

Original Article

^{18}F -FDG PET/CT and pain in metastatic bone cancer

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Abstract: This study aims to determine if the pain intensity of patients with oncologic bone metastases (BM) correlates with metabolic activity measured by ^{18}F -FDG PET/CT. Twenty-eight patients, ages: 21-89 years (mean: 58.8) with BM were included in the study between September 2011 to September 2013. All patients completed a detailed questionnaire regarding pain symptoms on the visual analog scale (VAS), analgesic use, and areas of chronic pain, prior to obtaining an ^{18}F -FDG PET/CT. Pain symptoms were queried for 11 body regions including limbs, head, torso, etc. and the corresponding SUV_{max} of BMs within that region were modeled with the corresponding clinical data using a linear mixed effects model and a linear regression model. Overall 64 areas in the 28 subjects were found to have BM. SUV_{max} was found to be a significant predictor of pain intensity as measured by the VAS, with a *P*-value of 0.045, with a modest effect-size on linear regression of R^2 of 0.11.

Keywords: ^{18}F -FDG, bone metastasis, SUV pain

Introduction

Cancer pain is a serious and prevalent problem occurring in 64% of patients with advanced cancer [1]. Pain secondary to BMs is common underlying etiology (47.1% in a recent survey) [2]. Pain from BM is not only a clinical challenge to manage, but also has prognostic significance. Patients with pain related to BM have an increased mortality [3]. Why some patients experience debilitating pain and others are spared remains an open question. 2-deoxy-2- ^{18}F fluoro-D-glucose positron emission tomography (^{18}F -FDG PET/CT) is a tool that may be able to provide insight into this clinical observation.

^{18}F -FDG PET/CT is commonly used for staging and monitoring of patients with cancer and it also provides unique functional data about the metabolic activity of tumors. FDG is a glucose analog that is transported into a cell like glucose. It is not fully metabolized, but is phosphorylated, and subsequently becomes trapped within the cell. ^{18}F -undergoes positron decay that causes an emission of two 511 KeV photons that are captured by photodetectors. The absolute number of positron decay pho-

tons within a tissue not only depends on metabolic activity, but it also depends on body mass and injected dose. The standardized uptake value (SUV) was developed to account for variations in these parameters, and it is used as a proxy for the overall metabolic activity of a tumor. It has never been systematically assessed if a correlation exists between the metabolic activity of a tumor and pain.

Studies have demonstrated that BMs are generally hypermetabolic when measured with SUV_{max} [4]. Somatic pain is associated with activation of several types of nerve receptors that respond to inflammation and local tissue deformation [5]. These factors are likely to be increased near tumors of higher metabolic activity and it follows that metabolic activity may be an indirect measure of the propensity for a bone metastasis to cause pain.

The purpose of this study is to see if imaging parameters that characterize the metabolic activity of a tumor i.e. the SUV_{max} correlate with a patient's pain intensity. Here we investigate the possible correlation using ^{18}F -FDG PET/CT and a pre-imaging pain questionnaire. A significant correlation may prove clinically useful by

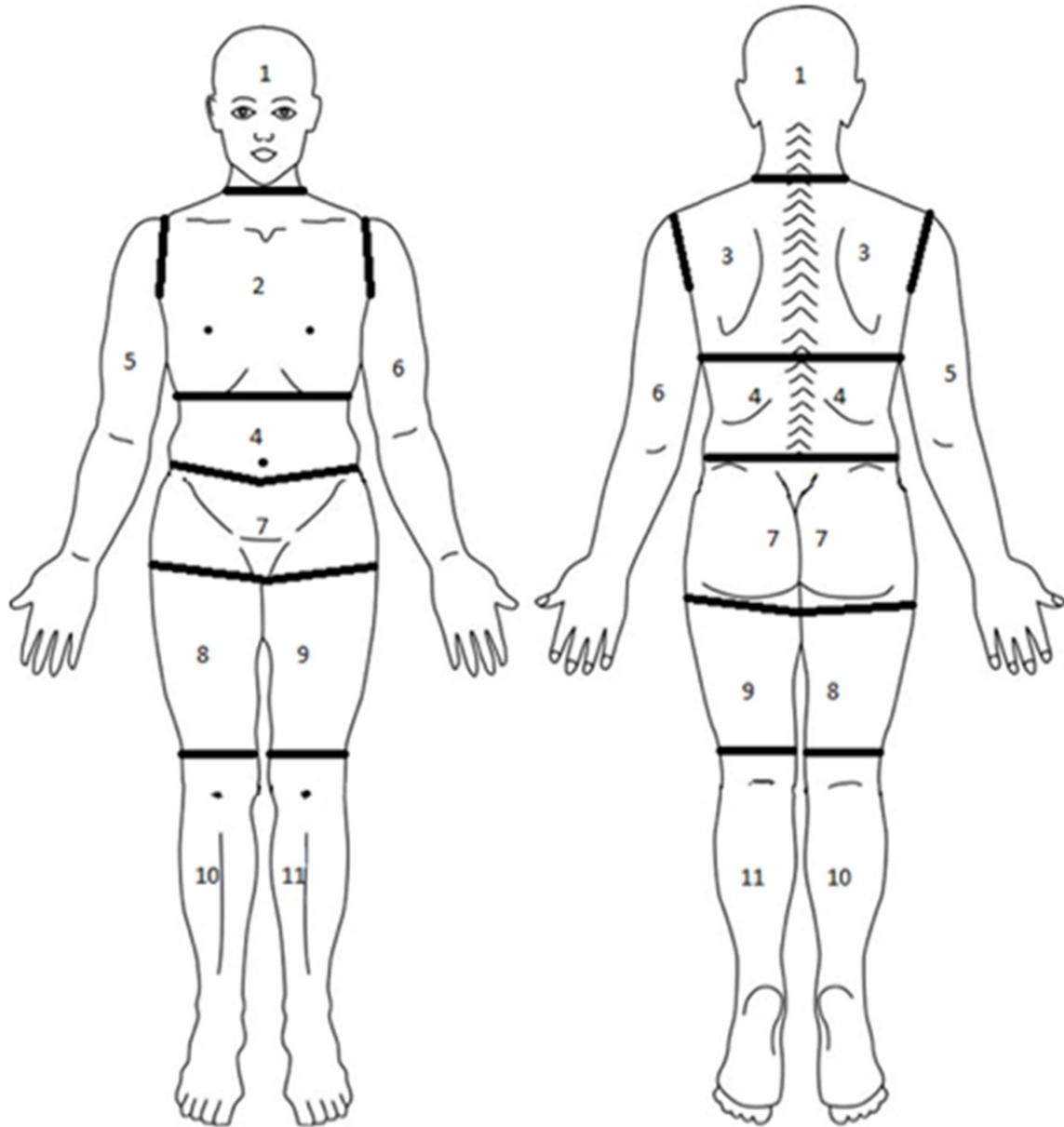


Figure 1. Diagram of body segmented into regions for assessment of pain.

helping clinicians delineate the most likely painful metastasis.

Materials and methods

Subjects

After approval by the University of Wisconsin Institutional Review Board, consecutive patients undergoing ^{18}F -FDG PET/CT were offered participation in this study. Enrollment began September 2011 and ended September 2013. If patients agreed to participate in the study

they were screened for eligibility requirements, including ability to consent to study and age > 18. Eligible patient for the study were offered a questionnaire. The results of the questionnaire were compared to the ^{18}F -FDG PET/CT results as reviewed by an experienced Nuclear Medicine physician (LH). The Nuclear Medicine physician was blinded to the questionnaire answers and only knew that the patient had enrolled in the study. Each body region was assessed for bone metastasis. If presence of bone metastasis was confirmed the highest

SUV_{max} within the region was measured. The first 41 patients in the study without BM were used as a control population; the remainder of the subjects without BMs were excluded from the study. Patients with BM and the control population had their medical charts reviewed for demographic factors as well as cancer diagnosis and type of cancer.

Procedures/data collection

Patients were given questionnaire that inquired about pain in 11 different regions (head and neck, chest, upper back, right shoulder and arm, left shoulder and arm, abdomen and lower back, pelvis and groin, right hip and upper leg, left hip and upper leg, right knee and lower leg/foot, left knee and lower leg/foot) and asked for the maximum intensity pain in the last 24 hours in that region. A diagram of the body regions is attached as **Figure 1**. Potential confounding factors were also assessed including use of pain medications, prior trauma, and pre-cancer chronic pain. Using a visual analog scale (VAS) subjects were asked if they experienced any pain in excess to typical daily aches and then they were asked to rate the most intense pain they have had in each region during the last 24 hours ("0" being no pain and "10" being the worst imaginable pain) [6]. Subjects were also asked about medication use and areas of long-standing chronic pain or recent traumatic injury. Areas of chronic pain were censored from further analysis. Similarly, if a patient had suffered trauma in the last year and had persistent pain, this area was not used in further analysis because of etiologic uncertainty. (Note this is true even if the patients have a pathologic fracture because the tissue damage can spread well beyond the vicinity of the tumor). In patients that were found to have bone metastasis medical records were interrogated for confirmation of cancer diagnosis and underlying oncologic pathology.

Imaging protocol

Patients fasted for 6 hours prior to injections. Patients received 0.14 mCi/kg (minimum of 10 mCi) ¹⁸F-FDG intravenously, and were imaged 60 minutes post-injection with a dedicated GE Discovery VCT. Scans were performed in the three-dimensional and two-dimensional modes and were reconstructed with and without attenuation correction.

Statistical analysis

Summary statistics (mean, standard deviation [SD], quartiles, minimum, maximum) were obtained for continuous measures; frequency counts and percentages were obtained for categorical variables. Summarizing data was compiled into tables and displayed in scatter plots. Differences between the BM and non-BM groups were assessed for continuous measures with a Mann Whitney U Test.

For the primary endpoint of SUV_{max} and its relation to pain more complex statistical analysis was used to control for confounding variables: a linear mixed effects model [7]. SUV_{max} was considered as a function of overall pain, any pain within the last 24 hours, region-specific pain, presence of bone metastases, body region, and being on any pain medication (fixed effects), and a subject-specific term (random effect). These models are able to account for possible correlation between body regions within the same subject. The models were fitted via maximum likelihood, so that a likelihood ratio F-test could be used to test whether the inclusion of additional terms significantly improved the model fit. Candidate terms with $P < 0.05$ were added to the model. Pairwise interaction terms between pain, region, being on any pain medication, and whether or not there were bone metastases in the region, were tested for inclusion. Initially, a "comprehensive" model was fitted to all observations, regardless of whether the subjects had bone metastases were present or not. A second, "reduced", model was fitted to the regions with bone metastases. $P < 0.05$ (two-sided) was the criterion for statistical significance. Exploratory and diagnostic plots were obtained to assess possible violations in model assumptions. All statistical graphics and computations were obtained in R 3.0.1 with the nlme package 3.1-110 for the mixed effects models [8]. Because effect-size measurements are not as widely used in medical literature, a linear regression of SUV_{max} and VAS was used to calculate an R^2 value.

Based on the expected number of eligible patients during the study period and investigator time constraints, we anticipate $n=25-50$ subjects would be the maximum feasible sample size to accrue during the 2-year study duration. The 95% confidence interval for a Pearson correlation coefficient, assuming values ranging from 0.3 to 0.7. PASS 11 [9] have confi-

Pain and SUV in bone metastasis

Table 1. Comparison of Patients with and without Bone Metastases

	No Bone Mets	Bone Mets	P-value
Age yrs (range)	58.8 (21-89)	64.5 (46-87)	0.246
Sex # female (%)	21 (51.2%)	15 (53.6%)	0.848
Hematologic CA	7 (17.1%)	8 (28.6%)	0.256
Overall Pain VAS (STD-DEV)	3.37 (3.25)	4.68 (3.07)	0.089
# of patients with pain (%)	22 (53.7%)	23 (81.1%)	0.015
Narcotic Use	7 (17.1%)	11 (39.3%)	0.039

*Comparisons done with Mann-Whitney U for ordinal/continuous variables, and Chi Square for categorical variables. P values < 0.05 were considered significant and placed in bold. Yrs = years, VAS = visual analog pain scale, STD-DEV = standard deviation, # = number, CA = cancer.

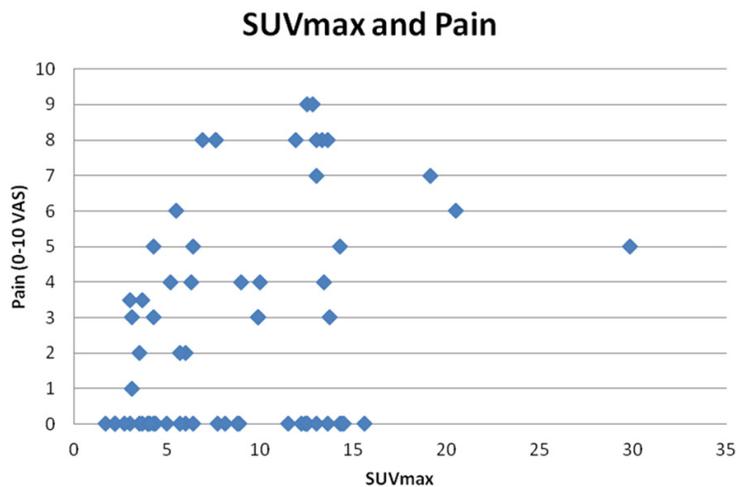


Figure 2. Scatter Plot of SUV_{max} and Pain Intensity (Visual analog scale [VAS] scale 0-10) of all 64 areas of 28 patients with Bone Metastasis.

dence intervals between 0.3 to 0.51 for 0.7 and 0.3 respectively. A mixed-effects model was utilized in this study because it is a robust and widely used statistical model used to assess for correlation between two variables as in the primary hypothesis in this experiment that pain and SUV_{max} are correlated and includes a random-effect term that helps to model subject specific variability.

Results

Pain in cancer patients with and without bone metastases

Twenty-eight patients with BM met the inclusion criteria including completing the questionnaire, and having a diagnosis of cancer. The first 41 patients that completed the questionnaire and had cancer, but did not have BM were used as a control population to compare demog-

graphics and overall pain. **Table 1** summarizes the comparison between patients with BM and those without BM. The age, sex, and percentage of patients with hematologic malignancies were not significantly different than the group of 28 patients with bone metastasis and the control group. The percentage of patients that were using narcotics was significantly different between the two groups as was the percentage of patients that had experienced any pain during the previous 24 hours. The number of regions in which the patients experienced pain and the overall pain on VAS were not significantly different between the groups, but the BM group trended toward higher overall pain intensity and greater number of regions with pain.

Pain intensity and SUV_{max}

The primary endpoint of the study was to compare the maximum regional pain intensity experienced during the last 24 hours with the SUV_{max} within that region. A mixed model (random and fixed effects) using

both the control and experimental groups along with modifying factors including pain medication use, areas of chronic pain prior to cancer, type of malignancy, and recent trauma was used to test the primary hypothesis. Overall 64 areas regions in the 28 subjects were found to have BMs. SUV_{max} was found to be a significant predictor of pain intensity as measured by the VAS. The P-value of 0.045 was calculated for this observation. A linear regression model was used to create an R^2 to assess effect-size with a resultant P-value of < 0.01 with an R^2 of 0.11. This is demonstrated graphically in a scatter plot as **Figure 2**.

Discussion

This is the first study of its kind to investigate the relationship between metabolic activity of bone metastasis and the associated pain. First a control population of patients with cancer

without BM was compared to the cohort of patients with BM. This study found that patients with bone metastasis use more narcotic pain medications, are more likely to experience pain and had a trend toward increased intensity of pain compared to the cancer patients without BMs. This finding confirms the importance that BMs have in the overall pain cancer patients' experience. Given the importance pain plays in the quality of life in cancer patients, investigating the primary mechanisms for pain caused by BMs is of salient importance.

The result of the primary investigation using a linear mixed effect model that included potentially confounding factors was statistically significant ($p=0.045$) for positive correlation between SUV_{max} and pain intensity. An R^2 measures from mixed-effects models are not as standardized or widespread in the medical literature so to quantify an effect-size a linear regression model between SUV_{max} and VAS was calculated. This model was also significant at $p < 0.01$ with an R^2 of 0.11. The findings of the second model indicate that while there is a significant correlation between pain and SUV_{max} these findings have a modest effect-size and this is likely related to a number of factors including the test-retest variability of SUV_{max} [10] as well as the other factors that modify the perception of pain and factors specific to the BM other than metabolic activity such as its location within the bone, as the majority of nociceptive sensory neurons are in the periosteum, and it may be that the periosteum needs to be involved for a BM to be symptomatic [11, 12].

The findings of this study were statistically significant in the mixed-effects linear model as well as the simple linear regression and while the effect-size was modest it needs to be considered within the context of the inherent limitations of a study of this design. Pain is ultimately a subjective experience and it can be somewhat difficult to localize by a patient. Pain can be referred to areas that are distant from the direct source. Pain is influenced by medications, mental state, activity, and prior chronic pain. The expression of pain is also influenced by patient specific factors like stoicism and denial. To try and limit the influence of these factors the mixed-effect model was used for the primary outcome and a well-validated pain scale the VAS was used. Questions regarding pain medication use and areas of chronic pain

were employed in the mixed effects model. To limit the influence of referred pain, the body was divided into broad regions. To minimize the influence of activity the maximum pain over the last 24 hours and not just at the time of questioning was interrogated. SUV_{max} is also not a perfect measure of metabolism.

SUV is a unitless measure $[FDG]/(\text{injected dose}/\text{body weight})$ that allows for inter-study comparison. There are several methods of calculating an SUV including SUV_{mean} , SUV_{peak} , and SUV_{max} . SUV_{max} is the most widely used in clinical practice. It is the simplest to use and subject to the least inter-reader variability, but it is the most affected by random imaging variation. SUV_{max} is the most widely validated and studied, but it can underestimate the metabolic activity of small tumors due to partial volume averaging [10]. This study was also limited by the small number of subjects, making further analysis into tumor specific and pathology specific factors limited. Despite these limitations and the inherent subjective of pain the results of this study were significant in both models suggesting that the underlying correlation is not trivial.

The finding that more metabolically active BM are associated with greater intensity of pain may prove clinically useful. It theoretically could help localize the BM most likely to cause pain help direct treatment (radiation/surgery), though this observation would need to be validated with a study using treatment related outcomes.

Conclusion

Cancer patients with BM are more likely to have pain ($p=0.015$). And, in patients with BM, a correlation between tumor metabolism, as measured with SUV_{max} , and the intensity of pain is significant ($p=0.045$), but with only a modest effect-size (R^2 0.11), suggesting that many factors contribute to the pain related to BM.

Disclosure of conflict of interest

None.

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