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Significance of Primary Tumor Volume and T-stage on Prognosis in Nasopharyngeal Carcinoma Treated with Intensity-modulated Radiation Therapy

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Objective: The aim of this study was to evaluate the effect of the primary tumor volume on prognosis in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy.
Methods: Between August 2003 and April 2005, 112 patients with Stage I–IVB nasopharyngeal carcinoma treated by intensity-modulated radiation therapy were included. Measurement of the primary tumor volume was based on contrast-enhanced computed tomography scans before treatment. A receiver operating characteristics curve was used to determine the best cut-off point of the primary tumor volume.
Results: The mean primary tumor volume for 112 patients with nasopharyngeal carcinoma was 33.9 ± 28.7 ml. Within the framework of UICC T-staging, all patients were divided into four groups according to the primary tumor volume. We call it the volume stage (V1 <15.65 ml, V2 = 15.65–24.25 ml, V3 = 24.25–50.55 ml and V4 >50.55 ml). The 5-year overall survival rates for V1, V2, V3 and V4 were 88.5, 83.3, 82.4 and 54.5% ($P = 0.014$), respectively. The cumulative survival curves for V1, V2 and V3 were very close, but clearly separated from V4. In addition, Cox proportional hazards regression model analysis showed that a primary tumor volume >50 ml was an independent risk factor for radiotherapy (risk ratio = 3.485, $P = 0.025$).
Conclusions: This study demonstrated that the primary tumor volume had significantly impacted on the prognosis of patients with nasopharyngeal carcinoma. We proposed that the primary tumor volume should be considered as an additional stage indicator in the new revision of the clinical stage of nasopharyngeal carcinoma.

Key words: nasopharyngeal carcinoma, intensity-modulated radiation therapy, primary tumor volume

INTRODUCTION

Nasopharyngeal carcinoma (NPC), a malignant tumor in the head and neck region, has a remarkably distinctive ethnic and geographic distribution. The highest incidence is found among Southern Chinese (25–30 per 100 000 persons per year), especially those of Cantonese origin (1). Radiation therapy is the mainstay treatment for NPC. Intensity-modulated radiation therapy (IMRT), which was developed in the late 20th century, is considered as a landmark development in radiation therapy. IMRT enables the delivery of higher radiation dose to the lesion while sparing the organs at risk (OAR), thus enhancing the therapeutic ratio, and has been accepted as an ideal radiation modality for NPC (2–4).

Currently, the TNM-staging system developed by UICC is the most widely used for NPC. However, according to the system, NPC is T-staged by local anatomic location and the peripheral cranial nerves involved, and no quantitative criteria of tumor volume are taken into account (5). So far, many scholars have confirmed the significant association between the head and neck carcinoma volume and disease control (6–8). The UICC-staging system of NPC was based

on conventional radiation therapy, but IMRT is generally acknowledged as a more advantageous technique. Further discussion needs to be proposed on whether it affects the staging system. Our study aimed to analyze the correlation between primary tumor volume and prognosis in NPC treated with IMRT within the current stage framework.

PATIENTS AND METHODS

Patient and Staging Evaluation

Between August 2003 and April 2005, 114 consecutive patients with NPC were treated primarily with IMRT at our institution. Excluding 2 patients with Stage IVc disease (UICC, sixth edition in 2002), 112 patients treated by IMRT were included. Patients' characteristics are listed in Table 1.

Primary Tumor Volume Measurement

Pretreatment contrast-enhanced computed tomography scan was performed with contiguous axial scans of 3 mm slices from the top of the head to the level of 2 cm below the sternoclavicular joint. Image data were input into a 3D treatment-planning system, and the primary lesion was manually outlined on each image using treatment-planning software. The gross tumor volume of the primary tumor plus retropharyngeal nodes was included in the primary tumor volume measurement. The system can automatically reconstruct a 3D image and calculate the primary tumor volume.

Treatment

Depending on curative intent, 112 patients in this study were treated with IMRT, while 79 of them had chemotherapy as a part of their treatment. The target volumes were delineated using an institutional treatment protocol defined as follows. The primary gross tumor volume (GTV-P) and the involved lymph nodes (GTV-N) included all gross disease as determined by imaging, clinical and endoscopic findings. The clinical target volumes (CTV-1, CTV-2) represented tissues felt to harbor the risk of microscopic disease. The CTV-1 was defined as the high-risk region that included GTV plus 5–10 mm margin, including the nasopharyngeal mucosa (5 mm submucosal volume). The CTV-2 was designed for potentially involved regions including the nasopharyngeal cavity, maxillary sinus, pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, anterior third of clivus and cervical vertebra, inferior spheniod sinus and cavernous sinus. Levels II–V can be incorporated into clinical target volume of the neck nodal regions (CTV-N), as recommended by the Radiation Therapy Oncology Group (RTOG) delineation consensus for head and neck malignancies. The planning target volume was created based on each volume with an additional 3-mm margin, allowing for setup variability. OAR include the brain stem, spinal cord, optic nerve, optic chiasm, temporal lobe, crystal, and parotid, pituitary and mandibular glands and so on. A total dose of 66 Gy in 30 fractions at 2.2 Gy/fraction to the planning target volume of GTV-P and GTV-N, 60 Gy at 2 Gy/fraction to the planning target volume of CTV-1, 54 Gy at 1.8 Gy/fraction to the planning target volume of CTV-2 and CTV-N were prescribed.

Seventy patients with UICC Stages III–IVB disease and nine patients with Stage II disease, whose neck adenopathy was >4 cm in diameter, received two cycles of cisplatin-based neoadjuvant chemotherapy. The total dosage of cisplatin was 80 mg/m^2. The dose was divided evenly into three parts and administered intravenously during days 1–3. The combination agent was 5-FU (800 mg/m^2 during days 1–5) or paclitaxel (100 mg/m^2 on the first day). Neoadjuvant chemotherapy was repeated every 2 weeks and the total number of cycles was two prior to the initiation of IMRT treatment. IMRT started within 1 week after the second administration of chemotherapy agents. Concurrent and adjuvant chemotherapy were not protocolized; nevertheless, one cycle of concurrent chemotherapy (the same dose of cisplatin described above) was given to 19 patients and two cycles of adjuvant chemotherapy were given to 15 patients at the discretion of the attending radiation oncologists. The adjuvant chemotherapy protocol was paclitaxel (135 mg/m^2 on the first day) plus the same dose of cisplatin described above. Concurrent and adjuvant chemotherapy were repeated every 21 days.

Table 1. Patients' characteristics

Characteristic	No. of patients (%)
Age (years)	
Median	43.5
Range	12–73
≤50	73 (65.2%)
>50	39 (34.8%)
Gender	
Male	89 (79.5%)
Female	23 (20.5%)
TNM stage [UICC (5)]	
T1/T2/T3/T4	20/42/33/17 (17.9/37.5/29.5/15.1%)
N0/N1/N2/N3	28/51/30/3 (25.0/45.5/26.8/2.7%)
I/II/III/IV	6/36/50/20 (5.4/32.1/44.6/17.9%)

Patient Evaluation

Survival, including 5-year local failure-free rate (LFFR), 5-year distant failure-free rate (DFFR), 5-year disease-free survival (DFS) and 5-year overall survival (OS), was calculated from the date of diagnosis to the most recent follow-up

or to the date of recurrence, metastasis or death. The pattern of failure was defined according to the first site of failure: local failure defined as recurrence of the primary tumor or metastasis to regional lymph nodes; and distant failure indicating metastasis to any site beyond the primary tumor and regional lymph nodes. In the analysis of OS, treatment related or unknown deaths are regarded as events. Similarly, in the analysis of DFS, all deaths including treatment related or unknown deaths and disease progression are regarded as events.

Statistical Methods

Statistical analysis was performed using SPSS statistical software. Different groups were compared with respect to baseline characteristics, with the *t*-test used for continuous variables and the χ^2 test for categorical variables. A receiver operating characteristics (ROC) curve was used to determine the best cut-off point of the primary tumor volume for clinical application. The Kaplan–Meier method was used for survival analysis. The log-rank test was used to calculate the significance of differences between multiple survival curves. Cox proportional hazards regression analysis was used to assess the independent significance of different prognostic factors. Statistical significance was accepted as a P value <0.05.

RESULTS

With a median follow-up of 62.0 months for all patients, the 5-year LFFR, DFFR, DFS and OS were 89.3, 87.5, 75.0 and 78.6%, respectively. The mean primary tumor volume for all NPC patients was 33.9 ± 28.7 ml (SD) with the range of 0.8–153.7 ml. Table 2 shows the T-stage distribution and primary tumor volume for each T-stage. The variation within the same T-stage was wide, and overlaps were observed in the different T-stages; but the mean tumor volume in an advanced T-stage was significantly different from the adjacent earlier T-stage ($P = 0.003$, $P = 0.004$ and $P < 0.001$ for T2 vs. T1, T3 vs. T2 and T4 vs. T3, respectively).

The ROC curve was used to determine the best cut-off point of the primary tumor volume for clinical application. The ROC curve is a plot of sensitivity (often called the true positive rate) vs. 1-specificity (often called the false positive rate) that offers a summary of sensitivity and specificity across a range of cut-off points for a continuous predictor. Within the framework of UICC T-staging, we assumed that all patients should be divided into four groups according to the primary tumor volume. We tentatively called it the volume stage which is based on the T-stage. The advanced volume stage is larger than the adjacent earlier volume stage; consequently we had the advanced T-stage as a positive parameter when we determined the best cut-off point. For example, we used T2 patients as the positive actual state and T1 as the negative state to make the ROC curve, and then determined the best cut-off point which was used as the standard to distinguish V1 and V2. The best cut-off point should satisfy the maximization of the true positive rate and the minimization of the false positive rate. The sensitivity and 1-specificity for the best cut-off points of the primary tumor volume are presented in Table 3. The best cut-off points are 15.65, 24.25 and 50.55 ml, respectively. Table 4 shows the distribution of T-stages among various volume stages ($P < 0.001$).

According to UICC staging, the 5-year OS for I–IV stages were 95.0, 85.7, 69.7 and 58.8%, respectively ($\chi^2 = 12.797$, $P = 0.005$). The 5-year OS for T1, T2, T3 and T4 were 95.0, 85.7, 69.7 and 58.8%, respectively ($\chi^2 = 9.950$, $P = 0.019$, Fig. 1). In accordance with the volume-based groups mentioned above, the 5-year OS for V1, V2, V3 and V4 stages were 88.5, 83.3, 82.4 and 54.5%, respectively ($\chi^2 = 10.686$, $P = 0.014$, Fig. 2). The cumulative survival curves for V1, V2 and V3 are very close, but clearly separated from V4. We found that the survival rate curves of T4 and V4 were difficult to separate during follow-up ($\chi^2 = 0.056$, $P = 0.813$). Table 5 summarized the treatment outcomes of the four groups according to the primary tumor volume.

Survival analysis demonstrated a significant difference in OS with a larger primary tumor volume (>50 ml). The 5-year OS for patients whose primary tumor volume >50 and ≤50 ml were 54.5 and 84.4%, respectively ($\chi^2 = 10.428$, $P = 0.001$, Fig. 3).

The Cox proportional hazards regression model was constructed to calculate the relative risks and confidence intervals for different prognostic factors (Table 6). Multivariate analysis revealed that a primary tumor volume >50 ml and N2–3 stage were adverse prognostic factors for OS [risk

Table 2. The T-stage and the primary tumor volume (PTV)

PTV (ml)	T1	T2	T3	T4	Total
No.	20	42	33	17	112
Mean ± SD	13.2 ± 9.3	24.2 ± 14.9	36.0 ± 19.0	77.9 ± 38.5	33.9 ± 28.7
Range	0.8–40.6	5.1–75.3	9.9–102.1	26.4–153.7	0.8–153.7
Median	13.7	22.1	33.7	71.8	24.3

Table 3. The best cut-off point of the V stage

Cut-off point (ml)	Sensitivity	1-specificity	Area	95% CI	*P* value
15.65	0.810	0.300	0.779 ± 0.063	0.655–0.902	<0.001
24.25	0.727	0.310	0.712 ± 0.062	0.591–0.833	0.002
50.55	0.765	0.182	0.837 ± 0.061	0.717–0.957	<0.001

CI, confidence interval.

Table 4. The distribution of stage among various volume-based groups

Volume stage	T1	T2	T3	T4
V1	14	8	4	0
V2	5	21	4	0
V3	1	10	19	4
V4	0	3	6	13

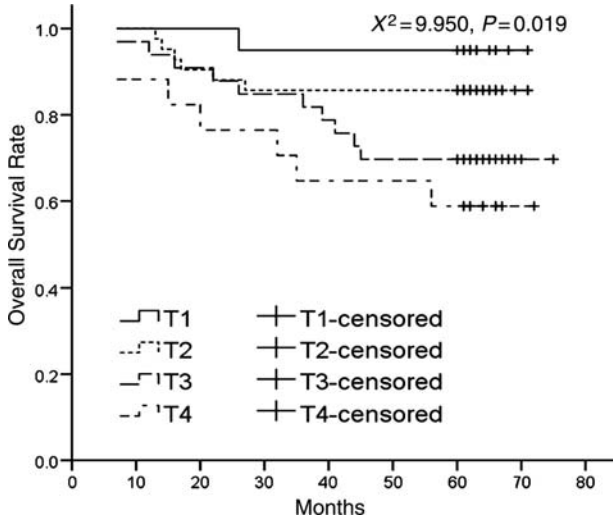

Figure 1. The cumulative survival curves by the T-stage.

ratio (RR) = 3.485, $P = 0.025$; RR = 4.979, $P < 0.001$, respectively].

DISCUSSION

The objectives of the staging system are to guide clinicians to make a reasonable treatment plan, estimate the prognosis, assess the treatment effect, exchange treatment information in different treatment centers and conduct further research in related fields. Due to the impact of anatomical location, nasopharyngeal lesions are very irregular and it is difficult to estimate its volume. The quantitative criterion of tumor

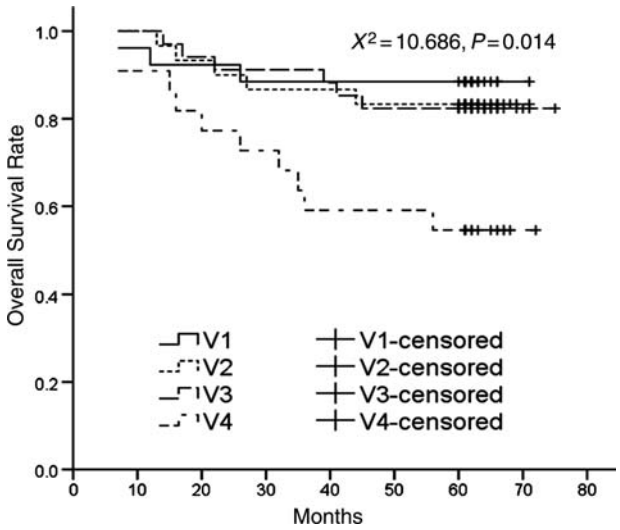

Figure 2. The cumulative survival curves by the primary tumor volume (PTV).

Table 5. Treatment outcomes of the different PTV

PTV (ml)	5-y LFFR (%)	5-y DFFR (%)	5-y DFS (%)	5-y OS (%)
<15.65	96.2	92.3	84.6	88.5
15.65–24.25	93.3	90.0	83.3	83.3
24.25–50.55	88.2	91.2	79.4	82.4
>50.55	77.3	72.7	45.5	54.5
χ^2, *P* value	8.311, 0.04	6.797, 0.079	16.497, 0.001	10.686, 0.014

5-y LFFR, 5-year local failure-free rate; 5-y DFFR, 5-year distant failure-free rate; 5-y DFS, 5-year disease-free survival; 5-y OS, 5-year overall survival.

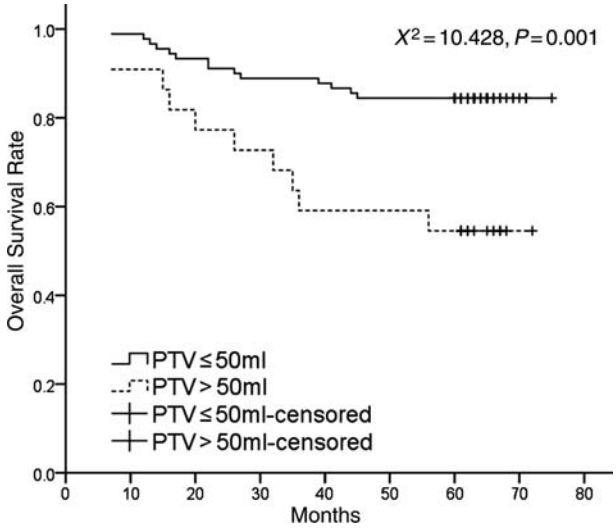

Figure 3. The cumulative survival curves by PTV (≤50 and >50 ml).

Table 6. The Cox proportional hazards model analysis

Variable	RR	95% CI	*P* value
Sex (female vs. male)	0.700	0.225–2.180	0.539
Age (≤50 vs. >50 years)	1.933	0.789–4.734	0.149
N-stage (N0–1 vs. N2–3)	4.979	2.086–11.884	<0.001
Chemotherapy (no vs. yes)	0.424	0.149–1.203	0.107
PTV (≤50 vs. >50 ml)	3.485	1.167–10.409	0.025
T-stage (T1–2 vs. T3–4)	1.498	0.458–4.897	0.504

CI, confidence interval; PTV, primary tumor volume; RR, risk ratio.

volume has not been included in the current UICC T-staging of NPC, too. However, tumor volume is associated with radiation tolerance, hypoxia and distant metastasis of cancer cells (9–11).

Some scholars have reported their findings on the relationship between tumor volume and prognosis of patients with NPC. However, how to divide reasonable the tumor volume and evaluate the effect of tumor volume on prognosis are inconclusive. Shen et al. (12) revealed that using four categories of the primary tumor volume (<20, 20–40, 40–60 and >60 ml), the 5-year LFFRs were 91.9, 89.5, 81.2 and 48.9%, respectively ($P = 0.002$). Lee et al. (13) reported that using four categories of primary tumor volume (<15, 15–25, 25–50 and >50 ml), cumulative survival curves were clearly separated ($P < 0.02$) and survival analysis demonstrated a significant difference in OS with a larger tumor volume (RR = 5.447, $P = 0.044$). Zhou et al. (14) correlated T-stage to tumor volume-based groups using a statistic-based analysis scheme. On the basis of their result, tumor volume could be used to indicate the following: tumors <12 ml, early disease; between 12 and 31 ml, intermediate disease; and >31 ml, advanced disease. But they have not analyzed the relationship between tumor volume and prognosis or verified whether it is suitable for clinical application.

In this study, we retrospectively analyzed the correlation between primary tumor volume and prognosis of NPC treated with IMRT. We believe that the amendment of the clinical stage should be within the existing framework, because the present UICC TNM staging has been implemented on a large scale. Unlike previous studies, our obtained tumor volume grouping was based on the current T-staging through statistical analysis. The ROC curve was applied to determine the best cut-off point of the primary tumor volume. Within the framework of UICC T-staging, all patients were divided into four groups according to the best cut-off points of the primary tumor volume (V1 <15.65 ml, V2 = 15.65–24.25 ml, V3 = 24.25–50.55 ml and V4 >50.55 ml). So we could test the value of such volume grouping by incorporating them into stage groups and correlating them with treatment outcome.

According to UICCstaging, the cumulative survival curves of the T-stage and the clinical stage were clearly separated, which indicated that the UICC TNM-staging system was a reasonable clinical staging. By four categories of the primary tumor volume, the 5-year OS for V1, V2, V3 and V4 groups were 88.5, 83.3, 82.4 and 54.5%, respectively($P = 0.014$).

The cut-off point to categorize patients into good and poor prognostic groups is still controversial. Chu et al. (15) reported that the large tumor volume (primary tumor volume >15 ml) was associated with more recurrence and a poor survival rate. Most scholars agreed that a tumor volume >50–60 ml would obviously affect the prognosis of patients. Shen et al. (12) showed that the 5-year LFFR was significantly reduced for patients with a primary tumor volume >60 ml. In our study, 5-year OS would be significantly reduced for patients with a primary tumor volume >50 ml. The Cox proportional hazards regression model analysis demonstrated a significant difference in OS with a primary tumor volume >50 ml (RR = 3.485, $P = 0.025$).

Some adverse biological factors, including hypoxia, radio resistance and the number of tumor clonogen cells, may be related to a poor OS rate of a large tumor volume. The tumor of more than a certain diameter will lack oxygen especially in the center of the mass. It is usually accepted that oxygenation is of paramount importance for the efficacy of radiation therapy. More clonogen cells exist with an increase in the tumor volume, and the sensitivity of the cloned cells responding to radiotherapy is low in a large tumor, which will lead to more difficulties in the treatment.

How much tumor volume can be included to the TNM system as an additional indicator of staging? Figure 2 showed that the cumulative survival curves for V1, V2 and V3 were close, but were clearly separated with V4. The survival rate curves of T4 and V4 were difficult to separate, and they even coincide with each other. This implied that there might be significantly lower OS for patients with a primary tumor volume >50 ml. In fact, survival analysis showed the 5-year OS for patients whose primary tumor volume >50 and ≤50 ml were 54.5 and 84.4%, respectively ($P = 0.001$). So it was concluded that the survival rate for patients with a primary tumor volume >50 ml was poor, which is different from that for a primary tumor volume ≤50 ml and was similar to that for patients with T4. Therefore, we recommend that patients with a primary tumor volume >50 ml should be classified as the T4 stage. However, we were unable to further explore how the primary tumor volume affected the prognosis in the same T-stage because the number of each group was relatively limited if 112 patients were divided into four groups according to the T-stage.

Since the primary tumor volume has significantly impacted on the prognosis of patients with NPC, how do

we improve the prognosis? In our study, all patients received primary IMRT. IMRT is an ideal radiation modality for NPC, due to its potential for excellent target coverage and normal tissue sparing. Kam et al. (2) found that IMRT achieved an improvement in the therapeutic ratio by delivering a higher dose to the target while keeping the normal organs below the maximum tolerance dose. Willner et al. (16) evaluated the correlation between tumor volume and the total dose necessary to obtain local control, and found a steep dose–response relationship after dose-volume modification. They stated that volumes larger than 64 ml were unlikely to be controlled with conventional radiation to a total dose of 72 Gy. Chen et al. (17) also considered that increasing the radiation dose was necessary for a primary tumor volume $>$ 60 ml. Although the COX proportional hazards regression model analysis showed that chemotherapy was not beneficial to survival in our study, Lee et al. (18) found that the subgroup with gross tumor volume of primary tumor plus retropharyngeal nodes (GTVprn) $\geq$13 ml revealed longer survival after $\geq$4 cycles of chemotherapy than after $<$ four cycles. Moreover, some studies confirmed that concurrent chemotherapy or concurrent chemotherapy plus adjuvant chemotherapy might improve the survival rate of patients with advanced NPC (19–20).

CONCLUSION

Our study demonstrated that the primary tumor volume had significantly impacted on the prognosis of patients with NPC. The 5-year OS was significantly reduced for patients with a large tumor volume ($>$50 ml), which is almost equal to that of T4. We proposed that the primary tumor volume should be considered as an additional stage indicator in the new revision of the clinical stage of NPC. At least patients with a primary tumor volume $>$50 ml should be classified as T4. Within the framework of the UICC TNM-staging system, we should consider the effect of the primary tumor volume on prognosis.

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Conflict of interest statement

None declared.

References

1. Lo KW, To KF, Huang DP. Focus on nasopharyngeal carcinoma. *Cancer Cell* 2004;5:423–8.
2. Kam MK, Chau RM, Suen J, Choi PH, Teo PM. Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation. *Int J Radiat Oncol Biol Phys* 2003;56:145–57.
3. Lee N, Xia P, Fischbein NJ, Akazawa P, Akazawa C, Quivey JM. Intensity-modulated radiation therapy for head-and-neck cancer: the UCSF experience focusing on target volume delineation. *Int J Radiat Oncol Biol Phys* 2003;57:49–60.
4. Chau RM, Teo PM, Kam MK, Leung SF, Cheung KY, Chan AT. Dosimetric comparison between 2-dimensional radiation therapy and intensity modulated radiation therapy in treatment of advanced T-stage nasopharyngeal carcinoma: to treat less or more in the planning organ-at-risk volume of the brain- stem and spinal cord. *Med Dosim* 2007;32:263–70.
5. Sobin LH, Wittekind CL, editors. *TNM Classification of Malignant Tumors*. 6th edn. New York: John Wiley & Sons, 2002.
6. Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Mancuso AA. Parameters that predict local control after definitive radiotherapy for squamous cell carcinoma of the head and neck. *Head Neck* 2003;25:535–42.
7. Chao KS, Ozyigit G, Blanco AI, Thorstad WL, Deasy JO. Intensity modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. *Int J Radiat Oncol Biol Phys* 2004;59:43–50.
8. Plataniotis GA, Theofanopoulou ME, Kalogera-Fountzila A, Haritanti A, Ciuleanou E. 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. *Int J Radiat Oncol Biol Phys* 2004;59:1018–26.
9. De JK, Merlo FM, Kavanagh MC, Fyles AW, Hedley D, Hill RP. Heterogeneity of tumor oxygenation: relationship to tumor necrosis, tumor size, and metastasis. *Int J Radiat Oncol Biol Phys*. 1998;42: 717–21.
10. Hill RP, De Jaeger K, Jang A, Cairns R. pH, hypoxia and metastasis. *Novartis Found Symp* 2001;240:154–65; discussion 165–8.
11. Evans SM, Koch CJ. Prognostic significance of tumor oxygenation in humans. *Cancer Lett* 2003;195:1–16.
12. Shen CY, Lu JD, Gu YJ, Zhu GP, Hu CS, He SQ. Prognostic impact of primary tumor volume in patients with nasopharyngeal carcinoma treated by definitive radiation therapy. *Laryngoscope* 2008;118: 1206–10.
13. Lee CC, Chu ST, Ho HC, Lee CC, Hung SK. Primary tumor volume calculation as a predictive factor of prognosis in nasopharyngeal carcinoma. *Acta Otolaryngol* 2008;128:93–7.
14. Zhou JY, Chong VF, Khoo JB, Chan KL, Huang J. The relationship between nasopharyngeal carcinoma tumor volume and TNM T-classification: a quantitative analysis. *Eur Arch Otorhinolaryngol* 2007;264:169–74.
15. Chu ST, Wu PH, Hou YY, Chang KP, Chi CC, Lee CC. Primary tumor volume of nasopharyngeal carcinoma: significance for recurrence and survival. *J Chin Med Assoc* 2008;71:461–6.
16. 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.
17. Chen MK, Chen TH, Liu JP, Chang CC, Chie WC. Better prediction of prognosis for patients with nasopharyngeal carcinoma using primary tumor volume. *Cancer* 2004;100:2160–6.
18. Lee CC, Huang TT, Lee MS, Hsiao SH, Lin HY, Su YC, et al. Clinical application of tumor volume in advanced nasopharyngeal carcinoma to predict outcome. *Radiat Oncol* 2010;5:20.
19. Chan AT, Teo PM, Ngan RK, Leung TW, Lau WH, Zee B, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol* 2002;20:2038–44.
20. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;16:1310–7.