Basic Principles of PET-CT Imaging

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5.1 Introduction

PET-CT imaging has become a very powerful tool in cancer imaging; it utilises the detection of the radiation emitted from radionuclides that decay by positron (β^+) emission. This chapter looks into the physical principles of this technique, factors that affect the quality of the images produced and some of the artefacts and problems that may be encountered.

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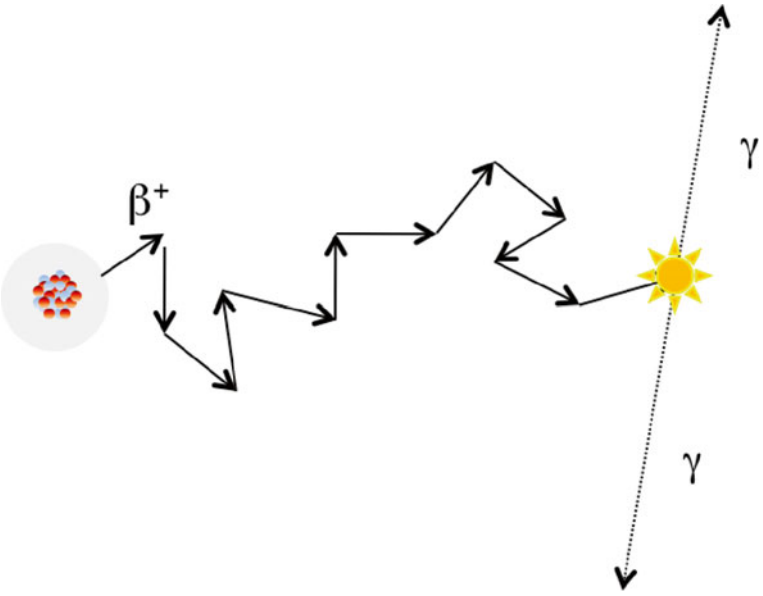

Fig. 5.1 During a nuclear decay, a positron is emitted from a nucleus and undergoes a series of interactions with atoms in the surrounding tissue. When its kinetic energy is almost zero, it and a neighbouring electron annihilate turning the mass of the two particles into energy in the form of two 511 keV photons. (Nucleus and random walk are not to scale)

5.2 Positron Emission Tomography (PET)

Positron emission tomography (PET) is the imaging of radiopharmaceuticals labelled with positron-emitting radionuclides. Positrons are the positively charged antimatter version of the electron and are ejected during the radioactive decay of a proton-rich nucleus; during this decay process, a proton in the nucleus is converted into a neutron. The positron is ejected from the nucleus carrying a lot of kinetic energy; it then travels a short distance and undergoes a number of interactions with the surrounding atoms. In each interaction, the positron loses some kinetic energy and changes its direction of travel, following a random path through the surrounding matter. When the positron is at rest, it annihilates with a nearby electron. Due to the conservation of energy, the energy associated with their combined mass (rest mass energy; $E = mc^2$) is converted to two annihilation photons each with energy of 511 keV. Conservation of momentum dictates that the two photons are emitted from the point of annihilation travelling in opposite directions (Fig. 5.1). These properties, the instantaneous production of two photons of equal energy travelling 180 degrees to each other, are the basis of the PET imaging technique used to localise where the original annihilation event occured within the patient.

A PET scanner is composed of several rings of small crystal scintillation detectors. Each detector is a few millimetres in size, and a group of them are formed

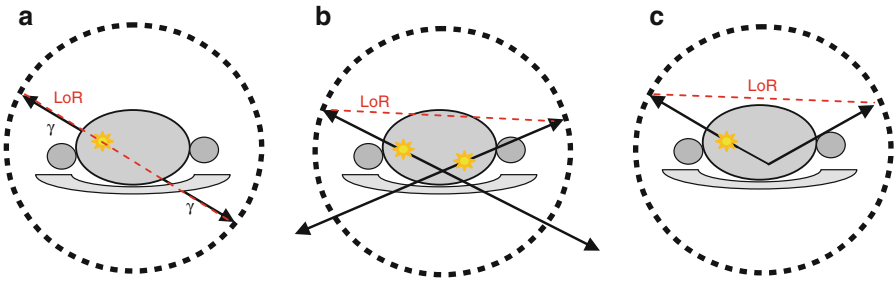

Fig. 5.2 Coincidence events in PET. (**a**) A true event with correct line of response (*LoR*), (**b**) a random event with two unrelated annihilations registering an incorrect line of response, (**c**) a scattered event where one photon has been scattered leading to an incorrectly positioned line of response

into a block that is typically connected to a group of four photomultiplier tubes. The scintillator detectors convert incoming photons into light before amplifying the signal using the photomultiplier tubes. When there is a positron emission within the ring of detectors, the two 511 keV photons, travelling at the speed of light, will be detected almost instantaneously (within approximately 10 ns). Photons arriving at different detectors within this coincidence timing window are called coincidence events. The line between the two detectors that detected each coincidence event is called the 'line of response'. Typically data are collected over several minutes and all detected coincidence events are grouped into parallel lines of response to form projections through the patient that are used for image reconstruction, typically using iterative reconstruction techniques. The great advantage of this type of localisation is that, unlike a gamma camera, it does not require collimators to provide positional information and therefore offers much higher sensitivity than single-photon emission tomography (SPECT).

The type of coincidence event described above is called a 'true' coincidence, and it is these signals that create the useful image. There are, however, other unwanted coincidence events that can occur (Fig. 5.2). A 'random' coincidence event is where multiple positron emissions and annihilations occurring in quick succession lead to a number of photons arriving at the detectors within the coincidence time window. If the wrong pair of detected photons is seen as the coincidence event, this will lead to an incorrect line of response. This process is called a random event as the line of response is not associated with a true annihilation event. The proportion of random events to total coincidence events increases significantly with higher activity concentrations and larger coincidence acceptance time windows, e.g., by moving from 10 to 15 ns. A 'scattered' event is where one or both photons coming from a positron-electron annihilation are scattered during their path to the detectors; the line of response will again be incorrect. The fraction of coincidence events that can be attributed to scatter increases with increased scattering material i.e. larger or denser tissue. Although unwanted coincidences can degrade image quality, all modern image reconstruction techniques use correction algorithms, which limit the effect of these types of event.

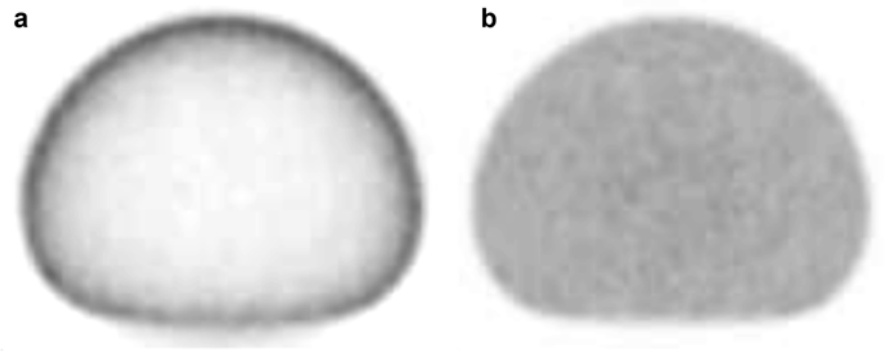

Fig. 5.3 Images of a transaxial slice through a phantom filled with a uniform solution of fluorine-18 (**a**) without correction for photon attenuation and (**b**) with attenuation correction

Along with adjustments for scattered and random events, there are other corrections that need to be applied during the reconstruction process to increase the accuracy of the final image. These include dead time corrections to deal with the high count rates found in PET, and a normalisation correction to correct for the difference in measured signal across pairs of detectors used to give the lines of response. However, the most dramatic of the corrections applied in PET is to correct for photon attenuation within the patient. Although the photons in PET are more energetic than those in single-photon tomography, both photons need to be detected for a signal to be registered; this means that the full thickness of patient tissue traversed by both photons affects the relative attenuation of signal from different parts of the patient. The effects of photon attenuation are therefore more dramatic in PET than in SPECT and lead to the classic 'hot' skin and lungs on uncorrected images (Fig. 5.3).

Exact attenuation correction (AC) is relatively straightforward so long as an accurate attenuation map is known. With the advent of PET-CT, the CT scan, which effectively is a map of attenuation at x-ray energies, can, with appropriate conversion factors, provide attenuation correction maps in a matter of seconds. The CT is mounted in the same gantry as the PET, and the bed moves the patient between the two scanners for sequential imaging. There are issues to be considered when using attenuation maps derived from CT, such as the accurate translation of attenuation coefficients from lower energy x-ray photons to 511 keV, the potential misregistration due to patient and respiratory motion, the use of contrast agents leading to incorrect attenuation maps owing to their enhanced attenuation only at the lower x-ray energies, the presence of metal artefacts and the additional radiation dose to the patient. Despite these limitations, the use of CT for AC has grown rapidly because of the low statistical noise in the attenuation maps and the addition of registered anatomical information; the fusion of CT with PET greatly enhances the interpretation of the functional information as will be seen through most of this book.

More recent technical advances include resolution (point-spread-function) modelling in PET image reconstruction resulting in significant improvements in image

resolution and contrast. Also modern fast crystal detectors are able to more precisely record the difference in the arrival times of the coincidence photons, known as time-of-flight (TOF) imaging. TOF helps localise the point of origin of the annihilation event along the line of response. The reduction in noise offered by TOF can be equated to a gain in sensitivity.

An advantage of applying a comprehensive set of corrections in PET-CT is that, with the inclusion of a sensitivity calibration, there is the possibility to calculate voxel values in terms of activity concentration per unit volume (kBq/ml). This activity concentration will change with patient size or administered activity, so it becomes more useful if this uptake is represented as a value normalised by the available activity concentration in the body. This is achieved by normalising injected activity and body size (weight or lean body mass), and this leads to the semi-quantitative index known as standardised uptake value (SUV). The SUV in each voxel will equal 1 for a uniform distribution. SUV is defined as

$$\mathrm{SUV}\left(\mathrm{g/ml}\right)=\frac{\text{activity concentration}\left(\mathrm{kBq/ml}\right)}{\text{administered activity}\left(\mathrm{MBq}\right)\Big/\text{weight}\left(\mathrm{kg}\right)}.$$

SUV was defined for use in PET whole-body oncology imaging with fluorine-18-fluorodeoxyglucose (usually abbreviated as [^{18}F]FDG or just FDG). Most PET display workstations will display PET images in SUV. Although the use of SUV is widespread, there are many factors that can affect its accuracy. It requires accurate measurement of administered activity, injection time, scan time and patient weight, and is affected by the performance characteristics of the PET scanner and image reconstruction factors. SUV also has a strong positive correlation with body weight. Heavy patients have a higher percentage of body fat that contributes to body weight but accumulates little FDG in the fasting state, so standardised uptake values (SUVs) in nonfatty tissues are increased in larger patients. SUV normalised to lean body mass or body surface area have been shown to have a lesser dependence on body weight, although SUV normalised to body weight is still the most clinically used parameter. Many physiological factors can affect SUV, including scan delay time (accumulation of FDG continues to increase over time), patient resting state, temperature, blood glucose level, insulin levels and renal clearance. In addition, FDG is not a specific tumour marker, and uptake will be high in areas affected by infective or inflammatory processes that are often seen immediately post-chemotherapy.

Several values of SUV can be quoted; the most common being $\mathrm{SUV}_{\mathrm{max}}$ which is robust and relatively independent of the observer, but as it refers to a single voxel value, it is strongly affected by image noise and can change significantly depending on count statistics and reconstruction parameters. It may also not be representative of the overall uptake in a heterogeneous tumour. $\mathrm{SUV}_{\mathrm{mean}}$ is more representative of the average tumour uptake and is less affected by image noise but can be prone to observer variability if freely drawn regions are used. Although the SUV formula has been criticised, the simplicity of the calculation makes it extremely attractive for routine clinical use.

Table 5.1 Properties of some radionuclides used in clinical PET imaging [1], [2]

Radionuclide	Half-life (min)	Average range (mm)	Positron fraction	Generator produced
Carbon-11	20.4	1.1	100	No
Nitrogen-13	9.96	1.5	100	No
Oxygen-15	2.03	2.5	100	No
Fluorine-18	110	0.6	97	No
Copper-64	762	0.6	18	No
Gallium-68	68	2.9	88	Yes
Rubidium-82	1.25	5.9	95	Yes

There is a wide range of positron-emitting radionuclides used in PET (Table 5.1). Many have a short half-life, which requires an expensive cyclotron production facility on the same site as the PET-CT scanner. Fluorine-18 has a slightly longer half-life, allowing it to be transported from the production facility to other imaging sites. This explains the popularity of fluorinated PET radiopharmaceuticals such as FDG. There are also longer half-life radionuclides such as copper-64 which allows imaging of pharmaceuticals with slower uptake kinetics. However, not all PET radionuclides require a cyclotron. Generators also exist, similar to the molydenum-99/technetium-99 m generator, which can produce PET radionuclides repeatedly on site. Gallium-68 and rubidium-82 are popular, short-lived, generator-produced PET radionuclides; gallium-68 comes from germanium-68 parent and rubidium-82 from strontium-82 parent.

Not all radioactive decays result in the emission of a positron; for example, with copper-64, only 18 % of decays produce positrons. This means that the sensitivity of the PET scanner to copper-64-labelled compounds is less than a fifth of that possible with fluorine-18. There may also be additional radiations resulting from the other decay routes or contaminants which can affect patient and staff radiation exposure and image quality.

The average range of the positron is important as it determines the distance the positron travels before the creation of the annihilation photons; this range is dependent on the initial energy of the positron following the radioactive decay. Because the positron moves through tissue in a random path, it is not possible to know the exact point in the tissue where the original decay took place. Spatial resolution in the images depends, to some extent, on the average range of the positron in that tissue. As a result, the spatial resolution of gallium-68 and rubidium-82 imaging will be worse than that from fluorine-18 tracers. The average positron ranges given in Table 5.1 are for soft tissue; the range of a positron will be much greater in air.

By far the most common radiopharmaceutical currently used in PET imaging is [F-18]FDG. Although FDG is a glucose analogue, it does not enter the glycolytic pathway after phosphorylation, but becomes trapped in the cell, allowing imaging of FDG concentration, which infers glycolytic rate. Both glucose and FDG are filtered by the glomeruli, but unlike glucose, FDG is not reabsorbed by the tubuli and therefore appears in urine. [F-18]FDG PET has become an important tool in oncology imaging for diagnosis and staging and to evaluate metabolic changes in tumours

at the cellular level. Although very sensitive for imaging many cancer types, it is also nonspecific, detecting many other physiological processes such as inflammation and infection.

5.3 PET Scanning

PET-CT imaging usually starts with a localising scan projection radiograph often known as a 'scout' or 'topogram' where the extent of PET scanning is defined. The patient then has a CT scan of this defined length that will be used for attenuation correction and possibly uptake localisation, before moving through the scanner bore for the PET scan. The axial PET field of view which defines the amount of body that can be scanned in one stop is normally around 15 cm, although systems are now available that scan 22 cm, or even 26 cm. For brain scanning or cardiac scanning, only one field of view is required; however, in oncology imaging where the extent of disease is often of interest, whole-body imaging can be performed. This is typically done by acquiring several fields of view with a slight overlap to allow for the detector sensitivity losses at the edges of the field of view (Fig. 5.4). Each of these

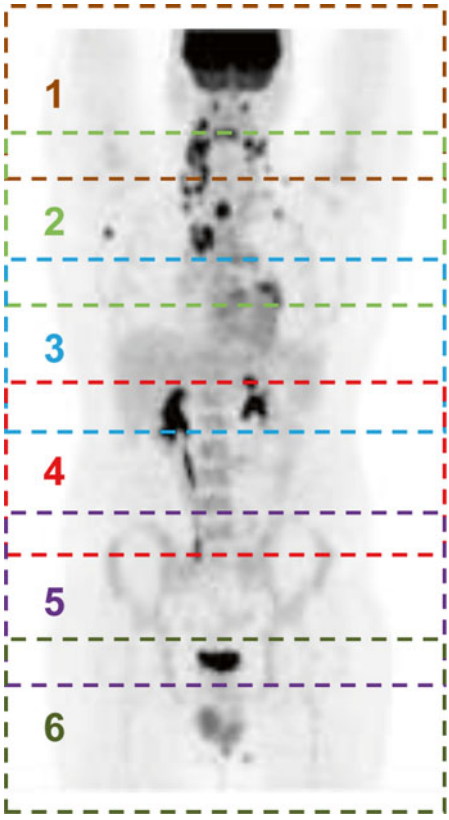

Fig. 5.4 A whole-body image is made up of multiple bed positions that are stitched together; in this example, six acquisitions are required to cover the desired length of the patient

fields of view are called a bed position, and the time of each scan at these bed positions can be between 1.5 and 5 min in duration, depending on the affinity of the radiopharmaceutical and the sensitivity of the scanner. Patients should be made comfortable and immobilised when necessary to keep the patient in the same position to maintain registration between the PET and the CT used for attenuation correction and localisation and limit movement artefacts.

For some applications, dynamic PET imaging over a single bed position can be useful to understand patient physiology. However, it is more typical to start PET imaging after a fixed period of time; this uptake or resting time is determined by the physiological uptake and excretion of the administered tracer with the aim to scan at the optimum time to have a good uptake in the target tissue with a low background circulation of the tracer in the rest of the body. For repeat imaging to assess disease progression, it is important to keep this uptake time duration similar for successive imaging, typically within +/– 5 min.

5.4 Imaging with [Fluorine-18]FDG PET

The patient must arrive well hydrated and have fasted for between 4 and 6 h to ensure blood glucose levels are low prior to injection with FDG. This is to ensure that there is limited competition between FDG and existing blood glucose, so that uptake of FDG is maximised in order to give the best possible image quality. Care needs to be taken with diabetic patients. A patient history should be taken to determine when the patient last had radiotherapy or chemotherapy. FDG uptake can be elevated as a reactive response to these treatments. It is also important to remember that FDG can be sensitive to inflammation/infection, so a general understanding of the patients' wellbeing and history of recent physical trauma (including biopsy) is necessary. For SUV calculations, patients' weight (and height if correcting for lean body mass) should be taken with reliable calibrated instruments to ensure accurate quantification of uptake. Injection of FDG should be intravenous through an indwelling cannula and the clocks used to record the injection and scan times should be calibrated; any discrepancies in the recorded times can lead to errors in the decay correction used for quantification of the uptake. All PET tracers are beta emitters (a beta particle is a high energy electron or positron), so particular care should be taken to reduce the likelihood of extravasation and local radiation burden. To assist in the quantification of FDG uptake, the exact injected activity of FDG should be recorded.

Imaging typically starts at 60 min post injection, and the patients must rest and be kept warm during this uptake period to avoid unwanted muscle or brown fat uptake. Patients are asked to void prior to imaging to reduce the activity in the bladder; full bladders containing high activity of FDG can cause difficulties in interpreting the images around this region and also increases the radiation dose to staff while the patient is positioned on the scanner bed. A multiple bed-position whole-body scan is normally performed from mid-thigh up to the base of the brain. FDG is processed via renal excretion, so it is important where possible to scan in this direction

to avoid scanning a bladder that has refilled with FDG during the scan. With the patient lying supine, whole-body imaging is performed with the arms raised above the patient's head to avoid CT beam hardening artefacts and to ensure that the patient's body fits within the transaxial field of view. If head and neck imaging is required, an additional arms down scan over the head and neck area can be helpful to reduce attenuation in this area.

5.5 Artefacts

There are several artefacts that can occur in PET imaging even when all reasonable precautions are taken. One of the hardest artefacts to control is due to respiratory motion that can occur if the patient takes a large breath hold prior to or during the CT. As can be seen in Fig. 5.5(a), the result can be a banana-shaped artefact caused by mismatch of PET and CT used for attenuation correction at the base of the lung and dome of the liver. The easiest way to avoid these artefacts is to ensure that the patient is relaxed prior to imaging and asking them not to take any large intakes of breath – particularly during the CT. Other motion-related artefacts are standard patient movement such as that seen in Fig. 5.5(b). Relatively common in head and neck imaging, the mismatch of CT and PET can lead to incorrect attenuation correction and difficulty in localising features. Making the patient feel relaxed, helping

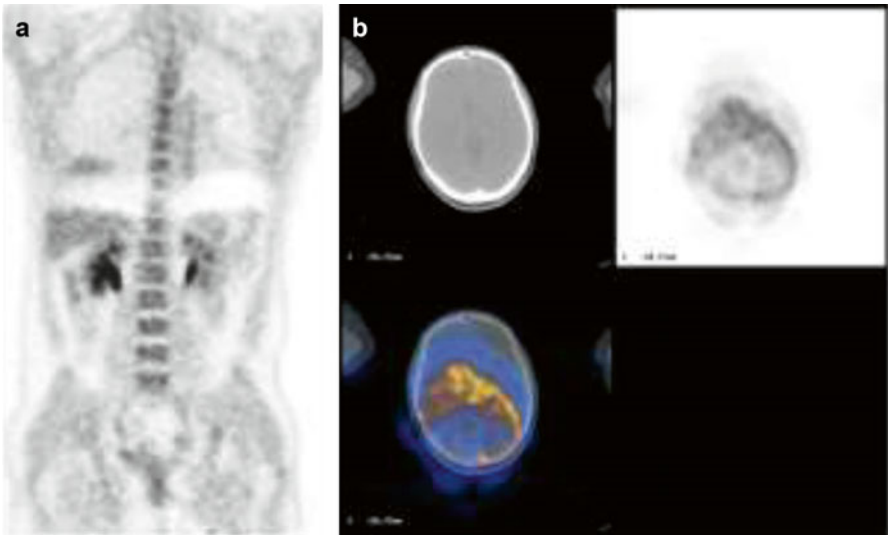

Fig. 5.5 (**a**) Respiratory motion artefact seen at the dome of the liver caused by mismatch of PET and CT for attenuation correction. (**b**) Patient motion between CT for attenuation correction and PET leading to poor correction for attenuation and localisation of tracer uptake

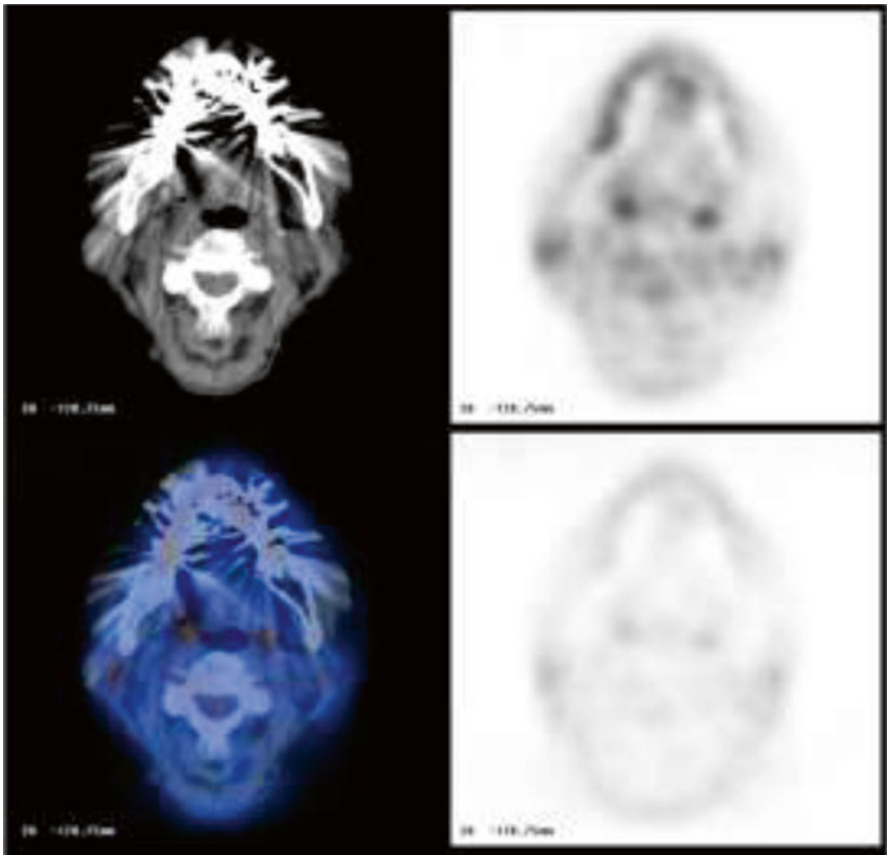

Fig. 5.6 Beam hardening artefacts on CT caused by dental amalgam. PET quantification and localisation can be difficult although non-attenuation corrected data (*bottom right panel*), may help with identifying artefacts in the attenuation corrected images (*top right panel*)

them understand the need to remain still and appropriate immobilisation can help reduce the likelihood of these artefacts.

An artefact that cannot be easily controlled is the CT x-ray beam hardening, and subsequent streaking aretefacts in the CT image, produced by metal prosthesis typically in the hip, or where the patient has metal dental work (Fig. 5.6). Many modern systems have algorithms that can help minimise these effects. Nevertheless, care must be taken when quantifying uptake in affected areas because inaccuracies in the attenuation map derived from the CT data can lead to inaccuracies in PET quantification. Another area where attenuation correction can fail is when CT contrast has been used. The conversion of the attenuation map derived from CT x-ray energies to attenuation values at PET photon energies can fail in areas of CT contrast accumulation. This is due to the elevated attenuation of contrast media, such as iodine and barium, at the lower x-ray energies due to the k-edge absorption peak; this peak does not affect the absorption of the 511 keV PET photons. As the reconstruction

algorithm cannot distinguish between tissue that has a high density and less dense tissue containing CT contrast, the attenuation correction over corrects areas containing contrast. This again can lead to errors in PET quantification. If quantification is particularly important, e.g., in a trial setting, the contrast CT should be performed last after the PET data is acquired, and the attenuation correction should be performed using a low-dose CT acquired before the contrast administration.

An important tool to identiy many artefacts introduced during the attenuation correction process is the reading of PET images without attenuation correction. Although these images are then not quantitative, they can be useful to highlight areas of artefact and to assess disease within the patient.

Careful consideration of radiation protection is important due to the high-energy annihilation photons. Over ten times the thickness of lead is required to shield PET photons compared to 140 keV photons, and, immediately post injection, the dose rate from a patient administered with fluorine-18 is ten times that of a patient administered with the same activity of technetium-99 m. Extremity dose to staff can be high when handling PET tracers due to the positron radiations.

The short physical half-lives of PET tracers result in a lower patient dose than might be expected. A typical administered activity of 350 MBq [F-18]FDG corresponds to an effective dose of approximately 7 mSv, and with ongoing improvements in PET detector technology and reconstruction methods, both imaging times and typical administered activities are decreasing. The required level of CT image quality (and therefore effective dose) depends on the use of the CT data. When the CT data are used solely for AC, patient doses can be extremely low (< 1 mSv). A notable improvement in image quality (and dose increase) is required if the CT data are to be used for AC and anatomical localization (typically 3–8 mSv), and a further increase in both image quality and dose is required if the CT images are to be used for diagnostic purposes, usually with the addition of contrast agents (typically > 15 mSv).

Key Points

- Positron emission tomography (PET) is the imaging of radiopharmaceuticals labelled with positron-emitting radionuclides.
- Positron decay leads to two 511 keV photons following annihilation of the emitted positron and a nearby electron.
- $E = mc^2$. Positron mass $= 9.109 \times 10^{-31}$ g, speed of light $= 2.9979 \times 10^8$ m/s, 1 eV $= 1.6 \times 10^{-19}$ J. You know you want to do the calculation.
- A PET scanner is composed of several rings of scintillation detectors.
- Coincident detection of the two photons in different detectors allows an image to be formed from information gleaned by tracking ‘lines of response’ between these detectors.
- TOF helps localise the point of origin of the annihilation event along the line of response. This helps to decrease noise, and thereby improve signal to noise ratio.

- The sensitivity of the scanner drops towards the edges of the axial field of view of the detectors. Adjacent bed positions need to be overlapped to account for this.
- A semi-quantitative index, the standardised uptake value (SUV) is commonly used in clinical PET.
- Several values of SUV can be quoted; the most common being SUV_{max} which is relatively robust, as it is less affected by the observer than SUV_{mean}, but it is strongly affected by image noise.
- SUV_{mean} is more representative of the average tumour uptake and is less affected by image noise but can be prone to observer variability.
- To assist in the quantification of FDG uptake, the exact injected activity of FDG should be recorded.
- For SUV calculations, patients' weight (and height if correcting by lean body mass) should be taken with reliable calibrated instruments to ensure accurate quantification of uptake.
- SUVs are affected by changes in reconstruction techniques and can vary between scanners; it is only semi-quantitative.
- Careful patient preparation is important to obtain good-quality PET images.
- All PET tracers are beta emitters, so particular care should be taken to reduce the likelihood of extravasation and local radiation burden.
- There are several artefacts that can occur in PET imaging even when all reasonable precautions are taken; knowledge of these is important when interpreting images.
- The effects of photon attenuation are more dramatic in PET, and attenuation correction is essential.
- A typical administered activity of 350 MBq F-18 FDG corresponds to an effective dose of approximately 7 mSv.
- Radiation doses to staff are much higher when exposed to PET tracers than from similar activities of other technetium-based nuclear medicine tracers.

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