

## Case Reports of Cutaneous and Subcutaneous Metastasis from Primary Solid Organ Tumors by <sup>18</sup>F-FDG PET/CT

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### Abstract

Skin metastasis from solid and soft tissue primary malignancies overall are rare. However, cutaneous metastases from certain soft tissue malignancies are seen not infrequently in clinic especially by dermatologists. Clinically, the presence of cutaneous metastasis is usually a finding of advanced disease stage and generally indicates a poor prognosis. Cutaneous lesions are often overlooked on <sup>18</sup>F-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT), with the appearance of radiotracer uptake not well appreciated. Common confounding factors are post-surgical changes or inflammatory lesions in the soft tissue body wall which can demonstrate nonspecific <sup>18</sup>F-FDG uptake. We present three cases of soft tissue metastases from primary solid organ malignancies spanning the range of clinical occurrence: a 62-year-old female with cutaneous metastasis from primary breast cancer which only became apparent on exams, a 59-year-old female with cutaneous and soft tissue metastatic nodules from a non-small cell lung carcinoma on presentation and finally, a case of sarcomatoid carcinoma arising from squamous cell carcinoma of the bladder with disease progression despite chemotherapy and radiation. In this last case, the patient developed a vesiculo-cutaneous fistula draining a malignant effusion along with a subcutaneous chest wall <sup>18</sup>F-FDG avid nodule, indicating widespread metastatic disease. All of these cases, demonstrated resistance to first-line therapy and a widespread metastatic disease state with poor prognosis overall. Additionally, in these cases, the recognition and subsequent biopsy of the cutaneous metastases led to changes in the clinical management.

### Keywords

Cutaneous metastasis, Soft tissue, Adenocarcinoma, Breast cancer, FDG PET/CT, Metastasis

### Introduction

Cutaneous manifestations of primary internal malignancies are often an overlooked site of oncologic disease with an overall incidence ranging from 0.6%-10.4% [1, 2]. Suspicion should be raised if there are soft tissue and cutaneous lesions that persist or grow on <sup>18</sup>F-FDG PET/CT studies despite systemic anti-neoplastic therapy. Soft tissue and cutaneous metastases can often be the first clinical manifestations of internal malignancy, and as such, their recognition plays an important role in the clinical management of the patient [3]. Breast carcinoma is a common solid tumor with distant metastasis occurring in 3.3% of newly

diagnosed cases [4]. Of those cases with distant metastases, cutaneous metastases occurred in 23.9% of cases, and of these, nodular cutaneous metastases are the most common presentation [1]. These usually appear as firm nodules, 1-3 cm in size and are pink to red-brown with ulcerations.

Tumor cells are typically arranged in glandular arrangements or linear distributions in the dermis with positive immunohistochemical staining with the molecular markers CK19, mammaglobin, E-cadherin, estrogen, and progesterone receptors [1]. Overexpression of the oncogene HER-2/neu can be seen in 20-30% of cutaneous metastases from invasive breast carcinoma and can be associated with treatment resistance [5, 6]. Firstline chemotherapy for HER-2 negative metastatic breast cancer usually involves anthracyclines and taxanes such as doxorubicin and docetaxel respectively. If the disease progresses despite this regimen often a pyrimidine analog such as gemcitabine is then utilized [7, 8]. Additional therapies with microtubule inhibitors such as eribulin or the topoisomerase I inhibitor irinotecan have also proven to be effective [9]. In addition, following initial surgical treatment in breast cancer, and is generally indicated unless there is evidence of distant metastasis [6, 10].

Non-small cell lung carcinoma (NSCLC) is one of the most common solid organ malignancies worldwide and is the most frequent type of lung cancer associated with cutaneous metastases with half of all cases arising from NSCLC. Small-cell lung cancer is the second most frequent lung malignancy with cutaneous metastases [11]. Interestingly, cutaneous metastases can be the first presentation of lung carcinoma, most commonly in men. In women, it is the fourth most common cause of cutaneous metastasis [12, 13]. In one study, skin metastases were found at autopsy in 15.4% of NSCLC cases [12]. Often portending an advanced disease state, cutaneous metastases in lung cancer can harbor mutations in EGFR, ALK, and KRAS where mutations in KRAS in particular are associated with a poor prognosis [14].

Primary NSCLC localized to one lung or ipsilateral lymph nodes is usually amenable to surgery, chemotherapy and radiation [15-17]. For disease that is advanced and involves distant metastases in the contralateral mediastinal lymph nodes, liver, or the brain, usually only chemotherapy, and targeted radiation is indicated [17]. In addition, genetic profiling is done to look for actionable mutations such as ALK or EGFR for treatment with specific inhibitors of these proteins [18]. A widely utilized example of an actionable molecular diagnostic is the treatment for metastatic lung carcinoma with the PD-L1 inhibitor pembrolizumab. Tumor analysis for PD-L1 protein expression is thus often performed [19].

Primary urological malignancies can give rise to cutaneous metastasis in rare cases. In one study, approximately 1% of primary urological malignancies showed cutaneous metastases, with 3.4% of the cases coming from renal cell carcinoma followed by 0.84% from bladder primary malignancies (mostly transitional cell carcinoma), and 0.36% associated with prostate carcinoma [20]. Cutaneous metastatic lesions can arrive by hematogenous or lymphatic spread, direct extension from the primary tumor, or with surgical site

seeding. The appearance of these metastases often appears as an infiltrating plaque or nodule. In previously seen cases with primary bladder carcinoma, the cutaneous metastases can be in a "zosteriform" or dermatomal pattern over the chest and abdominal walls [20] and may mimic keratoacanthoma [21]. Immunohistochemical stains to help identify bladder cancer metastasis include CD10, CK7, CK14, and uroplakin III [1]. As the prognosis is poor with cutaneous metastatic disease from a urologic primary tumor, treatment usually involves palliative radiation and chemotherapy.

Overall, skin lesions on FDG PET/CT are non-specific in appearance. The level of FDG activity in these lesions can vary and the etiology of such lesions can be elucidated only when taken together with the anatomic distribution, trend in FDG activity, and clinical history of any recent procedures [1, 22]. We present three cases that highlight features of soft tissue and cutaneous metastases that should alert radiologists, nuclear medicine physicians, dermatologists, and oncologists to this often-unexpected site of malignant metastases.

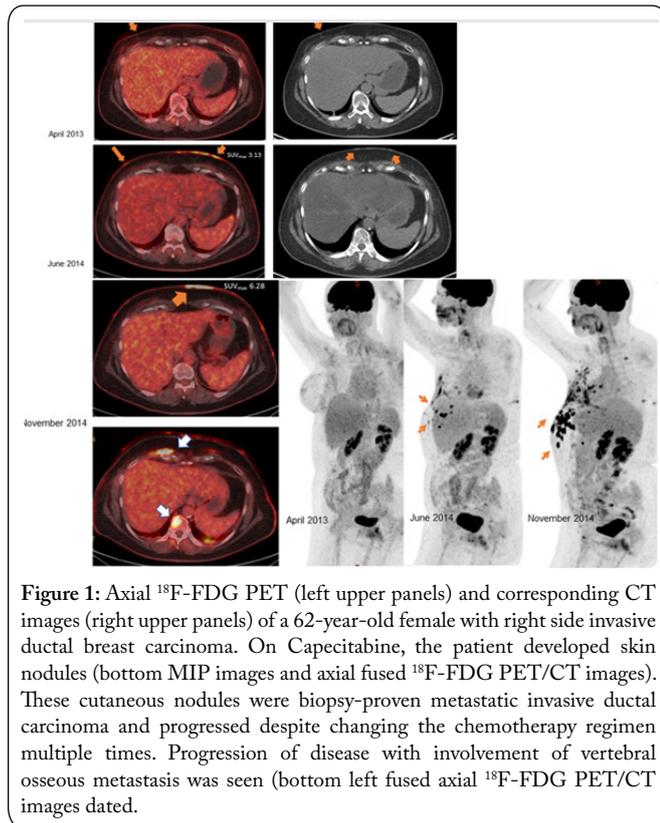
## Case I History

A 62-year-old female with right side invasive ductal breast carcinoma Stage IIA, T2N0M0 which was negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2), ER/PR/HER-2/neu (-). The patient was initially treated with a right side modified radical mastectomy and axillary lymph node dissection as well as prophylactic left mastectomy. The patient subsequently completed adjuvant chemotherapy with targeted radiation to the chest wall for local recurrence. While on capecitabine the patient developed skin nodules (Figure 1 upper row of axial fused PET/CT images dated April 2013, with disease progression seen in the middle axial fused PET/CT image dated June 2014).

The cutaneous nodules seen on the attenuation correction CT images, (lower right images in figure 1) showed an increase in FDG-activity in a timewise progression comparing the MIP FDG PET images (lower right column in figure 1). These cutaneous nodules were identified on biopsy to be metastatic invasive ductal carcinoma. Chemotherapy was changed from capecitabine to gemcitabine, then to eribulin, and finally to irinotecan. Despite changing the chemotherapy regimen, there was disease progression (SUVmax of the upper left abdominal wall cutaneous lesion in figure 1 increased from 2.14 in June 2014 to 4.29 on the November 2014 exam) along with increased soft tissue and rectus abdominis intra-muscular metastatic involvement and osseous metastasis of a vertebral body seen on the PET/CT exam dated November 2014 (bottom left axial fused images in figure 1 signifying advanced metastatic disease).

## Case II History

The second case is of a 59-year-old female with a right lower lobe Stage IV EGFR exon 19 deletion non-small cell lung carcinoma, brain, osseous, right thigh cutaneous and soft

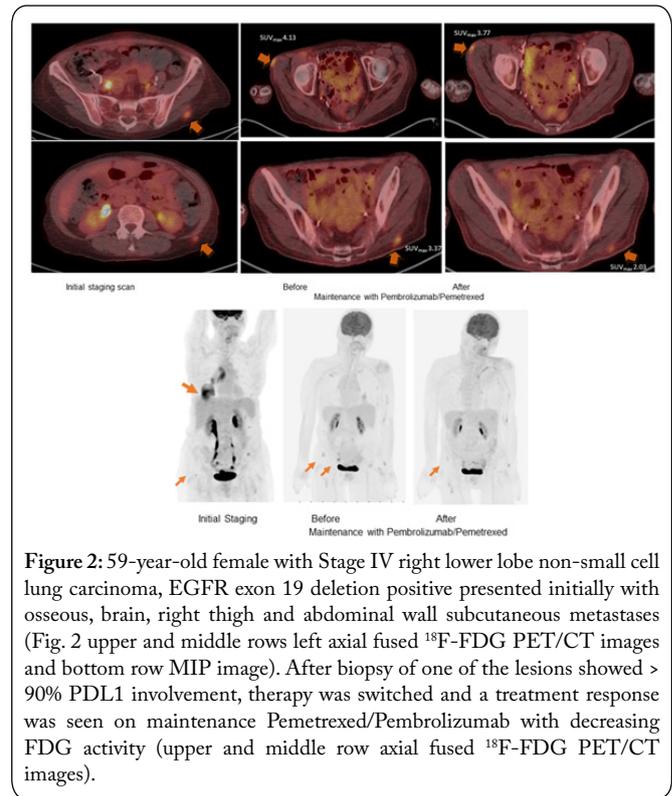


**Figure 1:** Axial <sup>18</sup>F-FDG PET (left upper panels) and corresponding CT images (right upper panels) of a 62-year-old female with right side invasive ductal breast carcinoma. On Capecitabine, the patient developed skin nodules (bottom MIP images and axial fused <sup>18</sup>F-FDG PET/CT images). These cutaneous nodules were biopsy-proven metastatic invasive ductal carcinoma and progressed despite changing the chemotherapy regimen multiple times. Progression of disease with involvement of vertebral osseous metastasis was seen (bottom left fused axial <sup>18</sup>F-FDG PET/CT images dated).

tissue abdominal wall subcutaneous metastases (upper row left axial fused images and lower left MIP image in [figure 2](#)). The patient had whole brain and right upper extremity external beam radiation. The metastatic disease progressed despite starting treatment with the oral targeted tyrosine kinase inhibitor osimertinib (<sup>18</sup>F-FDG PET/CT axial fused images in the upper middle column and MIP image lower middle column of [figure 2](#)). The patient was switched to carboplatin/pemetrexed/pembrolizumab based on biopsy results from a posterior left abdominal wall soft tissue nodule which showed expression of PDL1 > 90%. Subsequently, the patient was placed on the maintenance of pemetrexed/pembrolizumab. A right thigh cutaneous nodule and left buttock subcutaneous nodule showed treatment response (decrease in SUVmax from 4.13 to 3.77 and in SUVmax from 3.37 to 2.03 of the two lesions respectively). This response was seen while the patient was on the aforementioned combination chem-immunotherapy (axial fused <sup>18</sup>F-FDG PET/CT upper middle and right images and lower middle and right MIP images in [figure 2](#)).

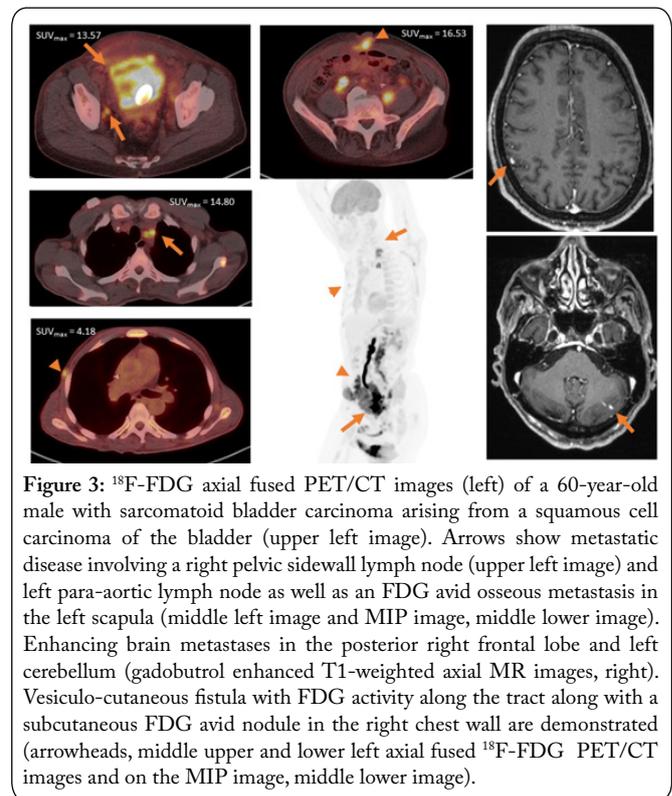
### Case III History

The third case is of a 60-year-old male presenting with abdominal pain, hematuria, and urinary retention. Diagnostic imaging work-up demonstrated a posterior bladder wall mass with pelvic lymphadenopathy as well as osseous sclerotic lesions on CT. Biopsy of the mass yielded bladder squamous cell carcinoma. The patient was initially treated with 4 cycles of chemotherapy as well as 10 cycles of external beam radiation. Subsequently, the patient returned with widespread metastatic disease which was seen on <sup>18</sup>F-FDG PET/CT, included intra-



**Figure 2:** 59-year-old female with Stage IV right lower lobe non-small cell lung carcinoma, EGFR exon 19 deletion positive presented initially with osseous, brain, right thigh and abdominal wall subcutaneous metastases ([Fig. 2](#) upper and middle rows left axial fused <sup>18</sup>F-FDG PET/CT images and bottom row MIP image). After biopsy of one of the lesions showed > 90% PDL1 involvement, therapy was switched and a treatment response was seen on maintenance Pemetrexed/Pembrolizumab with decreasing FDG activity (upper and middle row axial fused <sup>18</sup>F-FDG PET/CT images).

abdominal lymph nodes, osseous and brain metastases (seen on MRI primarily), and subcutaneous metastatic nodules ([Figure 3](#)). Repeat biopsy of the fungating bladder mass and cutaneous fistula tract demonstrated sarcomatoid bladder carcinoma arising from moderate to poorly differentiated keratinizing squamous cell carcinoma with 70% PDL1 expression, stage 4b cM1b. The patient was given 4 cycles of



**Figure 3:** <sup>18</sup>F-FDG axial fused PET/CT images (left) of a 60-year-old male with sarcomatoid bladder carcinoma arising from a squamous cell carcinoma of the bladder (upper left image). Arrows show metastatic disease involving a right pelvic sidewall lymph node (upper left image) and left para-aortic lymph node as well as an FDG avid osseous metastasis in the left scapula (middle left image and MIP image, middle lower image). Enhancing brain metastases in the posterior right frontal lobe and left cerebellum (gadobutrol enhanced T1-weighted axial MR images, right). Vesiculo-cutaneous fistula with FDG activity along the tract along with a subcutaneous FDG avid nodule in the right chest wall are demonstrated (arrowheads, middle upper and lower left axial fused <sup>18</sup>F-FDG PET/CT images and on the MIP image, middle lower image).

carboplatin and gemcitabine. However, the clinical course was complicated by a vesico-cutaneous fistula with the associated serosanguinous fluid. Sampling of this fluid by fine-needle aspiration demonstrated tumor cells (Figure 3). Pembrolizumab was planned for treatment given the high PDL1 expression on biopsy however, the clinical course was further complicated by pancytopenia, hypercalcemia of malignancy, cardiac effusion causing tamponade, and a urinary tract infection. Subsequently, the patient deteriorated clinically and was discharged home to hospice.

## Discussion

Although cutaneous metastases are rare, they are clinically significant and often herald advanced disease. Since these lesions are a measure of disease progression they have prognostic and therapeutic consequences and can help direct clinical management. Loco-regional recurrence of breast carcinoma is seen in 25-35% of patients. Additionally, the incidence of cutaneous metastases in breast carcinoma is about 23.9% [3] with a prevalence of 2.4% [1, 23]. Thus, recognition of cutaneous recurrence of breast malignancy is of paramount importance in the diagnosis of metastatic disease as well as in directing loco-regional disease treatment.

A possible confounding factor is that skin lesions in both inflammatory and malignant disease avidly take up FDG. In the first two cases, the patients were placed on chemotherapy which can cause an inflammatory skin rash [24]. Currently, direct clinical observation, temporal relationship to medication use, and the nature of the skin lesions following therapy can help decide if the activity seen on FDG PET/CT is from an inflammatory skin process or due to cutaneous metastases. It is therefore important to clinically and radiologically document skin lesions and any changes before, during and after treatment.

The anatomic distribution of cutaneous metastatic lesions is important in adding to the clinical suspicion for them. Approximately 50% of cutaneous metastases in lung cancer arise from non-small cell carcinoma and as such, demonstrate a particular anatomic distribution in the chest and abdomen. Interestingly, in female patients with soft tissue metastases from lung adenocarcinoma with driving mutations such as the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes, the anatomic distribution of these lesions is along the chest and abdominal walls [11]. Similarly, cutaneous breast carcinoma metastases have a predilection for the chest wall and abdomen [1]. Further, a specific anatomical distribution of metastases can be seen in up to 75% of all cutaneous metastases in women along the anterior chest and abdominal walls whereas the same proportion of cutaneous metastases are seen along the anterior head and neck regions in men [1].

The distribution of lesions in the first two cases presented were along the anterior chest wall as well as the anterior and posterior abdominal walls, consistent with the distribution pattern of metastases observed more often in female patients. In urologic malignancies, often cutaneous metastases occur

around the genitalia, inguinal region or along the abdominal wall [20]. Such cutaneous metastatic lesions can arrive by hematogenous or lymphatic spread, direct extension from the primary tumor, or surgical site seeding. In the third case presented, a cutaneous fistula tract developed to the primary tumor, and on biopsy was confirmed as metastatic disease. In addition, a body wall subcutaneous lesion that was also FDG avid was seen and likely also represented metastatic disease.

Cutaneous metastases often demonstrate significant genomic changes from the genetic profile of the primary solid tissue tumor that originally gave rise to them [25]. Such cutaneous metastases can be a harbinger of a significant shift in the genomic tumor characterization profile and can have therapeutic consequences especially in the era of personalized medicine. In the second case we presented, a biopsy of the skin lesions characterized them as being EGFR positive with an over-expression of PDL-1 which had therapeutic implications. Subsequently, the patient responded favorably to targeted therapy based on the biopsy results of these lesions (Figure 2).

In the third case presented, a biopsy of the cutaneous fistula lesion also demonstrated a specific tumor molecular signature that had the potential to change treatment management and it was only the patient's deterioration that prevented this from occurring. Molecular profiling of metastatic skin lesions is important as often cutaneous metastatic disease signals an aggressive stage of disease with the recruitment of certain driver mutations [25]. These driver pathways can be amenable to specific targeted therapies [26]. Since cutaneous metastases can be seen both on FDG PET as well as in the clinic, awareness of their existence is crucial in optimizing patient treatment.

The cases presented demonstrate the need for awareness of this category of metastatic lesions. Although overall rare in occurrence, cutaneous metastases have important clinical implications and should be brought to the attention of the clinical management team. This is especially true given that cutaneous and subcutaneous metastases can arise from all different types of internal solid malignancies. Since many of the chemotherapies themselves can cause inflammatory skin lesions, an overall view of these lesions and any changes in appearance both on imaging and within the clinical context is important to keep in mind.

## Conflict of Interest

The authors declare no conflict of interest.

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