients with squamous cell carcinoma of the upper aerodigestive tract. *AJNR Am J Neuroradiol* 2004;25:1425–32.
5. Willner J, Baier K, Pfreundner L, Flentje M. Tumor volume and local control in primary radiotherapy of nasopharyngeal carcinoma. *Acta Oncol* 1999;38:1025–30.
6. Sze WM, Lee AWM, Yau TK, Yeung RMW, Lau KY, Leung SKC, Hung AWM, et al. Primary tumor volume of nasopharyngeal carcinoma: prognostic significance for local control. *Int J Radiat Oncol Biol Phys* 2004;59:21–7.
7. Chen MK, Chen THH, Liu JP, Chang CC, Chie WC. Better prediction of prognosis for patients with nasopharyngeal carcinoma using primary tumor volume. *Cancer* 2004;100: 2160–6.
8. Chua DT, Sham JS, Kwong DL, Tai KS, Wu PM, Lo M, Yung A, et al. Volumetric analysis of tumor extent in nasopharyngeal carcinoma and correlation with treatment outcome. *Int J Radiat Oncol Biol Phys* 1997;39:711–9.
9. Cheng SH, Tsai SYC, Yen KL, Jian JJM, Feng AC, Chan KY, Hong CF, et al. Prognostic significance of parapharyngeal space venous plexus and marrow involvement: potential landmarks of dissemination for stage I–III nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2005;61:456–65.
10. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, Forastiere AA, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;16: 1310–7.
11. Breiman RS, Beck JW, Korobkin M, Glenny R, Akwari OE, Heaston DK, Moore AV, et al. Volume determinations using computed tomography. *AJR Am J Roentgenol* 1982;138:329–33.
12. Pameijer FA, Balm AJ, Hilgers FJ, Muller SH. Variability of tumor volumes in T3-staged head and neck tumors. *Head Neck* 1997;19:6–13.
13. Chong VFH, Zhou JY, Khoo JBK, Chan KL, Huang J. Correlation between MR imaging-derived nasopharyngeal carcinoma tumor volume and TNM system. *Int J Radiat Oncol Biol Phys* 2006;64:72–6.
14. Wu PM, Chua DT, Sham JS, Leung L, Kwong DL, Lo M, Yung A, et al. Tumor control probability of nasopharyngeal carcinoma: a comparison of different mathematical models. *Int J Radiat Oncol Biol Phys* 1997;37:913–20.
15. Teo PM, Leung SF, Lee WY, Zee B. Intracavitary brachytherapy significantly enhances local control of early T-stage nasopharyngeal carcinoma: the existence of a dose-tumor-control relationship above conventional tumoricidal dose. *Int J Radiat Oncol Biol Phys* 2000;46:445–58.