18F-FDG PET/CT is Valuable in Detecting Soft-tissue Metastasis of Lung Cancer

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Research article

Keywords: 18F-FDG, lung cancer, soft-tissue, metastasis, PET/CT

Posted Date: March 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16675/v1

Version of Record: A version of this preprint was published on June 26th, 2020. See the published version at https://doi.org/10.1186/s12885-020-07080-0.

Abstract

Background Soft-tissue metastasis (STM) is a relatively rare, but not exceptional, manifestation of lung cancer. Since the lesions of STM are usually asymptomatic, they are easy to miss during clinical evaluation. The aim of the study was to explore the incidence and characteristics of STM in lung cancer using fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (18 F-FDG PET/CT), and evaluate its effect on tumor staging and treatment. Methods We analyzed 4543 patients with lung cancer who underwent 18 F-FDG PET/CT in our hospital between January 2013 and September 2018. 85 were diagnosed with STM and included in the study group. Imaging characteristics, clinical symptoms, and survival time (from confirmed STM to death) were recorded for all study subjects. Results A total of 219 lesions were identified by 18 F-FDG PET/CT: 215 were detected by PET (maximum standardized uptake value = 6.12); 139 were detected by CT. Muscle STM were primarily found in the hip, upper limb muscle; whereas subcutaneous STM were mainly distributed in the chest and abdomen, back. In 68 patients (80%), STM were found incidentally during routine 18 F-FDG PET/CT staging. The lesions were symptomatic in 17 cases (20%); in 10 patients (11.8%) STM was the first manifestation. Other site metastases were detected in 79 patients (92.9%). Isolated STM were found in 6 patients (7.1%), whose tumor staging and treatment were affected by PET/CT findings. At the end of the follow-up period, 69 patients were dead (median survival time= 5.0 months) and 5 were lost to follow-up. Conclusions STM may be a sign of advanced stage and poor prognosis in lung cancer. 18 F-FDG PET/CT is highly valuable in the detection of STM, and can impact tumor staging and management of lung malignancies.

Background

Lung cancer is one of the most prevalent malignant tumors, and the leading cause of cancer-related death worldwide. In China alone, 700,000 new cases are diagnosed every year, resulting in 600,000 deaths per annum. Increasing environmental pollution has led to a surge in lung cancer incidence in recent years. Nearly 50% of patients are metastatic at diagnosis, with the bone, adrenal glands, brain, and liver being the most common distant metastatic sites of lung cancer [1–5]. Early diagnosis and treatment are essential for improving the survival of affected patients.

Soft-tissue metastasis (STM) refers to the growth of tumor cells in soft tissue that is not connected to the primary tumor or regional lymph nodes, and comprises metastases to skeletal muscle and subcutaneous tissue [6–8]. Although skeletal muscle and subcutaneous soft tissue account for more than 50% of the human body weight, STM is relatively rare [6–8]. Lung cancer is the most common primary tumor of STM, with adenocarcinoma being the most common histological variant [9–16]. A recent study by Kanaji et al [17] showed that STM is associated with poor prognosis and worse response to treatment in lung cancer. Therefore, timely detection of STM can affect tumor staging and outcome.

Magnetic resonance imaging (MRI) is the gold standard for evaluation of soft tissue diseases owing to its good soft tissue contrast [4]. However, it necessitates long acquisition times and is affected by movement artifacts [18]. Moreover, studies [19] have shown that MRI is less sensitive than fluorine-18

fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in identifying STM. The latter technique uses a radioactive glucose analog, ^{18}F-FDG, to image glucose uptake in tumors and adjacent healthy tissue, enabling improved localization and characterization of tumors. Thus, ^{18}F-FDG PET/CT is an important tool for evaluation of patients with cancer, including identification of primary and metastatic lesions, guidance of biopsy, and assessing efficacy of anticancer therapies.

The widespread use of ^{18}F-FDG PET/CT has led to increased detection of STM in various malignancies. However, reports on its use to identify STM of lung cancer are scarce, and most of them represent individual cases. The purpose of this study was to explore the incidence and characteristics of STM in a large cohort of patients with lung cancer using ^{18}F-FDG PET/CT. Additionally, we assessed the impact of ^{18}F-FDG PET/CT findings on tumor staging and patient treatment to evaluate its clinical value in lung cancer.

Methods

Patient selection

We retrospectively reviewed 4543 patients with lung cancer who underwent ^{18}F-FDG PET/CT examination at the Affiliated Hospital of Southwest Medical University between January 2013 and September 2018. Based on clinical, imaging, and histopathological data, 85 patients (1.87%) were diagnosed with STM and included in the study group. There were 58 male and 27 female subjects and the median age was 61.8 years (range 37–88). The type of primary tumor; clinical symptoms; location, size, shape, edge, density, and maximum standardized uptake value (SUVmax) of STM; presence of concomitant distant metastases; and survival time (from confirmed STM to death) were recorded for all study subjects. The patients were followed-up to assess health outcomes by telephone or electronic case inquiry until September 2019. All procedures were carried out in accordance with the principles of the Helsinki Declaration. This study was approved by the ethics committee of the Affiliated Hospital of Southwest Medical University. Because the study was retrospective, and included data from deceased patients, informed consent was waived.

Inclusion And Exclusion Criteria

The study inclusion criteria were as follows: 1) underwent ^{18}F-FDG PET/CT examination and had not been diagnosed with STM before; 2) primary lesion confirmed by puncture biopsy, fiberoptic bronchoscopy, or postoperative pathology; 3) STM confirmed by histopathology or clinical follow-up.

The exclusion criteria were as follows: 1) lymphoma, malignant melanoma, neurofibroma, or other soft tissue tumor; 2) STM caused by direct infiltration from primary lesion or bone metastasis; 3) presence of lymph nodes, infection, inflammation, and post-biopsy reactions.

Pet/ct Scanning

^{18}F-FDG was prepared using the Siemens Eclipse HD cyclotron and ^{18}F-FDG automated chemical synthesis system, and had radiochemical purity of > 95%. The patients were asked to avoid strenuous physical activity the day before the scan, and fast for at least 6 h prior to intravenous administration of ^{18}F-FDG (5.5 MBq/kg body weight) to ensure a blood glucose level of < 11.1 mmol/L. Following the injection, the patients rested for 40 min-1 h in the dark, drank 300–500 mL of lukewarm water, then underwent PET/CT scanning on a Philips Gemini TF 16 scanner after emptying the bladder. First, a 16-slice spiral CT scan was performed, ranging from the base of the skull to the middle upper thighs, with the arms raised above the head (120 kV, 100 mA, layer thickness 0.5 mm, matrix 512 × 512 pixels, window width 300–500 HU, window level 40–60 HU). If a patient was known to have abnormal lesions in the limbs, they were scanned from the top of the head to the feet, with the arms at the sides of the body. After CT was complete, three-dimensional PET was performed for 70–90 s per bed position, for a total of 7 bed positions. The resulting images were corrected by attenuation and reconstructed by iterative method to obtain transverse, coronal, and sagittal views of the PET/CT scans. Delayed imaging was performed 2 h after ^{18}F-FDG injection, if necessary.

Image Analysis

The images were analyzed for the presence of STM by 3 experienced PET/CT physicians and a radiologist, using a combination of semi-quantitative analysis and visual assessment. Any disagreements were settled through negotiation. For the semi-quantitative analysis, a region of interest was drawn and the SUVmax was measured in the most intense area of focal ^{18}F-FDG accumulation. The lesions were considered PET-positive if their ^{18}F-FDG uptake was greater than that of surrounding healthy muscle and subcutaneous soft tissue. CT-positive lesions were defined as obvious nodules, masses, or abnormal tissue structure. The density, maximum diameter, shape, edge, and SUVmax of each lesion were measured. The final diagnostic criteria were pathological results or clinical follow-up.

Results

Pathological type of lung cancer

The most common histological variant of primary lung cancer was adenocarcinoma (51 cases), followed by small cell lung cancer (12 cases), squamous cell carcinoma (11 cases), non-small cell carcinoma of unclear origin (6 cases), adenosquamous carcinoma (3 cases), and large cell carcinoma (2 cases). In 15 patients only, the presence of STM was confirmed by histopathology; in the remaining cases the diagnosis relied on clinical evaluation and imaging data.

Number And Imaging Characteristics Of Stm

Muscle STM occurred in 41 cases and subcutaneous STM in 34 cases. In 10 of the patients, both types of STM were present. A total of 219 metastases were located by ^{18}F-FDG PET/CT. Among them, 215 lesions were detected by PET (detection rate = 98.2%; median SUVmax = 6.12 (range 0.8–20.9)). CT identified 139 lesions (detection rate = 63.5%), out of which 109 were isodense and 30 were of low or slightly low density; 96 lesions were nodules or tissue masses, while 43 were accompanied by swelling and had unclear boundaries. Median lesion size was 2.12 cm (range 0.4–13.8).

There were 126 muscle metastases (57.5%), of which 125 were identified as hypermetabolic nodules by PET (detection rate = 99.2%; median SUVmax = 6.79 (range 2.1–20.9)) and 46 were identified as abnormal by CT (detection rate = 36.5%). There were 93 subcutaneous metastases (42.5%), of which 90 were identified as hypermetabolic nodules by PET (detection rate = 96.8%; median SUVmax = 5.36 (range 0.8–19.1)). All subcutaneous STM were identified as abnormal by CT (detection rate = 100%).

Location Of Stm

Muscle lesions were primarily distributed in the hip muscle, upper limb muscle, and dorsal muscle (Table 1), with the highest frequency in erector spinae, gluteus major muscle, and psoas muscle. Subcutaneous soft tissue lesions were most commonly located in the chest and abdomen, followed by back, head and neck, hip, and, occasionally, in the extremities (Table 2).

Table 1
Distribution of skeletal muscle metastases.

Location	No. of cases
Pelvic muscle	36 (28.6%)
Upper limb muscle	21 (16.7%)
Back muscle	20 (15.9%)
Abdominal muscle	16 (12.7%)
Pectoral muscle	14 (11.1%)
Head and neck muscle	11 (8.7%)
Lower limb muscle	8 (6.3%)
Total	126

Table 2
Distribution of subcutaneous tissue metastases.

Location	No. of cases
Chest and abdomen	26 (28.0%)
Back	22 (23.7%)
Head and neck	20 (21.5%)
Pelvis	19 (20.4%)
Extremities	6 (6.4%)
Total	93

Clinical Presentation

Most patients (80%) were asymptomatic and their STM were discovered incidentally during routine ^{18}F-FDG PET/CT. In the remaining cases, the lesions were symptomatic; STM to muscle were accompanied by local pain or swelling, while those to subcutaneous tissue were often painless, with some patients displaying redness, swelling, and pain. In 10 patients, STM was the first manifestation of primary malignancy (Fig. 1).

The vast majority of the patients (92.9%) had other distant metastases when STM was detected (Fig. 1), of which 3 received additional treatment for STM, mainly in the form of local surgical resection or radiotherapy. 6 patients (7.1%) had isolated STM, which was the only manifestation of metastatic disease (Fig. 2 and Fig. 3 – 1); their tumor staging and treatment were profoundly affected by PET/CT findings.

Survival Time

At the end of the follow-up period (September 2019), 69 patients were dead (81.2%), with a median survival time of 5.0 months (range 0.5–57); 11 were alive (12.9%); and 5 were lost to follow-up (5.9%).

Discussion

STM are defined as metastases to skeletal muscle and subcutaneous tissue [6–8]. Although soft tissue accounts for over 50% of the human body, and has abundant blood supply, it is a relatively rare site of metastasis. Factors such as changes to local blood flow; presence of various proteases and inhibitors; high partial pressure of oxygen; pH, pressure, and temperature changes; and local production of lactic acid are not conducive to the growth of tumor cells, making soft tissue relatively resistant to malignant

penetration [3, 7, 17, 20–24]. Although infrequent, STM are still encountered in clinical practice and warrant greater attention of radiologists and clinicians [13].

Lung cancer is the most common primary malignant tumor leading to STM [9–13]. More than half of lung cancer cases are diagnosed at an advanced stage [1, 2]. The most common sites of distant metastasis include the bone, brain, adrenal glands, and liver, with STM being much less common [3–5]. Usually, when lung cancer progresses to a certain extent, some of the tumor cells break away from the primary tumor and disseminate to remote sites through the bloodstream or lymphatic system [25–27]. If local tissue conditions are suitable, the cancer cells begin to divide and proliferate and gradually become metastatic foci [7].

^{18}F-FDG PET/CT can show metabolic changes before morphological abnormalities occur, and is used to screen for extra-pulmonary metastases in patients with lung cancer [10]. It is a whole-body imaging technique, with high tumor-to-background FDG uptake ratio, which allows detection of hidden STM [13, 28]. Despite these advantages, the use of 18F-FDG PET/CT for the detection of STM of lung cancer has not been widely researched. In previous studies, the prevalence of STM varied from 0.86–13% [13, 28]. In our review, we found that approximately 1.87% of patients with lung cancer had STM. Although this proportion is much lower than that for lung, liver, bone, or brain metastases, STM of lung cancer are not exceptional. Importantly, a more widespread use of ^{18}F-FDG PET/CT may allow detection of previously undetected STM.

The median age and sex distribution in our study population was similar to that in previous studies [16, 25] of STM of lung cancer, indicating that the disease is the most prevalent in middle-aged and elderly males. Further, existing literature [11, 14–16] suggests that STM mostly occurs in patients with lung adenocarcinoma, which is consistent with our findings. Muscle metastasis is reportedly more common than subcutaneous metastasis, with a ratio of 1.2–3.3:1 [7, 8, 14]) This was also observed in the current study; the overall incidence of skeletal muscle STM was 60%, while that of subcutaneous STM was 51.8%, i.e. a ratio of 1.2:1.

SUVmax is the most widely used parameter to measure the uptake of a radiolabeled tracer by tumor tissue [29]. In this study, the median SUVmax in STM was 6.12 (range 0.8–20.9); while that in skeletal muscle and subcutaneous metastases was 6.79 (range 2.1–20.9) and 5.36 (range 0.8–19.1), respectively. The vast majority of metastatic lesions (98.2%) had high FDG metabolism, and could be detected by visual inspection of PET scans. A total of 80 muscle STM (36.5%) were missed by CT, which was probably related to the low resolution of low-dose CT acquisition, and the isodensity of the lesions. The highest frequency of muscle metastases was in the hip, upper limb, and dorsal muscle, while subcutaneous metastases were mainly distributed in the chest, abdomen, and back. These findings are in line with those reported in the literature, and suggest that the staging of lung cancer should include a thorough examination of soft tissue [9, 11, 25, 30, 31].

Generally, STM are asymptomatic and easy to miss during clinical evaluation [9, 13]. Indeed, most of our patients (80%) did not present with symptoms related to their STM, and if ^{18}F-FDG PET/CT had not been performed, the lesions would have likely remained undetected. If STM is the only metastasis, tumor staging and treatment might change dramatically. In 20% of the patients, the lesions were symptomatic, with local pain or swelling in muscle STM and painless masses in subcutaneous STM. Thus, in patients with lung cancer, unexplained muscle pain or subcutaneous nodules should raise suspicion of STM, and comprehensive physical and imaging examination should be conducted [4]. STM may also be the initial manifestation of lung cancer, which was observed in 10 of our patients (11.8%). In such cases, in addition to active follow-up of medical history and physical examination, ^{18}F-FDG PET/CT imaging should be performed as soon as possible to locate the primary tumor and ensure optimal patient management.

STM, which was shown to have the same practical significance as other types of distant metastases of lung cancer, may be a manifestation of declining immunity and a sign of advanced-stage disease [7]. Most patients with STM of lung cancer display multiple organ and lymph node metastases, and since metastasis mostly occurs in patients with a high degree of malignancy, their prognosis is poor [5, 7, 8, 11]. Thus, ^{18}F-FDG PET/CT detection of additional STM does not have a significant effect on the staging of lung cancer patients with extensive metastases, but it can help delineate the target area for local radiotherapy [15]. ^{18}F-FDG PET/CT could also guide biopsies of soft tissue lesions, which usually occur in superficial areas. Among the 85 patients in our study, 79 had extensive metastatic diseases, which led us to believe that STM is a sign of advanced lung cancer.

A small proportion of patients (7.1%) showed solitary STM on ^{18}F-FDG PET/CT, which was the only manifestation of metastatic disease. ^{18}F-FDG PET/CT results completely changed tumor staging, treatment plan, and prognosis of these patients.

Increased ^{18}F-FDG uptake in soft tissue may be caused by a variety of physiological and pathological factors, and differential diagnosis should take into account muscle hyperactivity, infectious/inflammatory processes, post-surgical reactions, primary soft tissue tumors, lymphoma, etc [14, 32]. When ^{18}F-FDG PET/ CT of patients with lung cancer shows elevated ^{18}F-FDG uptake in soft tissue, especially in muscle tissue, and the above factors are excluded, the lesion should be regarded as suspicious STM even if there is no corresponding morphological abnormality on CT [8, 14]. In addition, some factors might result in decreased ^{18}F-FDG uptake in soft tissue and lead to false negative results, such as small lesions, tumors with low metabolic activity, elevated blood glucose levels, etc.

The treatment of STM of lung cancer can vary depending on the patient's age, overall health, metastatic status, and expected goal. Treatment options include palliative radiotherapy, systemic chemotherapy, and supportive treatment; resection can be considered if the metastasis is isolated [3, 4, 11, 14–16, 33]. Despite the different treatment strategies available, most patients diagnosed with STM die within months [34]. In this study, the median survival time was 5.0 months, which was similar to that reported in

previous studies [7, 33]. Therefore, we propose that STM is one of the strong predictors of lung cancer prognosis.

Limitations

First of all, our study was retrospective and only 17.6% of patients were confirmed to have STM by histopathology. While in line with patient care standards (most metastases do not need pathological diagnosis), the fact that not all lesions were verified by histopathology might have cause some deviation in the results [9, 12, 13].

Secondly, since the 4458 patients with no signs of STM on ^{18}F-FDG PET/CT were not followed-up in the same way as the 85 patients with STM, the actual incidence of STM in lung cancer may be higher than that observed in our study.

Thirdly, we performed low-dose CT scans, which have relatively low resolution and failed to detect lesions with small density changes.

In addition, the vast majority of our patients were scanned from the base of the skull to the middle upper thighs, which is not a true whole-body scan. Some studies have shown that a considerable proportion of STM may occur outside the scan range [8, 12]. Missed diagnosis of limb metastases can underestimate the extent of STM, leading to under-staging and mis-management of the disease. Newer PET/CT technology allows fast whole-body scanning without affecting imaging accuracy. In our future work, we will gradually adopt the whole-body approach to PET/CT imaging (from the top of the head to the soles of the feet) to prevent missed lesions.

Conclusions

STM in lung cancer are relatively rare, but not exceptional. Understanding their incidence and characteristics on ^{18}F-FDG PET/CT can deepen the understanding of the disease and help guide clinical staging and treatment decisions. The use of ^{18}F-FDG PET/CT to detect STM of lung cancer has not been well-studied, with the available data mostly derived from isolated case reports. Thus, this study makes a significant contribution to the literature. Our results suggest that STM is a sign of advanced-stage disease and poor prognosis in patients with lung cancer, and that ^{18}F-FDG PET/CT is a valuable technique for its detection. Integrated PET/CT imaging has synergistic advantages over CT or PET alone, and can display both primary and metastatic lesions, improving the accuracy of tumor staging, re-staging, and curative effect evaluation. Since ^{18}F-FDG PET/CT allows early detection of hidden STM, particularly in patients with solitary STM, it can profoundly impact the staging and treatment of these patients. In addition, it can also help outline the target area for local radiotherapy and guide lesion biopsy. To sum up, ^{18}F-FDG PET/CT is a valuable tool for detecting STM of lung cancer.

Abbreviations

^{18}F-FDG: Fluorine-18 fluorodeoxyglucose

PET/CT: Positron emission tomography/computed tomography

STM: Soft-tissue metastasis

SUVmax: Maximum standardized uptake value

MRI: Magnetic resonance imaging

Declarations

Ethics approval and consent to participate

All procedures were carried out in accordance with the principles of the Helsinki Declaration. This study was approved by the ethics committee of the Affiliated Hospital of Southwest Medical University (Luzhou, China). Because the study was retrospective, and included data from deceased patients, informed consent was waived.

Consent for publication

Not applicable.

Data Availability

The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

Acknowledgments

This work is supported by the Nuclear Medicine and Molecular Imaging Key Laboratory of Sichuan Province. We would like to thank Editage (www.editage.com) for English language editing.

Conflict of interest

The authors declare that they have no competing interests.

Funding

There is no funding relevant to this work to be declared.

Author contributions

X-TT and Z-XY contributed to the study design and X-TT wrote the manuscript. X-TT and Z-XY collected and analyzed the clinical data of patients and they contributed equally to this paper. Z-SM, L-CF, F-WH and Z-CR were responsible for the integrity of the data and the accuracy of the data analysis. C-Y was

responsible for revising for important intellectual content. All authors read and approved the final manuscript.

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Figures

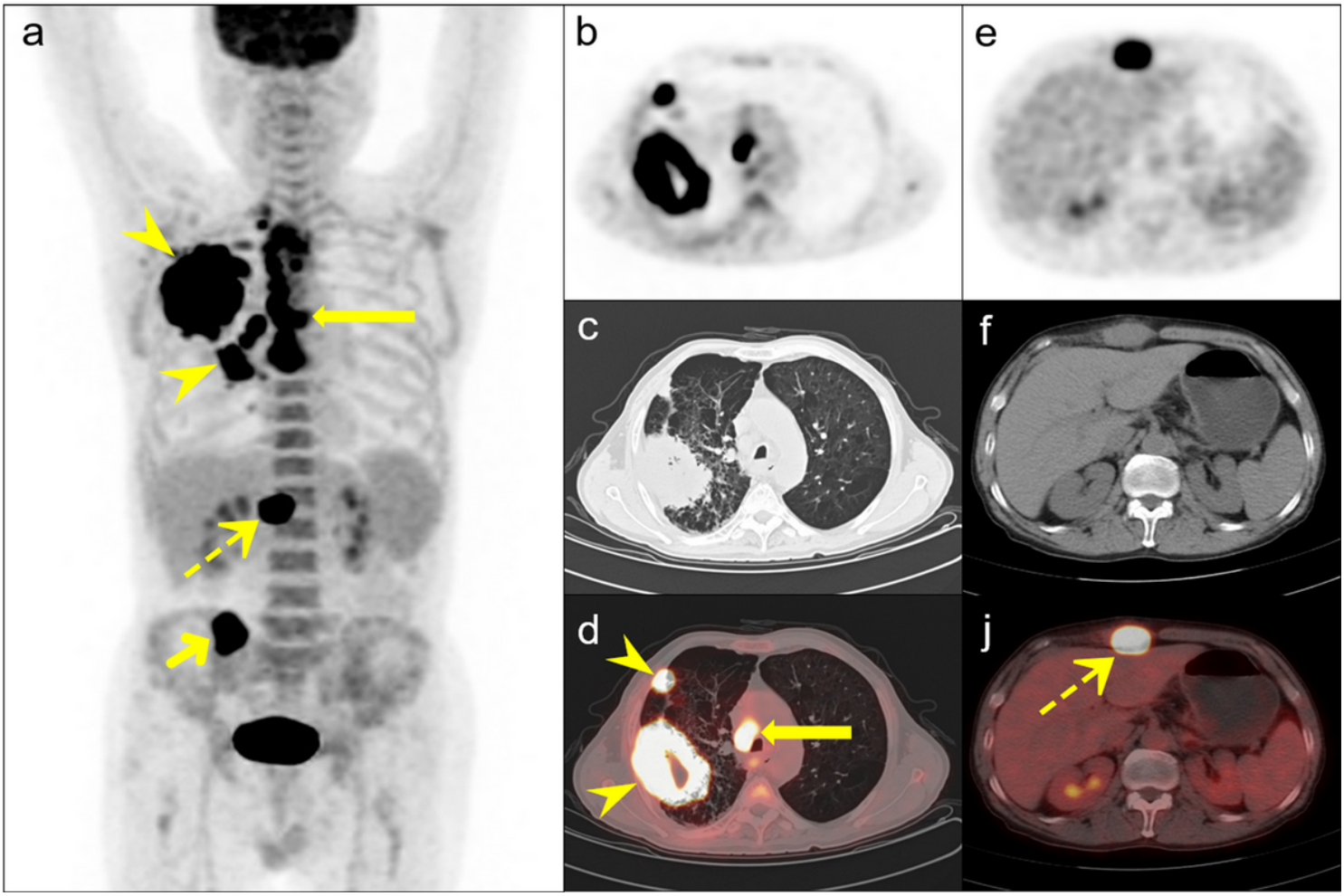

Figure 1

A case of lung adenocarcinoma with metastasis of right rectus abdominis as the first manifestation. A 64-year-old man presented with a 2-week history of a painful, tough mass in the upper abdomen, which was confirmed as metastatic adenocarcinoma by biopsy. 18F-FDG PET/CT imaging was performed to locate the primary tumor. MIP (a), chest axial images (b-d), and abdomen axial images (e-g) of PET/CT showed lesions in the upper lobe of the right lung (arrowheads), right rectus abdominis muscle (dotted arrows), multiple lymph nodes (long arrows) and right ilium (short arrow). Lung biopsy confirmed

adenocarcinoma of the right lung. Therefore, a diagnosis of right lung cancer with lymph node, bone, and right rectus abdominis metastases was made. The patient survived for 6 months on palliative chemotherapy.

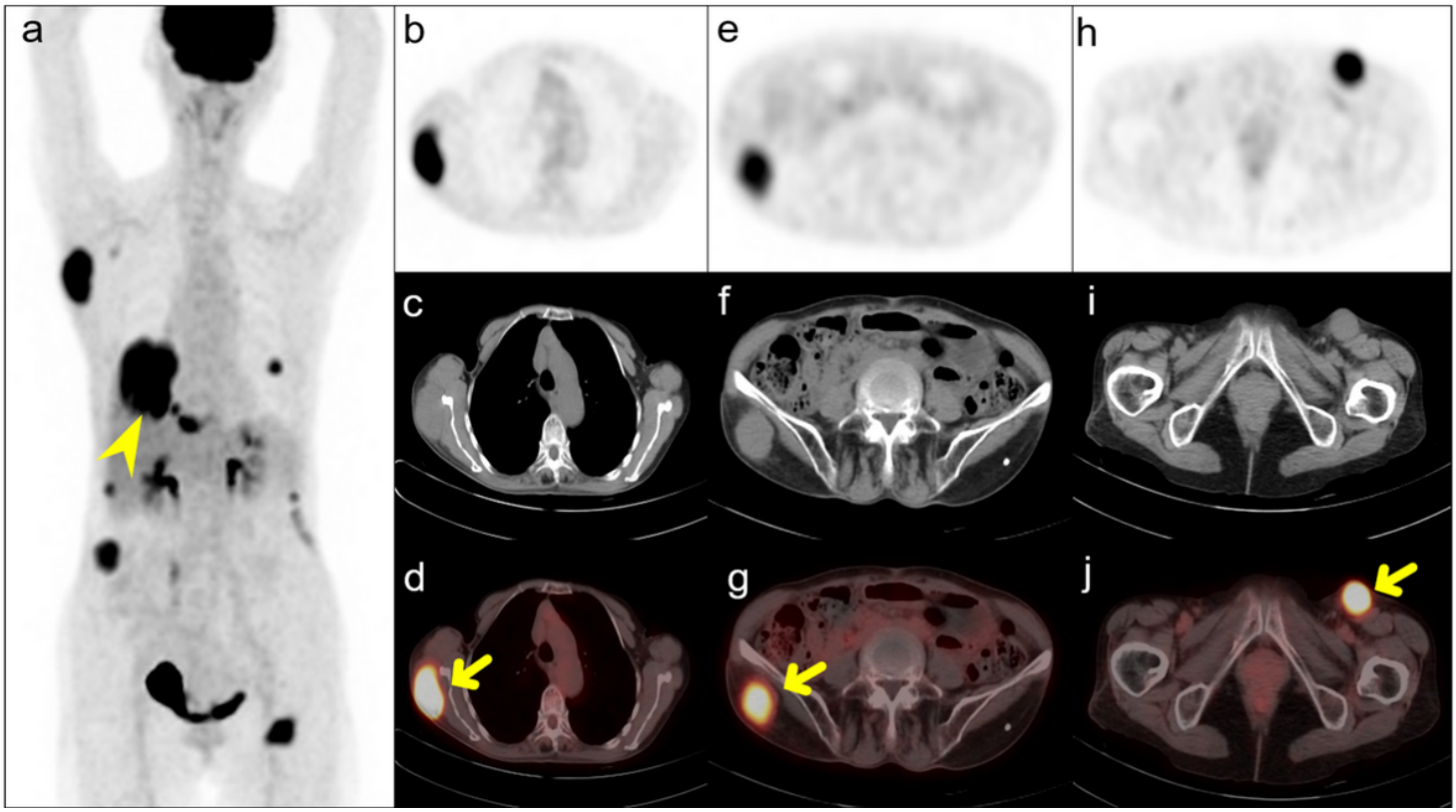

Figure 2

STM is the only manifestation of a small cell lung cancer. A 74-year-old woman presented with a 1-month history of a subcutaneous mass on the right side of her waist, which was confirmed as metastatic small cell carcinoma on biopsy. MIP (a) of 18F-FDG PET/CT showed a soft tissue mass in the lower lobe of the right lung (arrowheads), with elevated FDG uptake (SUVmax= 8.4). MIP (a), chest axial images (b-d), and pelvis axial images (e-j) revealed multiple nodules and masses throughout subcutaneous tissue and skeletal muscle (short arrows) with increased FDG uptake (SUVmax= 7.5). Subsequently, lung biopsy confirmed small cell lung cancer of the right lung. After 11 months of palliative chemotherapy, the patient died of respiratory failure.

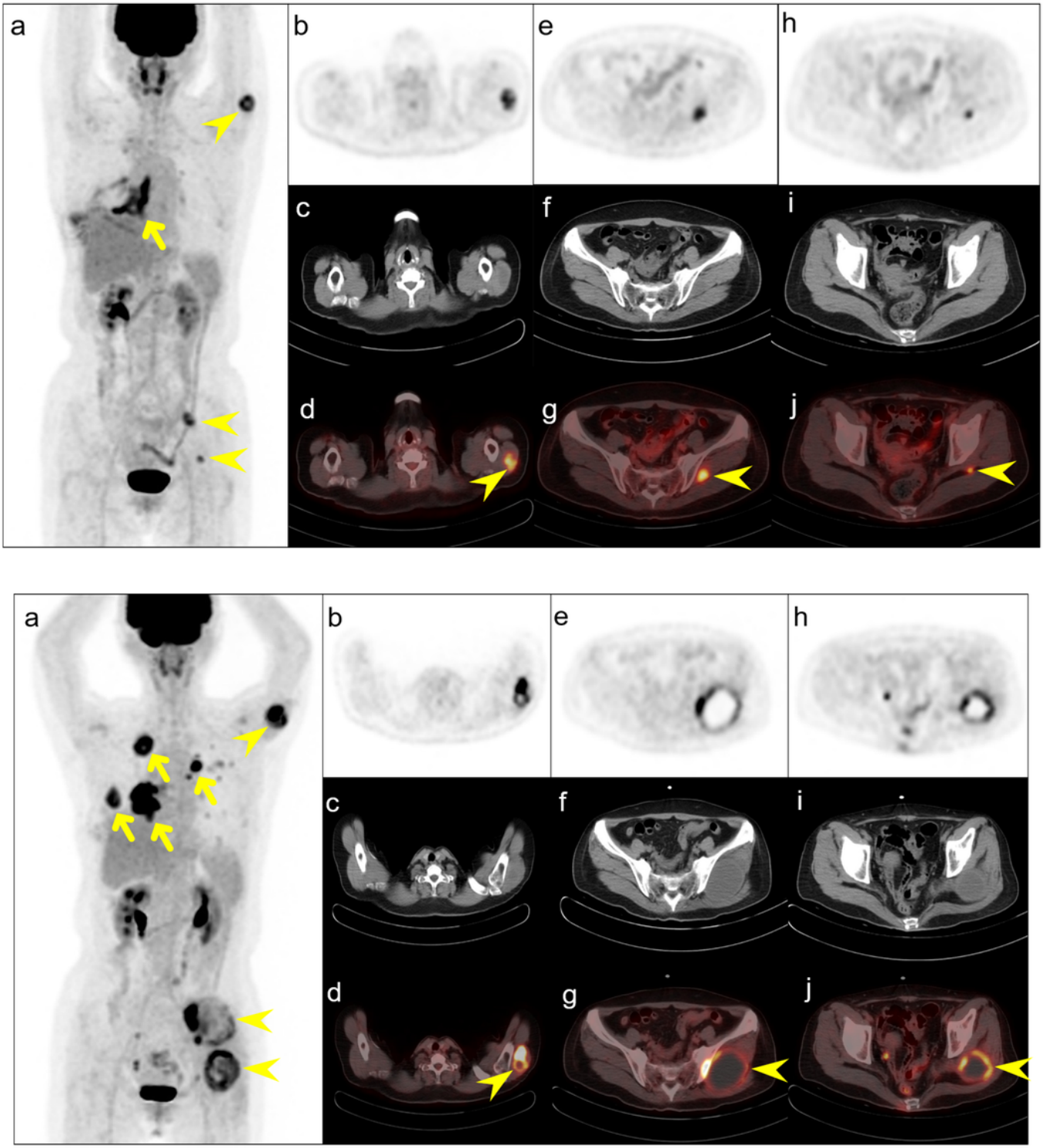

Figure 3

3-1: STM changed the postoperative stage of a lung squamous cell carcinoma. A 62-year-old woman was referred to our hospital with a 2-month history of cough. Squamous cell carcinoma of the lower lobe of the right lung was diagnosed by chest CT and lung biopsy. The general condition of the patient was good, and no metastases were found in head MRI or thoracic and abdominal CT. The patient underwent surgical resection and received adjuvant chemotherapy after the operation. Three months later, the

patient underwent 18F-FDG PET/CT to assess treatment efficacy. MIP (a) showed increased 18F-FDG uptake (SUVmax= 3.8) in the operative area of the right lung (short arrows). MIP (a), axial images of neck and pelvis (e-j) revealed localized reduced-density nodules in the left deltoid muscle, left gluteus medius muscle, and left gluteal muscle (arrowheads), with FDG uptake (SUVmax= 8.0). Therefore, a diagnosis of multiple STM after lung cancer resection was considered. The patient was treated with palliative radiotherapy and chemotherapy to control the disease. 3-2. Five months later, the patient complained of pain and swelling in her left shoulder. Physical examination revealed a painful mass approximately 4 cm in diameter in the left shoulder. MIP (a) showed multiple nodules and masses with increased 18F-FDG uptake (SUVmax= 6.8) in both lungs (short arrows). Axial images of neck and pelvis (e-j) revealed and multiple low-density masses with liquefaction and necrosis in the left deltoid muscle, left gluteus medius muscle, and left gluteal muscle (arrowheads), with increased FDG uptake (SUVmax= 8.7). Despite active treatment, the patient died of multiple organ failure.