Published in final edited form as:

Lung Cancer. 2015 July ; 89(1): 43–49. doi:10.1016/j.lungcan.2015.03.023.

A New PET/CT Volumetric Prognostic Index for Non-small Cell Lung Cancer

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Abstract

Objectives—Whole-body metabolic tumor volume (MTV_{WB}) has been shown of prognostic value for non-small cell lung cancer (NSCLC) beyond that of TNM stage, age, gender, performance status, and treatment selection. The current TNM staging system does not incorporate tumor volumetric information. We propose a new PET/CT volumetric prognostic (PVP) index that combines the prognostic value of MTV_{WB} and TNM stage.

Materials and Methods—Based on 328 consecutive NSCLC patients with a baseline PET/CT scan before treatment, from which MTV_{WB} was measured semi-automatically, we estimated hazard ratios (HRs) for $\ln(MTV_{WB})$ and TNM stage from a Cox proportional hazard regression model that consisted of only $\ln(MTV_{WB})$ and TNM stage as prognostic variables of overall survival. We used the regression coefficients, which gave rise to the HRs, as weights to formulate the PET/CT volumetric prognostic (PVP) index. We also compared the prognostic value of the PVP index against that of TNM stage alone and $\ln(MTV_{WB})$ alone with univariate and multivariate survival analyses and C-statistics.

Results—Univariate analysis C-statistic for the PVP index ($C = 0.71$) was statistically significantly greater than those for TNM stage alone ($C = 0.67$, $p < 0.001$) and for $\ln(MTV_{WB})$ alone ($C = 0.69$, $p = 0.033$). Multivariate analyses showed that the PVP index yielded significantly greater discriminatory power ($C = 0.74$) than similar models based on either TNM stage ($C = 0.72$,

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest and have not used writing assistance.

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$p < 0.01$) or $\ln(MTV_{WB})$ ($C = 0.73$, $p < 0.01$). Lower values of the PVP index were associated with significantly better overall survival (adjusted HR = 2.70, 95%CI [2.16, 3.37]).

Conclusion—The PVP index provides a practical means for clinicians to combine the prognostic value of MTV_{WB} and TNM stage and offers significantly better prognostic accuracy for overall survival of NSCLC patients than the current TNM staging system or metabolic tumor burden alone.

Keywords

^{18}F -FDG PET/CT; non-small cell lung cancer (NSCLC); TNM stage; tumor burden; metabolic tumor volume (MTV)

INTRODUCTION

Lung cancer is the most common cause of cancer death and the second most common cancer in men and women in the world [1]. In the United States, in 2014, an estimated 159,260 people will die from lung cancer, which is more than the number of deaths from colorectal, breast, and prostate cancer combined [2]. Non-small cell lung cancer (NSCLC) comprises 80–85% of all lung cancer cases [3].

The tumor, node, and metastasis (TNM) stage, defined by the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC), is the single most important piece of clinical information for making treatment choices and predicting prognosis of NSCLC patients [4–9]. Other clinical and pathologic factors such as age, gender, performance status, treatment received, and tumor histology, have also been shown to be associated with patient survival, but they are secondary in importance to TNM stage [10–12]. The standard of care for early-stage (stages-I and II) NSCLC in physically-fit patients is surgical resection [9]; for unresectable, locally-advanced, stage-III NSCLC is chemotherapy combined with thoracic radiation therapy; and for stage-IV NSCLC is systemic chemotherapy [9, 12]; all of which may be modified by consideration of other secondary clinical factors. However, unfortunately, substantial variation persists in patient survival even within the same TNM stage [13], suggesting that TNM stage alone (together with secondary clinical factors) is not completely satisfactory as a prognostic factor.

Metabolic tumor burden (MTB), such as the whole-body metabolic tumor volume (MTV_{WB}), has been shown to have prognostic value for NSCLC patients, beyond that of TNM stage and other factors such as patient age, gender, performance status, treatment type, and tumor histology [14–26]. Furthermore, MTV_{WB} has been shown of greater prognostic value than the standardized uptake value (SUV) [14–23]. In addition, MTV_{WB} is found to be relatively immune to the effect of inter-observer variability [17, 19, 20]. However, despite these promising findings, current clinical practice relies mainly on the TNM staging system, which does not incorporate volumetric tumor burden information [4, 5]. Only “T” descriptor includes a single linear measurement of primary tumor size, which may serve as a surrogate of the tumor volume on CT [27]. The “N” and “M” descriptors specify the existence of tumors in lymph nodes and distant organs, respectively, irrespective of tumor volume. For example, N2 and N3 span a wide spectrum from micro-metastatic deposit in a single node to

multiple metastatic extra-nodal extensions, and M1a and M1b span a similarly wide spectrum from a single intra-thoracic solitary metastatic focus to multiple distant extra-thoracic metastases.

We hypothesize that by combining the prognostic value of MTV_{WB} with that of the TNM system we can improve staging of NSCLC. In this report, we propose, and provide initial evaluation of, a new PET/CT-based volumetric prognostic (PVP) index that combines MTV_{WB} with the TNM stage based on a Cox proportional hazard regression model. Our objective is to investigate whether the PVP index can provide greater prognostic value than either MTV_{WB} or TNM stage alone, and whether it can provide a practical and quantitative approach for clinicians to take advantage of the combined prognostic value of MTV_{WB} and TNM stage for NSCLC patients.

MATERIALS AND METHODS

Patient Cohort and Imaging Study

This study was approved by our Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. There were a total of 1010 patients with NSCLC who were diagnosed and treated at our hospital from January 2004 to December 2008. About 41.0% (414/1010) of those cases had a baseline PET/CT scan and about 59.0% (596/1010) did not have the baseline PET/CT scan.

The inclusion criteria were: 1) baseline whole-body PET/CT scan before treatment, 2) no known brain metastasis (our standard PET/CT scan does not cover the entire brain), and 3) no concurrent, or history of, another cancer diagnosis. The study included a total of 328 consecutive NSCLC patients at the University of Chicago Medical Center for the analysis. The exclusion rate due to brain metastasis and history of second primary cancers was 20.8% (86/414) in the patients with the baseline PET/CT. Assuming there was a similar inclusion rate in patients with or without baseline PET/CT scans, there would have been about 79.2% (472/596) who did not have PET/CT but would otherwise have been eligible for the study. The primary endpoint of our analysis was overall survival. Survival duration was calculated from the date of the baseline PET/CT scan to the date of death from any cause. Surviving patients were considered as censored on the date of last known follow-up contact. Patient survival status was determined through clinical follow-up and the Social Security Death Index.

The PET/CT imaging protocol and MTV_{WB} measurement method have been described previously [14, 17]. Briefly, ¹⁸F-FDG PET/CT images were acquired with a high-resolution bismuth-germanate detector PET/CT scanner and a dual-slice CT system (Reveal HD, CTI, Knoxville, TN), in accordance with National Cancer Institute guidelines. Two board-certified radiologists with PET/CT imaging experience measured the MTV_{WB}, defined as the total MTV of all visible tumors in the whole-body scan, by using the PET-edge tool of the MIMvista software (MIMvista Corp, Cleveland, OH; version 5.1.2). Discrepancies between their assessments were resolved by consensus through discussion. TNM staging was according to the 7th edition definition [4, 5], and was extracted from written reports of

clinical history, physical examination, contrast infused CT of the chest and abdomen, and whole-body PET/CT scans.

Formulation of the PVP Index

We used a Cox proportional hazards regression model to obtain appropriate weightings when combining MTV_{WB} and TNM stage. The hazard ratio (HR) of a prognostic variable, obtained from a Cox regression model of overall survival, represents an estimate of the effect of that variable on the risk (or hazard) of death from any cause.

We estimated the HRs for $\ln(MTV_{WB})$ and TNM stage by using a Cox model that consisted of only $\ln(MTV_{WB})$ and TNM stage as prognostic variables. The natural logarithmic transformation of MTV_{WB} was applied because, for our data, $\ln(MTV_{WB})$ was closer to being approximately normally distributed than MTV_{WB} . The appropriateness of this transformation was confirmed using Martingale residuals. In the Cox model, $\ln(MTV_{WB})$ was treated as a continuous variable and TNM stage was treated as an ordinal variable (stage-I or II, stage-III, and stage-IV). The interaction between MTV_{WB} and stage was tested but was dropped from the final model since it was not statistically significant ($p=0.40$). We were limited by the number of patients in each TNM stage and further dividing the cases into more staging groups would have led to small numbers of cases in some staging groups, which would have resulted in imprecise estimates of the HRs. We defined the PVP index as a weighted sum of $\ln(MTV_{WB})$ and TNM stage with the Cox model regression coefficients (which gave rise to the HRs) as weights. Because the Cox regression model was fit with the method of maximum-likelihood estimation, the estimated regression coefficients are the most likely values on the basis of the observed data and, thus, should provide an optimal combination of $\ln(MTV_{WB})$ and TNM stage.

Prognostic Value of the PVP Index

We evaluated the PVP index, in comparison with either TNM stage or MTV_{WB} alone, with both univariate and multivariate Cox models [28, 29], which provided estimates of unadjusted and adjusted HRs, respectively, together with 95% confidence intervals (CIs). TNM stage was treated as a three-staging-group variable (I or II vs. III vs. IV). However, analysis of TNM stage as a seven-staging-group variable (IA, IB, IIA, IIB, IIIA, IIIB, and IV) was also included here to show that the results are not affected by the TNM staging groups used. The multivariate Cox models included the following prognostic variables: PVP index (or TNM stage or MTV_{WB}), age, gender, histology classification (adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, not-otherwise-specified carcinoma, and other carcinoma), and treatment (no cancer specific therapy; no surgery with chemotherapy, radiation or both chemotherapy and radiation therapy; and surgery). The proportional hazards assumption was assessed using Schoenfeld residuals. A quadratic age term was tested but was not included in the final models since it was not statistically significant. We further evaluated the discriminatory power of these models of the PVP index vs. either $\ln(MTV_{WB})$ or TNM stage alone in terms of the C-statistic [30]. Greater C-statistic values indicate greater discriminative power, and a value of 1 indicates perfect discrimination. Statistical comparison of C-statistics between models was based on a z-test constructed from 500 bootstrapped replications. We also plotted Kaplan-Meier curves by the median (based

on our entire patient cohort) of $\ln(MTV_{WB})$ in the patients with TNM stage IIIA NSCLC to illustrate the merit of combining $\ln(MTV_{WB})$ and TNM stage and formulating the PVP index. For illustrative purposes, Kaplan-Meier curves were also constructed after creating four equal sized groups using quartiles of the PVP index. Finally, we compared our estimates of HR values for $\ln(MTV_{WB})$ and TNM stage with values reported in the literature to provide preliminary validation of the weightings for the PVP index. Similar values of the HRs from our patient cohort compared with literature reports would support the validity of these weightings. Stata Version 13 (Stata Corp., College Station, TX) was used for all statistical analyses and $p < 0.05$ was considered statistically significant.

RESULTS

Patient and Tumor Characteristics

The patient-cohort and tumor characteristics are summarized in Table 1. The numbers of male and female patients were similar. The numbers of stage-I, III, and IV cases were similar, but there were far fewer stage-II cases. Thus, in the formulating PVP Index, stage-II cases were combined with stage-I cases into a single group. Patient age, distribution of histology diagnosis, and treatment were similar to other NSCLC patient cohorts reported in the literature. In all, 249 (75.9%) patients were known to have died, and the median follow-up of the 79 censored patients was 58 months.

Formulation and Prognostic Value of the PVP Index

Figure 1 shows Kaplan-Meier curves based on 52 stage-IIIA patients in our cohort stratified by the median (calculated from the entire study cohort of 328 patients) of the $\ln(MTV_{WB})$. These Kaplan-Meier curves, and those in our prior study in stage-IV nonsurgical NSCLC patients stratified by the median of $\ln(MTV_{WB})$ [18], show clearly that $\ln(MTV_{WB})$ provides prognostic value in patients of the same TNM stage. The prognostic value of MTV has been demonstrated in retrospective studies across different TNM stages of NSCLC [31]. This observation motivated our proposal for the PVP index, which combines $\ln(MTV_{WB})$ with TNM stage to allow clinicians to take advantage of the additional prognostic value from $\ln(MTV_{WB})$.

Estimates of the HRs and regression coefficients based on our patient cohort are shown in Table 2. Based on these estimates, we defined the PVP index as follows (Fig. 2):

$$PVP\ index = 0.360 \ln(MTV_{WB}) + 0.424 I(TNM = III) + 0.890 I(TNM = IV). \quad (Eq. 1)$$

In this equation, the indicator function $I(\cdot)$ yields a value of 1 when its argument is true and 0 otherwise, *i.e.*, for a stage-III patient, $I(TNM = III) = 1$ and $I(TNM = IV) = 0$; for a stage-IV patient, $I(TNM = III) = 0$ and $I(TNM = IV) = 1$; and for a stage-I or a stage-II patient, $I(TNM = III) = 0$ and $I(TNM = IV) = 0$. Therefore, Eq. (1) describes a formula for the calculation of a quantitative PVP index for each NSCLC patient who has a baseline ^{18}F -FDG PET/CT scan.

A univariate analysis of the prognostic value of the PVP index yielded a statistically significantly greater C-statistic value ($C = 0.71$) than those of $\ln(MTV_{WB})$ alone ($C = 0.69$, $p = 0.033$), TNM stage alone grouped into three staging groups of I or II, III, and IV ($C = 0.66$, $p < 0.001$), and TNM stage alone grouped into seven staging groups of IA, IB, IIA, IIB, IIIA, IIIB, and IV ($C = 0.67$, $p < 0.001$) (Table 3). Multivariate comparison of the prognostic value between the PVP index, $\ln(MTV_{WB})$ alone, and TNM stage alone, adjusted for age, gender, histology, and treatment, are shown in Table 3. There was no evidence of multicollinearity among the covariates. Not surprisingly, because the PVP index is a combination of $\ln(MTV_{WB})$ and TNM stage, it was a statistically significantly better prognostic variable (adjusted HR = 2.70, $p < 0.001$) than either $\ln(MTV_{WB})$ alone or TNM stage alone, both of which are statistically significant prognostic variables [13–25]. The C-statistic was statistically significantly greater for the multivariate model that included the PVP index ($C = 0.74$) than for the multivariate model that included $\ln(MTV_{WB})$ alone ($C = 0.73$, $p < 0.01$) or TNM stage alone, with TNM stage grouped either in three or seven staging groups ($C = 0.72$, $p < 0.01$, for both) (Table 3), indicating that, in this multivariate analysis with adjustment for age, gender, histology, and treatment, the PVP index produced significantly greater discriminatory power for prognostication of overall survival than either $\ln(MTV_{WB})$ or TNM stage alone.

Figure 3 shows Kaplan-Meier curves based on all 328 patients in our cohort stratified by the quartiles of the values of the PVP index. Clearly, increasing values of the PVP index was associated with worsening overall survival. Thus, the PVP index makes the additional prognostic value from MTV_{WB} available to clinicians to achieve, potentially, greater discriminatory power for the prognostication of overall survival than the current practice based on the TNM stage.

As a preliminary validation, we compared our estimated HRs for $\ln(MTV_{WB})$ and TNM stage, used for the formulation of the PVP index, with the HR values reported in the literature. The univariate analysis HR of $\log_2(MTV_{WB})$ for stage-I and II patients in our patient cohort ($n = 89$) ($HR = 1.21$) was similar to the HR value reported by Hyun SH *et al* based on 529 stage-I and II Korean patients ($HR = 1.264$) [22]. In a multivariate analysis that included age, gender, and histology, the HR for TNM stage in our patient cohort ($n = 328$) ($HR = 1.37$) was similar to the HR value reported by the IASLC Lung Cancer Staging Project (7th edition) based on 11,536 NSCLC patients ($HR = 1.38$) [13].

DISCUSSION

For patients of a single TNM stage, $\ln(MTV_{WB})$ was capable of differentiating between longer-surviving patients and those of poorer prognoses. This prognostic value is in addition to the TNM stage and is only available if $\ln(MTV_{WB})$ and TNM stage are used together clinically for the management of NSCLC patients. The PVP index provides a practical method for consideration of $\ln(MTV_{WB})$ and TNM stage together, thus making the additional prognostic value from $\ln(MTV_{WB})$ available to clinicians. Our analysis shows significantly greater prognostic value of the PVP index compared with $\ln(MTV_{WB})$ alone or TNM stage alone in both univariate and multivariate survival analyses, the latter of which, with

adjustment for age, gender, treatment and histology, indicates that the additional prognostic value of the PVP index comes from MTV_{WB} , and not from the secondary clinical variables.

Clinicians can potentially take advantage of the greater prognostic value of the PVP index in several clinical situations. First, the PVP index could be used to help make better treatment decisions for NSCLC patients. For example, at diagnosis, about two-thirds of NSCLC patients are in advanced stages (stages IIIA, IIIB, or IV), with only 1.3–15.9% five-year overall survival rate [13]. Stage-IIIA encompasses the stages of T3N1M0, T1-3N2M0, and T4N0-1M0, and is highly heterogeneous due to variations in the primary tumor size, and the extent and location of nodal metastases. The management of stage-IIIA patients is currently controversial and without a standard approach. Chemotherapy, radiation therapy and surgery either alone or in various combinations with chemotherapy and radiation, have all been studied, but without a uniform and conclusive winning treatment [32–40]. Further risk-stratification of stage-IIIA patients with the PVP index may lead to more appropriate treatment choices: e.g., more invasive surgical lobectomy for low-risk (low PVP index) patients, and chemoradiation therapy for high-risk (high PVP index) patients.

Second, the PVP index could also be used to help provide NSCLC patients with a better estimate of survival duration after diagnosis and treatment. How long a patient would likely live after NSCLC diagnosis and treatment is an important question for helping the patient and his or her family plan future care, resource allocation, and other end-of-life issues. However, unfortunately, there is limited guidance for medical professionals to address this question with an accurate estimate. The PVP index provides access to greater prognostic value from currently available clinical information and could lead to a more accurate estimate of patient survival, thereby benefiting the patients, their families, and their physicians.

Finally, the PVP index could be used in clinical trials to better define patient populations. In clinical trials, patients are selected and enrolled into experimental and control groups based on similarities of their risk profiles. Therefore, accurate characterization of risk is critical, and more accurate characterization of risk leads to more effective and more efficient trials. To date, volumetric MTV_{WB} has not been included commonly as a consideration in NSCLC treatment trials [41–43]. The PVP index makes it possible and practical for trial investigators to take advantage of the added prognostic value of MTV_{WB} , thereby potentially improving the likelihood of producing definitive trial outcomes or reducing the number of patients necessary for the trial.

To provide initial validation of the reliability of the weights that we used to formulate the PVP index based on our patient cohort (Eq. 1, Table 2), we compared our estimate of the HR values with those reported in the literature. We found similar HR values for $\log_2(MTV_{WB})$ [22] and for TNM stage [13]. The similarities in the HR values suggest that our formulation of the PVP index is potentially reliable and applicable to patient populations at other institutions. More extensive validation with larger patient cohort, and with multi-institutional data, is necessary to confirm the accuracy and reliability of the weights in the formulation of the PVP index.

This study has some limitations. First, this is a retrospective study within a single academic institution where formulation and assessment of the PVP index were performed on the same cohort of patients. Retrospective validation with data from other institutions and prospective validation are needed to further establish the prognostic value of the PVP index. Second, our study had a limited number of patients, especially limited number of stage-II NSCLC patients. This prevented us from formulating the PVP index with more than three TNM-stage groups. Even with the analysis of TNM stage limited to only three stage groups, the PVP index was shown to be more prognostic than TNM stage alone or $\ln(MTV_{WB})$ alone (Table 3); a larger patient cohort, which would allow us to analyze more TNM-stage groups, might yield greater prognostic value of the PVP index from more precisely defined TNM-stage groups than we report here. Further analysis and validation with a larger patient cohort will be necessary.

Third, performance status was not included in our multivariate analysis, because performance status was not recorded clinically at the time of PET/CT scan for all patients included this study. However, association between performance status and survival has not been demonstrated consistently [10, 15, 16], and poor performance status may be simply due to high tumor burden [15].

CONCLUSION

The new PVP index that we propose is a combination of TNM stage and whole-body metabolic tumor volume. It provides a practical approach for clinicians to combine the prognostic values of $\ln(MTV_{WB})$ and TNM stage for NSCLC and achieves improved prognostic accuracy for overall patient survival compared with current practice based on TNM stage alone.

Acknowledgments

1. This work was supported in part by a grant (R21 CA181885) from the National Cancer Institute of the National Institutes of Health.
2. The statistical analysis of this work was supported in part by the National Institutes of Health (NIH) through a University of Chicago Cancer Center Support Grant (P30 CA014599).
3. YJ was supported in part by NIH through grant R01 CA092361.
4. Special thanks to our chest oncological team at the University of Chicago for taking care of our study patients.
5. The authors have not used writing assistance.

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Summary

We propose a new PET/CT volumetric prognostic (PVP) index for NSCLC by combining the current TNM staging system and whole-body metabolic tumor volume based on Cox regression analysis of 328 consecutive NSCLC patients. Our analysis shows that the PVP index offers significantly better prognostic accuracy for overall survival of NSCLC patients than the current TNM staging system alone or whole-body metabolic tumor volume alone.

HIGHLIGHTS

- We propose a new PET/CT volumetric prognostic (PVP) index for NSCLC based on a Cox regression model.
- The PVP index is a combination of TNM stage and whole-body metabolic tumor volume.
- The PVP index was developed based on 328 consecutive NSCLC patients.
- It offers better prognostic accuracy than TNM stage or whole-body metabolic tumor volume alone.

Figure 1.

Kaplan-Meier curves of overall survival based on 52 stage-IIIa NSCLC patients stratified by the median value of $\ln(MTV_{WB})$ (calculated from the entire study cohort of 328 patients), showing that MTV_{WB} provides prognostic value in patients of the same TNM stage. This observation provides motivation for the proposed PVP index, which combines $\ln(MTV_{WB})$ with TNM stage to allow clinicians to take advantage of the additional prognostic value from MTV_{WB} .

Figure 2.

Graphical representation of the PET/CT volumetric prognostic (PVP) index as defined by Eq. (1). For patients within a single TNM stage, the PVP index is linearly related to $\ln(MTV_{WB})$, with a slope of 0.360. For a given value of $\ln(MTV_{WB})$, advanced stage yields greater PVP index. The values on the x-axis correspond to the 5th, 25th, 50th, 75th, and 95th percentiles of $\ln(MTV_{WB})$ for the entire study cohort.

Figure 3.

Kaplan-Meier curves of overall survival based on 328 stage-IA to stage-IV NSCLC patients stratified by the quartiles of the values of the PVP index, showing that increasing values of the PVP index are associated with worsening overall survival.

Table 1

Patient and tumor characteristics

Variables	N	Percentage (%)
All Patients	328	100
Gender		
Male	156	47.6
Female	172	52.4
TNM Stage		
Stage IA/IB	46/43	14.0/13.1
Stage IIA/IIB	19/18	5.8/5.5
Stage IIIA/IIIB	52/39	15.9/11.9
Stage IV	111	33.8
Histology		
Adenocarcinoma	129	39.3
Squamous cell carcinoma	92	28.0
Large cell carcinoma	21	6.4
Not otherwise specified	78	23.8
Others	8	2.4
Treatment*		
No cancer specific therapy	37	11.3
No surgery with chemo/XRT	180	54.9
Chemo only	55	
XRT only	28	
Both	97	
Surgery	111	33.8
Age (years: mean±SD, median [range])	67.5±10.5, 68.3 [30.0–89.9]	
MTV_{WB} (ml: mean±SD, median [range])	149.57±221.29, 66.33 [1.04–1566.88]	

Notes: N = number of patients; others = other types of non-small cell lung cancer; Chemo/XRT = chemoradiation; SD = standard deviation; MTV_{WB} = whole-body metabolic tumor volume.

* Surgery was always performed with curative intent, but the intent of non-surgical treatment was unknown.

Table 2

Estimated hazard ratio and Cox regression coefficients for formulation of the PET/CT volumetric prognostic (PVP) index.

	HR	Regression Coefficient
ln(MTV _{WB})	1.43	0.360
TNM stage		
Stage I+II	reference	
Stage III	1.53	0.424
Stage IV	2.44	0.890

Notes: HR = Hazard Ratio. ln(MTV_{WB}) is natural log-transformed whole-body metabolic tumor volume.

Table 3

Prognostic value comparison between the PET/CT volumetric prognostic (PVP) index, TNM stage, and whole-body metabolic tumor volume.

Variables	N	Univariate Analysis			Multivariate Analysis*				
		HR	[95%CI]	p-value	C	HR	[95%CI]	p-value	C
PVP index	328	2.72	[2.28,3.24]	<0.001	0.71 [†]	2.70	[2.16,3.37]	<0.001	0.74 ^{\$}
ln(MTV _{WB})	328	1.60	[1.46,1.75] [#]	<0.001	0.69	1.51	[1.36,1.67]	<0.001	0.73
TNM Stage	328			<0.001 [^]				<0.001 [^]	
I+II	126		(reference)				(reference)		
III	91	2.73	[1.96,3.79]		0.66	2.07	[1.44,2.97]		0.72
IV	111	4.55	[3.31,6.25]			3.55	[2.43,5.18]		
TNM Stage	328			<0.001 [^]				<0.001 [^]	
IA	46		(reference)				(reference)		
IB	43	2.24	[1.25,4.04]			1.94	[1.06, 3.55]		
IIA	19	2.04	[0.98,4.23]			1.94	[0.92, 4.08]		
IIB	18	3.04	[1.49,6.22]	0.67	1.97	[0.94, 4.12]	0.72		
IIIA	52	4.46	[2.56,7.79]		3.49	[1.93, 6.32]			
IIIB	39	5.35	[2.99,9.55]		3.20	[1.73, 5.92]			
IV	111	8.08	[4.83,13.51]		5.83	[3.28, 10.33]			

Notes: N = number of patients; HR = Hazard Ratio; CI = Confidence Interval; C= Gönen and Heller's K concordance statistic ln(MTV_{WB}) is natural log-transformed whole-body metabolic tumor volume.

* Adjusted for age, gender, treatment and histology.

[†] p=0.033 for PVP index vs. ln(MTV_{WB}); p<0.001 for PVP index vs. TNM stage (for both three- and seven-level staging).

^{\$} p<0.01 for PVP index vs. ln(MTV_{WB}); p<0.01 for PVP index vs. TNM stage (for both three- and seven-level staging).

[#] The HR for MTV_{WB} on the log10 scale would be exp(0.468*2.303) = 2.94, where 0.468 is the regression coefficient for ln(MTV_{WB}) in this model and 2.303 is a conversion factor. Thus, for a 10-fold increase in MTV, the hazard of death increases by a factor of 2.94.

[^] Based on a 2 degree of freedom test for the 3-level staging variable and 6 degree of freedom test for the 7-level staging variable.