Artefacts and pitfalls in PET-CT

The emergence of FDG-PET imaging has greatly improved methods for imaging cancer. Based on the uptake of fluorine-18 fluoro-deoxyglucose (FDG) by metabolically active cells, PET imaging provides functional information on the metabolic activity of tumors which is supplemental to the information acquired by conventional imaging such as CT. Radioactive fluorine-18, administered in the form of the glucose analogue F-18 fluoro-deoxyglucose, is taken up preferentially by malignant tissue because of an over-expression of GLUT-1 receptors on the surface of tumor cells and an up-regulation of hexokinase (a phosphorylating enzyme); malignant cells then sequester the F-18 FDG because of the inability of the glucose analogue to enter intracellular glycolytic pathways (due to a down-regulation of phosphatase). Because FDG-PET imaging has been shown to have the ability to detect metabolically-active tumor in clinically unsuspected sites, it has become an important additional tool in the initial staging of cancer, assessment of response to treatment, and surveillance for tumor recurrence. The development of integrated PET-CT scanning, which incorporates a combined PET scan and whole-body CT scan and provides fused PET/CT images in addition to the dedicated PET and CT images, has made it possible to acquire both morphological and functional information of the entire body in a single examination. This discussion will highlight some of the artefacts and pitfalls encountered when interpreting PET-CT images.

Patterns of physiological FDG uptake

F-18 FDG is taken up by tissues that are metabolically active and which have a blood supply. The most common normal sites of FDG uptake include the heart, brain, gastrointestinal tract, genitourinary tract, and salivary glands (Fig 1). These patterns of FDG uptake are readily recognized by their expected anatomical distribution. However, FDG uptake within the colon can often be patchy or focal rather than the typical diffuse appearance, which can cause diagnostic difficulties if the CT images are not inspected. FDG uptake within the ureters can also appear focal or asymmetrical. These variations in physiologic uptake of FDG can present as potential pitfalls in interpretation and should be recognized. Correlation of the PET findings with the corresponding CT and fused PET-CT images is crucial in avoiding interpretative errors.

Variants in the pattern of physiological uptake

- Striated muscle

FDG uptake by skeletal muscle may occur due to muscle activity immediately prior to or following injection of the isotope (within 30 minutes of tracer injection) [1] and can rarely cause diagnostic difficulty with intramuscular metastatic disease, particularly if the FDG uptake is asymmetrical or focal (which can occur at musculotendinous junctions). This phenomenon is most commonly observed in the muscles of the head and neck (particularly the genioglossus and

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sternocleidomastomoid muscles), the rotator cuff muscles, the proximal muscles of the legs, the intercostal muscles of the thorax and the vocal cord muscles, and is exacerbated by patient anxiety, movement, hyperventilation or speech. It is important to minimize muscle uptake by FDG by ensuring that the patient is relaxed and comfortable prior to injection of the radiotracer and during the subsequent waiting period prior to image acquisition (60-90 minutes) (Fig 2). Speech should be discouraged. The pattern of FDG uptake within striated muscle is typically bilateral, symmetric and may be extremely prominent. In adults, brown fat is most frequently seen in the supraclavicular regions, giving rise to the descriptive term, “USA fat” (Uptake in Supraclavicular Areas) (Fig 3) [3].

Although the classical distribution of FDG uptake in brown fat is easily recognized and should not be confused with metastatic disease, it can cause particular diagnostic difficulties in patients with head and neck cancer, in whom nodal metastases in the cervical regions need to be specifically excluded. Nodal metastases in the neck can co-exist with brown fat and it may not be easy to differentiate abnormal from physiological FDG uptake in these regions [2]. In such cases, it is necessary to pay careful attention to the co-registered PET-CT images (Fig 4).

Inflammatory Causes of Increased FDG Uptake

- **Atherosclerotic plaques**

  Atherosclerosis involving the aorta and its branches is a common cause of increased FDG accumulation (Fig 5) [4]. Although the pattern of uptake is usually linear, conforming to the trajectory of the vessel, focal uptake within atherosclerotic plaques can also be observed, especially in the aortic arch and descending aorta. Such uptake can simulate nodal metastatic disease in the mediastinum or retroperitoneum.

- **Degenerative osteoarthritis**

  Focal FDG uptake is also frequently seen in osteoarticular joints, particularly the shoulder and hip joints, and most likely represents inflammatory bursitis secondary to degenerative osteoarthritis. Careful examination of the corresponding CT images should always be undertaken to exclude osseous metastases in these regions (Fig 6).

- **Radiation inflammation**

  However, probably the most common – and definitely the most troublesome in terms of interpretative difficulties - inflammatory cause of increased FDG uptake is the inflammation that follows radiotherapy, which can persist

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**Fig 2 • Twenty-six year old woman with lymphoma currently free of disease. A. axial PET image; B. CT scan; C. integrated PET-CT. Axial PET-CT images demonstrate uptake in scalene and intercostal muscles.**

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**Fig 3 • Uptake in USA fat.**

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**Fig 4 • Co-registered PET-CT images demonstrate uptake in brown fat.**

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**Fig 5 • Focal FDG uptake in atherosclerotic plaques.**

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**Fig 6 • Focal FDG uptake in degenerative osteoarthritis.**
Radiation inflammation normally presents as an area of diffuse FDG uptake conforming to the irradiated area. In the esophagus, FDG uptake due to radiation esophagitis is commonly linear in distribution. However, FDG uptake can often appear heterogeneous in intensity and may simulate recurrent disease. In addition, the increasing population of 3D conformal radiotherapy techniques has meant that inflammation due to radiotherapy may also present with more unusual patterns of FDG accumulation that are even harder to distinguish from tumor activity. For these reasons, it is commonly advised to wait for a period of at least 3 months following the completion of radiotherapy before restaging PET-CT imaging is undertaken (Fig 7).

### Venous thrombus

Venous thrombosis is associated with an inflammatory reaction as it undergoes recanalization and fibrosis, and can be an uncommon cause of focal FDG uptake [6]. On CT, venous thrombus may be depicted as a focal area of high attenuation within a vein, but without IV contrast the definitive diagnosis may be impossible. FDG uptake may be observed within both bland and malignant thrombus (Fig 8). Similarly, FDG uptake may be seen within thrombus at the tip of a central venous catheter [7].

### FDG uptake due to hormonal changes

FDG uptake is normally observed within ovarian tissue in pre-menopausal women approximately 8-18 days prior to menstruation [8]. This period corresponds to the late follicular to early luteal phase of the menstrual cycle. Such ovaries may show cystic enlargement up to 3 cm in diam-
**Fig 6** • Sixty-one-year old woman with breast cancer. Coronal PET scan (A) shows bilateral symmetrical FDG uptake in hand region correlating on the CT (B) and fused images (C) to the distal phalanges of both thumbs (arrows). The patient also had a history of psoriasis, and benign disease was confirmed with plain films of the hands.

**Fig 7** • Seventy-one-year old woman 5 months after radiation treatment for non-small-cell lung cancer. Increased FDG activity is seen on the PET image (B) correlating to the paramediastinal right lung. CT (A) and fused images (C) show typical radiation changes with no mass. No recurrence was seen on two year follow-up.
ter. FDG uptake is also seen in the endometrium during the first 3 days of menstruation [8, 9]. These patterns of FDG uptake should not be misinterpreted as representing malignant disease, a pitfall that can be avoided by obtaining a careful menstrual history and assessing the corresponding CT images.

During the late follicular phase of the menstrual cycle, normal breast tissue may also exhibit physiological FDG uptake corresponding to the response of glandular breast tissue to variations in oestrogen and progesterone levels (Fig 9). In young patients with extremely glandular breasts, it can be difficult to differentiate this normal appearance from breast infiltration by tumors such as lymphoma or inflammatory breast cancer. However, the symmetrical distribution of FDG uptake within both breasts should dispel any concerns.

Another cause of increased FDG uptake within the breasts relates to rupture of a silicone breast implant or direct injection of silicone into breast tissue; in these patients, the dispersion of silicone within breast tissue leads to a chronic foreign-body type inflammatory reaction, with the infiltration of macrophages and giant cells and the formation of foreign body granulomas [10]. On CT, these granulomas appear as small soft tissue nodules which demonstrate increased FDG uptake on PET and fused PET-CT images; in addition, abnormal FDG accumulation can occur within draining axillary lymph nodes (Fig 10). Without a suggestive clinical history, differentiation from breast cancer can be extremely difficult, and further evaluation with ultrasound, MRI or even biopsy may be required.

**Bone Marrow**

Stimulation of the bone marrow may occur during periods of physiological stress (such as due to illness or trauma) or following the administration of chemotherapy or colony-stimulating growth factors. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are hematopoetic cytokines that are increasingly used in the oncology setting to stimulate recovery of bone marrow function following myeloablative chemotherapy. Bone marrow stimulation is accompanied by a marked increased in FDG accumulation on PET-CT, which can be recognized by its typically diffuse and symmetrical distribution within red marrow-containing regions of the body such as the proximal long bones, pelvis and vertebral bodies [11] (Fig 11). Unfortunately, such diffuse FDG uptake can often obscure underlying bone metastases; conversely, FDG uptake due to marrow stimulation may also appear patchy and heterogenous in intensity and thereby simulate metastatic disease. The resultant diagnostic difficulty is greatest in patients with malignancies that commonly metastasize to the bone marrow and which may not produce visible osseous changes on CT images; such cancers include lymphoma, lung cancer, melanoma, breast cancer and esophageal cancer. In such cases, it may be impossible for the interpreting radiologist to be confident about the presence or absence of metastatic disease within the bone marrow. Follow-up imaging after discontinuation of marrow-stimulating medication may be required; however, marrow activity can be seen for periods of up to 1 month following discontinuation of colony stimulating factors.
Iatrogenic causes of increased FDG uptake

Focal FDG uptake that is not due to malignant disease is commonly observed at sites of percutaneous tube placements (tracheostomy, gastrostomy, biliary drains, nephrostomy tubes, chest drains), and can persist following removal of the tube [12] (Fig 12). Recognition of the linear pattern of FDG uptake in regions commonly associated with percutaneous tubes and drains should help avoid confusion with malignancy; correlation with the CT images, and with the patient’s clinical history, provides additional useful information.

Other iatrogenic causes of focal increased FDG uptake include the injection of Teflon (polytetrafluoroethylene) into a vocal cord (performed for midline approximation of the vocal cord in cases of vocal cord paralysis) [13], and talc pleurodesis [14] (Fig 13). Although both Teflon and talc can be recognized by the presence of high-density material within the vocal cord and pleural cavity, respectively, this high-density material is not always seen, and diagnostic difficulty can arise if an accurate clinical history has not been provided. Pleural talc causes particular interpretative problems in patients with malignant mesothelioma or suspected malignant pleural effusions, many of whom have undergone pleurodesis for recurrent pleural effusion prior to PET-CT imaging. In such cases, increased FDG uptake in the pleural cavity due to talc may be impossible to differentiate from pleural malignancy.

Artefacts in PET-CT: technical considerations

Images acquired during the CT component of PET-CT have two primary purposes: firstly, they allow attenuation correction of the PET emission data by providing information regarding the density of the body tissue at each axial slice; secondly, they allow more accurate anatomical loca-
Fig 11 • Thirty four-year-old man with lymphoma, 10 days following G-CSF treatment. Coronal PET image (A) shows diffuse, homogeneous, symmetrical FDG uptake in the axial skeleton due to increased hematopoesis. CT image (B) shows normal appearance of bones. Increased FDG uptake in spleen is due to extramedullary hematopoiesis.

Fig 12 • Forty-nine-year old man with lymphoma. Coronal PET scan (B) shows FDG activity from the right lower neck (arrow) simulating a lymph node. Correlation with CT (A) and fused images (C) reveal this was due to inflammation along the insertion of the central line.
lization of PET abnormalities through fusion of the PET and CT images. The whole-body CT scan is performed at mid-expiration in suspended respiration, while the PET images are acquired with the patient breathing quietly. This makes conventional PET-CT susceptible to respiratory motion artefacts that manifest themselves in two ways:

✔ slight spatial mis-registration of the CT and PET data, particularly in the region of the diaphragm, most commonly recognized by a sliver of photopenia outlining the superior surface of the diaphragms in the coronal plane and caused by movement of the diaphragm during breathing (Fig 14);

✔ inaccurate attenuation correction in regions of the body subject to breathing motion, leading to an under-estimation of the intensity of FDG uptake within moving lesions and an over-representation of the volume of metabolically active tissue ("smearing").

Fig 13 • Sixty-three year old man with local recurrence of lung cancer. Multiple foci of increased FDG activity were seen along the pleura (A). These correlated with nodular pleural thickening with increased attenuation consistent with prior history of talc pleurodesis (B). Patient had talc pleurodesis performed three years prior to the PET-CT and CT appearance of the pleura was stable for three years.

Fig 14 • Fifty-four year old man staged for newly diagnosed esophageal cancer. Coronal PET image (A) shows an FDG avid focus projecting over the lungs (black arrow). However, CT images of the lungs (not shown) were normal. The dome of the liver showed a low attenuation lesion barely visualized on initial inspection (white arrow) (B) but readily seen with narrow windows (C). This represented misregistration of a liver metastasis due to differences in patient’s breathing at acquisition of CT (end-expiration) and PET (tidal breathing).
Both of these phenomena need to be recognized in order to avoid making mistakes in terms of diagnosis, assessment of treatment response and estimation of prognosis.

In particular, spatial mis-registration may be responsible for confusing hypermetabolic liver lesions with pulmonary metastases: due to diaphragmatic movement during breathing, lesions that are in the domes of the liver may appear on the PET images to be located in the lung bases; conversely and for the same reasons, FDG uptake in the lung bases may appear to be located in the liver. This has important implications for staging lung and liver tumors. However, attention paid to the corresponding CT images should avoid confusion in most cases.

For radiation physicists formulating a radiotherapy treatment plan on PET-CT images, it is important for them to appreciate the possible effect of respiratory motion artifact on their target volume, particularly when 3D conformal therapy is being employed with the aim of more focused irradiation that spares normal tissue adjacent to the target lesion. Any treatment plan that is based on the PET images must take into account possible spatial mis-registration of the target lesion. Similarly, inaccurate attenuation due to breathing will tend to make a lesion appear less hyper-metabolic and may affect edge determination. 4D PET-CT, a technique that acquires both CT and PET images while the patient is quietly breathing [15], will minimize these artefacts and lead to greater diagnostic accuracy, but such techniques are not yet in routine use in most centers.

PET-CT has also been proposed as a method for assessing the response of tumors to treatment by the degree of decrease (relative to baseline) in FDG avidity observed on a post-treatment scan, thereby helping to judge whether a specific treatment is effective or should be discontinued or changed. Such a response can also be used to estimate ultimate prognosis. However, respiratory motion can cause artefactual decreases in FDG accumulation and give a misleading impression of the effect of a particular treatment. In the future, PET-CT scanning techniques that employ methods that compensate for respiratory motion, such as respiratory gating and 4D PET-CT [15, 16], will hopefully lead to more reliable assessments of treatment response and eventual prognosis.

References


Conclusion

PET-CT is an exciting imaging modality that has rapidly become an integral tool for imaging patients with cancer. However, because PET-CT combines two different technologies – nuclear medicine imaging and diagnostic radiology – it has also posed challenges to the way in which PET-CT is performed and interpreted. A thorough understanding of the way in which PET-CT images are acquired and an appreciation of the limitations of PET-CT will help to avoid most diagnostic pitfalls. With increasing availability of PET-CT and its rising preeminence in oncological imaging, a much greater collaboration between radiologists, nuclear medicine physicians, radiation therapy physicists, and oncological clinicians will be required if the full benefits of PET-CT are to be optimized.