Chapter 1
Introduction

This introduction outlines what this book is about and just as importantly what it is NOT about. The fact is, if you want to stay up to date in medicine, you cannot avoid PET/CT. This discipline is exploding at the moment with new scanners being placed in hospitals all over the United States and throughout Europe. You can run but you can't hide from the impact this new technology is making, particularly within oncology but increasingly in many other medical disciplines.

This handbook offers a starting point for anyone interested in learning a little about PET/CT. The text is relatively straightforward and the book is stacked full of interesting images. We assume no background knowledge of the subject and give an enthusiastic, well informed basic introduction. This is PET/CT 1.1, nothing more and nothing less.

If you already have an interest in this field and a working knowledge of PET/CT, I would recommend buying a copy of Jadvar and Parker's excellent book *Clinical PET and PET/CT* (ISBN: 1-85233-838-5). Their small handbook is a great stepping stone for those who have attained a basic grasp of the subject, and the authors delve more deeply into the science of PET than I can in this book. No department should be without Sally Barrington's excellent, award-winning new PET/CT atlas. There are many other fine textbooks worthy of mention but few are aimed at individuals with little or no background in nuclear medicine and PET/CT.

Are you a radiologist or nuclear medicine physician with little or no experience with PET/CT? Are you experiencing more and more exposure to this subject at multidisciplinary meetings?

Are you a physician or surgeon with an interest in any of the following cancers? *Lung, Lymphoma, Gastro-oesophageal, Colorectal, Head and neck, Melanoma or Genitourinary*.

Are you about to acquire a PET/CT scanner in your hospital?

Are you a resident or medical student keen to learn about the latest technology?

If the answer to any of these is yes, then this book can provide a useful starting point for you.

The aim is to inform readers about the role of PET/CT in the big six cancers: lung, lymphoma, esophageal, colorectal, head/neck, and melanoma. Brief mention is also made of gynecological, and testicular cancer. The physics involved is skipped over lightly (Chapter 10), and an outline of normal and common variant uptake is included in Chapter 9.

Each big six chapter contains a summary of the associated staging scheme. The most common staging system used is the TNM (tumor, node, metastases); this will be familiar to most readers. In some tumor types, other staging schemes are used and these will be outlined within the relevant chapter. I hope to show how PET/CT fits into the staging process, where it is best used and, just as importantly, where it should not be used. This book contains a significant number of images and case scenarios to illustrate the use of PET/CT.

Throughout this book reference is made to PET/CT, but this is a misnomer. What I really mean is FDG-PET. FDG is only one of many radioactive tracers that can be used in PET/CT, but it the one most widely used in oncology imaging and the only tracer that is discussed in this book. For all intents and purposes, throughout this book, PET/CT means FDG-PET/CT.

WHAT IS PET AND PET/CT?

PET (Positron Emission Tomography) is an imaging modality that identifies the presence of a metabolically active tumor within the body after injecting a radioactive substance called FDG. This localizes within areas of metabolic activity around the body and emits radiation that allows us to image the distribution of metabolism, a so-called functional image. A CT (computed tomography) scan uses X-rays to provide an anatomical image of the patient. A PET/CT machine is a single device that combines both modalities to produce an image that shows the metabolic functional information from the PET image and the anatomical information from the CT scan. The resultant data is displayed as a combined, or fused, PET/CT image.

Top Tip

PET + CT = PET/CT
Metabolic function + Anatomy = Fused image

Before we begin to discuss the nature of PET/CT imaging, I would like to consider the basic cellular metabolism involved in tumor growth. From a simplistic point of view, tumors want to divide, multiply, grow, and invade their surroundings. If possible they will spread to distant sites and repeat the same process.

To achieve this objective, the tumor must have an energy source capable of fueling this division and growth. Otto Warburg, a German Biochemist noted more than 80 years ago that many tumors use glucose as their primary energy substrate for this process. As tumors grow, they often become starved of oxygen and, therefore, anerobic metabolism of glucose becomes easier to sustain than aerobic metabolism within the Tricarboxylic acid cycle. The result of this is increased utilization of glucose within tumor cells in relation to most other cells.

Of course normal cells also use glucose for their day-to-day function but in general the glucose uptake in most normal cells is relatively low. Active tumors tend to have a much greater metabolic rate than most normal cells and consequently use considerably more glucose.

Some cells within the body can use several different energy sources to fulfil their metabolic needs. Cardiac muscle, for example, preferentially uses free fatty acids as an energy source, but it can also use glucose, lipids, or amino acids if required. As a result, the glucose uptake within the heart varies among people and can change considerably within an individual over a short period in relation to the blood glucose. Brain cells do not have the ability to use any fuel other than glucose and consequently the glucose activity within the brain is always high.

Top Tip
Tumor cells often use more glucose than normal cells.

In a fasting state, most body tissues (with the exception of the brain) actually use free fatty acids as their preferred energy source. After a glucose rich meal, these will temporarily switch from free fatty acids to glucose metabolism because they are under the influence of rising insulin levels.

The uptake of glucose into cells is facilitated by transmembrane proteins called glucose transporters. At least 12 different glucose transporters have been identified and are known as GLUT 1, GLUT 2, and so on. When the glucose molecule enters the cell, it is phosphorylated under the influence of the enzyme

hexokinase. The resultant compound is called glucose-6-phosphate. Under normal circumstances, the glucose-6-phosphate will undergo further enzymatic change and be converted into energy, a process called glycolysis. Alternatively the glucose-6-phosphate may be stored as a future energy reserve in the form of glycogen, a pathway called glycogensis, or it may possibly be converted into either lipid or protein form.

The increased energy demands of a dividing tumor cell necessitate a faster and more efficient delivery of glucose to allow rapid growth. As the cellular division and growth proceed, the tumor cell finds ingenious ways of meeting its energy requirements. Firstly, the cell will increase the number of transmembrane GLUT transporters to aid glucose delivery. If this is still insufficient to meet demand, the cell can increase the rate of phosphorylation by upgrading hexokinase activity. The resultant effect is that many tumor cells demonstrate marked increases in glucose metabolism when compared to normal cells (see Figure 1.1).

Metabolic Changes in Tumor Cells
Increased cell division
Increased glucose turnover
Increased activity of glucose transporters
Increased hexokinase activity

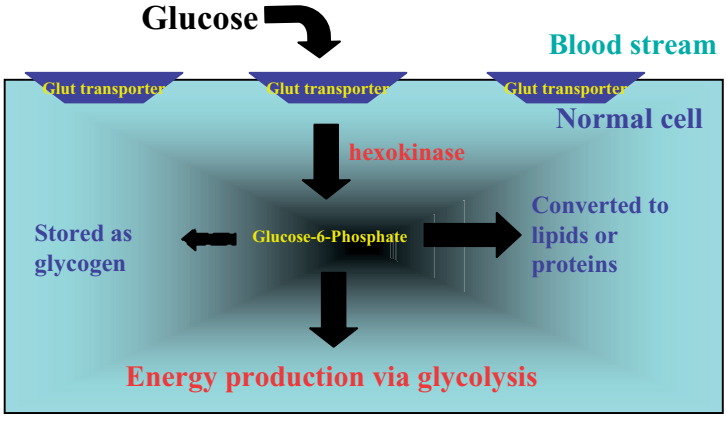


FIGURE 1.1. Uptake and metabolism of glucose in a normal cell

HOW CAN WE IMAGE GLUCOSE METABOLISM?

Fluro-deoxy-glucose (FDG) is an analog of glucose that is labeled to the radioactive positron emitter Flourine-18. The FDG is injected intravenously and is taken up by normal and tumor cells alike in a fashion similar to glucose. In fact, FDG and glucose actively compete with each other for cellular uptake and transport using the GLUT transporters.

When within a cell FDG will be converted into FDG-6-phosphate under the action of hexokinase. The pattern of uptake and phosphorylation being identical for both glucose and FDG. Beyond this point however their pathways diverge, whereas glucose is converted into either energy or stored as glycogen, FDG undergoes no further reaction and by in large remains trapped in the cell.

FDG is a radioactive substance and emits radioactive particles called positrons (see Chapter 10 for a basic description of the physics involved in PET/CT and a brief mention of some other positron emitters and their possible medical usage). FDG has a half-life of approximately two hours, meaning that the amount of radioactivity within the body will halve every two hours. Practically speaking. this means that approximately 3% of injected activity will remain in the patient after 10 hours (or 5 half-lives).

The distribution of radioactivity within the body can be imaged using a specialized camera called a PET scanner. The resultant image gives a picture of the areas of the body which have FDG (and therefore glucose) uptake. The intense accumulation of FDG within many tumor cells allows those cells to be identified when compared to the less intense uptake in normal cells. Patients are imaged in the fasting state because most normal cells will continue to use free fatty acids as their energy substrate. FDG will primarily be taken up into tumor cells as these cells often lack the ability to effectively use other substrates for energy production (see Figure 1.2). Figure 1.2 is a PET scan showing the normal distribution of glucose (as identified by FDG uptake). This image is called the maximum intensity projection image or MIP and is the 2 dimensional representation of the accumulation of FDG uptake in the body as a whole. The appearances are sometimes likened to that of a glass man.

We can see that the brain has intense uptake, with less marked uptake in the heart, liver, and spleen. What we also see is intense uptake in the renal system, kidneys, ureters, and bladder. As you will be aware, normal individuals do not excrete glucose through the renal system, but FDG is excreted renally. We must remember that FDG is not glucose; it is only an analogue of glucose, and it

FIGURE 1.2. The distribution of FDG within a normal individual (MIP).

is handled in a different way than normal glucose. Whereas most normal glucose is freely filtered within the renal glomeruli and rapidly reabsorbed by the nephron, the FDG filtered is poorly reabsorbed and a large proportion is excreted in the urine.

Top Tip
FDG distribution reflects the glucose metabolism in the body (except for the renal system).

As explained earlier the cardiac uptake of glucose can be variable. Figure 1.3 shows a different patient with more intense cardiac uptake (which can indicate a recent glucose meal). In addition this patient shows bilateral uptake in the neck muscles, a common finding in tense patients and representative of physiological glucose uptake due to muscular contraction.

FIGURE 1.3. Normal MIP with more intense cardiac and physiological neck muscle uptake.

Figures 1.4–1.8 are examples of abnormal scans, with the abnormality highlighted by arrows.

It is difficult to believe that the patient in Figure 1.8 had a normal CT scan of the chest, abdomen, and pelvis. The patient had a previous history of colorectal cancer and had a recent rise in tumor markers. The PET/CT scan revealed multiple bony deposits as well as an unsuspected subcapsular liver secondary.

Figure 1.9 is an axial image through one of the bony vertebral metastases identified on the MIP image seen in Figure 1.8. The CT component is viewed in the top left hand corner and the PET in the top right. The more intense the FDG (or glucose) uptake the blacker it appears on the PET scan. The fused PET/CT scan is seen in the bottom left hand corner of the image. This image combines both the anatomical data from the CT and the metabolic data from the PET; the color scale chosen shows the FDG uptake as increasingly orange with increasing activity. Technology allows the PET and CT images to be viewed separately or as a combined PET/CT or "fused" image. In this case the normal appearance of the CT scan hides the fact that a metastatic deposit exits in the vertebral body. This patient had multiple osseous metastases that were not identified by CT and only some of which were found on a subsequent MRI scan.

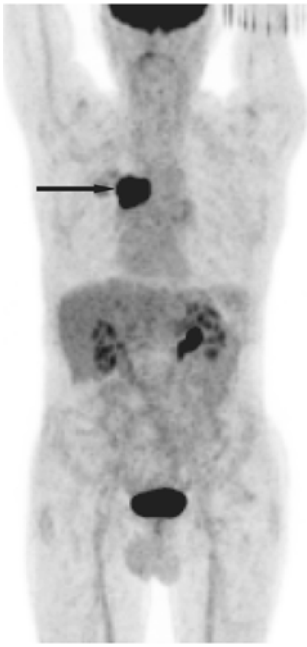


FIGURE 1.4. A FDG positive right hilar squamous cell carcinoma.

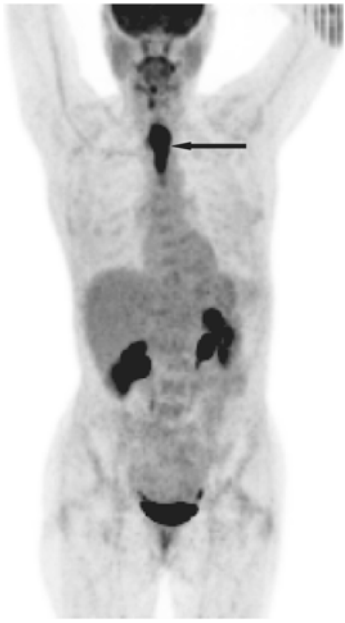


FIGURE 1.5. An upper oesophageal squamous cell cancer.

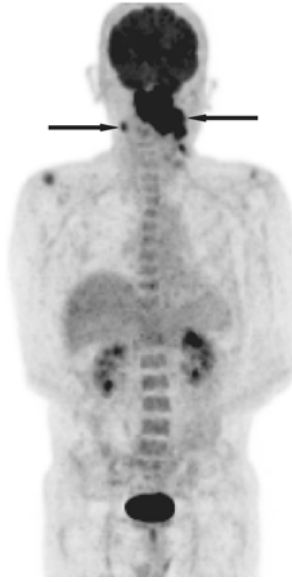


FIGURE 1.6. A nasopharyngeal lymphoma with bilateral neck node involvement.

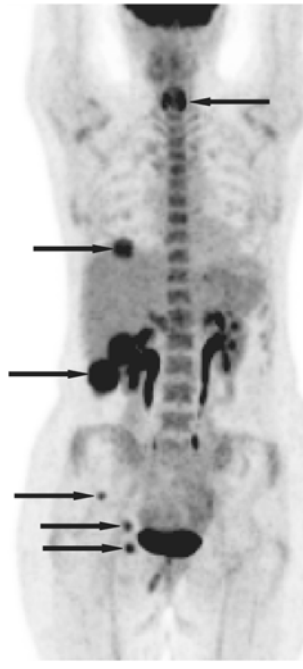


FIGURE 1.7. Recurrent colorectal cancer with metabolically active deposits in the liver and right hemipelvis. The uptake in the neck is due to a coincidental thyroiditis.

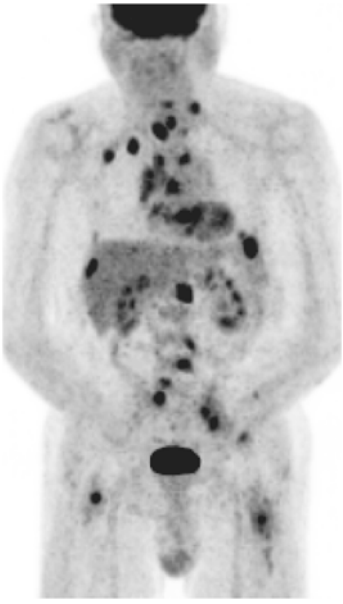


FIGURE 1.8. Multiple bony metastatic deposits.

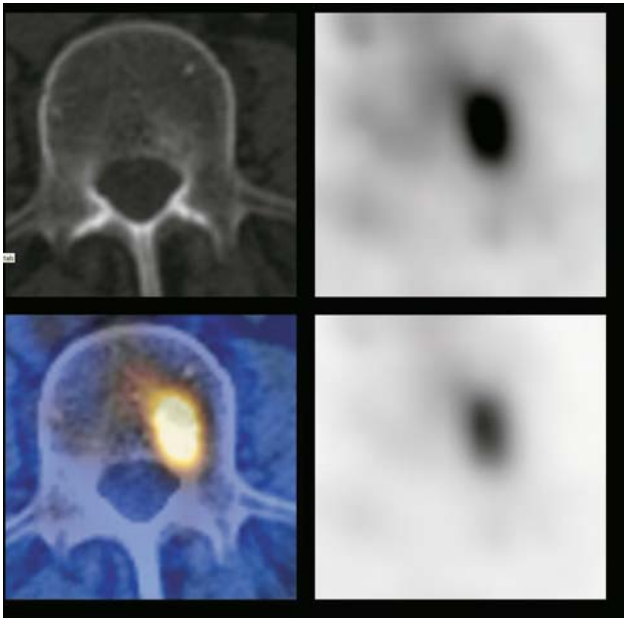


FIGURE 1.9. An axial image through one of the bony vertebral metastases seen in Figure 1.7.

NORMAL SCANNING PROTOCOL AND DESCRIPTION OF IMAGING SEQUENCE

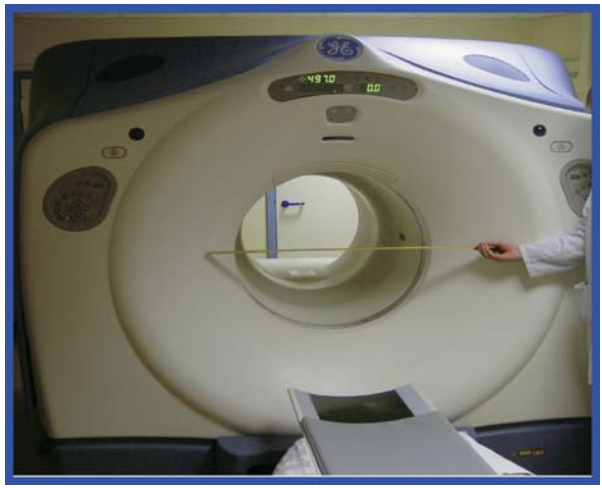
Patients should arrive at the nuclear medicine department having fasted for at least four hours. This ensures that most tissues are using free fatty acids as their energy source. Diabetic patients are advised to take their normal insulin or medication prior to arriving at the department.

After the staff have made all the necessary patient checks, including correct patient identification and a check of blood glucose level, the injection of radioactive FDG can take place. The patient is advised to lie still for approximately 45 minutes to allow the FDG time to accumulate in metabolically active cells. Any unnecessary patient movement during this uptake period can result in muscular uptake which can cause confusion with later scan interpretation. Patients who are tense during this time often show physiological uptake within the muscles of the neck. Some other patterns of normal uptake are illustrated below and a list of normal and variant uptake is found at the end of this chapter.

Following the uptake period, the patient is taken into the scanning room and lies supine on the table. A picture of a GE discovery lightspeed PET/CT scanner is shown in Figure 1.10. The CT scan is performed first, normally without intravenous contrast but increasingly after the administration of oral contrast to outline the normal bowel. The CT scan is normally carried out from the base of skull to mid-thigh level, the so-called half body scan. The reasons for this are:

- Brain metastases are difficult to detect using FDG as any brain lesion must have an intensity greater than or less than the surrounding brain tissue to be identified.
- Generally speaking, few tumors that have metastatic deposits that disseminate to the distal lower limbs.
- There is a decreased radiation burden to the patient.
- There is a considerable amount of time saved if we do not have to perform a whole body scan.

Whole body scans are carried out in some patient groups. For example, patients with melanoma have a whole body scan from skull vertex to feet. This is because of the widespread and unpredictable lymphatic dissemination that characterises this disease. A similar problem is encountered with the pattern of disease spread in non-Hodgkin's lymphoma, which often requires a larger scanning volume.



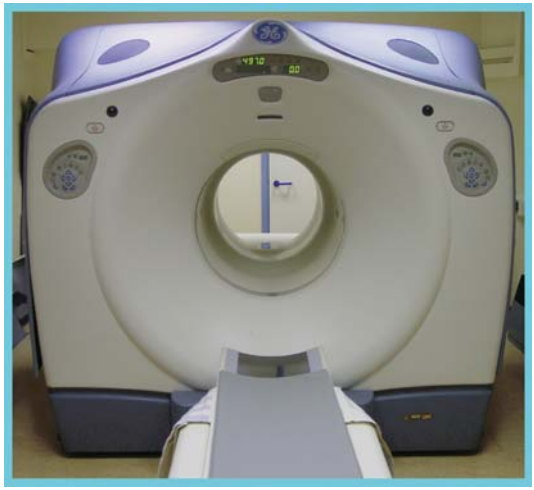


FIGURE 1.10. GE PET/CT scanner.

Patients with head and neck disease often have scans that include the entire skull, and patients with soft tissue sarcomas may also require additional views. After the CT images are acquired (which only takes a minute or so when using a modern multislice scanner), the patient is then scanned again using the PET component of the machine. The detectors on the PET scanner can identify radioactive emissions from the FDG within the body. A ring of detectors surrounds the patient. This ring is

approximately 15 cm long, and images are therefore acquired in blocks of 15 cm from the base of the skull to mid-thigh. In most individuals, this area is covered in about 5 blocks (approximately 75 cm); taller or shorter individuals will take more or less imaging time. The time required for each 15 cm image of the patient is between 3 and 5 minutes. This means that the PET component of the study can take at least 45 minutes to acquire. Any patient movement during this time will degrade the quality of the images obtained.

After the PET scan has been acquired the patient is free to go but is given warnings about exposure to individuals during the next few hours as the radioactivity decays and is excreted from the body.

Figure 1.11 is another axial image in a patient with lymphoma who had received chemotherapy. The clinician wanted to out rule residual active disease. As you can see, there is a metabolically active soft tissue mass in the left axilla which was later shown to be residual follicular non-Hodgkin's lymphoma.

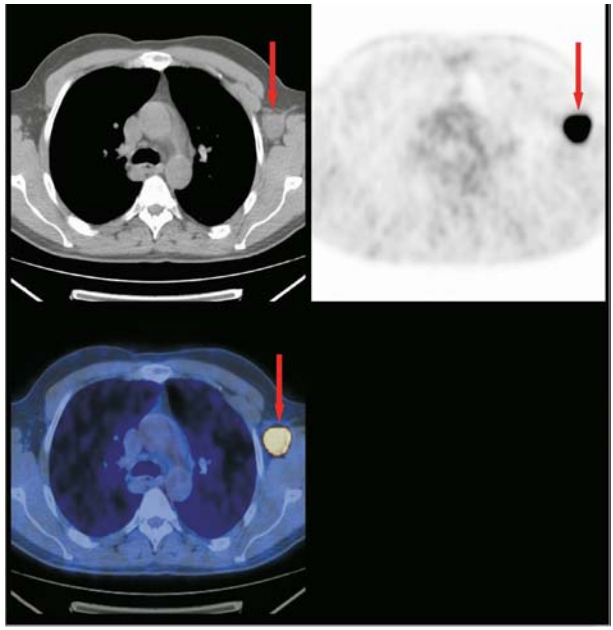


FIGURE 1.11. An axial image. Top left: CT image showing a 3 cm nodal mass in the left axilla (red arrow); top right: PET scan showing intense uptake; bottom left: fused PET/CT image shows active nodal recurrence in a patient with previous follicular non-Hodgkin's lymphoma.

Standardized Uptake Value

A semiquantitative method is available to calculate the intensity of FDG uptake within a range of interest on the PET scan. This value is called the Standardized Uptake Value (SUV) and takes account of such factors as injected activity, patient weight, and time from injection. Simply speaking, the SUV assumes that if there is an even distribution of radioactivity throughout the body the SUV would be measured as 1. Obviously this is not the case, but we can calculate the relative uptake within different parts of the body and relate them to each other. An area with an SUV of 5 means this area has five times the average uptake. Certain modifications can be made to the SUV calculation to take into account, for example, the patient's body fat (since FDG is not generally taken up into fatty tissue).

The SUV allows comparisons to be made between different parts of the body and between different scans on the same patient over a period of time. It must be emphasized that the SUV is only a semiquantitative measurement and can vary considerably with changes in patient's plasma glucose levels.

Many clinicians prefer to avoid numbers and simply use visual interpretation to compare the intensity of one area to another suing the background blood pool as a guide to normality. There is evidence to suggest that both methods are equally accurate. Figures 1.12 and 1.13 demonstrate the change in intensity of an esophageal tumor following chemotherapy

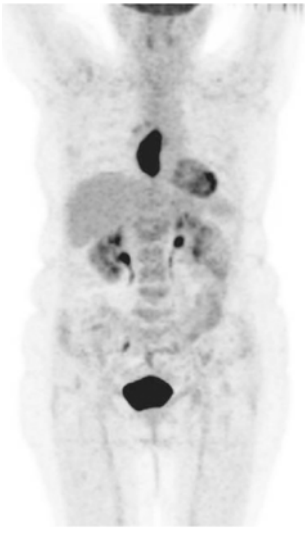
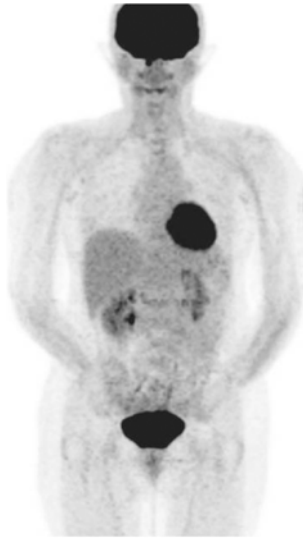


FIGURE 1.12. Pretherapy SUV 15.

FIGURE 1.13. Posttheray SUV 2.



the maximum SUV had decreased from 15 pretherapy to 2 post-therapy. Recent literature would suggest a response of this magnitude correlates with a better prognostic outcome.

List of Normal and Variant Uptake

See Chapter 9 for a list and illustrations of common patterns of normal uptake and examples of some variant uptake.

NOTE ON ILLUSTRATIONS

Please note that throughout this book the above orientation is used on all axial images. Top left corner is the CT image; bottom left the fused PET/CT and top right is the PET image. There are however some images that contain a fourth image in the bottom right corner. This appears very similar to the PET image above it. The bottom right image when present is the nonattenuated correction image and is slightly different from the PET image above it (top right) which represents an attenuation corrected PET image, (see Chapter 10 for a more detailed explanation).