How can we Use PET/ CT More Accurately for Characterization of Asbestos-related Pleural Thickening?

Type
Research paper

Keywords
desothelioma, Cut-off value, pleural thickening, 18F-FDG-PET

Abstract

Introduction
There is no consensus about standardized uptake value maximum (SUVmax) cut-off value to characterize pleural thickening worldwide. Sometimes, this causes unnecessary invasive diagnostic procedures. Our first aim is to determine a cut-off value for SUVmax. Secondly, we try to answer this question “If we use this cut-off value together with morphological parameters, can we differentiate benign thickening from Malignant pleural mesothelioma (MPM) more accurately”.

Material and methods
Thirty-seven patients with performed 2-deoxy-2-[18F]-fluoro-D-glucose ([18F]FDG-PET/CT) before pleural biopsy included the study. All of patients had histopathologically proven primary pleural disease. Their [18F]FDG-PET/CT imaging reports were re-assessed. If patient’s SUVmax or size of the thickening was not mentioned in report, we calculated them with their [18F]FDG-PET/CT.

Results
Age, pleural effusion, size, and SUVmax were found a relationship with MPM. We found the size>14 mm, and SUVmax>4.0 as cut-off values for MPM. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for size>14 mm were found as 86.4%, 85.2%, 82.6%, 88.5%, respectively. For SUVmax>4.0; sensitivity, specificity, PPV, NPV were 90.9%, 87.0%, 85.1%, 92.2%, respectively.

Conclusions
If a patient has SUVmax>4.0 and/or size>14 mm, the risk of MPM is high. These patients should be undergone biopsy. If patient’s SUVmax<4.0, size<14 mm and does not have pleural effusion, he/she has low risk for MPM. These patients can be undergone to the follow-up. If a patient's SUVmax<4, Size<14, and has pleural effusion MPM risk is approximately 4%. These patients can be undergone biopsy/cytology/follow-up. Novel studies are needed for these patients.
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**Results:** Age, pleural effusion, size, and SUVmax were found a relationship with MPM. We found the size >14 mm, and SUVmax >4.0 as cut-off values for MPM. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for size >14 mm were found as 86.4%, 85.2%, 82.6%, 88.5%, respectively. For SUVmax >4.0; sensitivity, specificity, PPV, NPV were 90.9%, 87.0%, 85.1%, 92.2%, respectively.

**Conclusion:** If a patient has SUVmax >4.0 and/or size >14 mm, the risk of MPM is high. These patients should be undergone biopsy. If patient’s SUVmax <4.0, size <14 mm and does not have pleural effusion, he/she has low risk for MPM. These patients can be undergone to the follow-up. If a patient's SUVmax <4, Size <14, and has pleural effusion MPM risk is approximately 4%. These patients can be undergone biopsy/cytology/follow-up. Novel studies are needed for these patients.
Introduction: Malignant pleural mesothelioma (MPM) or benign pleural thickenings (BPT) are rare diseases originating from mesothelial cells. Both of them mostly associated with asbestos exposure. MPM has aggressive behavior with very poor prognosis. Its median survival rate is around 12 months. Recent studies reported that, the incidence of disease has increased [1-5]. MPM is generally detected in advanced stages after the long latency period. Early diagnosis is crucial for prolongation of survival [6-9] and can be achieved with imaging procedures. On the other hand, sometimes BPT and MPM cannot differentiate properly with imaging methods. This causes unnecessary invasive approaches such as cytological examination or more invasive procedures [10].

Enhanced or unenhanced computed tomography (CT) is the most commonly using method for differentiate asbestos related pleural pathologies. Nonetheless it has not enough accuracy. Magnetic resonance imaging (MRI) is not commonly used for pleural lesion characterization due to its limited availability, costs and longtime of the imaging. Moreover, if invasion does not exist in surrounding tissues, it is also not a reliable method [11]. Because of we cannot reach high accuracy with morphological techniques, 2-deoxy-2-[18F]fluoro-D-glucose ([18F]FDG-PET/CT) have been used nowadays for this purpose. Although it has better results than morphological imaging modalities,[18F]FDG-PET/CT also has not enough accuracy. In addition, there is not any consensus for standardized uptake maximum (SUVmax) cut-off value for characterize pleural thickening [12, 13]. Because of all these difficulties, pleural thickening with suspected MPM is described as ‘challenging disease to image by any modality’ by some scientists [7, 10]. At this point, radiologists/nuclear medicine specialists’ reports become very important to patient management. However, due to ambiguity of the imaging results in some patients, they undergo unnecessary cytological examination or biopsy [10].
Our first aim in this study is to determine a cut-off value for SUVmax in patients with asbestos related pleural thickening. Secondly, we try to answer this question “If we use this cut-off value together with morphological parameters, can we differentiate benign thickening from MPM more accurately”. If we achieved a simple and practical diagnostic approach for these patients, it can provide us to avoid unnecessary invasive diagnostic procedures. It can reduce costs of Medicare system, save time for medical professionals and decreased complication rates caused by invasive methods.

**Material and Methods**

**Patient selection**

The results of 98 patients whom underwent [18F]FDG-PET/CT imaging for asbestos related pleural thickening between 01 January 2013 and 31 December 2017 were reviewed. Thirty-seven patients who had not distant metastasis in pre-biopsy [18F]FDG-PET/CT included in the study. All of these patients had pathologically proven primary pleural disease. Thirty-one patient’s pleural lesion’s SUVmax were >2.5 and these patients directly underwent to biopsy. Six patient’s SUVmax <2.5; however, three of them had pleural effusion and three of them had increasing size of the thickening in follow-up. These patients were also underwent biopsy. Their anamnesis, demographic parameters, [18F]FDG-PET/CT and pathology results were found from our database. If size of the thickening, or lesions’ SUVmax value was not mentioned in previous report, we calculated them from their re-examined [18F]FDG-PET/CT. Pathological results accepted as gold standard.

**PET/CT Imaging**

After at least 6-hours fasting, if patient’s blood glucose level was appropriate for injection, approximately 6-8 millicuries [18F]FDG were administered intravenously (iv). Patients rested in a warm and quiet room about 60 minutes and then [18F]FDG-PET/CT (General Electric D600 16 slice, GE Healthcare, USA) was performed. Initially, morphologic
imaging was performed with ‘Care dose’ CT with 5 mm thickness from the vertex to the mid-thigh. Then, PET imaging was performed in 7-8 bed positions for approximately 3 minutes for each position. The patients underwent shallow breathing during the PET imaging. CT data were used for attenuation correction and anatomical localization. We did not use oral or iv contrast agents. Images were evaluated by us and SUVmax values of each suspicious lesion were measured.

**Statistical Analysis**

Data were analyzed by Statistical Package for the MedCalc Statistical Software version 18.10.2 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). The numerical and categorical data were expressed as mean ± standard deviation and percentage, respectively. Kolmogorov-Smirnov and Shapiro-Wilk tests were used as tests of normality for continuous variables. Fisher exact test was used for determining the relationship between two groups and \( p < 0.05 \) was considered as statistically significant. Receiver operating characteristic (ROC) curve analysis was performed with Hanley&McNeil methodology. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

**Results**

Fourteen (37.8%) patients were female. Total number of the MPM diagnosis was twenty-five (67.6%). Approximately 61.0% of male, and 78.0% of female patients were diagnosed MPM. Although, females had higher rate of MPM, this was not statistically significant (\( p=0.27 \)). Patients mean age was 62.8 years (31-90; SD: 13.1). Mean age of the MPM and BPT patients were 65.6 and 62.6 years, respectively. Due to twelve patients with BPT, we also calculated geometric mean for them. This value was 56.0 years (41-75 and 95% CI was 43.7-65.9). Age had statistically significant relationship with MPM (\( P=0.049 \)). Results were summarized in table 1.
Approximately 2 out of every 3 (66.7%) diffuse thickening patients had MPM. This rate was very similar for nodular thickening patterns (65.2%). The differences were not statistically significant. Approximately 44.4% of MPM patients had pleural calcification. This rate was 55.6% for patients with BPT. Although BPT patients had higher pleural calcification rate, this also was not statistically significant. On the other hand, 83.3% of the patients with pleural effusion diagnosed MPM. Differences between MPM and BPT were statistically significant (p=0.01). However only 56.0% of MPM patients had pleural effusion. Mean size of the thickening and mean SUVmax values also had statistically significant differences between groups. Results were summarized in table 2.

We found size >14 mm and SUVmax >4.0 as cut-off values for MPM. The sensitivity, specificity, PPV and NPV of size >14 mm was calculated as 85.7%, 83.3%, 90.0% and 76.9%, respectively. Area under the ROC curve, standard error and confidence interval were 0.887, 0.05 and 95.0% (0.772-1.0), respectively. This cut-off value had 12.0% false negativity, and 8% of them were epitheloid, 4% of them non-epitheloid subtype MPM. For SUVmax >4.0; sensitivity, specificity, PPV and NPV were found as 88.0%, 83.3%, 91.7%, 76.9%, respectively. Area under the ROC curve, standard error and confidence interval were 0.895, 0.05 and 95% (0.789-1.0), respectively. It had also 12.0% false negativity. All false patients in this group were epitheloid subtype. On the other hand, false positive results were associated with inflammation. For example, one patient who diagnosed pleurit had 5.8 SUVmax value. ROC analysis was shown at figure 1. 24 out of the 25 (96.0%) MPM patients had SUVmax >4.0 or size >14 mm. Remaining one patient with MPM had SUVmax <4.0 and size <14 mm. However, he had pleural effusion. If we examined BPT patients, 58.3% (7/12) of them had SUVmax <4.0, size <14 mm and had not pleural effusion. Figure 2 was an example for this.

Discussion

MPM is an aggressive tumor originating from mesothelial cells of the pleura. This malignity mostly related to asbestos exposure and the incidence of it has been increasing [1, 3,
Early diagnosis is crucial for prolongation of survival and it can be achieved with imaging procedures. On the other hand, sometimes benign pleural thickening patients undergo unnecessary invasive procedures due to uncertainty of the imaging techniques’ reports. In such situations, cytological examination, which has low NPV, or more invasive procedures can be applied [10]. This increases costs of Medicare system and causes time consuming. Moreover, it can cause unnecessary morbidity, and increased complication rates in lots of patients.

Radiography is usually used the first imaging method to evaluate respiratory system [15]. If there are any suspicious findings, CT is the next step. Studies reported that, CT imaging provides helpful information for pleural pathologies. However, CT parameters do not have enough accuracy for characterization of them. For example, Seely et al. reported that, %43 of the MPM patients had calcified pleural pathology, but 57% had not [16]. Leung et al. studied circumferential pleural thickening, nodular pleural thickening, parietal pleural thickening greater than 1.0 cm, and mediastinal pleural thickening patterns, and their relationship between MPM. Authors found these parameters could be useful [17]. Hierholzer et al. reported that, if a patient had one or more of these four parameters, the sensitivity was 72% and specificity was 83% [18]. A research, which published 2016, reported circumferential thickening occurs in 31.1% of MPM patients. This rate was 59.2% for nodular thickening [19]. Kato et al. aimed to achieved more accurate results with irregularity. Authors found that, low level pleural irregularity and BPT relationship. Scientists were also reported that, high level irregularity, or mass formation and MPM relationship [20]. Finally, a recent study reported overall sensitivity, specificity, PPV and NPV of the CT imaging was 68.2%, 78.0%, 80.4% and 64.9%, respectively [21]. Due to lacking of the highly reliable results with morphological CT imaging, some researchers studied contrast-enhanced CT parameters. Lots of studies reported venous phase contrast-enhanced CT imaging provide more accurate results for pleural lesions evaluation [22,23]. However, in a recent study, even if venous phase applied, and CT reported
by thoracic radiologist; the sensitivity, specificity, PPV and NPV were found as 69%, 73%, 78% and 63%, respectively. If arterial phase imaging applied, these values calculated as 27%, 69% 53% and 40%, respectively [24]. Moreover Kato et al. reported that, there were not any significant differences between contrast enhanced and unenhanced CT imaging for characterized asbestos related pleural thickening [20]. For overwhelm this difficulty, some other authors studied different MRI techniques. For example, Koc et al. aimed to more reliable results with diffusion contrast enhanced MRI scanning. However, it could not provide high accuracy [25]. Selina et al. used early contrast enhanced-MRI, which is a novel technique, to reach high accuracy. With this method authors reported sensitivity, specificity, PPV and NPV as 83%, 83%, 68% and 92%, respectively. Although it has higher accuracy compared to conventional ones, low PPV is noteworthy [26].

Our study had similar findings with the literature. 66.7% of the patients with diffuse thickening and 65.2% of the patients with nodular thickening were diagnosed as MPM. In addition, 44.4% of patients with pleural calcification had MPM, and 56.4% had BPT. These results were not statistically significant (p >0.1). On the other hand, two CT parameters could differentiate BPT from MPM significantly. The first one was presence of the effusion. In our patient population, 83.3% of the patients with pleural effusion diagnosed MPM and only 16.7% of them had BPT. This was statistically significant (p=0.01). A recent study also mentioned this relationship [27].Ökten et al. reported that, 83% of the pleural effusion patients had MPM. This value was very similar to our results [28]. Nonetheless, only 56.0% of the MPM patients had pleural effusion in our patient population. Chen et al. found that, 60.0% of the MPM patients had pleural effusion [29]. According to findings, if a patient has pleural effusion and history of asbestos exposure, he/she has high risk of MPM. However, if a patient has not pleural effusion, this finding cannot exclude the MPM. The second CT parameter related to MPM was size of the thickening. Moore et al reported, if a lesion >10 mm, the likelihood of malignancy increases
significantly [30]. In another study, if pleural thickening >10 mm, sensitivity was found as 56% and specificity was 88% [17]. We calculated size >14 mm as an optimal cut-off value for pleural thickening characterization. With this cut-off value; the sensitivity, specificity, PPV and NPV were found as 85.7%, 83.3%, 90.0% and 76.9%. When we evaluated all unenhanced CT parameters, pleural thickening pattern (circumferential or nodular) or calcification could not differentiate benign lesions from MPM. On the other hand, presence of effusion, and size of the thickening were able to characterize it. However, if they used alone, they are not reliable for differentiate BPT from MPM.

At this point, [18F]FDG-PET/CT is a useful modality. Terada et al. reported that, mean SUVmax was 5.3 for MPM and 1.2 for benign pleural disease [8]. Yeom et al. found that, mean SUVmax was 2.0 in benign tumors, while it was 3.6 in malignant cases [31]. We calculated the mean SUVmax of BPT was 2.96, and mean SUVmax of MPM was 10.6. Our findings supported previous researches. On the other hand, this is not the main problem in characterization of asbestosis related pleural thickening with [18F]FDG-PET/CT. The main problem is that, lacking of the consensus of the SUVmax cut-off value. Abe et al. accepted the SUVmax >2.0 as a cut-off value, and 30/31 (96.7%) patients of MPM had positive uptake. The remaining one patient's SUVmax value was above 2.0 after the delayed image [13]. However, this value has not enough NPV. Elboga et al. reported that, the sensitivity, specificity, PPV, NPV and accuracy of [18F]FDG-PET/CT were 91.8%, 61.5%, 87.1%, 72.7% and 84%, respectively [32]. In this study SUVmax >2.5 accepted as a cut-off value. Terada et al. accepted SUVmax >3.5 as optimal value. With this, they found 59.6% sensitivity, 93.1% specificity, 93.3% PPV and 58.7% NPV [8]. There are also some other studies performed to reach more satisfactory results with SUVmax. For example, Yamamoto et. al found sensitivity, specificity, PPV and NPV as 88% for each with qualitative analysis [33]. Yildirim et al. determined the SUVmax >2.2 as a cut-off value. Scientists reported that, the sensitivity, specificity, PPV, and NPV were found as
The methodological differences between studies may have caused the differences. We found SUVmax >4.0 as an optimal cut-off value by ROC analysis. The sensitivity, specificity, PPV and NPV were 88.0%, 83.3%, 91.7%, 76.9%, respectively. We think, although SUVmax >4.0 has high PPV, and moderately high NPV, if used alone, it is not a reliable parameter for pleural lesion characterization.

On the other hand, when we used either SUVmax >4.0 or size >14 mm, 24 out of 25 (96.0%) MPM patients had one of them. Remaining one patient had pleural effusion. When we used SUVmax <4.0, size <14 mm, and lacking of the pleural effusion altogether, all of these patients had BPT. We think, these results are within acceptable range. When this criterion was applied to our patient population, 58.3% of BPT was correctly diagnosed without biopsy. This approach could also allow us to avoid one out of every five (7/37) invasive diagnostic methods.

Our study has some limitations. First of all, it has a retrospective nature and inherently has limitations due to this kind of design. Secondly, although our patient population exposed asbestos with long period of their life, due to features of the region, the number of biopsies proven BPTs were still low. We think our biopsy selection criteria caused this. Thirdly, we did not include the MRI or contrast-enhanced CT results in the study. However, [18F]FDG-PET/CT examination mostly performed without iv contrast and current study design was not included these techniques. In addition, as mentioned in the text, enhanced CT or MRI techniques also had not enough accuracy for characterization.

**CONCLUSION**

Before deciding the invasive diagnostic approaches for asbestos related pleural thickening patients, according to unenhanced CT and [18F]FDG-PET/CT findings, we should check firstly SUVmax value and size of the thickening. If a patient has SUVmax >4.0, or size >14 mm these patients must undergo to the biopsy. If a patient’s SUVmax <4.0, size <14 mm and he/she has not pleural effusion, likelihood of MPM is low. These patients can be undergoing to the follow-
If a patient’s SUVmax < 4.0, size < 14 mm but has pleural effusion, this patient has BPT with high likelihood. However, we cannot exclude MPM with this result. Due to risk of the misdiagnosing of them, he/she maybe biopsy or cytology is appropriate for them. This is another research’s subject. Figure 3 summarized this approach. Finally, we think multicentric and high-volume prospective studies can will put forth the recommended approach’s usefulness.

Conflict of interests None

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|                          | MPM (n=25; 67.6%) | BPT (n=12; 32.4%) | P value |
|--------------------------|-------------------|-------------------|---------|
| Mean age (years)         | 65.6              | 62.6              | 0.049   |
| Female                   | 78%               | 22%               | 0.27    |
| Male                     | 61%               | 39%               |         |

MPM: Malignant pleural mesothelioma; BPT: Benign pleural thickening
Table 2: The Relationship of Some Morphological/Metabolic Parameters and Final Diagnosis

|                     | BPT 95.0% CI (%) | MPM 95.0% CI (%) | P value |
|---------------------|------------------|------------------|---------|
| Pleural effusion    | 16.7             | 83.3             | P=0.01  |
| Calcification       | 55.6             | 44.4             | P >0.1  |
| Diffuse pattern     | 33.3             | 66.7             | P >0.1  |
| Nodular pattern     | 34.8             | 65.2             | P >0.1  |
| Size of thickening  | 11.8 (SD±3.2)    | 25.6 (SD±12.5)   | P <0.01 |
| (mm)                |                  |                  |         |
| SUVmax value        | 2.96 (SD±1.37)   | 10.6 (SD±7.4)    | P <0.01 |

(MPM: Malignant pleural mesothelioma; BPT: Benign pleural thickening; CI: Confidence Interval; SD: Standard Deviation)
Figure 1: ROC analysis of size and SUVmax
Asbestosis related pleural thickening

SUVmax >4.0 or size >14 mm
- Biopsy

SUVmax <4.0 and size <14 mm
- Pleural effusion(-)
  - Follow-up
- Pleural effusion(+)
  - Follow-up/Cytology/Biopsy

Figure 2: Suggested diagnostic Approach for Asbestos Related Pleural Thickening
Figure 2: 58 years old female patient. She had a pleural thickening in the right lung. Lesion's size was 13 mm, and SUVmax value was 3.4. There was no sign of pleural effusion. After the histopathological examination the diagnosis was benign pleural thickening.