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Risk Stratification of Metastatic Neck Nodes by Computed Tomogram and Positron Emission Tomogram in Patients with Head and Neck Cancer Receiving Definitive Radiotherapy

Running title: images on metastatic neck node

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CONFLICT OF INTEREST:

None.

ABSTRACT

To investigate the prognostic impact of computed tomogram (CT) and ^{18}Fluoro-deoxyglucose PET/CT on the outcome of metastatic neck node (MNN) in patients with head and neck cancer receiving definitive radiotherapy (RT) or chemoradiotherapy (CRT).

Methods: This patient-based study included 91 patients diagnosed with pharyngeal cancers with MNN (N1: 15, N2: 70, N3: 6). All had pretreatment CT and PET/CT before definitive CRT/RT. Parameters of MNNs for each patient, including maximal diameter, nodal volume, radiological central necrosis, maximum standardized uptake, metabolic tumor volume, and total lesion glycolysis (TLG) were retrieved for the analysis. Nodal relapse-free survival (NRFS) and survivals were calculated using the Kaplan-Meier method. Independent predictors were identified using Cox regression analysis.

Results: After a median follow-up of 18 months, 64 patients remained nodal relapse-free, and 27 experienced neck recurrence. Multivariate analysis showed that the application of 40% of the maximal uptake of nodal TLG (N-TLG40%) $\geqq$ 38 g [P = 0.03, Hazard ratio (HR) 2.63, 95 % Confidence interval (CI) 1.10 ~ 6.30] and radiological necrosis on CT scan (P = 0.001, HR 10.99, 95% CI 2.56 ~ 47.62) were two adverse features for NRFS. Patients who had a N-TLG40% $\geqq$ 38 g and central radiological necrosis had

significantly inferior 2-year NRFS (53% vs. 77% and 45% vs. 95%, respectively).

Conclusion: The outcome of MNNs in patients with head and neck cancer receiving CRT/RT can be predicted according to radiological necrosis and N-TLG40% value. The two adverse features should be validated in future trials. By this way, patients can be treated alternatively or aggressively.

Key words: ^{18}Fluoro-deoxyglucose PET/CT, computed tomogram, head and neck cancer, metastatic neck lymph node, radiotherapy.

INTRODUCTION

Organ preservation with definitive chemoradiotherapy (CRT) has become a treatment option in patients with head and neck cancers. In case of residual or recurrent diseases after initial therapy, salvage surgical intervention will be indicated. Although the status of the neck disease is a major determinant of prognosis in head and neck cancers, the optimal management of the metastatic neck node (MNN) remains an issue of debate. A planned adjunctive neck dissection has been suggested in patients with N2 or N3 disease, which was based on some studies which demonstrated that radiotherapy (RT) combined with surgery might improve neck control rates compared with one modality alone (*1-3*). However, several studies advocated surveillance of the neck diseases because a complete remission can be achieved when assessing the response using ^{18}Fluoro-deoxyglucose positron emission tomography (PET) (*4-7*). In patients with regional recurrence after CRT/RT, salvage neck dissection would be possible, but was associated with additional morbidity and worse prognosis (*8, 9*). Therefore, there is a need to identify pretreatment predictors that can foresee the outcome earlier when a decision of organ preservation, or treatment modification should be discussed.

Although computed tomogram (CT)-based tumor volume or PET/CT has been used to predict treatment outcome in patients with head or neck cancers, there is still a lack of

studies implementing comprehensive knowledge of the two images to identify imaging features which can be used to predict treatment outcomes for patients with MNN. Knowledge of imaging features which predict poor response to non-surgical management could assist clinicians in selecting surgical therapy or considering dose escalation schemes for patients with such high risk features. In order to address this issue, we conducted a patient-based study to examine pretreatment parameters from both images.

MATERIALS AND METHODS

Patient Population

From January 2007 through June 2012, a cohort of 91 patients with pharyngeal cancers with histological proof of squamous cell carcinoma, who had been treated with an organ preservation scheme at China Medical University Hospital were included in this retrospective analysis after institutional review board approval. The institutional review board (IRB or equivalent) approved this retrospective study and the requirement to obtain informed consent was waived. [Certificate number of local institutional review board (IRB): DMR99-IRB-010-1]. The origin of the tumors was oropharynx in 49 patients and hypopharynx in 42 patients. The median age was 52 years. All received pretreatment CT and PET/CT for initial staging within 4 weeks before initiating treatment. Because this

study also aimed to recognize the association between nodal control and survival, a patient-based rather than a node-based analysis was carried out. The characteristics of the 91 patients are shown in Table 1.

Definition of CT-based Parameters

Each patient underwent a pretreatment contrast-enhanced CT of the neck with 3-mm thick contiguous sections. Neck nodes were considered pathological when their smallest axis diameter was >1 cm. The CT images from the picture archiving and communication system were then transferred to a commercial planning system (Eclipse Version 8.1, Varian Medical system Inc, CA, USA). Radiation oncologists then delineated the pretreatment gross tumor volume of the primary tumors and the MNN (*10*).

Three parameters including gross tumor volume of MNN (N-GTV), maximal nodal diameter, and radiological central necrosis were retrieved from pretreatment CT image. Nodes in groups close together were scored as multiple node conglomerates. If there were multiple nodal sites on CT scan, we selected the largest N-GTV for this patient-based analysis. The radiological central necrosis was confirmed by radiologists. Because of lacking consistent consensus about extranodal spread, this parameter was not analyzed in

this study.

PET/CT Image Acquisition

None had abnormal serum glucose level before the PET/CT images were captured. All patients were required to fast for at least 4 h before ^{18}F-FDG PET/CT imaging. The images were captured using a PET/CT scanner (PET/CT-16 slice, Discovery STE, GE Medical System, Milwaukee, Wisconsin, USA) approximately 60 min after the administration of 370 MBq of ^{18}F-FDG. After determining the axial imaging range, a spiral non-contrast-enhanced low–radiation dose CT scan (0.8-second rotation time, 120 kVp, variable mA with AutomA technique, 3.75-mm slice thickness, and 1.75:1 pitch) was performed for anatomical reference and attenuation correction. PET emission images were then acquired sequentially after CT scan at 1.5 minutes per field of view in 3-dimensional acquisition mode with a 11-slice overlap at the borders of the field of view. The CT images were reconstructed onto a 512 × 512 matrix with a section thickness of 3.75 mm, then reconstructed onto a 128 × 128 matrix, and converted into 511-keV-equivalent attenuation factors for attenuation correction of the corresponding PET emission images. The PET images were reconstructed using 3-dimensional iterative algorithms (VUE Point). The PET/CT workstation provided a quantification of FDG

uptake for SUV. This procedure has been described in our prior study (*11*). The maximum standardized uptake value of the target node was abbreviated as N-SUVmax.

Measurement of metastatic tumor volume (MTV) and total lesion glycolysis (TLG)

We used the auto-segmentation process of PET to define the volume of interest (VOI) to reduce inter-observer variability in image evaluation. MTVs and TLGs were measured from attenuation-corrected FDG-PET images using a SUV-based automated contouring program (Advantage Workstation Volume Share version 2, GE Health). The MTV was defined as the sum of the metabolic volumes of the primary tumors. The volume boundaries were sufficiently wide to incorporate each target lesion in the axial, coronal, and sagittal FDG-PET images. To define the contouring margins around the tumor, we used SUVmax of 2.5 (MTV2.5), 50% of SUVmax (MTV50%), as reported in our previous study (*11*). The TLG was calculated according to the following formula: TLG = Mean SUV x MTV (*12*). We used threshold levels that were equivalent for the MTVs; that is, TLG40%, and TLG50%. Each patient had 2 sets of TLG: P-TLG for the primary tumor and N-TLG for the MNN. Similarly, the largest one was selected for the analysis in case of multiple MNNs.

Treatment

RT was performed using a sequential intensity-modulated radiotherapy technique (*10*). All patients received doses of 1.8 Gy daily, up to a total dose of between 68.4 and 73.8 Gy (median: 70.2 Gy). Two clinical target volumes (CTV) were considered for various risks: CTV1 encompassed the primary tumor, MNLNs, 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 of CTV1 and CTV2 were 70.2 and 54.0 Gy, respectively. The median RT duration was 53 days. Seventy patients received concurrent chemotherapy; their regimen consisted of cisplatin (80–100 mg/m2 on Days 1, 22, and 43). Fourteen patients received combined cetuximab (400 mg/m2 loading dose and 250 mg/m2) weekly. Seven received RT alone.

Follow-up

According to the guidelines of the Response Evaluation Criteria in Solid Tumors (*13*), the initial treatment response was assessed by the CT scan done 1 to 2 months after the completion of therapy. Thereafter, patients were followed every 2 to 3 months

thereafter. A physical examination and laryngoscopy were performed during each follow-up examination, and CT scan was conducted every 3 to 6 months over 2 years. The definition of neck failure was based on the PET/CT, or progression of tumor on the CT scan. If patients had persistent tumors or recurrence after initial complete remission, salvage surgery was suggested if technically feasible and allowable by the condition of the patient.

Statistical Analysis

This study used the median values of the N-SUVmax, N-GTV, N-MTVs, and N-TLGs as cut-off points. The results of the statistical analysis are presented as the mean ± standard deviation (SD). To examine the correlations between the parameters and recurrence, receiver operating characteristic (ROC) curves were created to evaluate the optimal predictive performance among the MTVs and TLGs. The primary endpoints were the predictors for initial treatment response and nodal relapse-free survival (NRFS). The secondary endpoints were overall survival (OS), disease-free survival (DFS). These rates were calculated using the Kaplan-Meier method. Logistic regression analysis was used to identify predictors for initial responders. Cox regression was performed to examine the effects of explanatory variables on OS, DFS, and NRFS. Although this study was to

examine the impact of images on treatment outcome for MNL, PET/CT parameters describing primary and nodal tumors, as well as clinical parameters, were all included in the analysis when analyzing the survivals. Two-tailed tests were used, and *P* values of < 0.05 were considered statistically significant. All calculations were performed using SPSS 13.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Parameter Measurement

Four methods of calculating nodal MTV (N-MTV) and nodal TLG (N-TLG) values were retrieved for all patients. The mean N-GTV was 18.1 ± 27.8 ml, whereas the mean N-SUVmax was 6.5 ± 4.4. The distributions of N-SUVmax, N-GTV, and various N-MTV and N-TLG with respect to N classification are shown in Table 2. A trend of increasing values of PET/CT- or CT-related parameters was observed at an advanced N stage.

Treatment Outcome

According to the first CT scan after the treatment, 56 of the 91 MNNs (62%) obtained

a complete response, whereas 35 (38%) had a partial response. After a median follow-up duration of 18 months (range, 6 to 69 months), 37 patients were alive without known recurrent disease, and 16 patients had locoregional recurrence; however, they were alive after salvage or palliative treatment. Thirty-one patients died of tumor recurrence. Seven died of intercurrent diseases or other malignancies. Table 3 shows the detailed failure patterns of the cohort. In summary, 64 patients remained nodal relapse-free, while 27 patients experienced neck recurrence. Overall, the 2-year OS, DFS and NRFS were 51% [95% confidence interval (CI) 42% - 60%], 42% (95% CI 33% - 51%), and 66% (95% CI 57% - 75%), respectively.

Comparison of Predictive Ability for Nodal Failure among Different Threshold Methods

The ROC curves were analyzed to compare the efficacy of various PET/CT-related parameters and threshold methods for determining the optimal approach for autosegmentation contouring. The results showed that N-MTV2.5, and N-TLG40% predicted the residual or recurrent nodes most accurately among the corresponding threshold methods (Appendix 1). Based on the results, biological tumor volumes using N-MTV2.5, and N-TLG40% methods combined with N-SUVmax and CT-related

parameters were selected for the analysis.

Factors Associated with Initial Nodal Response

According to the first follow-up CT scan, patients were classified into complete and partial responders. The logistic analysis showed N-GTV ≧ 8.9 ml [*P* = 0.025, Odds (OR) 3.32, 95 % Confidence interval (CI) 1.16 ~ 9.48] and radiological central necrosis (*P* < 0.001, OR 10.10, 95% CI 3.03 ~ 34.48) were two factors associated with partial remission of the MNNs (Appendix 2).

Prognostic Factors for Nodal Relapse and Survival

The Cox regression analysis showed that N-TLG40% ≧ 38 g [*P* = 0.03, Hazard ratio (HR) 2.63, 95 % CI 1.10 ~ 6.30] and radiological central necrosis (*P* = 0.001, HR 10.99, 95% CI 2.56 ~ 47.62) were two predictors for neck recurrence (Table 4). The 2-year NRFS for patients who had tumors with N-TLG40% ≧ 38 g and < 38 g was 53% and 77%, respectively (Figure 1). Patients with radiological central necrosis had a lower 2-year NRFS compared with those without this feature (45% vs. 95%; Figures 2). Although a large N-GTV, or a higher N-SUVmax was also associated with higher risk of recurrence, there was no statistical significance in the multivariate analyses. In addition,

no difference of NRFS curves was found between the origin of the primary tumors (Appendix 3). Using N-TLG40% ≧ 38 g as a cut-off to predict nodal failure, the sensitivity, specificity, and accuracy were 44%, 85%, and 65%, respectively. When applying the central necrosis to forecast recurrence, the sensitivity, specificity, and accuracy were 47%, 93%, and 67%.

As also shown in Table 4, two predictors for inferior OS were T3-T4 (P = 0.01, HR 2.68, 95% CI 1.27 ~ 5.64), and central necrosis (P = 0.02, HR 2.59, 95% CI 1.13 ~ 5.26). T-MTV2.5 (metabolic tumor volume of primary tumor defined by SUV=2.5) showed a marginal impact on OS. The prognosticators of DFS were T3-T4 (P = 0.001, HR 3.63, 95% CI 1.75 ~ 7.50), central necrosis (P < 0.001, HR 3.62, 95% CI 1.79 ~ 7.35), and N-TLG ≧ 38 g (P = 0.02, HR 2.12, 95% CI 1.13 ~ 4.00).

Subgroup Analysis in Patients with N2-N3 Neck Disease

Because some studies advocated a planned neck dissection for patients with N2-N3 disease, we carried out a subgroup analysis for these patients (N = 76) to examine the performance of the parameters mentioned above. The Cox regression analysis showed a similar finding that N-TLG40% > 38 g (P = 0.04, HR 2.22, 95 % CI 1.04 ~ 4.79) and central necrosis (P = 0.002, HR 4.99, 95% CI 1.83 ~ 13.69) were two prognostic factors

for nodal relapse.

Risk Stratification of Nodal Relapse According the Major Adverse Factors

When nodal diseases were stratified with the two prognostic factors, patients can be evenly stratified with three groups. Group A comprised 28 patients without any adverse features. Group C included 33 patients having both risk factors, whereas Group B consisted of 30 patients having one of the two. The estimated 2-year NRFS was 92% for group A, 78% for group B, and 33% for group C, respectively (Figure 3).

DISCUSSION

An advanced nodal stage in patients with head and neck cancers is a well-known adverse factor for the survival (*14*). When investigating the prognostic role of the image-related factors, it would be appropriate to examine all the parameters derived from the primary tumors and MNNs, respectively. Because of the insufficiency of using T- or N-classification alone in assessing the final outcome, we previously reported the clinical implication of CT- and PET/CT-based findings on the control of primary tumor (*11*). This study further disclosed the efficacy of implementing image-related factors on the neck

control. Before the evolution of organ preservation, neck nodes could be usually dissected at the same time as excision of primary tumors. To date, neck dissection is commonly reserved for those with residual or recurrent disease following the initial therapy. Therefore, the evaluation of nodal response became crucial to the adequate performance of salvage neck dissection. Although post-treatment CT or PET had a high accuracy in determining the regional control (*4-7, 15*), early recognition of patients at risk for nodal failure after curative non-surgical treatment can optimize the individual-treatment schemes by reducing the number of patients undergoing unsuitable treatment.

The role of several prognostic factors for nodal recurrence after RT has been investigated. Previous studies showed that nodal size, radiological signs of extranodal spread, and central necrosis are prognostic factors for regional control (*16-20*). Through comprehensive CT- and PET/CT-related parameters with various threshold methods, we first showed that the N-TLG40% combined with radiological central necrosis, the risk of residual or recurrent neck diseases can be stratified. Particularly for patients with any MNNs categorized as Group C, alternative modalities can be taken into account prior to a decision of definitive CRT/RT. In addition, for patients having chosen organ preservation scheme, a planned neck dissection for the high-risk patients can be discussed earlier.

Certainly, further studies are warranted to test our results because of the low sensitivity presented in this study.

A unique advantage of FDG-PET/CT is its ability to automatically create a tumor contour using quantitative information on glucose uptake within the tumor. In patients with head and neck cancers receiving definitive CRT/RT, the use of pretreatment biological tumor volume as a predictive factor is not novel. However, few studies have compared comprehensive volumetric and threshold methods to define the optimal approach for MNN. Using ROC analysis, we first examined the efficacy of various threshold methods for determining the best approach. Then, their predictive abilities were compared to those derived from CT-related and clinical parameters. To identify the optimal cut-off values where the sum of sensitivity and specificity was the greatest; undoubtedly, it is essential to enroll more participants prospectively, and to use standardized protocols for FDG PET acquisition and processing. Nonetheless, this is a pilot study to clarify the N-TLG40% method was better than nodal volume or MTV approaches in predicting NRFS or DFS for these patients. Although other threshold approaches for N-TLG or N-MTV failed to show a superior predictive power in NRFS compared with the N-TLG40%, all tested threshold methods exhibited a biological phenotype trend for nodal recurrence. In the era of considering dose escalation for

FDG-avid tumors, Jeong et al. (*21*) reported a novel outcome-equivalent dose analysis method to estimate the dose-response modifying effect of FDG uptake variation. By this way, they provided a rational starting point for selecting IMRT boosts for FDG-avid tumors. Their study indicated FDG-avid tumors are likely to require 10% to 30% more dose than FDG-non-avid tumors to reach equal response rates. Our study presented a clinical basis when considering dose-escalating scheme to the nodes.

A previous study showed that the presence of central hypodense zones on CT correlated well with a high incidence of nodal necrosis (*22*). Based on the same radiological definition, we demonstrated that nodal control and survivals were significantly associated with central necrosis, as described in previous studies (*17, 20*). Interesting, our data also showed that radiological central necrosis was positively associated with several CT- and PET/CT- parameters including N-GTV, SUVmax, and N-TLG. Theoretically, the hypodense necrotic zones on contrast image CT infer areas of hypovascularity, and could harbor hypoxic cells, which could expect the negative impact on nodal control as hypoxic cells are less radiosensitive (*20*). Nakajima et al. (*23*) analyzed tumor cells grown as xenograft in nude mice after identification of the metabolic response to hypoxia and found 2-deoxyglucose uptake in hypoxic regions of the tumors was approximately 2 times higher compared to the whole tumor. They

concluded hypoxia is associated with increased intratumoral metabolic heterogeneities on FDG-PET. Given the metabolic heterogeneity within the tumors might be an indicator of tumor hypoxia, it is warranted to correlate the heterogeneities with clinical outcome in the future. In addition, the radiological necrosis needs to be scored and the association between the score and extent of heterogeneities of FDG uptake should be investigated further.

This study was subject to numerous limitations, such as a lack of magnetic resonance image (MRI) information. The ability of diffusion-weighted MRI (DWI) in improving target volume delineation, early tumor response assessment, and differentiation between normal post-treatment changes suggests an important clinical role in RT (*24*). It would be interesting to compare the impact of DWI on the treatment outcome. In addition, post-treatment PET/CT was not routinely performed for relevant prognostic information. Thus, the changes of PET/CT-related parameters before and after therapy could not be assessed accordingly. Finally, the impact of human papillomavirus (HPV) related oropharyngeal cancer on prognosis has gained great interest. The effect on prognosis might be stronger than many other factors investigated before, including stage or FDG uptake. Despite the lower prevalence of human HPV-related oropharyngeal cancer in Asia (*24, 25*), the results would be more robust if information about the HPV

status could be included in this analysis. Future studies must use more imaging studies and information of HPV status, and adjust for potential confounders in the analysis. In addition, FDG uptake variability in human tumors may be an indicator of tumor hypoxia, and prognosis, and therefore could be validated in prospective clinical trials. Based on our finding, we recommend that treatment modification or an alternative treatment can be considered for patients with a pretreatment N-TLGw40% $\geqq$ 38 g, or radiological central necrosis. Such treatment modification may include dose escalation, novel cytotoxic drugs, or the use of adjunctive neck dissection. In this manner, patients for individual-treatment schemes can be selected more appropriately.

In summary, this pilot study shows the control rate of MNN in patients with head and neck cancer receiving RT/CRT for organ preservation can be predicted according to radiological central necrosis on CT scan and N-TLG40% value on PET/CT. The result should be validated in future clinical trials. By this way, patients with the adverse features may be considered to be treated alternatively or aggressively.

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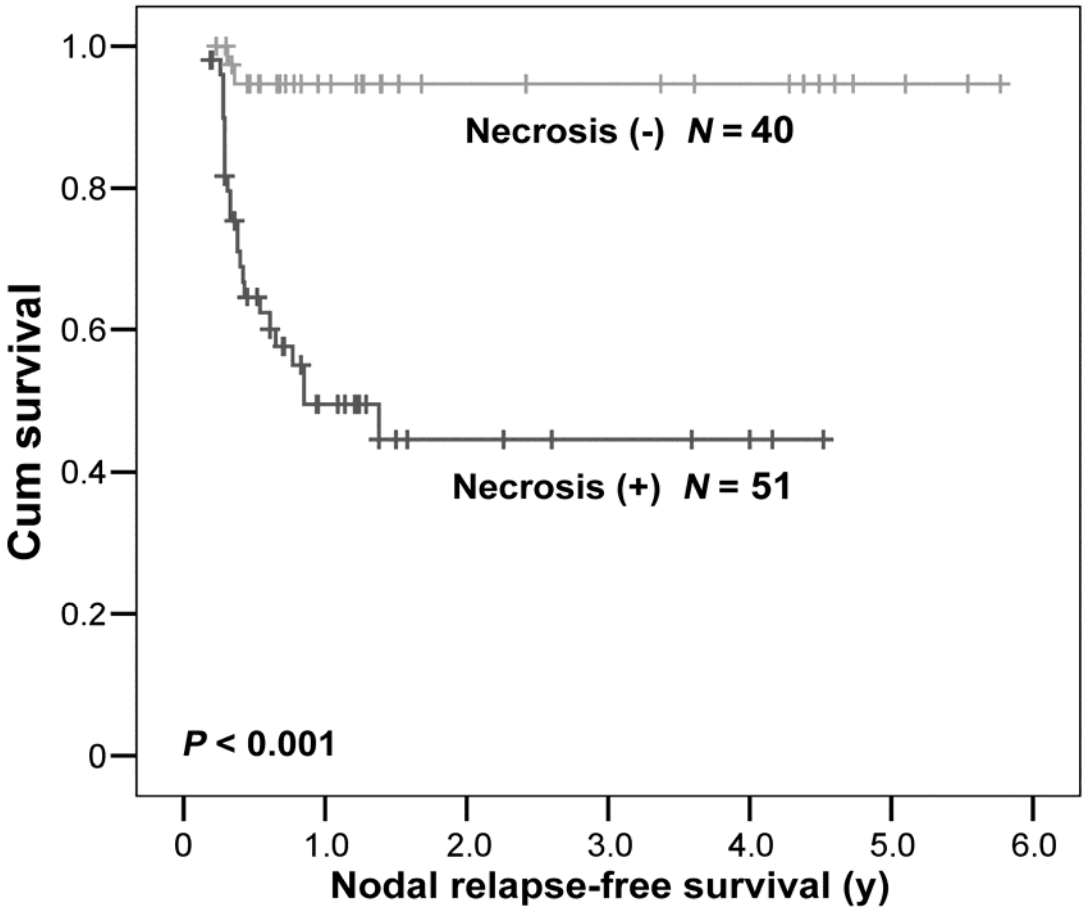

Figure 1. Nodal relapse-free survival according to central necrosis on CT scan ($P <$ 0.001).

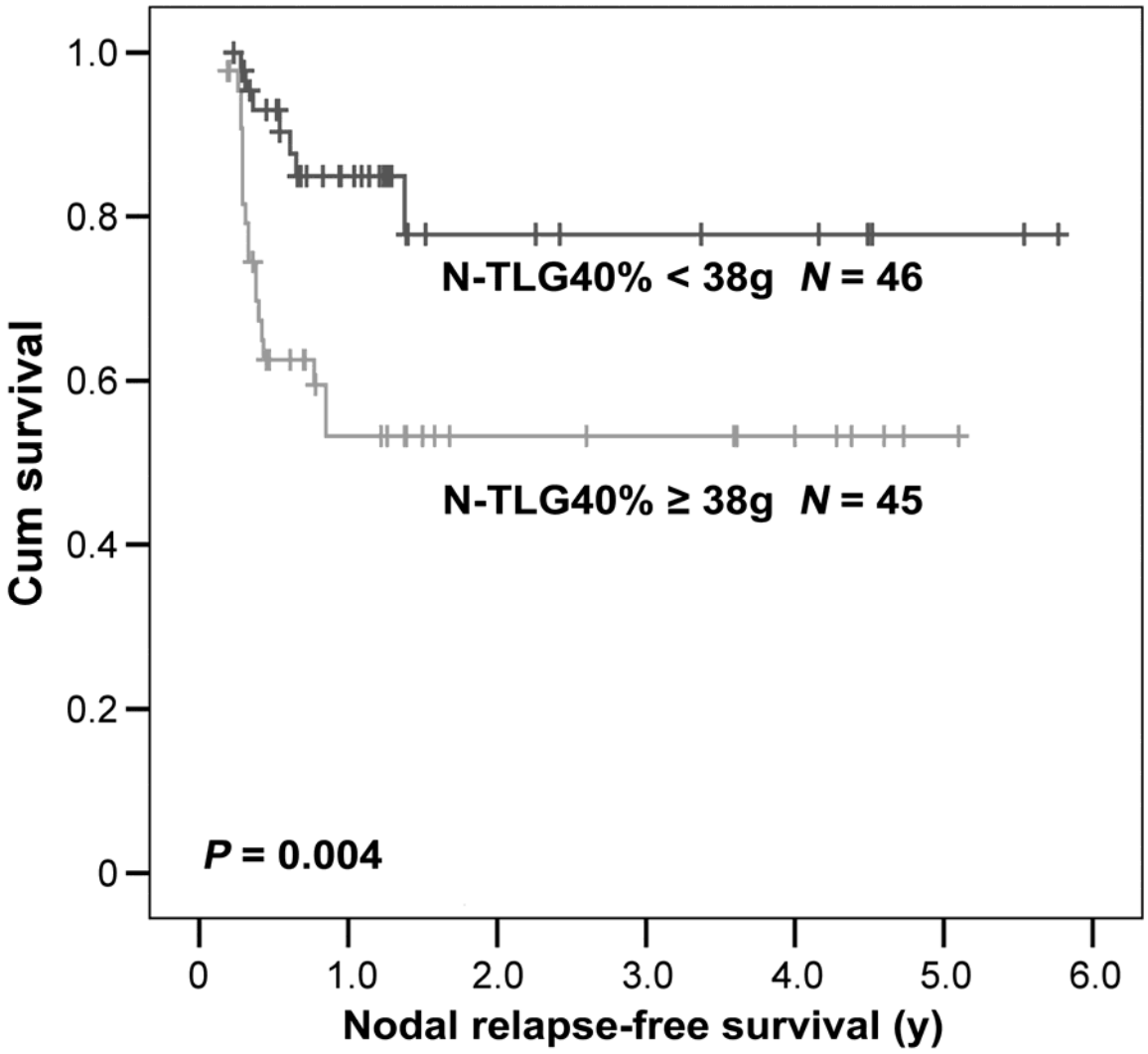

Figure 2. Nodal relapse-free survival according to nodal TLG40% ≧ 38 g and < 38 g (*P* = 0.004).

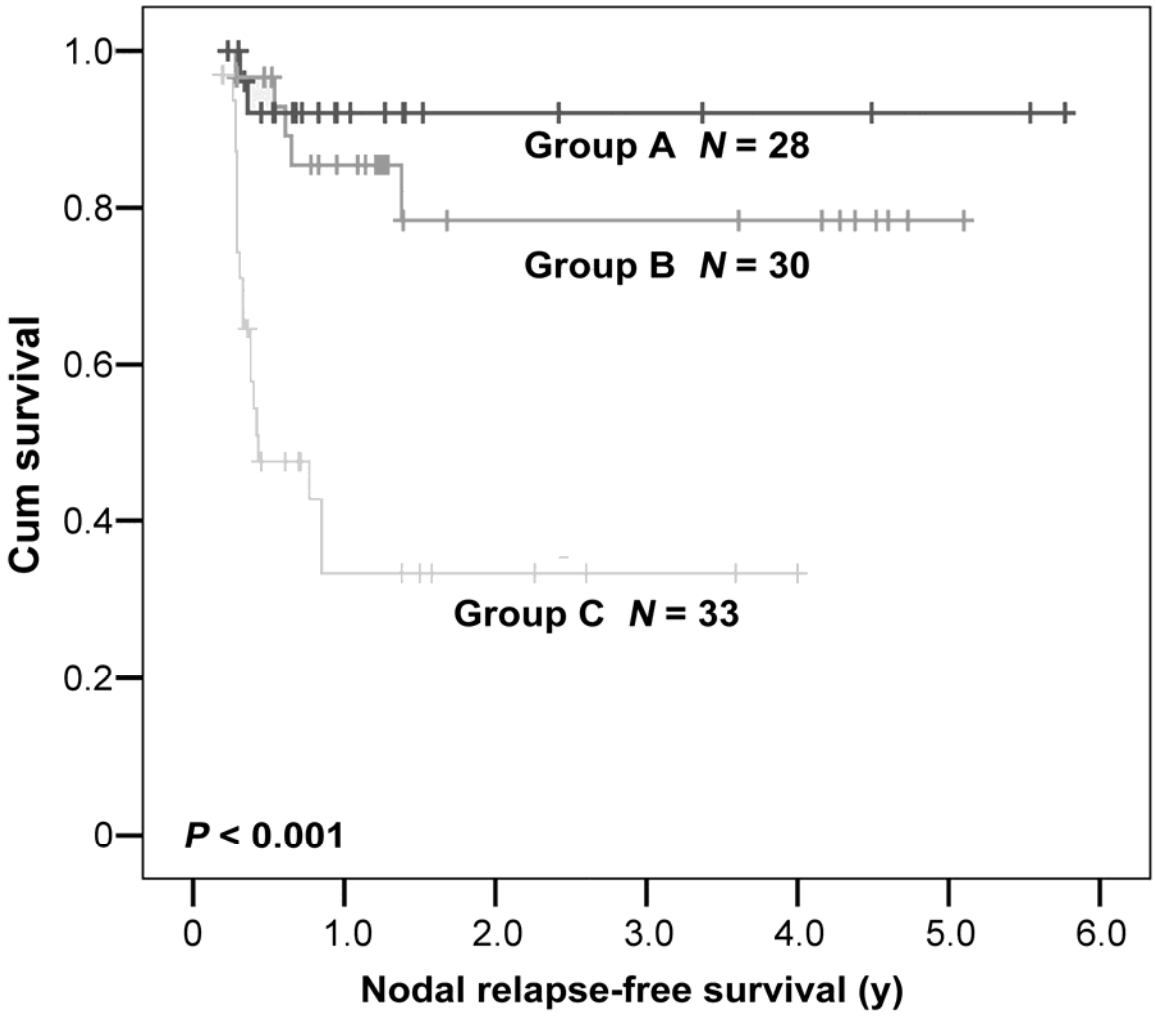

Figure 3. Nodal relapse-free survival according to nodal groups ($P < 0.001$).

TABLE 1

Patient characteristics (N = 91)

Characteristic	Value
Age (years)	37-78 (median, 52)
Gender	man 90; woman 1
Smoking	Yes: 80 ; No : 11
Betel nut squid	Yes: 64 ; No: 27
Alcoholism	Yes: 59 ; No: 32
Primary lesion site:	
Oropharynx	49
Hypopharynx	42
AJCC 7th Stage	III: 10; IV: 81
T- stage	T1: 7; T2: 36; T3: 27; T4: 21
N- stage	N1: 15; N2: 70; N3: 6
Total radiation dose (Gy)	66 ~ 74 (median, 70)
Overall radiation interval (day)	43 – 82 (median, 53)
Concurrent chemotherapy or drug	
cisplatin-based	70
weekly cetuximab	14
none	7
PET/CT-related parameters	
N-SUVmax	6.5 ± 4.4(1.2-28.5), median 6.1
N-MTV2.5 (ml)	11.5 ± 25.6(0.1-178), median 3.0
N-MTV40% (ml)	10.0 ± 18.4(1.0-153), median 5.1
N-MTV50% (ml)	7.1 ±1 4.2(0.5-119), median 3.6
N-TLG40% (g)	112.8 ± 168.5(0-855.3), median 38.0
N-TLG50% (g)	87.3 ± 134.9(664.7), median 29.0
CT-based volume parameters	
N-GTV (ml)	18.1 ± 27.8 (1-185), median 8.9
maximal diameter (cm)	2.9 ± 1.9 (1.1-10.8), median 2.4
central necrosis	51 / 91
Follow up (months)	3-69 (median: 18)

Abbreviation: AJCC = American Joint Committee on Cancer; N-SUVmax: pretreatment nodal maximum standard uptake value(SUV); N-MTV2.5: pretreatment nodal metabolic tumor volume defined by SUV=2.5 ; N-MTV40%: pretreatment nodal metabolic tumor volume defined by 40% of maximal SUV; N-MTV50%: pretreatment nodal metabolic tumor volume defined by 50% of maximal SUV ; N-TLG40%:

pretreatment nodal total lesion glycolysis defined by 40% of maximal SUV ; N-TLG50%: pretreatment nodal total lesion glycolysis defined by 50% of maximal SUV ; N-GTV: nodal gross tumor volume.

TABLE 2.

Distribution of the CT- and PET/CT-related parameters with respect to N classification

Variable	N1	N2	N3	All	Median
CT-based parameters					
N-GTV (ml)	4.1 ±2 .8(1.7-11.2)	14 ± 14.1(1.0-64.5)	101 ± 46.3(51.2-185.4)	18.1 ± 27.8(1-185)	8.9
maximal diameter (cm)	1.7 ± 0.5(1.2-2.6)	2.7 ± 1.5(1.1-7.1)	7.6 ± 1.9(5.8-10.8)	2.9 ± 1.9(1.1-10.8)	2.4
central necrosis	4 / 15	41 / 70	6/6	51 / 91	
PET/CT-based parameters					
N-SUVmax	4.2 ± 2.3(1.2-8.6)	6.9 ± 4.4(1.3-28.5)	8.6 ± 5.8(1.3-15.9)	6.5 ± 4.4(1.2-28.5)	6.1
N-MTV2.5 (ml)	2.4 ± 2.7(0.1-8.9)	8.3 ± 11.8(0.1-59.1)	72.3 ± 71.1(0.1-178)	11.5 ± 25.6(0.1-178)	3.0
N-MTV40% (ml)	6.2 ± 2.9(2.1-12.8)	7.3 ± 6.9(1.0-32.5)	51 ± 56.9(4.0-153)	10.0 ± 8.4(1.0-153)	5.1
N-MTV50% (ml)	3.8 ± 1.4(1.5-6.8)	5.1 ± 5.2(0.5-25.5)	8.4 ± 44.4(3.6-119)	7.1 ± 14.2(0.5-119)	3.6
N-TLG40% (g)	60.4 ± 74.9(0-226.8)	100.4 ± 150.6(0-855.3)	388.3 ± 283.9(0-763.2)	12.8 ± 168.5(0-855.3)	37.9
N-TLG50% (g)	45.2 ± 56.2(0-170.7)	77.7 ± 119(0-664.7)	305.3 ± 244.8(0-634.7)	87.3 ±134.9(0-664.7)	29

Note: all values are presented with mean ± standard deviation.

Abbreviation: as table 1.

TABLE 3

Patient outcome (N = 91)

Outcome	Patient number
Alive without evidence of recurrence	37
Alive with evidence of disease recurrence	16
primary relapse alone	5
neck lymph node relapse alone	4
primary and lymph node relapse	5
distant metastasis alone	2
Died of cancer	31
primary and neck lymph node relapse	12
primary relapse alone	9
primary relapse and distant metastasis	1
neck lymph node relapse alone	2
distant metastasis alone	3
primary, neck and distant metastasis	4
Died of intercurrent diseases or other malignancies	7

TABLE 4

Association between PET/CT- and CT-based tumor parameters and survivals using Cox regression model

Variables	OS			DFS			NRFS		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
TNM classification									
T stage									
T1-2 vs. T3-4	2.68	1.27-5.64	0.01	3.63	1.75-7.50	0.001	2.40	0.90-6.46	0.07
N-stage									
N1-2 vs. N3	1.40	0.36-4.50	0.71	1.34	0.4- 4.03	0.60	1.25	0.21-3.01	0.56
N1 vs. N2-3	1.02	0.40-2.62	0.98	1.09	0.44-2.74	0.85	1.43	0.38-5.40	0.60
CT-related parameters for MNL									
central necrosis									
no vs. yes	2.59	1.13-5.26	0.02	3.62	1.79-7.35	< 0.001	10.99	2.56-47.62	0.001
maximal diameter (cm)									
< 2.4 vs. ≧ 2.4	1.24	0.48-3.27	0.66	2.16	0.78-6.01	0.14	1.80	0.55-5.92	0.34
N-GTV (ml)									
< 8.9 vs. ≧ 8.9	1.56	0.21-1.91	0.42	1.01	0.41-2.47	0.98	1.02	0.25-4.22	0.98
PET/CT-related parameters									
N-TLG40% (g)									
< 38.0 vs. ≧ 38.0g	1.71	0.77-3.78	0.19	2.12	1.13-4.00	0.02	2.63	1.10-6.30	0.03
N-SUVmax									
< 6.1 vs. ≧ 6.1	1.68	0.72-3.92	0.23	1.36	0.55-3.36	0.51	1.57	0.22-1.80	0.40
N-MTV2.5 (ml)									
< 3.0 vs. ≧ 3.0	1.62	0.75-3.50	0.22	1.20	0.57-2.56	0.64	1.19	0.51-2.75	0.69
T-TLG40% (g)									
< 53.3 vs. ≧ 53.3	1.09	0.47-2.09	0.97	1.75	0.71-4.32	0.22	1.72	0.70-4.24	0.24
T-SUVmax									
< 10.7 vs. ≧ 10.7	1.39	0.61-3.22	0.43	1.55	0.58-4.09	0.38	1.67	0.64-4.33	0.29
T-MTV2.5 (ml)									
< 14.5 vs. ≧ 14.5	2.43	0.99-6.05	0.06	1.11	0.38-2.72	0.88	0.93	0.36-2.42	0.88
Primary tumor origin									
oropharynx vs. hypopharynx	1.11	0.56-2.17	0.77	0.99	0.47-2.13	0.99	0.98	0.46-2.09	0.95

Abbreviations as Table 1; OS: overall survival; DFS: disease-free survival; NRFS: node relapse-free survival; HR: hazard ratio; CI: confidence interval; P-TLG40%: pretreatment primary total lesion glycolysis defined by 40% of maximal SUV T-SUVmax: pretreatment maximum standard uptake value of primary tumor; T-MTV2.5: pretreatment primary metabolic tumor volume defined by SUV=2.5.

Note: This study used the median values of the T-SUVmax, T-MTVs, and T-TLGs as cut-off points.