

Pitfalls and Artifacts in ^{18}F FDG PET and PET/CT Oncologic Imaging

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It is estimated that in excess of one million positron emission tomography (PET) scans are performed each year and PET can now truly be regarded as a routine imaging procedure in clinical management. Many potential pitfalls and artifacts have previously been described with ^{18}F -fluorodeoxyglucose PET imaging, but more continue to become apparent as worldwide expe-

BECAUSE ^{18}F FDG behaves as an analog of glucose, its distribution closely follows that of glucose-metabolizing cells and organs but with some differences. It enters cells by membrane glucose transporters, which are commonly overexpressed in cancer cells, and undergoes phosphorylation by hexokinase to form ^{18}F FDG-6-phosphate. Unlike glucose, this undergoes minimal further enzymatic reactions and is effectively trapped in the cell, accumulating in most tissues at a rate proportional to glycolysis. Most tissues and tumors have relatively low levels of glucose-6-phosphatase activity and therefore little ^{18}F FDG-6-phosphate escapes the cell. The liver, and possibly primary liver tumors, have higher activities of this enzyme and may consequently show reduced uptake of ^{18}F FDG over time.¹ Although clinical ^{18}F FDG PET imaging is commonly performed at 60 minutes after injection, there is evidence in some tumors that uptake as measured by standardized uptake values continues for several hours.² Increased glycolysis is not specific to tumor tissue, and a number of benign processes, particularly inflammation, may result in uptake of ^{18}F FDG that is higher than background tissues.³⁻⁵ It would appear that many benign processes do not continue to accumulate ^{18}F FDG at the same rate as malignant tumors, and some groups have exploited this phenomenon by performing imaging at dual time points, eg, at 1 and 2 hours.^{6,7} Malignant tissue

experience increases. In addition, the advent of combined PET/CT scanners in clinical imaging practice has brought their own specific pitfalls and artifacts. It is essential that we learn these potential pitfalls so that patients can be optimally prepared for their scans and that accurate interpretation can be made.

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shows an increase in uptake but benign lesions do not.

In the brain, there is high uptake of ^{18}F FDG into cortical tissue and basal ganglia irrespective of substrate conditions, glucose being the predominant substrate for brain metabolism. The liver, spleen, and bone marrow normally show homogeneous low-grade uptake, with bone marrow and spleen appearing less intense than the liver under normal conditions. Some normal lymphatic tissue may show uptake of ^{18}F FDG and this may be of a moderate intensity in the tonsils in adults as well as the adenoids in children. It is possible that there is seasonal variability in tonsillar uptake, with more prominent uptake within the winter months, presumably associated with upper respiratory tract infections (Fig 1).⁸ Thymic activity is commonly seen in children and can also be seen in young adults and occasionally older adults after chemotherapy, probably as a result of the thymic rebound phenomenon.⁹ It has been reported in as many as 19% of scans of patients with Hodgkin's disease.¹⁰ The typical pattern is of low to moderate uptake in the shape of an inverted "V" in the anterior mediastinum (Fig 2).

In the thorax, there is low uptake of ^{18}F FDG in lung tissue, although scans that are not corrected for attenuation effects result in lungs with artifactually high activity. Cardiac activity is very variable, ranging from no discernible activity above background blood pool activity, to intense activity throughout the left ventricular myocardium. The degree of uptake depends on substrate availability, and in a fasted patient in whom insulin levels are low, the predominant myocardial substrates are fatty acids. For oncology imaging of the thorax, it is preferable to minimize cardiac activity by fasting the patient for 4 to 6 hours so that any malignant mediastinal nodes or pericardiac nodules are clearly visualized. Some institutions also minimize cardiac glucose and ^{18}F FDG uptake by

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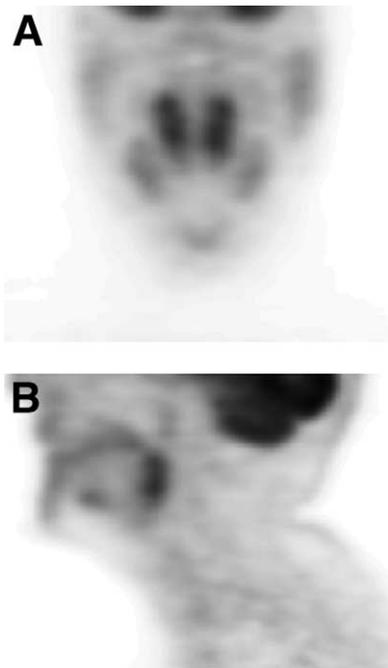


Fig 1. ¹⁸F FDG scan of the head and neck demonstrating physiological uptake in the tonsils. Coronal (A) and sagittal (B) views.

giving the patient a drink with high caffeine content that encourages fatty acid metabolism in the myocardium. It is unusual to see atrial or right ventricular activity unless there is cardiac disease affecting those chambers (Fig 3).¹¹

Glandular breast tissue may show moderate uptake of ¹⁸F FDG and is relatively increased in premenopausal subjects and postmenopausal subjects taking hormone replacement therapy compared with postmenopausal subjects. The degree of uptake is not such that it would be mistaken for malignancy but it is possible that a low-grade breast cancer might not be detected against this background activity. Marked uptake of ¹⁸F FDG may be seen in lactating breasts.

Uptake within the gastrointestinal tract can be highly variable. Apart from lymphatic tissues within the oropharynx, salivary glands also often show low to moderate diffuse uptake of ¹⁸F FDG. The esophagus does not usually show significant activity unless inflamed or malignant but homogeneous uptake of tracer within the stomach wall is relatively common. Higher grades of uptake may be associated with *Helicobacter pylori* infection.¹² Small intestinal uptake is variable and usually of low-grade when visible but colonic activity may be

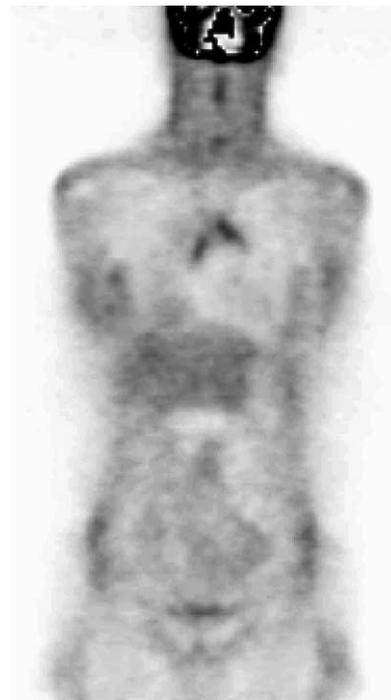


Fig 2. Nonattenuation-corrected ¹⁸F FDG scan. The coronal image demonstrates physiological ¹⁸F FDG uptake in the thymus.

quite marked and may affect part or all of the colon. It is commonest to see activity at the caecum and in the rectosigmoid region (Fig 4). It is unusual to see focal uptake within the colon unless this is associated with pathology.

The actual cause of intestinal uptake of ¹⁸F FDG is

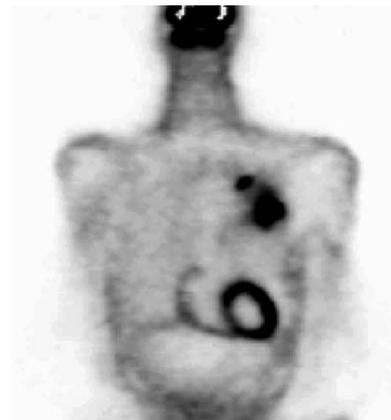


Fig 3. Nonattenuation-corrected ¹⁸F FDG scan performed for staging of lung cancer. Coronal image demonstrating prominent left and right ventricular FDG uptake, as well as the known malignancy in the left lung.

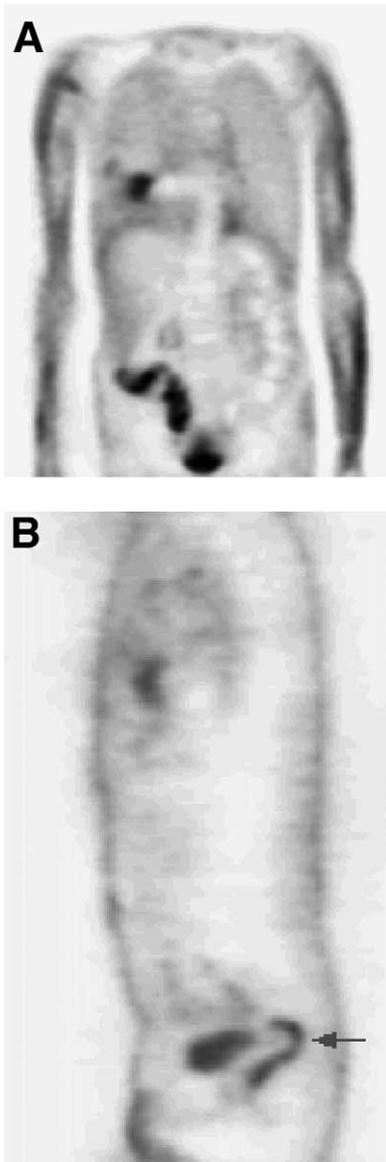


Fig 4. Nonattenuation-corrected ^{18}F FDG scans of two patients, demonstrating physiologic bowel activity on the coronal image (A) in the caecum and on the sagittal image (B) in the rectosigmoid region (marked by an arrow).

not fully understood and may be multifactorial. In rat studies it appears that only a minority of uptake is associated with intestinal smooth muscle but that the majority is associated either with the intestinal mucosa or with the luminal contents.¹³ It may not be possible to eliminate bowel activity completely but various groups have tried smooth muscle relaxants including glucagon and anticholinergics as well as bowel prep including laxatives with or without colonic cleansing.^{14,15} It is possible that

PET/CT imaging will reduce diagnostic uncertainty with respect to physiologic bowel activity by allowing more confident interpretation related to areas of anatomically normal intestine. This may be further enhanced by using bowel contrast agents.^{16,17}

The urinary tract is another source of potential pitfalls with regard to the interpretation of ^{18}F FDG PET images. Unlike glucose, ^{18}F FDG is not reabsorbed by the renal tubules and so may show significant activity in any part of the urinary tract or surgical urinary diversions such as ileal conduits. Now that iterative reconstruction techniques are used widely for PET imaging of the body, reconstruction artifacts, as a result of areas of high activity concentration, are less common than when filtered back projection was used more widely. Nevertheless, it is often of benefit to minimize urinary stasis in the renal collecting systems, ureters or bladder that might mimic or obscure pathology. It is possible that PET/CT will be of benefit in correctly ascribing focal areas of urinary activity to the urinary tract but in our experience it is often helpful to minimize urinary stasis in the ureters by keeping the patient well-hydrated and giving intravenous diuretic. This can be especially helpful when there is pathology in the pelvis. Rather than trying to empty the bladder by drainage or washout, it is our preference to image the pelvis with a full bladder with dilute ^{18}F FDG activity. This enables easier differentiation of perivesical lymphadenopathy from small pockets of urinary activity. Some groups catheterize the bladder and perform washouts but we have found this unnecessary in the majority of patients and have found that it can be associated with measurable radiation exposure to technologists.

Testicular activity of a moderate degree is commonly encountered and is probably inversely related to age.¹⁸ Ovarian uptake is not normally seen but has been described in benign corpus luteum cysts.¹⁹ Uptake in the uterus has been reported during menstruation and in relation to fibroids but in practice is an uncommon finding.^{20,21}

Probably the commonest area for interpretative pitfalls is related to ^{18}F FDG uptake in active skeletal muscle. In relaxed and rested patients, no significant skeletal muscle uptake is noted. Most skeletal muscle activity can easily be recognized as such but it is important to minimize activity that might obscure peripheral primary tumors, eg, soft tissue

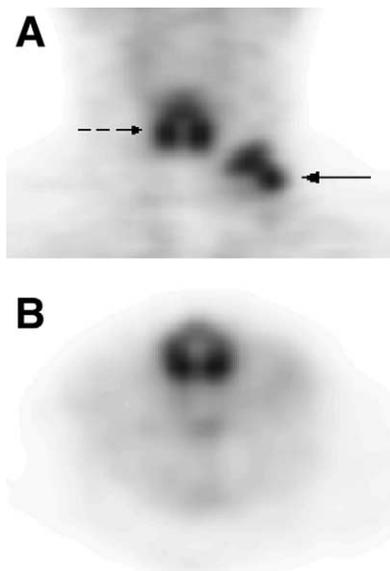


Fig 5. ¹⁸FDG scan performed for staging of head and neck cancer. The patient did not maintain silence during the uptake period. Coronal image (A) demonstrating the malignancy (solid arrow) and physiological laryngeal uptake (dashed arrow) and transaxial image (B) of the laryngeal uptake.

sarcoma or metastases that have an unusual peripheral or cutaneous distribution, eg, melanoma. Specifically, laryngeal muscle activity should be minimized in patients with head and neck cancer by maintaining silence before and after injection of ¹⁸FDG²² (Fig 5). Chewing of gum should also be forbidden as uptake in the muscles of mastication may mimic cervical lymphadenopathy (Fig 6). It is common to see activity in the floor of the mouth related to the genioglossus muscles, used to keep the tongue forwards while the patient is supine (Fig 7). This can be reduced by allowing the patient to sit upright during the uptake period.

In the early days of clinical PET, a symmetrical pattern of intense uptake was noted in the neck, supraclavicular, and paraspinal regions and attributed to muscle tension.²³ Since the advent of PET/CT it now seems that this appearance is probably as a result of metabolic activity in brown fat.^{24,25} Even when recognized as a benign variant, the degree of uptake can easily obscure malignant lymphadenopathy in the region (Fig 8).

PATIENT PREPARATION

The key to successful PET imaging is to adequately prepare the patient to minimize the appearance of potential artifactual uptake patterns that

make interpretation difficult. As previously discussed, it is important that a patient is relaxed at the time of injection and has not taken vigorous exercise in the hours leading up to the scan. In oncology patients considered at risk of showing activated brown fat or “muscle tension” then oral benzodiazepines should be considered at least 30 minutes before ¹⁸FDG injection. Chewing and talking should be forbidden when pathology in the head and neck is suspected.

For oncology studies it is common to starve the patient, except for water, for 4 to 6 hours before injection. This will keep insulin levels low and minimize uptake into muscle, fat, and the myocardium. If the pericardiac region is of particular interest then a caffeine containing drink may reduce left ventricular myocardial activity further. In insulin-dependent diabetic patients who have high blood sugar levels, it is better to reschedule the appointment rather than be tempted to give insulin because this will increase background activity in muscle and fat and reduce tumor conspicuity (Fig 9). Diet-controlled or noninsulin-dependent diabetics can be treated similarly to nondiabetics. The latter are best given an early morning appointment

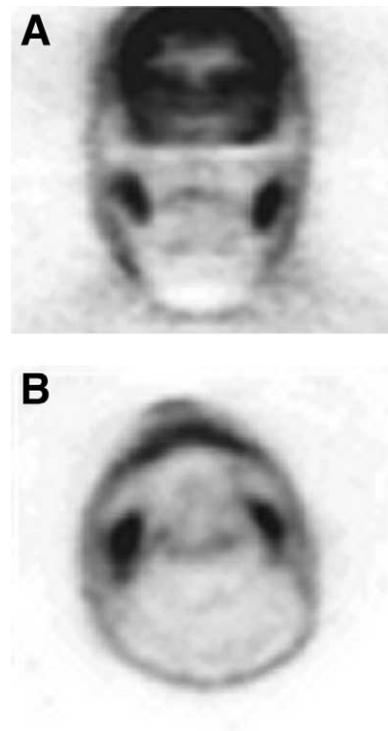


Fig 6. Symmetrical masseter muscle uptake due to chewing gum during the ¹⁸FDG uptake period.

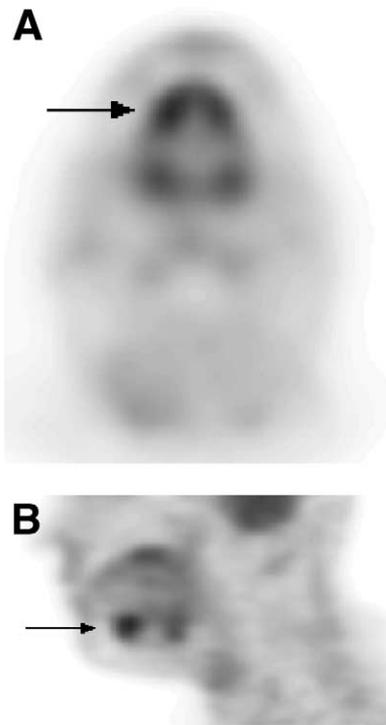


Fig 7. ^{18}F FDG scan of the head and neck demonstrating genioglossus muscle uptake (arrows). Transaxial (A) and sagittal (B) views.

so that breakfast and medication can be given when the scan is complete. For cardiac imaging preparation protocols are more variable and discussed in more detail elsewhere.^{26,27} Agents that lower fatty acids, such as acipimox, may be helpful in maximizing ^{18}F FDG activity, even in diabetic patients.

When malignant disease is suspected close to the urinary tract then good hydration and the use of intravenous diuretics should be considered to minimize urinary stasis and to dilute ^{18}F FDG activity in the bladder. Some units prefer to catheterize the bladder to aid urinary drainage or to perform bladder washout.

SCANNING AFTER THERAPY

Most oncologic ^{18}F FDG PET scans are performed at 1 hour postinjection but uptake in some tumors may not be maximal until some hours after this.² It is likely that a 1-hour scan is likely to continue to be the most widely used protocol for practicality, patient convenience, and because of the relatively short half-life of ^{18}F FDG. However, if serial measurements are being made, for example to monitor

therapy, then it is important to scan patients at exactly the same time after injection of ^{18}F FDG, as it is possible that differences in timing alone could cause differences in standardized uptake values between studies, independent of any therapy affect.

Controversy exists as to the best time to perform scans after chemotherapy and radiotherapy. To some extent optimal timing may depend on the clinical question being asked. For example, if there is a residual mass after completion of chemotherapy for lymphoma, the timing of the scan after the

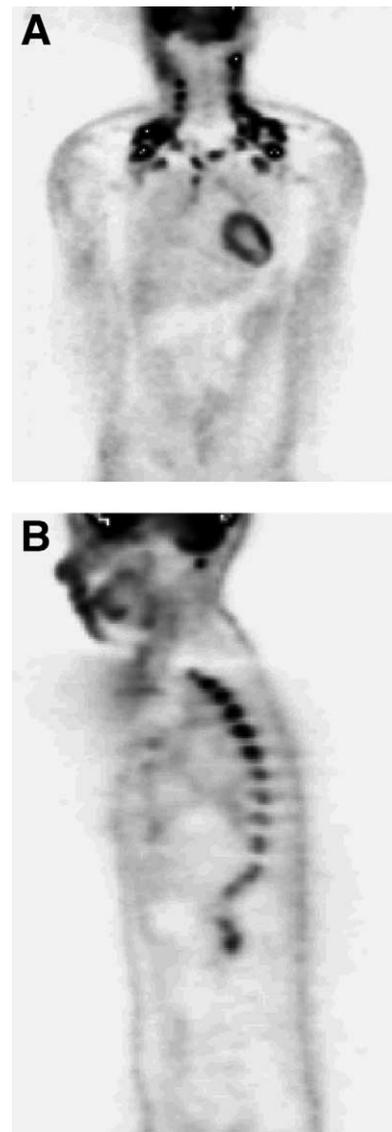


Fig 8. Nonattenuation-corrected ^{18}F FDG scan demonstrating physiological brown fat uptake in the neck, supraclavicular fossae and upper mediastinum on the coronal image (A) and paraspinal region on the sagittal image (B).



Fig 9. Nonattenuation-corrected FDG scan (coronal view) of a patient given insulin just before FDG administration. Prominent skeletal muscle uptake is demonstrated.

last course of chemotherapy might be different from when ¹⁸F PET is being used to assess the efficacy of chemotherapy after one or two cycles. It is possible that a “stunning” phenomenon occurs in some tumors after chemotherapy whereby ¹⁸F uptake is reduced or absent for a period of 2 weeks but subsequently increases again.²⁸ This phenomenon might explain the apparently poor sensitivity of ¹⁸F PET after neoadjuvant chemotherapy in some cancers.²⁹ A flare response has also been described after hormone therapy in breast cancer³⁰ and in brain tumors³¹ after chemotherapy, occurring a few days after therapy and possibly related with an influx of inflammatory cells as a response to tumor cytotoxicity. A number of publications have suggested that it is possible to predict response to chemotherapy at 1 to 2 weeks after treatment but that scans delayed to 5 to 6 weeks are more accurate.³²⁻³⁵ Further research is required in

this area but with the current state of knowledge it would not seem unreasonable to scan patients after one or two cycles of chemotherapy at least 10 days after the last treatment to measure whether the therapy is being effective or not. When there is a residual mass at the end of therapy, then it would seem better to wait approximately 6 weeks for the most accurate measure of residual viable tumor and prediction of relapse. Allowing for measurement imprecision of approximately 10% and the expected effect of chemotherapy on ¹⁸F uptake after one or more cycles of chemotherapy, the EORTC PET group have suggested guidelines for categorization of treatment response into progressive metabolic disease, stable metabolic disease, partial metabolic response, and complete metabolic response (Table 1).³²

After radiotherapy, there is an inflammatory reaction that may persist for some months and that is associated with uptake of ¹⁸F. It has been suggested that in rectal cancer and head and neck cancers that inflammatory ¹⁸F uptake may persist for 4 to 6 months after radiotherapy and that accurate diagnosis of residual tumor viability is best made after this time interval.^{36,37} A negative scan before this interval is clinically helpful but it may not be possible to differentiate residual tumor activity from inflammatory reaction in positive scans.

SPECIFIC PROBLEMS RELATED TO PET/CT

One of the most exciting technological advances in recent years is the clinical application of combined PET/CT scanners. However, this new technology has come with its own particular set of artifacts and pitfalls, most of which have been, or are currently being, addressed.

One of the biggest problems related to PET/CT imaging in a dedicated combined scanner is related to differences in breathing patterns between the CT and the PET scans. Although CT scans can be acquired during a breath hold, PET acquisitions are taken during tidal breathing and represent an aver-

Table 1. Suggested Response Measurement Parameters³²

Response Grade	Change in Standardized Uptake Value
Progressive metabolic disease	>25% increase ± new lesions or >20% increase in metabolic dimension
Stable metabolic disease	<15% reduction, <25% increase
Partial metabolic response	After one cycle of chemotherapy, >15% reduction After two cycles of chemotherapy, >25% reduction
Complete metabolic response	Complete resolution of lesions

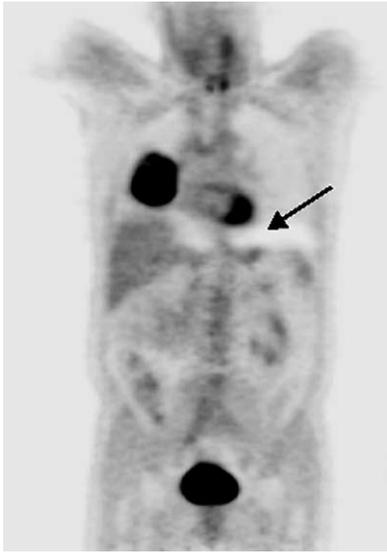


Fig 10. Coronal CT attenuation-corrected ^{18}F FDG scan demonstrating an apparent loss of activity at the level of the diaphragm (arrow) due to differences in breathing patterns between the CT and PET scans.

age position of the thoracic cage over 30 minutes or more. This may lead to mis-registration of pulmonary nodules between the two modalities particularly in the peripheries and at the bases of the lungs where differences in position may approach 15 mm.³⁸ Misregistration may be minimized by performing the CT scan during normal expiration.^{39,40} It has been noted that deep inspiration during CT acquisition can lead to deterioration of the CT attenuation-corrected PET image with the appearance of cold artifacts and can even lead to the mis-positioning of abdominal activity into the chest⁴¹ (Figs 10 and 11). CT acquisition during normal expiration minimizes the incidence of such artifacts and also optimizes coregistration of abdominal organs.

High-density contrast agents, eg, oral contrast (Fig 12), or metallic objects (Fig 13) can lead to an artifactual overestimation of activity if CT data are used for attenuation correction.⁴²⁻⁴⁸ Such artifacts may be recognized as such by studying the uncorrected image data. Low-density oral contrast agents can be used without significant artifact^{16,17} or the problem may be avoided by using water as a negative bowel contrast agent. Algorithms have been developed to account for the overestimation of activity when using CT-based attenuation correction that may minimize these effects in the future.⁴⁸



Fig 11. Coronal fused ^{18}F FDG PET (CT attenuation correction) and CT demonstrating a liver lesion that has been "misplaced" into the lung base due to differences in breathing patterns between CT and PET scans.

The use of intravenous contrast during the CT acquisition may be a more difficult problem. Similarly, the concentrated bolus of contrast in the large vessels may lead to overcorrection for attenuation, particularly in view of the fact that the concentrated column of contrast has largely dissipated by the time of the PET acquisition. This may lead to artifactual hot spots in the attenuation corrected image⁴⁵ or quantitative overestimation of

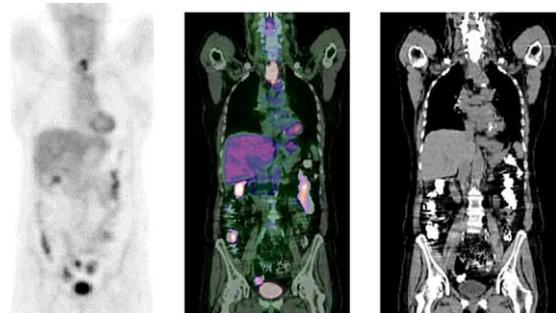


Fig 12. Coronal ^{18}F FDG PET with CT attenuation correction (left), fused PET/CT (center) and CT (right). High density bowel contrast from a previous barium examination leads to over correction in the PET image with an artifactual increase in bowel activity.



Fig 13. Coronal ¹⁸F-FDG scan with CT attenuation correction (A), CT alone (B), uncorrected ¹⁸F-FDG (C), of a patient with a metallic pacemaker placed over the left upper chest demonstrating artifactual increased uptake on the corrected images.

¹⁸F-FDG activity. If intravenous contrast is considered essential for a study then the diagnostic aspect of the CT scan is best performed as a third study with the patient in the same position, after first, a low current CT scan for attenuation correction purposes and second, the PET emission scan.

Although many centers have found low current CT acquisitions to be adequate for attenuation correction and image fusion,⁴⁹ it may be necessary to increase CT tube current in larger patients to minimize beam-hardening artifacts on the CT scan that may translate through to incorrect attenuation

correction.⁴⁶ This effect is commonly caused by the patient's arms being in the field of view and can also be minimized by placing arms above the head for imaging (Fig 14). Differences in the field of view diameter between the larger PET and smaller CT parts of combined scanners can lead to truncation artifacts at the edge of the CT image but these are generally small and can be minimized by the use of iterative image reconstruction methods.⁴⁸

Despite new artifacts being introduced by combined PET/CT imaging, it is likely that many

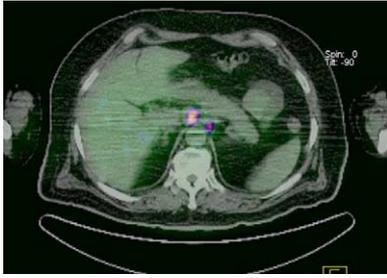


Fig 14. Transaxial fused PET/CT image demonstrating beam hardening artifact from the patient's arms that were by his side. The CT scan was performed with a tube current of only 70 mAs. Malignant celiac nodes are also noted in this patient with esophageal cancer.

pitfalls caused by normal variant uptake may be avoided by the ability to correctly attribute ^{18}F FDG activity to a structurally normal organ on CT. This may be particularly evident in the abdomen when physiological bowel activity or ureteric activity can otherwise cause interpretative difficulties. PET/CT also has the potential to limit false negative interpretations in tumors that are not very ^{18}F FDG avid by recognizing uptake as being related to structurally abnormal tissue and increasing the diagnostic confidence in tumor recognition by the use of the combined structural and functional data. Similarly, it may be possible to detect small lung metastases on CT lung windows that are beyond the resolution of ^{18}F FDG PET. The full use of the combined data, including the corrected and non-corrected PET emission data, and the inspection of soft-tissue, lung and bone windows on the CT data, may also allow the description and correct diagnosis of pertinent ^{18}F FDG negative lesions, eg, liver cysts, and incidental ^{18}F FDG negative CT abnormalities, eg, abdominal aortic aneurysm, to provide an integrated interpretation of all the available data resulting from this technology.

FALSE-POSITIVE AND -NEGATIVE ^{18}F FDG UPTAKE

Many benign conditions that can cause high uptake of ^{18}F FDG and have the potential for false positive interpretation in oncologic studies have previously been described and are too numerous to include here.³⁻⁵ Many of these are related to inflammatory, infective or granulomatous processes but some selected alternative potential false positives are briefly described. The reader is directed to previous publications for more complete summaries.³⁻⁵

Thyroid

Although homogeneous uptake of ^{18}F FDG is frequently seen in the thyroid (Fig 15) and is commonly associated with autoimmune thyroiditis, Graves' thyrotoxicosis, or autoantibody positivity, it is not uncommon for focal thyroid uptake to be present. In one large series approximately 2% of studies showed this pattern.⁵⁰ Approximately 50% of focal abnormalities turn out to be malignant and so such findings cannot be ignored and require further investigation.

Musculoskeletal

Skeletal muscle activity is commonly seen but rarely causes diagnostic difficulties unless it obscures peripheral tumors or metastases, eg, soft tissue sarcoma or melanoma. If patients talk during the uptake period then symmetrical laryngeal muscle activity is seen and the asymmetric appearance of muscle activity has been described following recurrent laryngeal nerve palsy.⁵¹ We have noted a similar appearance in the larynx following Teflon injection of the vocal cord.

As mentioned above, it is not uncommon to see a pattern of intense symmetrical multifocal and linear uptake of ^{18}F FDG in the neck, supraclavicular and paraspinal regions because of activated brown fat. It is likely that this represents increased glucose usage in brown fat, a vestigial organ of thermogenesis that is sympathetically innervated and driven. To support this hypothesis it has been

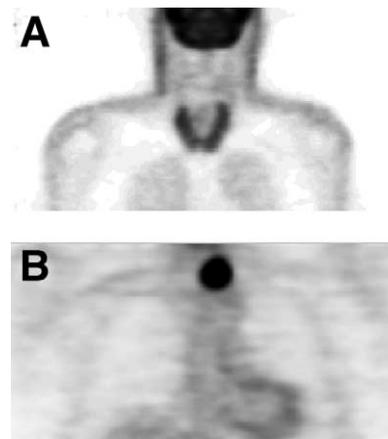


Fig 15. Nonattenuation-corrected ^{18}F FDG scan (coronal view) demonstrating thyroiditis (A) and attenuation corrected ^{18}F FDG scan (coronal view) demonstrating an incidental finding of focal uptake within the thyroid gland (B), which on biopsy proved to be papillary carcinoma.

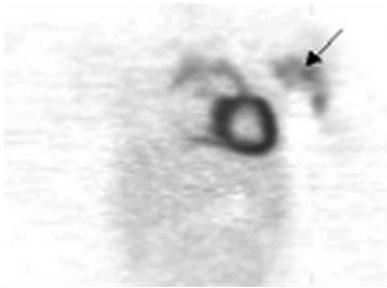


Fig 16. Attenuation-corrected coronal ¹⁸F-FDG scan of a child with sickle cell disease demonstrating uptake of tracer into left humeral osteomyelitis (arrow). Note the physiological thymic activity.

noted that this pattern is commoner in winter months and in patients with lower body mass index.²⁵ It appears that benzodiazepines are able to reduce the incidence of this potentially confusing appearance, possibly due to a generalized reduction in sympathetic drive but it would be interesting to evaluate the effects of pharmacological sympathetic block.

In the skeleton, the diffuse increase in bone marrow activity seen as a result of chemotherapy or colony stimulating factors, is now well recognized.⁵² It would appear that benign fractures can also lead to false positive uptake of ¹⁸F-FDG⁵³ but it would appear that abnormal uptake is relatively short-lived and usually returns to normal by 3 months, and often considerably sooner, after the fracture.⁵⁴ A number of other focal benign skeletal pathologies may result in high ¹⁸F-FDG uptake, including Paget's disease,⁵⁵ fibrous dysplasia⁵⁶ and osteomyelitis (Fig 16).⁵⁷

Because ¹⁸F-FDG activity is seen in a number of infective and inflammatory disorders it is now being considered as a useful radiopharmaceutical

specifically for this indication.⁵⁸ A number of benign neoplasms have been described as showing intense ¹⁸F-FDG activity, including Warthin's tumors of the salivary gland, colonic adenomas, enchondroma, and uterine fibroids,^{21,59-61} among many others. Conversely, there are a number of malignant tumors that show little or no uptake of ¹⁸F-FDG. In the chest, very small lung metastases may be beyond the resolution of current PET scanners, a problem made worse by "blurring" of the activity due to respiratory movement. Bronchioalveolar cell carcinoma notoriously shows only low-grade activity that may be inconspicuous. Other tumors, including mucosa-associated lymphoid tissue lymphomas, small lymphocytic cell lymphoma,³³ some neuroendocrine tumors,⁶² sclerotic bone metastases,⁶³ renal cell carcinoma, and brain metastases,⁶⁴ can be inconspicuous on occasion, either because of low uptake or high neighboring background activity.

With the large number of reports and observations of potential pitfalls in ¹⁸F-FDG PET oncologic imaging, it is not practical to give a comprehensive list of all within one article, but we have concentrated on what we believe are some of the more important pitfalls and those that have come to the attention of the PET community since we last wrote on this subject.^{3,4} It is hoped that as the knowledge and dissemination of potential pitfalls, and hence their avoidance, increases this will assist clinical PET and PET/CT's progression in establishing itself as an indispensable investigation in the management of cancer patients.

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