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PET/CT for the staging and follow-up of patients with malignancies

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ABSTRACT

Positron emission tomography (PET) and computed tomography (CT) complement each other's strengths in integrated PET/CT. PET is a highly sensitive modality to depict the whole-body distribution of positron-emitting biomarkers indicating tumour metabolic activity. However, conventional PET imaging is lacking detailed anatomical information to precisely localise pathologic findings. CT imaging can readily provide the required morphological data. Thus, integrated PET/CT represents an efficient tool for whole-body staging and functional assessment within one examination. Due to developments in system technology PET/CT devices are continually gaining spatial resolution and imaging speed. Whole-body imaging from the head to the upper thighs is accomplished in less than 20 min. Spatial resolution approaches 2–4 mm. Most PET/CT studies in oncology are performed with ^{18}F-labelled fluoro-deoxy-D-glucose (FDG). FDG is a glucose analogue that is taken up and trapped within viable cells. An increased glycolytic activity is a characteristic in many types of cancers resulting in avid accumulation of FDG. These tumours excel as "hot spots" in FDG-PET/CT imaging. FDG-PET/CT proved to be of high diagnostic value in staging and restaging of different malignant diseases, such as colorectal cancer, lung cancer, breast cancer, head and neck cancer, malignant lymphomas, and many more. The standard whole-body coverage simplifies staging and speeds up decision processes to determine appropriate therapeutic strategies. Further development and implementation of new PET-tracers in clinical routine will continually increase the number of PET/CT indications. This promotes PET/CT as the imaging modality of choice for working-up of the most common tumour entities as well as some of the rare malignancies.

1. Introduction

In patients with suspected malignancies both prognosis and therapeutic management particularly depend on the tumour stage. Thus, accurate tumour staging preferably encompassing the entire body is of high importance.

PET is a very sensitive modality to depict the spatial whole-body distribution of positron-emitting biomarkers that indicate molecular processes underlying tumour metabolic activity [1]. The average F-18-FDG PET sensitivity and specificity across all indications in oncology are estimated at 84% (based on 18,402 patient studies) and 88% (based on 14,264 patient studies), respectively, according to Gambhir et al. [2] from a collection of 419 articles from 1993 to 2000.

However, sole PET images are lacking detailed anatomical information. Reliable localisation of a lesion within a segment of an organ or even within a certain organ itself can be challenging. Thus, conventional stand-alone PET has mostly been replaced by PET/CT. PET/CT combines the complementary information of functional PET and morphological CT images in one imaging session for improved patient comfort, patient throughput, and most importantly the gain in diagnostic accuracy. FDG-PET/CT has been found superior to both imaging procedures acquired separately in tumour staging and restaging of different malignant diseases [3–5]. Furthermore, PET/CT potentially supports volume delineation in radiation therapy planning [6]. This may be particularly useful in the head and neck region where a multitude of sensitive structures is confined to a small area of the body. The close vicinity necessitates optimised definition of the treatment volume to minimise the risk of treatment-related toxicities. Another indication for PET/CT in radiation therapy planning is lung tumours where separation of viable tumour from atelectasis can be challenging with morphology alone [6].

While PET imaging has been available since 1980, PET/CT has first been introduced into clinical routine in 2001. Thus, there are many data on PET in oncological applications available in the literature, while data on PET/CT are still limited for some tumour entities. However, depending on the indication and the radionuclide in question data on PET imaging may in all likelihood also apply to PET/CT.

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This review will (1) cover methodological issues in PET/CT and (2) focus on the main oncological indications of FDG-PET/CT.

2. Methodological and technical issues in PET/CT

Two separate scanners, a PET and a CT scanner, are installed in series with a single gantry and examination table serving both imaging devices. Prior to the examination a positron-emitting biomarker is administered. The examination is then performed by positioning the patient on the examination table followed by sequential acquisition of the CT and of the PET images. Both data sets can be combined into a single superposed (coregistered) image. Differences between PET/CT systems apply to the number of detector rows with which the CT component is equipped. Currently up to 128 detector rows have been integrated in PET/CT and an increase to 256 rows seems possible. However, it is not clear how much CT capabilities have to be integrated in a PET/CT device to receive the best results. Current systems seem quite adequate for oncological imaging with the main limitation in systems performance being the data acquisition speed of PET [7].

2.1. Positron emission tomography (PET)

PET is based on the radioactive decay of neutron-deficient isotopes that are introduced into the body. These isotopes emit positrons, which are the antimatter counterpart of electrons, during their decay. The emitted positrons will interact with nearby electrons within a few millimetres from their origination (depending on positron energy). Electron and positron are mutually annihilated to form two photons taking paths 180° apart. The photons almost simultaneously reach opposite sides of a detector ring surrounding the subject. This detector ring can be fitted with various types of crystals (bismuth-germanate (BGO), luthetium-oxyorthosilicate (LSO), gadolinium-oxyorthosilicate (GSO)) that convert the annihilation photons to light signals (scintillation). The scintillation event is then converted to an electric signal via photomultiplier tubes. Two events that are simultaneously perceived by opposed detectors are assumed to originate from the same annihilation (coincidence detection). The size of the detector crystals defines the spatial resolution of the tomograph, which may range from 2 to 4 mm. A reconstruction algorithm is used to calculate the point of origin of coincident events to form images. Depending on their depth of origination the annihilation photons suffer from attenuation by intervening body tissue until reaching the detector. Thus, photons originating from structures deeper in the body are more highly attenuated than those originating closer to the surface. The effect of attenuation can be accounted for by correction with measured attenuation maps. In PET/CT these maps are calculated based on the CT transmission scan.

Evaluation of the PET part of a PET/CT scan is usually performed both visually (qualitative image analysis) and semiquantitatively. Initially, the reader visually assesses the PET images for areas of increased tracer uptake other than those of known physiologically high tracer accumulation. A region of interest may then be defined encompassing a "hot spot" offering semiquantitative analysis of the tracer activity in that area. The most commonly used technique is estimation of the standardised uptake value (SUV) as an index of tumour uptake normalised to the injected activity and a measure of the total volume of distribution, such as the patient's body weight. This method is often criticised for being subject to many sources of variability as body composition and blood glucose level that have to be taken into account. Nevertheless, SUV measurement turned out to be highly reproducible. Therefore, most institutions currently use SUV estimation as an add-on to support visual image analysis. Moreover, the estimation of an SUV provides a valuable tool for cancer therapy monitoring as a certain decrease from a pretherapeutically measured SUV can indicate tumour response to a treatment applied.

2.2. PET-radiotracers

A radiotracer is a substance that contains a radioisotope to enable detection and measurement. Some radioactive isotopes or their combination with a biologically active molecule or drug that acts as a carrier and determines biodistribution will lodge in specific metabolic pathways. They can be administered in subpharmacologic doses to trace a particular physiologic or pathologic process in the body without causing any perturbation of function. Isotopes such as carbon [^{11}C], gallium [^{68}Ga] and fluorine [^{18}F] are in use for such purposes. Among the [^{18}F]-labelled compounds 2′-[^{18}F]-fluoro-2′-deoxy-D-glucose (FDG) is the most widely used in oncology. FDG is a glucose analogue that follows a metabolic pathway partially similar to glucose by being taken up but being only partially metabolised and then trapped within the cells. An increased glycolytic rate is a characteristic feature of many types of malignant cells and is partially related to an over-expression of the GLUT-1 glucose transporters and an increased hexokinase activity. These tumours excel as "hot spots" in FDG-PET/CT imaging. Some difficulties in interpretation may be caused by other processes that are characterised by an increased glucose metabolism as well, such as metabolic activity in brown adipose tissue, physiological enteric and gynaecologic activity, infectious and inflammatory processes, physiologic or pathologic sequelae of surgical or interventional procedures, etc. Moreover, highly differentiated tumours and certain tumour entities such as prostate cancer and mucinous carcinomas may exhibit only insignificant FDG-uptake due to only modest hexokinase activities and may thus not be detected with FDG-PET/CT. Tracers binding to specific receptors or entering different metabolic pathways can act as an alternative for imaging. Such tracers are (among others) ^{11}C-/^{18}F-choline for prostate cancer [8] (v. Fig. 1), ^{68}Ga-DOTATOC for neuroendocrine tumours [9] (v. Fig. 2), and ^{124}iodine for differentiated thyroid cancer [10] (v. Figs. 3 and 4).

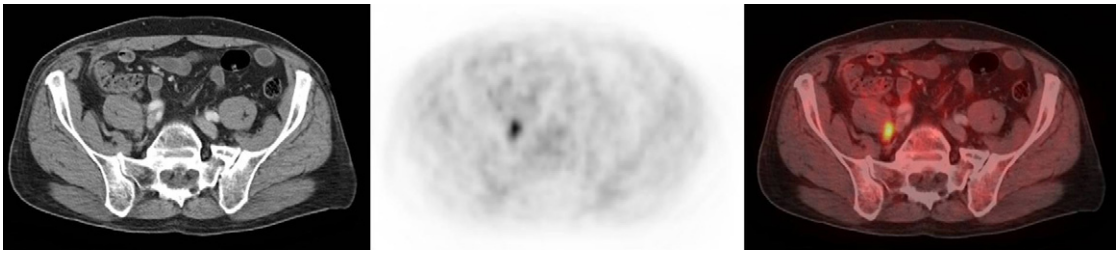

Fig. 1. 67-year-old patient with biochemical relapse after radical prostatectomy. ^{11}C-choline-PET/CT localised metastatic disease to a solitary lymph node metastasis that not fulfilled morphologic size criteria. Left: contrast-enhanced CT, middle: ^{11}C-choline-PET, right: ^{11}C-choline-PET/CT fusion.