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Original Article

Prognostic value of FDG PET/CT-based metabolic tumor volumes in metastatic triple negative breast cancer patients

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Abstract: FDG PET/CT-based measures of tumor burden show promise to predict survival in patients with metastatic breast cancer, but the patient populations studied so far are heterogeneous. The reports may have been confounded by the markedly different prognosis of the various subtypes of breast cancer. The purpose of this study is to evaluate the correlation between tumor burden on FDG PET/CT and overall survival (OS) in patients within a defined population: metastatic triple negative breast cancer (MTNBC). FDG PET/CT scans of 47 consecutive MTNBC patients (54±12 years-old) with no other known malignancies were analyzed. A total 393 lesions were identified, and maximum standardized uptake value (SUV_{max}), mean SUV, metabolic tumor volume (MTV), total lesion number (TLN) and total lesion glycolysis (TLG), were measured and correlated with patient survival by Mantel-Cox tests and Cox regression analysis. At a median follow-up time of 12.4 months, 41 patients died with a median OS of 12.1 months. Patients with MTV less than 51.5 ml lived nearly three times longer (22 vs 7.1 months) than those with a higher MTV (χ^2=21.3, P<0.0001). In a multivariate Cox regression analysis only TLN and MTV were significantly correlated with survival. Those with an MTV burden in the 75th percentile versus the 25th percentile had a hazard ratio of 6.94 (p=0.001). In patients with MTNBC, MTV appears to be a strong prognostic factor. If validated in prospective studies, MTV may be a valuable tool for risk stratification of MTNBC patients in clinical trials and to guide patient management.

Keywords: Triple-negative metastatic breast cancer, FDG PET/CT, metabolic tumor volume, breast cancer prognosis

Background

Triple negative breast cancer (TNBC) is a subtype of breast cancer defined by the absence of estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2). Metastatic triple negative breast cancer (MTNBC) has the worst prognosis of all subtypes of breast cancer. Median survival of patients with MTNBC is 13 months [1]. This is considerably shorter than patients with metastatic breast cancer (MBC) where the primary tumor is positive for ER (21.0 months), PR (24.7 months) or HER2 (25.1 months) [2-5]. For breast cancer patients with expression of ER, PR or HER2, endocrine treatment or Her2 targeted monoclonal therapy markedly improves survival in the setting of metastatic disease. However, in the nearly 15% of all breast cancers that have a triple-negative phenotype, efficacious targeted treatments are not available.

Clinical trials with poly ADP-ribose polymerase (PARP) inhibitors [7], epidermal growth factor receptor (EGFR) inhibitors [8], and platinum containing regimens are ongoing with mixed results [9]. Even a moderate imbalance in prognostic factors between the arms of a random-

ized study may affect treatment efficacy. Few predictors of survival or treatment response within the triple-negative phenotype exist, limiting means to stratify patients beyond TNM stage [6].

Intuitively, a quantitative measurement of total tumor burden should differentiate disease severity among breast cancer patients of the same stage and molecular phenotype. FDG PET/CT has been recognized to have an ever-expanding role in guiding the clinical management of breast cancer [10, 11]. FDG PET/CT has quantitative capabilities, however, in most studies FDG PET scans are interpreted in a qualitative way and the quantitative information of the PET scans is not fully utilized.

Various quantitative measures are easily derived clinically from whole body FDG PET/CT scans. The most common is the standard uptake value (SUV), used in practice as either the mean (SUV_{mean}) or maximum (SUV_{max}) metabolic signal from a given tumor lesion. Another parameter is metabolic tumor volume (MTV), calculated by determining all voxels that show FDG uptake above a certain percentage of SUV_{max}. MTV can be multiplied with the mean or maximum SUV from that lesion and results in a parameter called total lesion glycolysis (TLG) [12].

Studies of breast [13], multiple myeloma [14], lung [15, 16], pharyngeal [17], esophageal [18] and gastrointestinal cancers [19] have shown that MTV or TLG are significantly correlated with survival and that their prognostic value is often higher than SUV measurements. Two studies have shown this prospectively, suggesting MTV and/or TLG may have utility as stratification tools in assessing treatment efficacy [19, 20]. For example, *Song et al.* demonstrated that an MTV cut-off value of 160 ml was significantly predictive of survival in patients with gastrointestinal B-cell lymphoma. Post-hoc analysis further showed those with MTVs above the cut-off had significantly different responses to treatment with chemotherapy alone versus chemotherapy with surgery [19].

For studies assessing treatment efficacy in MTNBC, a reliable prognostic tool that enables more finely tuned patient stratification would be extremely valuable [21]. Thus, we investigated whether quantitative FDG PET/CT derived parameters of tumor burden are correlated with survival of MTNBC patients.

Methods

Patient selection

This was an IRB approved HIPAA compliant retrospective study. Patients were selected using Darwin, an electronic medical records filtering database at MSKCC, that searched and compiled a list of patients with a metastatic breast cancer diagnosis, triple negative pathology findings, and who underwent a FDG PET/CT from 2001-2012. Patients with synchronous, invasive non-breast tumors or no evidence of metastasis on FDG PET/CT were excluded. No restrictions were made regarding the number of prior palliative therapies. Of 47 patients meeting this criteria 18 received therapy prior to PET/CT, four in the past month. In 31 patients initial MTNBC diagnosis was made within two months of FDG PET/CT. Thirteen patients had had a previous diagnosis of breast cancer before their metastatic diagnosis. The basis of referral for FDG PET/CT was not recorded.

FDG PET/CT

Before injection of radiotracer patients were fasted for at least six hours. If plasma glucose levels were <200 mg/dl, patients were injected with 444-555 MBq of IV radiotracer. After injection patients were rested for 60-90 minutes before image acquisition. FDG PET/CT scans were performed on various systems (*GE Discovery Series, Siemens Biograph Series)* but patient preparation and image acquisition followed a standardized protocol. Using an IEC image quality phantom the medical physics group have made efforts to ensure iterative reconstruction parameters are comparable, minimizing SUV differences between scanners, generally within 10%. All patients followed the protocol described above. Measured lesions were those corroborated by the radiologist's report and included only primary tumors and lesions that had the typical characteristics of metastatic disease on FDG PET/CT. Lesion MTV was defined as the region enclosed by a 42% isocontour around the maximum PET voxel of a lesion using PET VCAR software (Advanced Workstation 4.4, GE Medical Systems, Milwaukee, WI). This method of calculating MTV has been well described by others [14,

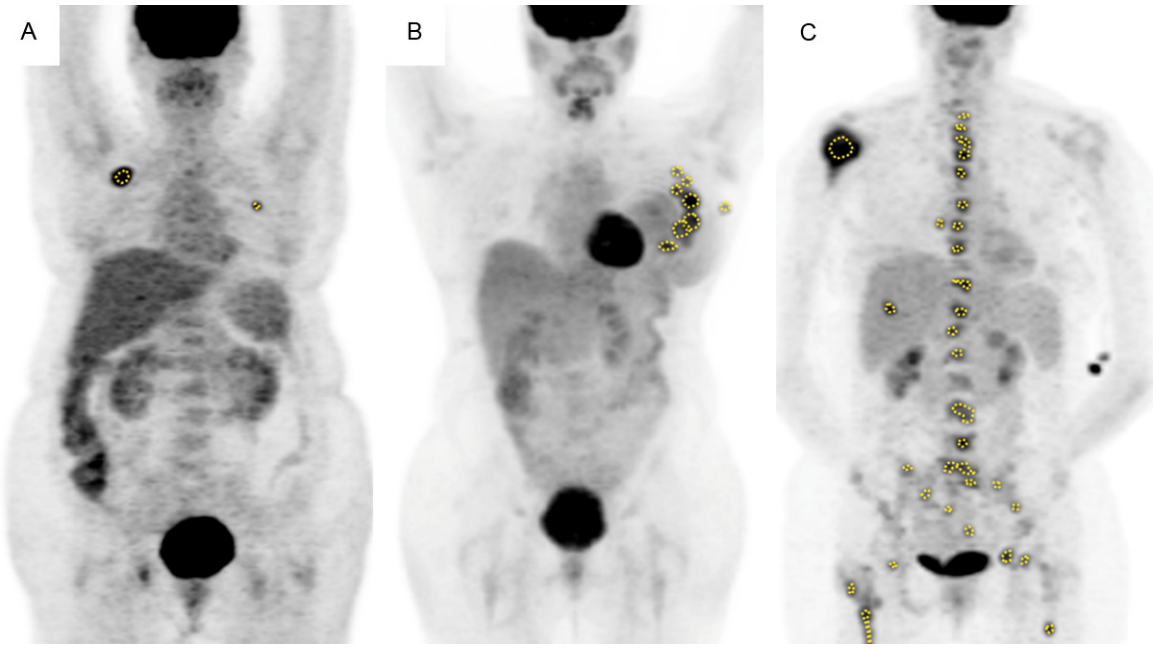

Figure 1. Measurement of Metabolic Tumor Volume. Representative PET MIP of two patients at time of FDG PET/CT: (A) Low tumor burden: MTV of 36.0 ml, with survival of 669 days; (B) Medium burden: MTV of 58.3 ml and survival of 393 days; and (C) high tumor burden: MTV of 137.0 ml with survival of 16 days.

Table 1. FDG PET/CT Measurement Summary

	Value[a]
Age	53±14
SUV_{max}	14.4±10.0
SUV_{mean}	6.6±4.8
TLG	292.5 [81.4-800]
MTV	51.5 [27.0-123]
TLN	7.9±6.4
Time from Diagnosis to PET-CT	40 [10-144]

[a]Values are presented as the means ± standard deviation or median [interquartile range].

22, 23]. Patient MTV represents the sum of every individual lesion MTV. Occasional adjustments of the 42% threshold were performed if the volume extended beyond the lesion as seen on CT [12]. Patient SUV_{mean} and TLGs constituted the average and sum, respectively, of all lesion SUV_{mean} and lesion TLG measures. Patient SUV_{max} was reported as the highest lesion SUV_{max}, and TLN was defined as the total number of malignant lesions per patient (**Figure 1**).

Visualization of bone and bone marrow metastases is one of the major strengths of FDG PET/CT in staging of breast cancer patients and were identified in half of all study subjects [24]. Also, alkaline phosphatase has been reported as prognostic of survival in patients with MTNBC [1]. Therefore, we performed the same multivariate analysis excluding bone lesions to assess if our approach may have been influenced by the unique ability of FDG PET/CT to detect such lesions. Measurements were also grouped separately for seven patients with only lymph node metastases to assess if metastatic site might influence the prognostic strength of these measures. There were no patients with only bone or only liver lesions from whom we could perform a similar grouping.

Statistical analysis

Overall survival (OS) was determined by chart review and defined as the time from FDG PET/CT to death or last recorded encounter. Prism GraphPad 6 (GraphPad Software, LaJolla, CA) was used for graphical representation of measurements and univariate Cox-Mantel survival analysis statistics. Cox regression analysis was performed using IBM SPSS 20 (IBM Corporation, Armonk, NY). Distributions of continuous values were assessed for normality with a one-sample Kolmogorov-Smirnov Test (**Table 1**).

Age, SUV_{max}, SUV_{mean}, TLG, MTV, and TLN were analyzed for their correlation with survival. To

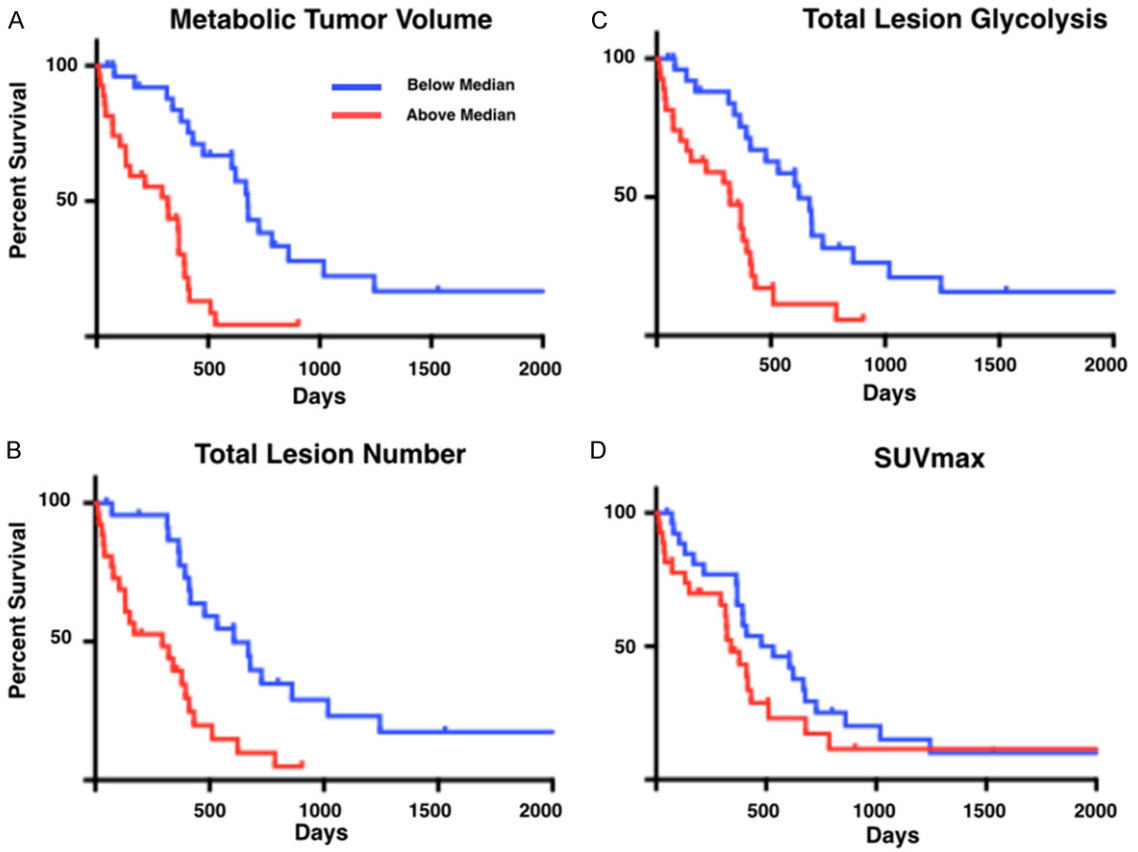

Figure 2. Univariate Analysis of FDG PET/CT Measurements. Mantel-Cox survival analysis for three measurements demonstrated significant differences (all $p<0.001$) when grouped by relationship to the median value. Metabolic tumor volume (MTV) (A) had the largest difference ($X^2=24.0$) between groups based on a median of 51.5 mL. Total lesion number (TLN) (B) ($X^2=15.6$) with a median value 7, and total lesion glycolysis (TLG) (C) ($X^2=15.6$) with a median value of 292.5 grams also demonstrated significant differences in survival. SUV max (D) ($X^2=1.9$, $p=0.167$) with a median of 12.5 grams per milliliter did not show a significant difference in survival.

distinguish between instances of early diagnosis versus slowly evolving disease the time from diagnosis to FDG PET/CT was also included. All measurements first underwent univariate analysis as continuous variables as well as their dichotomized versions using median-split. Those found to be significant were entered into a multivariate Cox Regression model using Backward Wald selection. Finally, to better illustrate clinical relevance a Cox model was refit with MTV dichotomized to compare patients with tumor burden of the 75th percentile to those of the 25th percentile. As patient data was collected over the span of twelve years, and management of MTNBC patients has changed notably in this time, analysis was repeated using the same median value cut-off excluding the six oldest patients, reducing the time range of patient data to eight years.

Results

Forty-seven patients with metastatic triple negative breast cancer met the inclusion criteria. The average age was 55 (SD, 12.4) years-old. Of those included, 26% of patients had undergone prior curative intent surgery, 26% had received adjuvant or neoadjuvant chemotherapy and 9% adjuvant radiotherapy. A majority of patients (59%) had not received breast cancer specific treatment prior FDG PET/CT and there was no significant difference in survival between these patients and those who did. There was also no difference in survival between those with a prior breast cancer diagnosis (13) and those without (34) a prior diagnosis. A total of 393 lesions were measured and their location noted. Manual adjustments of the MTV were only required for 12 of these

Table 2. Multivariate Analysis of FDG PET/CT Measurements for Predicting Survival

	HR	95% CI	p
TLG[a]	0.70	0.23-2.15	0.536
MTV	3.66	1.73-7.72	0.001*
TLN	3.28	1.57-6.84	0.002*
MTVWoBL	3.74	1.79-7.86	<0.001*
TLNWoBL	2.13	1.04-4.34	0.038*

[a]TLG dropped from Backward Wald Selection after first of two steps. *Denotes statistically significant hazard ratio.

lesions. In seventy-nine percent of patients (37) both primary and metastatic lesions were identifiable on FDG PET/CT.

SUV_{max}, SUV_{mean}, TLG, MTV, TLN and time from diagnosis to PET-CT values are reported in **Table 1**. Univariate Cox regression of measures as continuous variables demonstrated a significant correlation with survival only for MTV, TLG, and TLN. Mantel-Cox survival analysis demonstrated significant differences in OS for patient measures of MTV, TLN, and TLG when compared about their respective medians (**Figure 2A-C**). For example, median survival of patients with a MTV below the median was 3-times longer than for patients with a MTV above the median (**Figure 2A**). Both SUV_{mean} and SUV_{max} (**Figure 2D**) were not significantly correlated with survival. In patients with only lymph node metastases the median MTV was 47.0 mL compared to 52.4 mL in the remaining subjects. Median TLN was eight and seven, respectively, between these same two groups. Survival was also comparable with a median survival of 322 in the lymph node only group versus 386 days in all other patients.

Measures found to be significant on univariate analysis were tested in a multivariate Cox regression and only MTV and TLN connoted a significant ability to predict survival with the following hazard ratios (HRs): MTV (HR: 3.66, CI: 1.73-7.72, p=0.001) and TLN (HR: 3.28, CI: 1.24-13.23, p=0.002) (**Table 2**). These measures were also analyzed as continuous variables and, again, only MTV and TLN were significant: MTV per 100 ml (HR: 2.44, CI: 1.54-3.82, p=0.001) and TLN per lesion (HR: 1.11, CI: 1.03-1.19, p=0.004). As a dichotomous value representing the 25^{th} (27.0 mL) and 75^{th} percentiles (121.3 mL) of tumor burden MTV demonstrated a hazard ratio of 6.94 (CI: 2.15-22.39, p=0.001).

To address if FDG PET/CT's ability to identify bone lesions influenced our findings analysis was performed without bone lesions. This revealed only a small change in MTV (HR: 3.74, CI: 1.79-7.86, p=0.021) and moderate change in TLN (HR: 2.13, CI: 1.04-4.34, p=0.038) to predict survival. With some patient records extending back nearly twelve years analysis was performed excluding the six oldest records as management of MTNBC may have changed. This smaller cohort, representing records compiled across just eight years (2005-2012), still demonstrated significant correlations between survival and both MTV (HR: 3.90, CI: 1.91-8.12, p=0.001) and TLN (HR: 3.63, CI: 2.04-6.64, p=0.001).

Discussion

In our patient population tumor burden as assessed quantitatively by MTV and TLN on FDG PET/CT was a strong predictor of survival. The median OS for the whole group of patients included was 12.1 months, which is in line with previous studies of MTNBC [1]. Yet, OS was only 7 months with a MTV above the median whereas it was more than 20 months for patients with an MTV below the median. Thus, survival of triple negative breast cancer patients with a low metastatic volume was comparable to the survival of patients with estrogen receptor positive tumors.

Measures of breast cancer tumor burden from FDG PET/CT have been studied before and MTV has been shown to be able to predict post-surgery disease-free survival, and OS in early stage disease [24, 25]. In MBC patients of all phenotypes, *Ulaner et al*. [13] demonstrated MTV and TLG have prognostic strength when stratified by site of metastasis. However, intensity of FDG uptake is correlated with molecular subtype [26] and the molecular subtype is strongly correlated with prognosis. Therefore, studies of the prognostic value of MTV and SUV_{max} in mixed breast cancer populations can easily be confounded by the distribution of molecular phenotypes in the study population. Specifically, high SUV_{max} and high MTV may closely correlate with a more aggressive molecular phenotype and therefore not provide independent prognostic information. In order to confirm the prognostic value of measurements of tumor burden on FDG PET/CT we therefore studied a well-defined patient group of MTNBC patients.

Few studies have investigated predictors of survival exclusively in the MTNBC population. *Kassam et al.* [1] reported previous chemotherapy and an alkaline phosphatase level of more than 120 U/L to be predictive of survival with HRs of 2.40 and 2.77, respectively. This is substantially lower than the HR of nearly 7 for MTV values in the 75th percentile compared to the 25th percentile of tumor burden examined in the present study. Groups focused on triple-negative populations, metastatic and non-metastatic, have published HRs for OS as high as 4.2 [27, 28], however, all of these measures are confounded by TNM staging and may not be able to be extrapolated to the MTNBC population in a meaningful way.

The survival difference for patients above and below the median was nearly 15 months, which is high when compared to the typical median survival of MTNBC (13 months) and effects of current therapies on survival differences. Recent trials with PARP and EGFR inhibitors show survival changes on the order of 4 months, just a third of the difference observed here [8, 29].

Unexpectedly, our analysis showed SUV_{max} and TLG were not significantly predictive of survival yet MTV and TLN were. One explanation could be that the metabolic activity of the tumor cells (assessed by SUV_{max}) is relatively similar in all MTNBC patients and therefore not correlated with survival. In contrast, there are marked differences in SUV_{max} between the different molecular subtypes of breast cancer. For example, ER/PR positive primary breast cancers have been shown to demonstrate an almost 2-times lower FDG uptake than triple negative tumors [30]. In MTNBC patients, physical size and extent of tumor burden may therefore be stronger determinants of future breast cancer outcomes than metabolic signal strength.

In addition to MTV, TLN was also significantly correlated with patient survival. This raises the question if other imaging modalities, such as CT may provide similar prognostic information as FDG PET/CT. However, TLN was much less correlated with survival when bone (marrow) lesions were excluded from analysis. A study comparing the ability of FDG PET/CT and CT to detect extra-hepatic metastases in hepatocellular carcinoma demonstrated FDG PET/CT is twice as sensitive in detecting bone and bone marrow lesions [31]. If similarly true for breast cancer patients then CT imaging is unlikely to provide prognostic information as accurate as FDG PET/CT. However, future studies comparing CT and FDG PET/CT in patients with MBC are required to definitively address this point.

This study demonstrates promise for MTV and TLN measured with FDG PET/CT as useful prognostic indicators in MTNBC, but there are limitations. First, different PET machines were used, likely with various reconstruction algorithms, and coupled with the large number of small lesions measured inconsistent values for SUV_{max} and SUV_{mean} from partial volume effects may have influenced results. Yet, this also may highlight the relative robustness of MTV and TLN for application in future studies using disparate PET scanners. Second, as with all retrospective studies there are possibly confounding factors. For example, FDG PET/CT was performed at various times after diagnosis of MTNBC and, thus, concerning for bias towards longer survival times in patients who underwent FDG PET/CT scans earlier after the diagnosis of MTNBC. However, we saw no contribution to our multivariate survival analysis when time from diagnosis to FDG PET/CT was added. There was also considerable variability in the types and number of therapies employed, and our sample size was too small to account for these differences in a meaningful way. Also, as clinical use of serum tumor markers and measurements of circulating tumor cells (CTCs) become more common future studies would benefit from inclusion of these tests so that they could be compared to the PET/CT-based measures examined here. Nevertheless, a larger multicenter, prospective study is needed to validate the utility of MTV and TLN.

Conclusion

MTV and TLN appear to be strong prognostic factors in MTNBC. These parameters can be obtained from routine whole-body FDG PET/CT studies using commonly available software. If confirmed in prospective studies, MTV and TLN may be valuable predictors of survival in MTNBC and provide data for risk adaptive treatment.

Disclosure of conflict of interest

All procedures performed in studies involving human participants were in accordance with

the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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