Advances in Medical Radiation Imaging for Cancer Diagnosis and Treatment

A. Introduction

1.   Cancer management requires reliable diagnosis in order to identify the primary tumour and assess its dissemination to surrounding tissues, as well as to other organs and structures throughout the body. This process, technically called 'staging', is of paramount importance in deciding the therapeutic approach to be taken, since staging dictates prognosis and consequently therapy. Imaging by means of radiation medicine techniques is usually the first step in clinical management and diagnostic radiology and nuclear medicine studies play important roles in screening, staging, monitoring of treatment, and in long term surveillance of cancer patients.

2.   Until a few decades ago, medical imaging was dominated by planar (projection view) X-ray radiography aimed at detecting changes in tissue density that may result from disturbances in cell function, possibly due to cancer. More recently, as a result of improvements in computer technology applied to imaging, digital techniques were introduced into medical radiation imaging. Powerful diagnostic tomographic (cross-section view) modalities were made available to clinicians, namely X-ray computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) (see Fig. 1). Diagnostic radiology techniques such as CT and conventional MRI depend on structural or anatomical abnormalities to detect disease whereas nuclear medicine techniques, in particular PET, and to some extent advanced MRI techniques, have the ability to detect cancer based on molecular and biochemical processes within the tumour tissue.
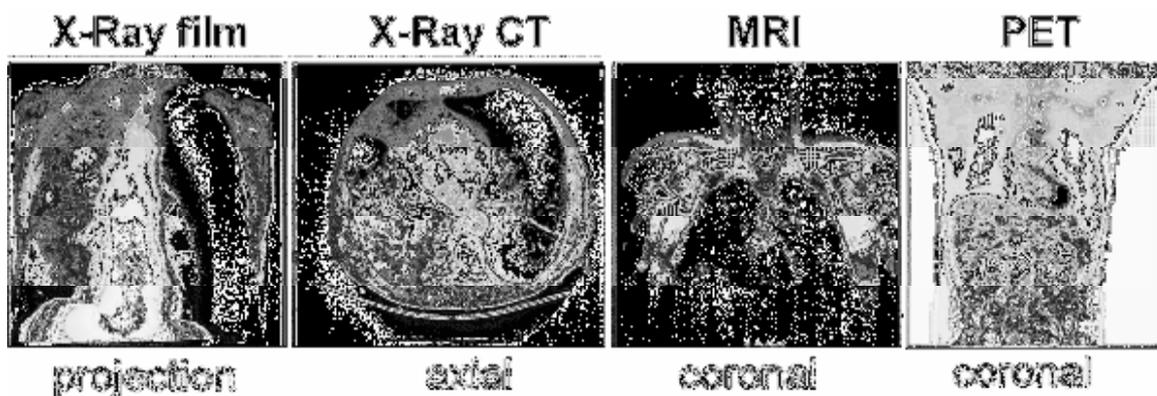

Figure 1. Overview of the most common medical imaging techniques. From left to right, the images correspond to the classical planar X-ray radiography (projection view), and to the tomographic images (cross-section view) created by X-ray computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET).

3.   The capacity of X-ray, CT and MRI to detect millimetre-sized abnormalities is greater than that of nuclear medicine techniques, but the ability of nuclear medicine to highlight functional abnormalities complements the resolution of CT and MRI. Owing to the inherent resolution limitations of nuclear medicine, its imaging applications, initially unique for many diseases, have either been fully substituted or much less employed for some years, particularly those modalities aimed at investigating

anatomic structure in cancer management. Instead, new applications appeared to be specifically aimed at in vivo detection of abnormalities in processes that cannot be effectively investigated in other ways. Among these, some examples are SPECT imaging of myocardial perfusion (blood supply to the heart muscular tissue) during physical or pharmacologic stress, receptor expression and density at the cellular level and antigen expression in cancer cells.

4.   The following review will briefly describe these techniques, including MRI and ultrasound (US), which, since they utilize non-ionizing electromagnetic radiation and sound waves respectively, are not ordinarily considered part of radiation medicine, but their role is so important that they cannot be excluded. The main focus, however, will be given to PET, one of the most powerful diagnostic techniques that has appeared in the last 10 years, which after the appearance of hybrid machines (PET-CT scanners) gave this technique a very important role to play in cancer management. It will not replace CT as first-line investigation, because of its cost and resolution limitation, but it appears to be very helpful in situations where CT does not provide all the information required by clinical oncologists. These could be: differentiating tumoural masses from benign lesions; identifying lymph nodes already invaded by cancerous cells; differentiating residual tumour or local tumour relapses from scarring and necrosis and detecting unsuspected distant metastases (Fig. 2) that would affect patient prognosis and treatment. The ability of PET, and other upcoming techniques, to investigate diseases at the molecular level will produce a 'molecular imaging revolution' which will lead to a much greater ability to characterize diseases, diagnose them at a very early stage, treat them effectively, and monitor the clinical outcome of such treatment.
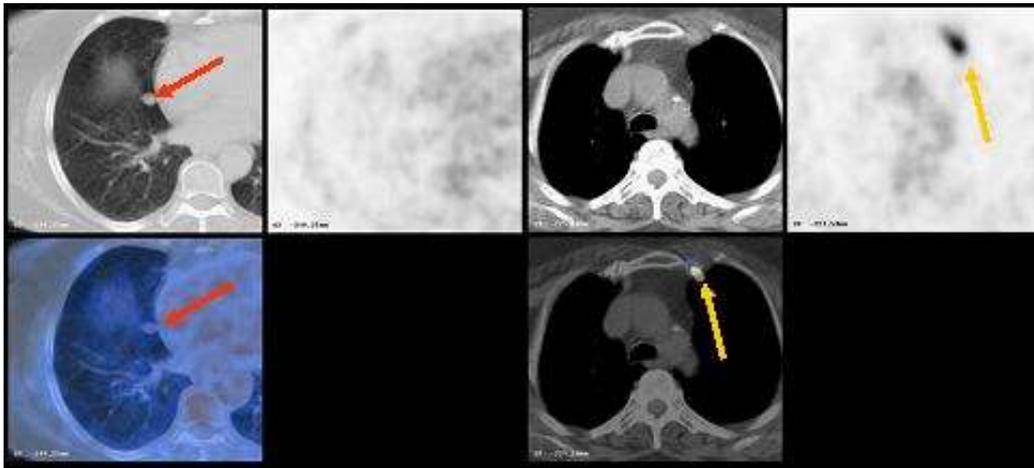

Figure 2. Breast cancer suspected of recurrence. CT identifies a possible metastasis in the right lung (yellow arrows) that does not show any FDG (see para. 20) uptake in PET imaging. PET, on the other hand, identifies an unknown metastasis on the contra-lateral side (red arrows).

B. The Role of Medical Radiation Imaging in Cancer Management

5.   Cure rate in cancer patients is strongly dependent on the stage of the disease at the time of its diagnosis, and early detection remains a key issue. In medical imaging, early detection depends on many factors, including spatial resolution, i.e. the ability to discriminate cancer lesions from normal tissue when their volumes are still very small. A considerable range of spatial resolutions can be

achieved within the spectrum of medical imaging. They range from fractions of a millimetre in MRI and CT to a few millimetres in PET and several millimetres in SPECT.

6. Although the distinction is somewhat arbitrary, medical radiation imaging techniques can be divided into anatomical (structural) and functional. Imaging can be called anatomical to the extent that it reports on macroscopic pathology, guides decisions based on disease stage, has tissue biopsy as its reference standard, and provides information regarding surgical decisions. In contrast, functional imaging has the ability to detect cancer based on molecular and biochemical processes within the tumour tissue, in some cases prior to any tissue alterations becoming detectable using anatomical imaging.

C. Structural Imaging

C.1. X-ray Computed Tomography (CT)

7. The most important imaging technique in detecting and diagnosing cancer remains X-ray CT, which is based on the principle that when X-rays pass through the body they are absorbed or attenuated at differing levels, according to the density and atomic number of the different tissues, creating a matrix or profile of X-ray beams of different strength. This X-ray profile is registered on a detector, thus creating an image. Radiographic film has been the main medical radiation imaging detector for many years, and is now being replaced by digital X-ray detector types. In the case of CT, the film is replaced by a detector which measures the X-ray profile. Inside the CT scanner is a rotating frame that has an X-ray tube mounted on one side and the detector mounted on the opposite side. A fan beam of X-rays is created as the rotating frame spins the X-ray tube and detector around the patient. Each time the X-ray tube and detector make one complete rotation, an image or slice is acquired. This slice is collimated (focused) to a thickness that ranges from less than 1 mm to 10 mm using special diaphragms in front of the X-ray tube and X-ray detector. As the X-ray tube and detector make this rotation, the detector takes numerous snapshots (called profiles) of the attenuated X-ray beam. Typically, in one lap, about 1000 profiles are sampled. Each profile is then backwards reconstructed (or back-projected) by a dedicated computer into a two-dimensional image of the slice that was scanned.

8. Since its development in the early 1970s, CT has become the standard for the evaluation of patients with malignancies because of its excellent definition of anatomical details. The slip ring technology and faster computer systems have laid the foundations for helical data acquisition, allowing fast volumetric scanning and multiphase enhancement techniques. State-of-the-art multi-slice helical CT permits fast acquisition of volumetric and CT angiographic images, and spiral CT scanners can now image entire anatomic regions, such as the lungs, in 20 to 30 seconds (Fig. 3). Instead of acquiring a stack of individual slices that may be misaligned due to slight patient motion or breathing (and lung/abdomen motion) between each slice acquisition, spiral CT acquires a volume of data with the patient anatomy all in one position. This volume data set can then be computer-reconstructed to provide three-dimensional pictures of complex structures. The resulting 3D CT images allow medical physicists and radiation oncologists to visualize tumour masses in three dimensions, which help them plan the treatment. Recently, to overcome problems imposed by respiratory movements, respiration-correlated, or 4-dimensional CT (4dCT) has been introduced. As regards CT scanning, this represents a breakthrough in imaging, because 4dCT generates both spatial and temporal information on organ mobility. In this technique, the respiratory waveform is synchronously recorded with CT acquisition,

and multiple CT slices are acquired at each table position for at least the duration of one full respiratory cycle. This yields CT datasets for up to 20 phases of the respiratory cycle. Multi-slice CT scanners equipped with respiratory gating hardware, and 4-dimensional imaging software are now commercially available. Preliminary studies indicate that a single 4dCT scan is sufficient to replace the use of 6 rapid CT scans for generating the internal tumour volume of mobile peripheral lung tumours.
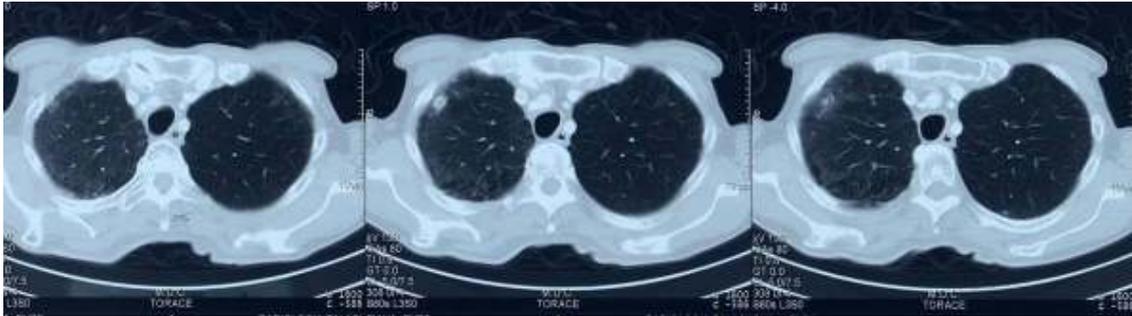

Figure 3. Lung CT examination showing a solitary nodule in the right lung.

C.2. Magnetic Resonance Imaging (MRI)

9.   Research on MRI was initially conducted in the early 1970s and the first MRI prototypes were tested on clinical patients in 1980. The use of MRI to visualize morphological alterations rests on its ability to detect changes in proton density and magnetic spin relaxation times, which are characteristic of the environment presented by the diseased tissue. During the examination, a radio signal is turned on and off, and subsequently the energy that is absorbed by different atoms in the body is echoed or reflected back out of the body. These echoes are continuously measured by the MR scanner and a digital computer reconstructs these echoes into images. The benefit of MRI is that it can easily acquire direct views of the body in almost any orientation, while CT scanners typically acquire images perpendicular to the long body axis. MRI is one of the best diagnostic exams for imaging the brain, the vessels of the brain, the eyes, the inner ear, the neck, the cervical, thoracic and lumbar spine, the upper abdomen (including liver, kidney, spleen, pancreas and abdominal vessels), the pelvis and hips, the male and female reproductive systems, and the bladder (Fig. 4). This is because MRI can provide exquisite contrast details between different tissues with very similar structural densities, for instance grey and white brain matter. Also for MRI, where the response is proportional to proton density, the high water content of tissues provides for a strong inherent signal enabling the resolution of small differences in hydrogen concentration. The anatomical definition of organs is therefore very good with MRI, which is commonly used for better characterization of lesions and for patients allergic to the iodinated contrast agents used with CT. MRI is also developing a tremendous potential for not only showing the structure or anatomy of the body, but also the functions or workings of the body. The advancements in MRI (e.g. fast acquisition protocols with multiple new pulse sequences and new MRI contrast agents) are beyond the scope of this discussion. Applications of MRI in functional imaging (advanced MRI) will be briefly presented below.

Figure 4. Pelvic MRI examination, showing excellent anatomical detail of pelvic structures.

C.3. Ultrasound

10. Ultrasound does not involve the use of ionizing radiation and hence ordinarily it would not be covered in a review on radiation medicine. However, its role in medical imaging and in cancer management cannot be overlooked. The ultrasound process involves placing a small device, called a transducer, against the skin of the patient near the region of interest, for example, against the back to image the kidneys. This transducer produces a stream of inaudible, high frequency sound waves that penetrate into the body and reflect from the organs inside. The transducer detects sound waves as they echo back from the internal structures and contours of the organs. Different tissues reflect these sound waves differently, causing a signature that can be measured and transformed into an image. These waves are received by the ultrasound machine and turned into live pictures with the use of computers and reconstruction software. Since high-frequency sound waves cannot penetrate bone or air, they are mostly used in imaging soft tissues and fluid-filled spaces. Ultrasound is good at non-invasively imaging a number of soft tissue organs without X-rays, namely; heart, pelvis and reproductive organs, kidneys, liver, pancreas, gall bladder, eye, thyroid, blood vessels and the foetus.

D. Functional Imaging

11. Anatomical imaging modalities such as CT and conventional MRI rely on structural changes or anatomical abnormalities to detect cancer. In some instances, however, this is not sufficient and false negative results may be found. A typical example is lymph node involvement in metastatic disease. In these cases, nodal invasion by cancer cells may be suspected when CT or MRI is used, only when nodes are found to be enlarged and therefore stand out as being abnormal. However, this is not always the case, as cancer dissemination can be found even in normal sized lymph nodes. In contrast, functional imaging techniques have the ability to detect cancerous involvement based on molecular and biochemical processes within the tumour tissue. It includes visualizing variations in the tissue

levels of specific bio-molecules and their turnover, and this information is directly linked to the tissue's biochemistry.

12.   In recent years, the major advances in imaging and the combination of molecular biology and the imaging sciences have merged into a new research field named 'molecular imaging'. It includes all imaging modalities used in cancer imaging, and new applications continue being developed. Technologies which are being used include PET, SPECT, MR spectroscopy, functional MRI, dynamic MRI, dynamic CT, etc.

13.   Although this review has its focus on nuclear imaging techniques, the role played by magnetic resonance in the field of molecular imaging cannot be disregarded. Recent advances in dynamic MR imaging (diffusion-weighted imaging, perfusion imaging), and spectroscopic imaging all have in common the ability to provide quantitative cellular, haemodynamic (blood dynamic) and metabolic information that may enhance understanding of tumour biology, improve the assessment of treatment response, more accurately determine tumour activity more accurately during therapy, and differentiate between recurrent tumours and treatment-related complications. The two most widely used MR spectroscopy techniques involve acquiring resonance signals from hydrogen-1 nuclei in molecules other than water, or phosphorus-31 containing molecules. Functional MRI makes it possible to analyse the response of the brain to different external stimuli, and thereby to study normal brain function and different brain diseases.

14.   Nuclear medicine functional imaging techniques such as gamma camera imaging, SPECT, and PET, have the ability to detect cancerous involvement based on molecular and biochemical processes within the tumour tissue. SPECT and PET procedures involve the injection of an appropriate radionuclide usually bound to a biologically active ligand (an extracellular substance that binds to receptors). Imaging is performed after a suitable time for the ligand to be incorporated into the target organ(s).

D.1. Single Photon Emission Computed Tomography (SPECT)

15.   SPECT is an imaging technique that relies on drugs that are labelled with atoms that emit at least one gamma ray when they decay. The most commonly used radionuclides in SPECT imaging are technetium-99m, gallium-67, iodine-131 and thallium-201. Since gamma rays are normally emitted equally in every direction, it is necessary to use a collimator in front of the detector that allows only the gamma rays emitted in the direction of the detector to be registered. In this way, the collimator defines the direction of the radiation when it is detected. By moving the detector completely around the patient, a 360º image is obtained. Mathematical methods are used to trace the emitted gamma rays back in the direction that they were emitted in order to produce the image.

D.2. Positron Emission Tomography (PET)

16.   PET is a very similar technique to SPECT in that they both provide information about the metabolism of a disease. Isotopes used in PET imaging are typically produced in a cyclotron by bombarding a stable element with protons, deuterons, or helium nuclei. The resulting isotope will decay by positron emission. PET imaging then utilizes physiologic substrates labelled with these positron emitting isotopes. The emitted positron travels only a minimal distance (about 2 mm maximum distance for fluorine-18) before it undergoes an annihilation reaction with the production of two 511 keV photons that travel in opposite directions to one another. Localization of the annihilation event is achieved by placing two detectors on opposite sides of the patient. When the photons are detected at the same time, the position of the emitted positron can be traced back with a straight line. (Fig. 5). In this way, the spatial position of the emitted photons is defined without the use of

collimators. This represents the greatest advantage of PET over SPECT. The result is enhanced resolution (by a factor of 2-3).
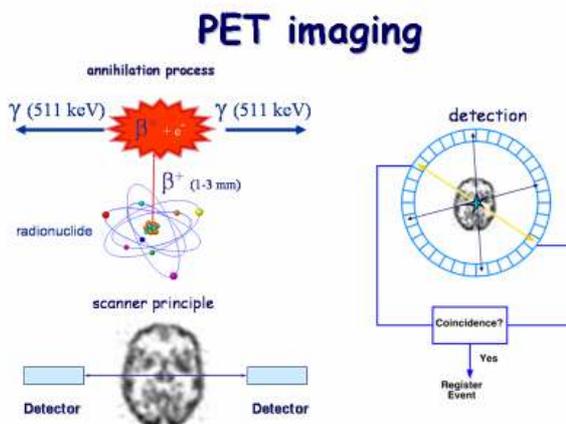

Figure 5. Physical principles of the positron emission tomography (PET).

17. Nuclear medicine imaging does not have the resolution of anatomical imaging such as MRI or CT. If detailed anatomical information is required, then nuclear medicine by itself is not the imaging modality of choice. However, great advances have been made with the fusion of nuclear medicine images with CT or MRI and the combination gives accurate anatomical localization of function. The great advantage of nuclear medicine imaging is its functional nature, for example, its ability to assess whether a residual mass after therapy for lymphoma contains viable tumour or its ability to detect small melanoma metastases. In such situations, anatomical imaging alone relies on size, which has been shown to have suboptimal accuracy.

E. Recent Advances in Cancer Nuclear Imaging Techniques

18. In the last decade, the most rapidly advancing modality of clinical functional imaging has been PET, which has moved from being a research tool into a common clinical practice with the use of fluorine-18(F-18)-2-fluoro-2-deoxyglucose (FDG) as a technique for evaluation of lung cancer and lung nodules. In this field, PET was found to be able to provide additional information to the clinicians dealing with this type of cancer. The same model was subsequently applied to other cancer settings and the application of PET in many different tumour types has been extensively evaluated and proved to be beneficial.

19. The introduction of hybrid PET-CT scanning technology in 2000 and early 2001 was a further step. Clinicians became more aware of the functional information supplied by PET when the 'unclear' background was substituted by a clear CT anatomical roadmap. This led to the final acceptance of PET into clinical oncology and other aspects of medicine like cardiovascular disease. With regard to cancer patient management, PET is affecting treatment strategy and planning, leading to more aggressive therapy in potentially curable cases and preventing operative procedures or guiding

palliative radiation therapy in those cases that are no longer deemed curable. The ability to combine the functional information from SPECT and PET imaging with the structural information obtained from CT or MRI studies provides a powerful tool for the clinician to make an accurate diagnosis. Mathematical techniques are used to combine the two sets of data into a single image. Several algorithms are in use, each adopting different approaches. Applying combined SPECT-CT or PET-CT systems to conduct functional and anatomical imaging during one session spares precious time and resolves many of the problems encountered during the process of image registration and image fusion by avoiding changes in the patient's position during data acquisition. Co-registration of the PET and CT data is a benefit of combined PET-CT units. The combined PET-CT images are more effective than PET images alone in localizing neoplastic (tumour) lesions precisely and in distinguishing normal uptake from juxtaposed neoplastic lesions. The evidence shows that PET-CT fusion data can lead to a significant change in diagnosis in about 20% of oncological cases. Even in cases where no major change in diagnosis occurred, there is greater diagnostic confidence, improved diagnostic accuracy, and fewer equivocal lesions for which management decisions remain difficult. PET-CT may affect patient treatment significantly and improve specificity more than sensitivity. The results of PET-CT exams can impact on patient management in 25–35% of patients. Settings in which PET-CT imaging is particularly useful include radiation therapy planning, preoperative surgery/biopsy planning, evaluation of head and neck tumours, and the detection of recurrent abdominal and pelvic malignancies. PET and CT examinations can be acquired on separate units. However, in such cases, consistent patient positioning and sophisticated image fusion software programs are required to ensure proper co-registration of the images.

E.1. Radiopharmaceutical Aspects of PET Functional Imaging

20. Image analysis or processing is only one of the technical areas that influence the clinical success of PET. The production of radionuclides that emit positrons and the development of molecules that can be labelled with these radionuclides are also active areas of research. Although nearly all the PET studies around the world are performed with [18F]2-fluoro-2-deoxyglucose (FDG), other radiopharmaceuticals labelled with 18F such as [18F]fluoroethyl-tyrosin, [18F]fluromethyl-thymidine or different positron emitters, for example gallium-68 as [68Ga]DOTATOC or 11C as [11C] choline (Fig. 6) or methinione, etc., are used to provide probes with increased selectivity and specificity for different functions and diseases. The patho-physiological basis for the application of radiopharmaceuticals in clinical PET comes from the consideration that chemical disturbances will almost always precede structural abnormalities. The result of diagnostic procedures using imaging probes aimed at detecting these biochemical abnormalities will allow an earlier detection of disease. Like conventional nuclear medicine, the principle of PET is based on the concept of tracer kinetics, which is a measurement of physiological activities resulting from biochemical changes. Unlike conventional nuclear medicine, PET measures biochemical activity at a more basic molecular level because the probe is by itself a simple molecule identical to or indistinguishable from the basic biochemical substrates. The common positron emitters (fluorine-18, carbon-18, nitrogen-13, oxygen-15) are basic elements of the backbone in organic chemistry, implying that there is an unlimited potential in the investigation of various biochemical pathways. These radioisotopes retain their normal biological function and allow the synthesis of numerous positron-emitting radiopharmaceuticals.
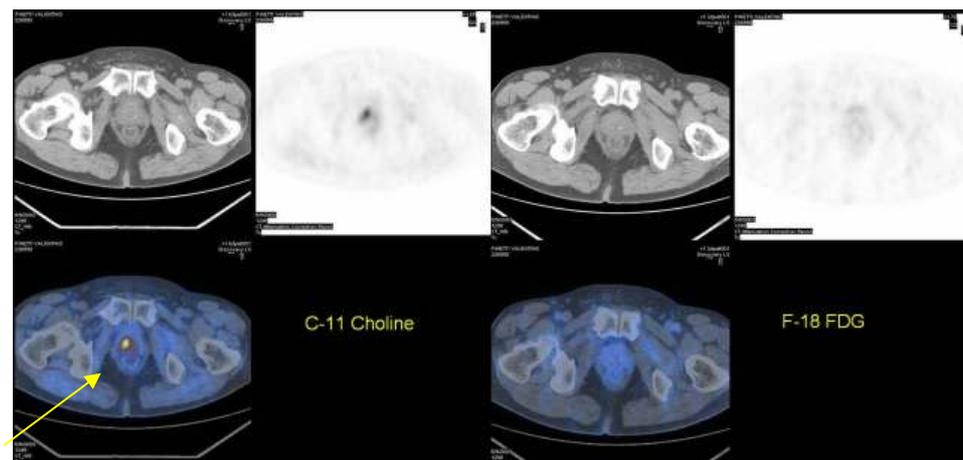
Figure 6. Prostate cancer: relapse after radiation therapy treatment; PET scan using C-11 choline detects a recurrence that went undetected both after CT scan and FDG PET (arrow).

21. Because of the short half-life of positron emitters, ranging from nearly 2 hours to a few seconds, hospital-based biomedical cyclotrons with low energy, typically 10–18 MeV, are often installed at clinical sites to take advantage of the full spectrum of available PET isotopes. These are usually referred to as 'baby-cyclotrons', and approximately 20–25% of the PET medical institutions in the USA and Western Europe have one installed. Financial considerations for installing and running even a low energy cyclotron have led to the design of networks consisting of a large PET medical centre having its own cyclotron, and four or five 'satellite' clinics equipped with PET scanners. Hereby, production costs are reduced, the large PET centre offers the full range of clinical procedures, even those based on short-lived isotopes, and the satellite clinics offer PET scans based only on FDG, which remains the most widely used PET radiopharmaceutical at the present time.

E.2. Clinical Applications of PET

22. The pivotal role of techniques such as CT, MRI and US are undoubtedly first-line modalities to be employed in patients affected by cancer. However, they rely on anatomical landmarks (i.e. morphological alterations due to the tumour) to identify tumour involvement and this leaves the clinicians with a grey area of cases that require further investigation. This is the area where PET proves most useful because of its capability of detecting cancer involvement in otherwise normal tissues and structures. The following is a concise description of already established applications of PET in cancer management. Many others, including non-cancer related conditions such as cardiovascular and brain degenerative diseases are under investigation and look promising.

E.2.1. Lung Cancer

23. Until the advent of PET, a consistent percentage of patients undergoing surgery for non-small-cell lung cancers (NSCLC) experienced a tumour relapse due to the presence of metastases undetectable by available staging modalities (CT; US; mediastinoscopy). This was the first proven clinical application of FDG-PET and it was found to be significantly more accurate than structural imaging methods such as CT scanning for determining whether pulmonary nodules are benign or malignant, and for investigating tumour dissemination (staging). High levels of uptake of 18F-2-deoxy-2-fluoro-D-glucose (FDG) are very accurate in characterizing pulmonary mass lesions that are either unsuitable for, or that have failed, histopathological (microscopic study of diseased tissue) characterization. PET has also been shown to be more accurate than CT for staging mediastinum (central compartment of the thoracic cavity) involvement. The best non-invasive results have been

obtained by correlating the results of both PET and CT images. They conclusively prove that when PET is used in addition to CT to evaluate intrathoracic lymph nodes for malignancy, the accuracy of the assessment is significantly greater than for CT alone. In addition, PET can detect unsuspected distant metastasis in patients with potentially-resectable stage I-II disease.

E.2.2. Lymphoma

24.   The incidence of non-Hodgkin's lymphoma (NHL) has been increasing approximately 3%-4% per year for the last three decades. Hodgkin's disease is much less common than NHL. Both Hodgkin's disease and NHL are amenable to curative therapy and many of the affected patients are young with otherwise good life expectancies. FDG PET imaging can play a significant role in the staging and management of patients with lymphoma. Treatment for NHL is dependent on several factors, including tumour grade, and for this purpose it is broadly grouped into low-, intermediate-, and high-grade disease subgroups. There is a direct correlation between the degree of FDG uptake and the histological grade of lymphoma. High-grade tumours demonstrate greater metabolic activity (and greater FDG accumulation) than low grade tumours. For Hodgkin's disease, the stage at presentation and tumour cell type determine the patients' overall prognosis and optimal method for treatment. Since the anatomical extent of disease is the single most important factor influencing the relapse-free duration and overall survival in patients with Hodgkin's disease, accurate staging prior to the initiation of therapy is essential for proper patient management. The optimal staging method for lymphoma should be able to identify all sites of disease non-invasively.

25.   Conventional imaging with CT or MR has been the primary means to evaluate and stage patients with lymphoma. These modalities can reveal anatomical abnormalities suggestive of tumour involvement. Conventional imaging is primarily dependent on lymph node size for the determination of tumour involvement. Generally, lymph nodes greater than 1 cm in size are considered suggestive of tumour involvement (depending on anatomical location). Unfortunately, normal-sized lymph nodes can harbour malignancy and enlarged nodes may be reactive. Furthermore, infiltrative involvement of the liver, spleen, and bone marrow cannot be accurately detected by conventional imaging modalities. As a result of these limitations, up to 36% of lesions seen on PET images may not be visible on CT or MRI examinations and, overall, FDG PET examinations are more sensitive in the evaluation of lymphoma patients.

E.2.3. Breast Cancer

26.   Routine evaluation for recurrent or residual disease after breast cancer treatment includes physical examination and imaging tests such as mammography, CT, MRI, sonography, and radionuclide whole-body imaging. These tests are frequently performed as routine clinical follow-up or are prompted by rising levels of tumour markers or, in some cases, by patient symptoms. Some metastatic sites such as lymph nodes or bone marrow are not easily depicted by conventional imaging modalities, resulting in delayed diagnosis and therapeutic interventions. Several authors have provided evidence that PET is more sensitive for establishing the extent of metastatic breast cancer involvement. A prospective survey showed PET to have a considerable impact on staging and managing breast cancer patients. The use of PET altered the clinical stage in 36% of patients and the clinical management in 60%. The results are in keeping with a previous report suggesting that FDG PET added information on the extent of disease in 29% of patients studied, mainly through detection of additional lymph node involvement. Importantly, PET can uncover unknown lymph node metastases and unknown distant metastases in 20% of the entire population studied. It is noteworthy that there was a consistent fraction of patients whose stage was not altered by PET but whose treatment nevertheless was managed differently after PET. This suggests that PET provided the referring physicians with additional pertinent staging information. For instance, in patients with stage

IV disease, additional nodal or distant metastatic disease detected by PET may not result in a stage change but may result in different management plans.

E.2.4. Head-and-Neck Cancer

27.   Clinical studies have demonstrated that FDG-PET scans provide additional information for the pre-treatment detection of lymph node metastases, localization of unknown primary tumours in patients with cervical lymph node metastases, and for the detection of tumour recurrence after radiotherapy. FDG-PET proved to be more sensitive (78–100% probability of a positive test among patients with disease) than CT-MRI (57–85%) in detecting primary tumours in the head and neck area. Some false negative PET results were observed in micrometastatic disease, while false positive findings occurred in inflammatory lymph nodes. In addition, anatomical structures like tonsils and salivary glands can take up considerable amounts of FDG leading to false positive results. Thus, sensitivity and specificity (probability of a negative test among patients without disease) of FDG-PET in lymph node staging is higher than for MRI or CT. However, FDG-PET cannot replace invasive diagnostic procedures.

E.2.5. Cervical Cancer

28.   PET scanning is increasingly used in the initial evaluation of patients with invasive cervical cancer using FDG. Abnormal uptake can be anticipated in 91% of the primary tumours. Compared with surgical staging, PET scanning has a sensitivity of 72% and a specificity of 92% in detecting para-aortic metastasis. FDG-PET is useful in re-evaluating women with cervical cancer after therapy. Whole-body FDG-PET is a sensitive and specific tool for the detection of recurrent cervical cancer in patients who have clinical findings implying the presence of a recurrence. A larger prospective trial would be needed to determine whether this modality should be used routinely in conjunction with, or in lieu of, other imaging studies to detect recurrent disease in a broader population of cervical cancer patients. However the impact of routine PET scanning in patient treatment and in terms of tumour control and survival remains to be established. The cost-benefit of routine PET scanning in cervical cancer patients is a matter that will require future research as well.

E.2.6. Prostate Cancer

29.   This is an area where the ability of PET to utilize different biological substrates to investigate cancer proves of great value. Indeed, although FDG imaging proved very effective in investigating almost all types of cancer, diagnosis of primary prostate cancer is hampered by the low glucose metabolic rates and low FDG tumour uptake. In addition, a significant number of metastatic lesions from prostate cancer will also not accumulate FDG (probably due to a low glucose metabolic rate). 11C-choline is a PET tracer that can be used for prostate cancer imaging, since choline is one of the essential elements of phospholipids in cell membranes. Malignant tumours show a high cell proliferation rate and increased metabolism of cell membrane components, which will lead to an increased uptake of choline. Another benefit of PET imaging is that it can identify lymph node metastases that are outside the field of modified lymphadenectomy surgery. 18F-fluorocholine has been developed in order to overcome difficulties associated with the short half-life of carbon-11 labelled compounds. The sensitivity, specificity and accuracy of 11C-choline-PET in the diagnosis of lymph node metastasis of prostate cancer are superior to traditional radiological imaging using CT and MRI.

E.2.7. Brain Tumours

30.   In general, FDG PET is of little value in primary brain neoplasms (abnormal, disorganized growth in tissue) because of the great glucose uptake in normal brain tissue. There are, however, some fields where PET proved helpful such as assessing tumour extension and in detecting some malignant transformations. The general approach to treatment of brain neoplasms is surgical resection of solitary lesions or limited disease, followed by radiation therapy (with or without chemotherapy). Solitary lesions may alternatively be treated with local field radiotherapy or stereotactic radiosurgery, while multiple or metastatic lesions receive whole-brain radiation. Anatomical alterations and scarring after therapy can impair proper identification of residual or recurrent neoplasms in conventional imaging studies. PET studies with FDG have shown that recurrent tumour exhibits hypermetabolism of glucose, while non-necrotic irradiated brain shows hypometabolism, and necrotic brain has no detectable metabolic activity.

E.3. PET in Radiation Therapy Planning

31.   The definition of target volume in radiation treatment planning is based essentially on CT and MRI, both having a very high resolution and describing anatomical structures with accuracy. The concept of 3-dimensional radiotherapy is based on morphological data delivered by these imaging techniques. However, in the last few years new methods of tumour visualization have been introduced into radiation oncology practice. Techniques like PET, SPECT or MRS are able to visualize biological pathways in tumours, giving additional information about the metabolism, physiology and molecular biology of tumour tissue. A new class of biological images, showing specific biological characteristics, complements the anatomical information of traditional radiological techniques. These imaging techniques, having the property to show biological characteristics, are also called molecular imaging or functional imaging techniques.

32.   The integration of FDG-PET in radiation treatment planning is still at the investigational stage. In one study the advantage of FDG-PET was the detection of additional lymph node metastases. While the integration of FDG-PET in radiation treatment planning led to an enlargement of the radiation field sizes in some cases, it led to a reduction in other cases. This meant that the parotid gland could be spared in the case of head and neck tumours. The image fusion between FDG-PET and MRI-CT was useful in both tumour volume determinations, and for the sparing of the normal tissue. In the majority of treatment planning studies for lung cancer patients, significant implications of the value of FDG-PET in lymph node diagnosis were confirmed, which were in agreement with the results of meta-analyses. These showed that the mean sensitivity and specificity for FDG-PET were 85% and 87% respectively, while for CT they were 66% and 71%, respectively. It was also shown that PET was superior to CT in differentiating malignant tissue from atelectasis (collapse of a part of the lung or the whole lung). This may help to spare normal tissue and to reduce the subjective judgement of the radiation oncologist in target delineation (Fig. 7).

33.   There are no data in the literature concerning the use of PET investigations in radiation treatment planning of prostate cancer. However, there are data about the use of another biological imaging method, namely hydrogen-1 magnetic resonance (1H-MR) spectroscopy. In trials comparing the tumour volume defined using MRI, with the tumour volume defined using 1H-MR spectroscopy and the histo-pathologically-determined volume, the addition of 1H-MR spectroscopy showed a significant improvement in tumour volume demarcation.
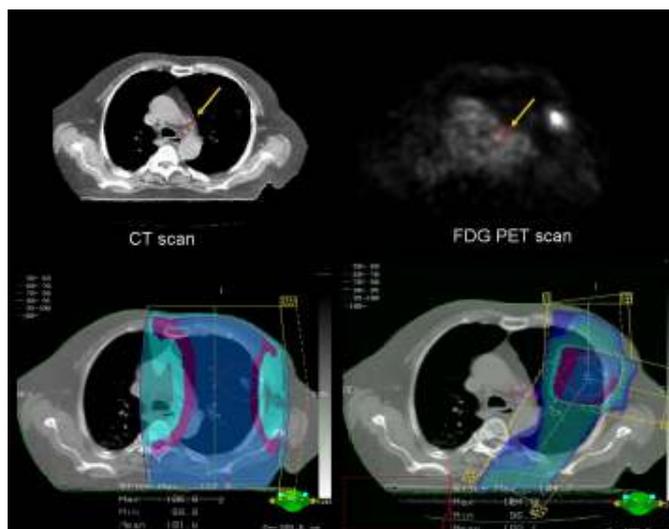
Figure 7. Lung cancer: target volume reduction after PET examination. On a CT scan (upper left) mediastinal lymph nodes appear enlarged (arrow) and are included in the treatment plan (bottom left). An FDG-PET scan, however, does not confirm such a finding, as no FDG uptake is detected (arrow). The target volume is therefore modified to exclude the mediastinal lymph nodes in the new treatment plan (bottom right).

E.4. Post-treatment Evaluation

34. The objective evaluation of the response to treatment (either chemo- or radiation therapy or both) remains an elusive goal in clinical oncology. Conventional imaging with CT and MRI does not always provide sufficient evidence of therapeutic results since volumetric changes, on which these techniques rely, take place later on during therapy, or because tumour mass can be replaced with fibrotic tissue with no significant volume reduction. These modalities are not sufficient to discriminate between residual malignant and still-viable cancer tissue. Also, fibrotic/necrotic tissue that often results from radiotherapy may not be distinguishable from cancer itself.

35. This ability to discriminate viable from non-viable tissue was extensively evaluated in lymphomas (both Hodgkin's disease and non-Hodgkin's lymphomas) where PET is a strong predictor of progression-free and overall survival. This proved to be particularly useful in selecting patients for resective surgery which is associated with considerable morbidity. It was also found that PET is useful for early treatment evaluation, following the completion of a few chemotherapy cycles whose metabolic effects are detected before tumour shrinkage could be detected by CT. Early detection of subclinical response could be used to adapt specific treatment options for individual patients.

F. Conclusions

36. Radiation medicine imaging techniques continue to play a major role both in cancer management, aiming to achieve earlier diagnoses, more accurate staging and therefore more accurate treatment decisions and planning, and in monitoring treatment effects. Of these modalities, CT scanning and, where appropriate MRI, will remain first-line modalities. PET is also one of the major breakthroughs in this area in the last decade.

37. It was a long journey that led PET from a purely scientific method of probing important physiological variables to an imaging tool of recognized value in clinical practice. More recently, the appearance of hybrid machines (PET-CT scanners) gave this technique a very important role to play in cancer management. It will not replace CT as first-line investigation, because of costs and resolution limitations, but it seems to be very helpful in situations where CT scans do not provide all the information required by clinical oncologists: differentiating tumour masses from benign lesions, identifying lymph node invasion by cancerous cells, differentiating residual tumour from scarring and necrosis, and detecting unsuspected distant metastases that would affect patient prognosis and treatment. The ability of PET to investigate diseases down to the molecular level will bring about the 'molecular imaging revolution' making it easier to diagnose cancer at a very early stage, characterize disease conditions and treat various diseases effectively. In addition, it is an effective tool for monitoring the effectiveness of treatment strategies in a more individual approach to patient management.