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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 ($C = 0.67$, $p < 0.01$) 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 ($C = 0.72$, $p < 0.01$) 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.

1. 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

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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 the "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.

2. Materials and methods

2.1. 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, ^{18}F-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.

2.2. 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.

2.3. 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