Pretreatment Maximal Standardized Uptake Value of the Primary Tumor Predicts Outcome to Radiotherapy in Patients with Pharyngeal Cancer

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FDG PET-CT/SUV/Pharyngeal carcinoma/Radiotherapy/Tumor volume.

This study aimed to investigate whether the combination of clinical information, tumor volume and pretreatment SUVmax at the primary tumors might improve the prognostic stratification in pharyngeal cancer (PC) patients treated with radiotherapy (RT). Sixty-two patients with PC (35 oropharynx; 27 hypopharynx) treated with RT were enrolled in this retrospective analysis. All patients received pretreatment FDG- PET or PET/CT. The primary tumor relapse-free survival (PRFS) was calculated according to different variables. The median values of the SUVmax for the primary tumors (SUVp-max) and the gross tumor volume (GTVp) were used to divide patients into two groups. Independent prognosticators were identified by the Cox regression analysis. In this study, the median SUVp-max and GTVp was 11 and 15.5 ml. Patients having tumors with SUVp-max > 11 had a significantly inferior 2-year PRFS (41% *vs.* 75%, $p = 0.003$) compared with patients having lower uptake tumors. Multivariate analysis of the PRFS showed two prognostic factors: SUVp-max > 11 ($p = 0.04$, hazard ratio = 2.67) and GTVp > 15.5 ml ($p = 0.03$, hazard ratio = 2.88). For patients with a GTVp less than 15.5 ml, there was a more significant impact of SUVmax-p on their PRFS compared to that for those with large ones. We disclosed a higher pretreatment SUVp-max is a predictor for primary recurrence in PC patients treated with RT, particularly for those with smaller tumor volumes. Patients with a large tumor volume or a higher SUVp-max should be considered for requiring more aggressive treatment approaches.

INTRODUCTION

Over the past decade definitive radiotherapy (RT) or concurrent chemoradiotherapy (CCRT) has been increasingly employed in organ preservation scheme for oropharyngeal and hypopharyngeal cancers. Despite recent advances in the high-precision delivery of RT, such as intensity-modulated radiotherapy (IMRT), implementation of individualized therapy is limited by a lack of comprehensive knowledge about individual response to a given RT until treatment has been completed. Although the traditional TNM classification or computed tomogram (CT)- based tumor volume has been used as a predictor of prognosis in head and neck patients,[1,2)] this parameter may not accurately reflect RT outcome because of the greater variations in the radiosensitivity between tumors, even with the same origins.

Several methods for assessing tumor response before RT have been applied; one of the most easily or increasingly used is positron emission tomography and computed tomogram (PET/CT) or PET scan, which have the potential to improve treatment outcome by providing improved lymph node staging, and perhaps predictive factors. Theoretically, a high SUV value of the tumor probably implies a higher chance of tumor aggressiveness. Based on the results of 17 studies identified; however, the predictive value for head and neck cancer patients treated with RT or CCRT was not

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Conflicts of Interest: All authors declare there were no actual or potential conflicts of interest in this study.

doi:10.1269/jrr.11174

conclusive. Eight investigators indicated that the maximal standardized uptake value (SUVmax) could play a role in predicting RT/CCRT outcome,[3–10] whereas the others showed that it does not.[2,11–18] These inconsistencies could be a result of the heterogeneity of treatment modalities, the heterogeneity of tumor sites, the use of several endpoints and the use of various SUVmax cut-off points.[11] Furthermore, substantial numbers of patients in theses studies were treated with surgery. In particular, most published studies did not examine the impact of tumor volume when investigating the predictive value of the SUVmax. Possibly studies with homogeneous tumor types, treatment characteristics and stratified for tumor volumes would be able to establish a real role for an optimal SUVmax cut-off for future treatment individualization.

This study aimed to investigate whether the combination of clinical information, tumor volume and pretreatment SUVmax at the primary tumors might improve the prognostic stratification in pharyngeal cancer (PC) patients after definitive RT or CCRT. We hypothesized that a higher pretreatment SUVmax would adversely affect the local tumor control following RT. By this way, radiation oncologists might be able to assess the feasibility of salvage surgery earlier, or conduct a dose escalation scheme for those who have great probability of local failure.

MATERIALS AND METHODS

Patient population

Between Jan 2007 and Dec 2010, a cohort of 62 newly diagnosed oropharyngeal or hypopharyngeal cancer patients, who would undergo definitive CCRT or RT with IMRT at China Medical University Hospital, were enrolled in this retrospective study (certificate number of local institutional review board: DMR99-IRB-010-1). The median age was 51 years (range, 37 to 76 years). Fifty-nine patients were male and 3 were female. They received a pretreatment PET or PET/CT for pretreatment staging. The interval between the images and the commencement of RT was less than 2 weeks. No patient was known to have a history of diabetes and all had a normal serum glucose level before taking the PET/CT image. Nasopharyngeal cancer was not included in this study because of its relatively higher radiosensitivity and the difference in staging strategy compared to the other pharyngeal cancers. The characteristics of the 62 patients are listed in Table 1.

Table 1. Patient characteristics (totally 62)

Characteristic	Value
Age (years)	37–76 (median, 51)
Sex	Male 59, Female 3
Smoking	Yes: 53, No: 19
Betel nut	Yes: 42, No: 20
Alcoholism	Yes: 43, No: 19
Pathology	
W-D/M-D squamous cell carcinoma	44
P-D squamous cell carcinoma	8
Unclassified squamous cell carcinoma	10
Primary lesion site:	
Oropharynx:	35 (56.5%)
Hypopharynx:	27 (43.5%)
AJCC 7th Stage	II: 12, III: 20, IV: 30
GTV of the primary tumor (mL)	
mean ± SD,	25.3 ± 24.8
median (range)	15.5 (2.3–130.2)
SUVmax of the primary tumor	
mean ± SD,	11.9 ± 4.8
median (range)	11.0 (3.9–30.5)
Concurrent chemotherapy or drug	
Cisplatin-based chemotherapy	54
Cetuximab	4
None	4
Follow up (months)	6–80 (median, 24)

Abbreviation: W-D = well-differentiated; M-D =moderately-differentiated; P-D = poorly-differentiated; AJCC = American Joint Committee on Cancer; SD: standard deviation.

PET/CT image acquisition

All patients were asked to fast for at least 4 hours before ^{18}F-FDG PET/CT imaging. Approximately 60 minutes after the administration of 370 MBq of ^{18}F-FDG, images were taken by PET scanner (Advance NXi PET scanner, General Electric Medical Systems, Milwaukee, WI, USA) before December 2008 or PET/CT scanner (PET/CT-16 slice, Discovery STE, GE Medical System, Milwaukee, Wisconsin USA) after December 2008. During the uptake period, patients were asked to rest. The PET/CT workstation provided the quantification of FDG uptake in terms of SUV. Nuclear medicine physicians identified the locations and values of SUVmax for all the primary tumors (SUVp-max). Then radiation oncologists reviewed the consistency of PET/CT images with nuclear medicine physicians. They also reconfirmed the allocated point of the SUVmax within the tumors. This procedure has been addressed in our previous report.[19]

Delineation of CT-based tumor volume

CT-based tumor volume definition was previously described.[20] Briefly, contouring of the tumor volume and normal and critical structures was performed without knowledge of the PET results in an effort to reduce bias. Radiation oncologists, who had clinical experiences of more than

10 years, delineated the primary gross tumor volume (GTVp) and the metastatic lymph node volume. Neck lymph nodes were considered pathological when their smallest axis diameter was > 1 cm. To reduce inter-observer variations, at least 2 different radiation oncologists carried out the contouring of the tumors for each patient. An average of the readings was used as the measured volume.

Treatment

RT was performed using a sequential IMRT technique as reported previously.[20] 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 volumes (CTV) 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 56 days. Because a phase 3 trial showed a survival benefit of CCRT in patients with unresectable head and neck cancers,[21] patients with age less than 70 years and suitable renal function were suggested to have CCRT. In all, 54 patients had concurrent chemotherapy. The regimen consisted of cisplatin (80–100 mg/m^2 on Days 1, 22, 43). Four patients had combined Cetuximab (400 mg/m^2 loading dose, then 250 mg/m^2 weekly). Four patients received RT alone.

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. The follow-up period for all patients ranged from 6 to 80 months (median, 24 months). Following RT, the definition of primary failure was based on

Table 2. Patient outcome

Outcome	Patient number (totally 62)
Alive without evidence of recurrence	29
Alive with evidence of recurrence	11
Primary relapse alone	8
Neck lymph node relapse alone	2
Primary relapse with distant metastasis	1
Died of cancer	18
Primary relapse	12
Primary relapse and distant metastasis	1
Primary and neck lymph node relapse	3
Neck lymph node relapse	2
Died of complication without evidence of recurrent cancer	1
Died of concurrent disease	3

Table 3. The distribution of the SUVp-max and GTVp with respect to T classification

	No	Mean GTVp ± SD ml (range)	Mean SUVp-max ± SD (range)
ALL	62	25.3 ± 24.8 (2.3–130.2)	11.9 ± 4.8 (3.9–30.5)
T1-2	24	11.4 ± 5.8 (2.3–25.5)	9.9 ± 3.6 (3.9–18.7)
T3	10	31.5 ± 24.4 (3.6–72.0)	12.3 ± 3.9 (6.7–20.1)
T4	28	32.4 ± 29.1 (5.1–130.2)	13.7 ± 5.4 (5.1–30.5)

Abbreviations: GTVp = gross tumor volume of the primary tumor; SD= standard deviation; SUVp-max= maximal standard uptake value of the primary tumor.

Table 4. Result of univariate, multivariate analysis and estimating hazard ratio of for primary relapse-free survival

Variables	Univariate		Multivariate	
	p value	HR	(95% CI)	*p* value
Age				
≦ 51 vs.> 51	0.03	1.83	(0.68–4.92)	0.22
smoking				
yes vs. no	0.30	2.72	(0.16–40.41)	0.38
Betel nut				
yes vs. no	0.22	0.59	(0.14–2.46)	0.31
Alcoholism				
yes vs. no	0.03	0.25	(0.03–2.21)	0.10
Tumor sites				
OPC vs. HPC	0.60	1.39	(0.52–3.75)	0.59
T-stage				
T1-2 vs. T3-4	0.001	1.43	(0.69–2.93)	0.33
T1-3 vs. T4	0.52	0.67	(0.19–2.37)	0.58
N-stage				
N0-1 vs. N2-3	0.24	0.62	(0.22–1.77)	0.68
GTVp (mL)				
≦ 15.5 vs. > 15.5	0.012	2.88	(1.08–6.59)	0.03
SUVp-max				
≦ 11.0 vs. > 11.0	0.004	2.67	(1.04–6.84)	0.04

Abbreviations: HR = hazard ratio; CI = confidence interval; OPC= oropharyngeal cancer; HPC = hypopharyngeal cancer; GTVp = gross tumor volume of the primary tumor; SUVp-max= maximal standard uptake value of the primary tumor.

the laryngoscopy results, a CT scan of the neck, or both. The RECIST criteria were used to assess the follow-up image findings.[22] When the patient had a persistent tumor or local recurrence after initial complete remission, salvage surgery was suggested when this was technically feasible and the patient's condition allowed it.

Statistical analysis

In this study, median values for the SUVp-max and the GTVp were used as cut-off points. Because we hypothesized a positive impact of pretreatment SUVmax on local control by RT, the study endpoint simply focused on primary tumor relapse-free survival (PRFS) instead of other parameters such as nodal failure. The PRFS was calculated using the Kaplan-Meier method. A successful surgical salvage for any recurrence in primary sites or neck lymph nodes was not taken into account when labeling the relapse-free. The log-rank test and the Cox regression were performed to explore the impact of explanatory variables on PRFS. Statistical significance was defined as two-sided, $p < 0.05$. A correlation test between the SUVp-max and the GTVp was also done using the Pearson's correlation with significance at 0.01. All calculations were performed with SPSS 13.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

At the time of analysis, 29 patients were alive without

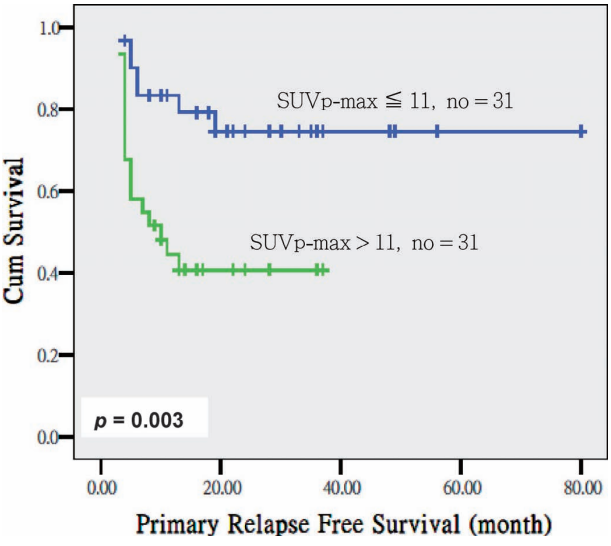

Fig. 1. Primary relapse-free survival according to the SUVp-max > 11 and ≦ 11.

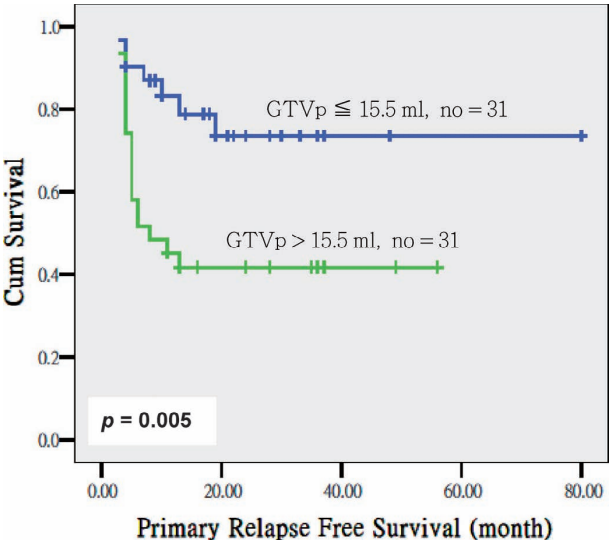

Fig. 2. Primary relapse-free survival according to the GTVp > 15.5 ml and ≦ 15.5 ml.

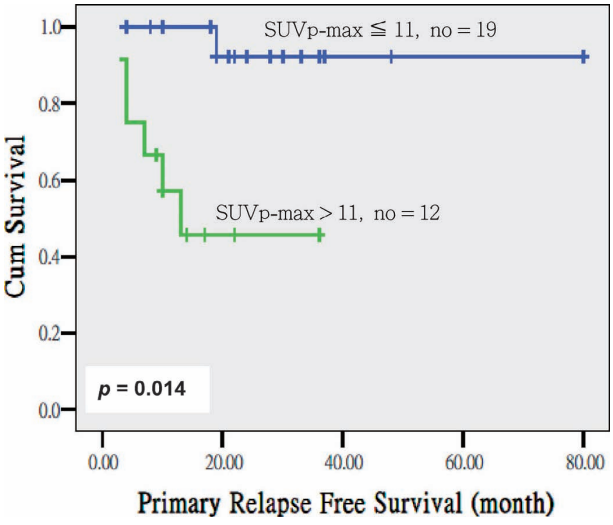

Fig. 3. Primary relapse-free survival divided by the SUVp-max > 11 and SUVp-max ≦ 11 for patients with GTVp ≦ 15.5 ml.

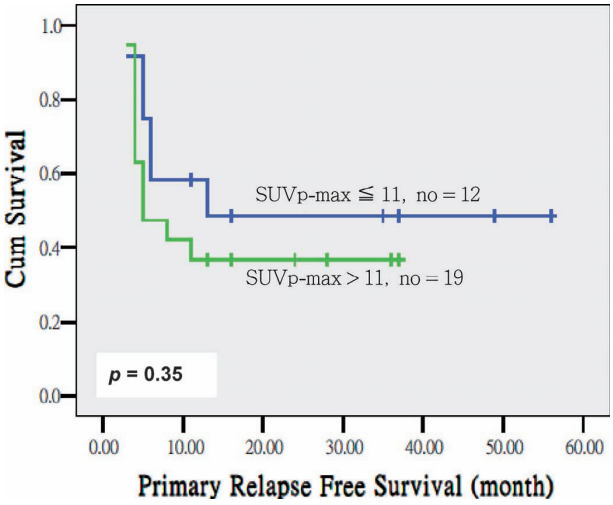

Fig. 4. Primary relapse-free survival divided by the SUVp-max > 11 and SUVp-max ≦ 11 for patients with GTVp > 15.5 ml.

known recurrent disease. Eleven patients had primary or nodal relapse but were still alive after salvage or palliative treatment. Eighteen patients had died of tumor recurrence. One had died of complication. Three patients were dead due to metachronous esophageal cancer. Table 2 summarizes the outcome of patients in this study. When initial treatment response was assessed at 1 to 2 month after the completion of treatment, complete remission of the primary tumor was observed in 42 patients (67.7%). With a median follow-up interval of 2 years, 25 patients (40.3%) developed recurrences at the primary site with or without nodal failure. For all patients, the 2-year overall survival and 2-year PRFS were 60% and 57%, respectively.

The mean SUVp-max was 11.9 ± 4.8 (median 11.0; range, 3.9 to 30.5), whereas the mean GTVp was 25.3 ml $\pm$ 24.8 (median 15.5 ml; range, 2.3 to 130.2 ml). The distribution of the SUVp-max and pGTV with respect to T classification in is shown in Table 3. The correlation test showed there was no obvious association between the GTVp and the SUVp-max values ($p = 0.24$).

The impact of the tumors and the patient-related parameters on the PRFS was analyzed by univariate and multivariate analyses, and is presented in Table 4. As illustrated in Figs. 1 and 2, patients having tumors with SUVp-max > 11 had a significantly worse 2-year PRFS (41% *vs.* 75%, $p = 0.003$) compared with those having lower uptake tumors. Subjects having tumors with GTVp > 15.5 ml had an inferior 2-year PRFS (42% *vs.* 74%, $p = 0.005$) compared with those having smaller tumor volumes. Multivariate analysis of the PRFS showed two prognostic factors: SUVp-max > 11 ($p = 0.04$, hazard ratio = 2.67, 95% CI 1.04–6.84) and GTVp > 15.5 mL ($p = 0.03$, hazard ratio = 2.88, 95% CI 1.08–6.59). When using the SUVp-max > 11 in predicting primary recurrence at 2 year, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy was 69.2%, 72.0%, 72.0%, 69.2% and 70.6%, respectively.

When the PRFS curve was further stratified by the median value of the GTVp, the 2-year PRFS for SUVp-max $\leqq$ 11 and SUVp-max > 11 were 92% and 47% ($p = 0.014$) for patients with GTVp $\leqq$ 15.5 ml, whereas that for those with large volumes were 49% and 37% ($p = 0.35$), as depicted in Figs. 3 and 4. The predictive value of the SUVp-max did better for patients with smaller tumor volumes.

To minimize the confounding variables from the treatment modalities, a subgroup analysis was carried out for 54 patients treated with CCRT. Similarly, multivariate analysis of the PRFS showed SUVp-max > 11 was a predictor with a HR of 5.84 ($p = 0.006$, 95% CI 1.65 to 20.66).

DISCUSSION

Identification of factors predictive of treatment outcome in cancer patients is of great potential interest, because such research may allow therapy to be tailored to the characteristics of individual tumors. The fact that pretreatment tumor volume can be a predictive factor is not novel. Because of variation in the radiosensitivity between tumors, treatment results might be optimized if prognostic factors, such as information from molecular image or other biomarkers could be used to supplement the clinical stage. Our study implemented patient- or tumor-related, volumetric and PET/CT data when investigating the RT outcome in PC patients. All the subjects were treated with a consistent IMRT scheme. The result demonstrated that FDG uptake of the primary tumor, as mainly measured by the SUVmax, was associated with worse PRFS in PC patients treated by IMRT. A SUVp-max > 11 represents a biological phenotype for predicting recurrence of primary tumor, particularly for those with the GTVp < 15.5 ml. This finding is consistent with a notion that within a limited tumor burden a higher FDG uptake might represent tumor aggressiveness such as proliferative activity, hypoxia, low apoptosis rate and p53 overexpression as described in some molecular studies.[23–25] These characteristics could be potentially adverse factors in patients treated with RT/CCRT.

Our findings need to be compared with some earlier RT studies for head and neck cancers. Allal *et al.*[3] showed the SUVmax of the primary tumor remained significant adverse factors, either by considering the median value of 4.76 or the best cut-off of 3.5 in terms of local control or disease-free survival. However, 39.2% (47/120) of the patients were treated with surgery in their study. On the other hand, the investigation by Brun *et al.*[4] is the only study indicating that SUVmax is a prognostic factor in a patient population treated with definitive RT/CCRT. They found that disease-free survival was worse when SUVmax was > 9. Because these studies included some proportion of patients with oral cavity cancers, which are always treated mainly by surgery with or without adjuvant RT, direct comparison might not be straightforward due to the heterogeneity of tumor sites. In addition, both studies analyzed the impact of clinical stage alone without CT-based tumor volumes information. In contrast, Ohnishi K *et al.*[2] reported an RT study for PC patients with a combination of comprehensive pretreatment parameters. In their study, SUVmax > 12 was significantly associated with local failure in univariate analysis, but only tumor volume > 10 ml remained an adverse factor in multinivariate analysis. To clarify the predictive value and an optimal cut-off point for SUVmax, previous and our studies highlighted the importance of working out comprehensive in-house data, including patient-related or volumetric information for those institutions using pretreatment FDG uptake as a biomarker for RT.

Another approach of implementing pretreatment PET/CT as a predictor is the measurement of metabolic tumor volume (MTV). Chung *et al.*[12] has investigated the outcome of RT for PC and suggested the MTV > 40 ml was only a significant predictor for the disease-free survival. Another

study indicated a higher MTV of 9.3 mL is significantly associated with an increased risk of recurrence and death.[13] In the two studies, the regions of the MTVs were defined on the pretreatment PET/CT by a fixed SUV value of 2.5. While the debate between fixed and adaptive threshold still exits despite it has been discussed for a long time. In particular, our previous investigation showed the latter approach could obtain a better match with the presumed tumor volumes.[19] Also, Schinagl *et al*.[11] conducted a predictive trial of 77 head and neck cancer patients with eligible for definitive RT/CCRT. Five PET segmentation methods were applied: interpreting FDG PET visually, applying an isocontour at a SUV of 2.5, using fixed thresholds of 40% and 50% of the maximum FDG activity and applying an adaptive threshold based on the signal-to-background. They concluded there is no role yet for pretreatment FDG PET as a predictor of RT outcome. However, this potential application needs further exploration, focusing both on PET-based tumor volume and SUVmax of the primary tumor.

Despite the limitation, such as short follow-up duration, this study provides a reference value of SUVmax for optimizing an organ preservation scheme for PC when both PET/CT and primary tumor volume become a part of pretreatment workup. Based on our data, we recommend the best treatment modification, such as dose escalation or consideration of adjunctive surgery, should be considered for tumors with a pretreatment SUVp-max more than 11 or with large tumor volumes. Certainly, the results have to be examined further with longer follow-up interval and PC patients could not be classified simply by this model. Nonetheless, some progress of prognostic stratification could be done by this approach and might lead to a more appropriate selection of suitable candidates for organ preservation scheme.

CONCLUSION

The pretreatment SUVp-max > 11 is a predictor for recurrence of primary tumor in PC patients treated with RT/CCRT, particularly for those with smaller tumor volumes. PC patients with a large tumor volume or a higher SUVp-max should be considered for requiring more aggressive treatment approaches, such as RT dose escalation or adjunctive surgery.

ACKNOWLEDGEMENTS

We want to thank the grant support of the study projects (DMR-94-080 and DMR-98-052) in our hospital and Taiwan Department of Health, Cancer Research Centers for Excellence (DOH100-TD-C-111-005).

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Received on September 8, 2011
Accepted on February 7, 2012
J-STAGE Advance Publication Date: May 11, 2012