

IAEA-TECDOC-1605

***A Guide to Clinical PET  
in Oncology:  
Improving Clinical Management  
of Cancer Patients***



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International Atomic Energy Agency

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## FOREWORD

Positron emission tomography (PET) has an approximately 50 year-history. It was developed as a tool of medical science to quantitatively measure metabolic rates of bio-substances in vivo and in particular the number of receptors in neuroscience. Until the late 1990s PET was, in most cases, research oriented activity.

In 2001, positron emission tomography/X ray computed tomography (PET/CT) hybrid imaging system became commercially available. An era of clinical PET then emerged, in which PET images were utilized for clinical practice in the treatment and diagnosis of cancer patients. PET imaging could recognize areas of abnormal metabolic behaviour of cancers in vivo, and the addition of CT imaging underlines the site of malignancy. More accurate and precise interpretation of cancer lesions can therefore be performed by PET/CT imaging than PET or CT imaging alone.

Clinical PET, in particular with fluorine-18-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG), has already proven itself to have considerable value in oncology. The indications include malignant lymphoma and melanoma, head and neck cancers, oesophageal cancer, breast cancer, lung cancer and colorectal cancer, and it is still being expanded. The roles of clinical PET could be for 1) preoperative staging of cancers, 2) differentiation between residual tumour and scarring, 3) demonstration of suspected recurrences, 4) monitoring response to therapy, 5) prognosis and 6) radiotherapy treatment planning.

Clinical PET can be used to illustrate exactly which treatment should be applied for a cancer patient as well as where surgeons should operate and where radiation oncologists should target radiation therapy.

An almost exponential rise in the introduction of clinical PET, as well as the installation of PET/CT has been seen throughout the world. Clinical PET is currently viewed as the most powerful diagnostic tool in its field.

This IAEA-TECDOC presents an overview of clinical PET for cancer patients and a relevant source of information on clinical PET in oncology for nuclear medicine physicians, radiologists and clinical practitioners. Possible ideas for cost effectiveness of clinical PET in oncology are mentioned. The information is also intended to be useful in decision making to improve clinical management of cancer patients when allocating resources dedicated to the health care system. This is a critical issue that is important for the development of both clinical oncology and nuclear medicine in IAEA member states. The IAEA can be instrumental in the advancement of programmes which focus on the IAEA's coordinated research projects and technical cooperation projects.

The IAEA wishes to express its thanks to all experts who have contributed to this publication. The IAEA officer responsible for this publication was N. Watanabe of the Division of Human Health.

### *EDITORIAL NOTE*

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## CONTENTS

1.	OVERVIEW OF PET TECHNOLOGY.....	1
1.1.	Production of radionuclides.....	1
1.1.1.	Accelerators .....	1
1.1.2.	Generators .....	2
1.2.	Radiolabelling.....	3
1.3.	Quality control of radiopharmaceuticals .....	3
1.4.	PET and PET/CT scanners .....	3
1.5.	Information technologies.....	5
1.6.	Methodology for oncological PET/CT investigation .....	6
1.7.	Radiation protection .....	7
1.8.	Legal consideration.....	8
2.	MODELS OF CLINICAL PET FACILITIES.....	9
2.1.	Location of PET/CT scanner .....	9
2.1.1.	Inside a hospital .....	9
2.1.2.	Stand-alone facility .....	10
2.1.3.	Mobile facility.....	10
2.1.4.	Non-clinical research institution.....	11
2.2.	Location of radiopharmaceutical production.....	11
2.2.1.	Supply from distance .....	12
2.2.2.	On-site individual preparation .....	12
2.2.3.	Satellite concept.....	12
2.3.	Number of installed scanners .....	13
2.4.	Example of PET centre.....	13
2.4.1.	General concept .....	13
2.4.2.	Building outline and equipment.....	13
2.4.3.	Personnel.....	15
2.4.4.	Workflow and overall performance of the clinic.....	15
2.4.5.	Radiation protection.....	17
3.	ADVANTAGES AND DISADVANTAGES OF PET COMPARED TO OTHER DIAGNOSTIC IMAGING MODALITIES.....	18
3.1.	Historical overview of diagnostic imaging.....	18
3.2.	Advantages and disadvantages of each imaging modality .....	20
3.2.1.	Simple radiography with and without contrast agents.....	20
3.2.2.	CT .....	20
3.2.3.	Magnetic resonance images (MRI).....	21
3.2.4.	Ultrasonography (US).....	22
3.2.5.	Nuclear medicine imaging including SPECT and PET .....	23
3.3.	Correlative imaging and image fusion.....	24
4.	PET APPLICATIONS IN ONCOLOGY .....	24
4.1.	<sup>18</sup> F-FDG-PET for evaluating mass lesions .....	27
4.2.	<sup>18</sup> F-FDG-PET for cancer detection.....	27
4.3.	<sup>18</sup> F-FDG-PET for staging of cancer.....	28
4.4.	<sup>18</sup> F-FDG-PET for treatment planning.....	28
4.5.	<sup>18</sup> F-FDG-PET for therapeutic monitoring .....	28

4.6.	<sup>18</sup> F-FDG-PET for restaging .....	30
4.7.	Use of <sup>18</sup> F-FDG-PET as a biomarker .....	30
4.8.	Alternative tracers for cancer evaluation.....	31
4.9.	Conclusion .....	31
5.	USE OF TRACERS OTHER THAN <sup>18</sup> F-FDG IN ONCOLOGY .....	31
5.1.	Some examples of clinical use of non <sup>18</sup> F-FDG radiopharmaceuticals.....	33
5.1.1.	Brain tumours .....	33
5.1.2.	Lung cancer.....	33
5.1.3.	Liver tumours.....	33
5.1.4.	Neuroendocrine tumours.....	33
5.1.5.	Prostate cancer and urological malignancies .....	34
5.1.6.	Breast cancer .....	34
5.1.7.	Hypoxia studies.....	35
5.1.8.	Cell proliferation studies.....	35
5.2.	Conclusions .....	36
6.	PRINCIPLES OF COST-BENEFIT ANALYSIS AS APPLIED TO PET/CT.....	36
6.1.	PET/CT- A rapidly evolving technology.....	36
6.2.	Is PET/CT too expensive for the developing world?.....	37
6.3.	The basis of economic evaluation .....	38
6.4.	Health technology assessment (HTA) on PET/CT.....	40
	BIBLIOGRAPHY .....	45
	CONTRIBUTORS TO DRAFTING AND REVIEW .....	51

## 1. OVERVIEW OF PET TECHNOLOGY

The chemical and biological properties of a substance administered to a patient result in a specific organ distribution. The replacement of a stable element of such a substance by radionuclide creates a radiochemical with the same chemical and biological properties as the non-radioactive agent. When it fulfils qualitative parameters defined by regulations, it is termed a radiopharmaceutical.

A special subcategory of radiopharmaceuticals in nuclear medicine is comprised of those that emit positrons — particles similar in their properties to electrons but positively charged. Positrons are a form of anti-matter, incapable of existing permanently in a mass environment. When emitted, the length of the positron's trajectory depends on its energy. The positron of the most commonly used radionuclide, fluorine-18 ( $^{18}\text{F}$ ), has a median range of only 0.2 mm in tissue and a maximum range of 2.4 mm. At the end of its trajectory, the positron interacts with an electron in a nearby atom and both are annihilated. Annihilation is a process that is accompanied by the emission of two quanta of  $\gamma$  radiation, each with an energy of 511 keV. These quanta move away from the point of annihilation in opposite directions along an almost straight line.

Positron emission tomography (PET) is a volumetric technique optimized for detection of these annihilation photons. It thereby allows precise tracking of the spatial and temporal distribution of positron emitting radiopharmaceuticals in patients. Thus, it represents a unique functional tomographic imaging modality based on the biochemical handling of chemicals by tissues of the body.

### 1.1. PRODUCTION OF RADIONUCLIDES

#### 1.1.1. Accelerators

The radionuclides most commonly used in PET are generated by bombardment of an appropriate target by charged particles accelerated either within a cyclotron or, less commonly, using a linear accelerator. Several manufacturers operate in the marketplace, offering a range of accelerators with differing energies. The energy of an accelerator determines the spectrum of radionuclides that can be produced and the production capacity, i.e. the amount of activity produced. The size and shielding requirements of these accelerators varies markedly. The range extends from mobile linear accelerators that can be housed on trailer, through self-shielded baby cyclotrons and up to massive commercial cyclotrons housed in heavily-shielded vaults.

Typical examples of radionuclides produced by accelerators are listed in Table 1. Clinically, the dominant radionuclide is  $^{18}\text{F}$ , which has a half-life of approximately two hours. It is produced by proton bombardment of a stable oxygen-18 ( $^{18}\text{O}$ ) enriched water target, thanks to nuclear reaction  $^{18}\text{O}(p,n)^{18}\text{F}$ . Thus,  $^{18}\text{O}\text{-H}_2\text{O}$  represents a strategic resource for a clinically oriented accelerator unit. Commercial suppliers are now available for this material.



TABLE 1. ACCELERATOR PRODUCED POSITRON EMITTING RADIONUCLIDES AND THEIR DECAY HALF-LIVES

Radionuclide	Half-life
$^{11}\text{C}$	20.385 min.
$^{13}\text{N}$	9.965 min.
$^{15}\text{O}$	2.037 min.
$^{18}\text{F}$	109.77 min.
$^{61}\text{Cu}$	3.33 hours
$^{64}\text{Cu}$	12.7 hours
$^{86}\text{Y}$	14.74 hours
$^{124}\text{I}$	4.176 days

### 1.1.2. Generators

There are various radionuclides that decay themselves into ‘daughter’ radionuclides with much shorter half-lives. The system, where a ‘parent’ radionuclide is chemically bound to column and the ‘daughter’ radionuclide (because of different chemical property) can be eluted, is called a radionuclide generator. Table 2 shows examples of generator-produced positron emitting radionuclides of medical interest. In oncology, special attention should be paid to the germanium-68/gallium-68 ( $^{68}\text{Ge}/^{68}\text{Ga}$ ) generator. The very long half-life of  $^{68}\text{Ge}$  combined with short half-life of  $^{68}\text{Ga}$  make it ideal for nuclear medicine practice. A disadvantage is the currently limited number of chemical compounds that can be labeled with  $^{68}\text{Ga}$ . At present, clinical use of  $^{68}\text{Ga}$  is largely limited to receptor-mediated peptide imaging using somatostatin-analogues. These are primarily used for various neuro-endocrine tumours, which are relatively rare. Thus, generators cannot be currently considered as a sufficient stand-alone source of radionuclides for an oncologically oriented PET Centre.

TABLE 2. PARENT AND THEIR DAUGHTER POSITRON EMITTING RADIONUCLIDES PRESENTED IN GENERATORS AND THEIR DECAY HALF-LIVES

Parent		Daughter	
Radionuclide	Half-life	Radionuclide	Half-life
$^{62}\text{Zn}$	9.26 h	$^{62}\text{Cu}$	9.73 min.
$^{68}\text{Ge}$	270.8 days	$^{68}\text{Ga}$	67.71 min.
$^{82}\text{Sr}$	25,0 days	$^{82}\text{Rb}$	1.273 min.

## 1.2. RADIOLABELLING

The different chemical reactions (e.g. nucleophilic substitution) that are used to radiolabel non-radioactive compounds depend on the nature of the chemical precursor and the chosen radionuclide. These reactions are generally performed in a compact system of storage vials, connected by tubes and valves, which are controlled by a computer. Such systems are known as synthesis modules. Various models are commercially available from a number of suppliers. Increasingly, these units are automated and use pre-prepared consumables in the form of cassettes or replaceable vials. Even though these synthesis modules can be modified for labelling of a range of radiotracers, further development of automated synthesis modules would be desirable to augment the clinical application of positron emission tomography/X ray computed tomography (PET/CT) in oncology.

Depending on its properties, a radiolabelled compound requires final purification (e.g. by high pressure liquid chromatography (HPLC)), sterilization by microfiltration or high-pressure steam, and dispensing into vials, completed with a stopper. Because of the high activity, all above-mentioned procedures must be performed in enclosures with appropriate radiation protection shielding. Such enclosures are termed 'hot cells'. Increasingly, the production of radiopharmaceuticals is performed robotically to avoid the need for manual handling.

## 1.3. QUALITY CONTROL OF RADIOPHARMACEUTICALS

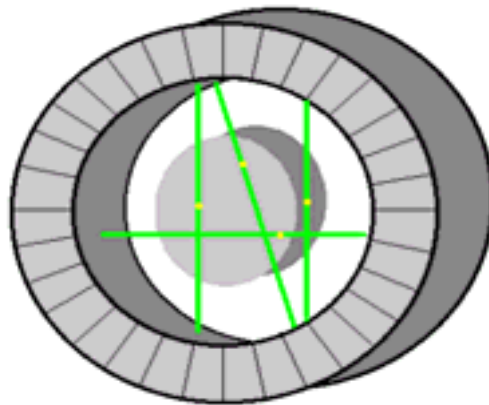
The final radiochemical is tested for radionuclide impurity (to define contamination by undesirable radionuclides) and for radiochemical impurity (to define the fraction of unbound or undesirably bound precursor). The residual concentration of additives, sterility and apyrogenicity must also be tested. Some of these parameters must be tested before administration of radiotracer, while others can be tested *post hoc*. The conversion of radiochemicals into radiopharmaceuticals is a semantic rather than physical process. It involves an administrative process, involving an individual who is authorized and responsible for checking and documenting that the product has met the requisite standards for usage in humans.

## 1.4. PET AND PET/CT SCANNERS

The PET scanner is a device with external appearances similar to those of a CT or magnetic resonance imaging (MRI) (Fig. 1), but it operates on completely different principles. It consists of a few parallel rings comprised of many small scintillation crystals. The patient is placed within the rings. As pairs of annihilation photons are emitted, they may or may not interact with these crystals to cause a scintillation (Fig. 2). Connected photomultipliers and preamplifiers amplify the signal and coincidence circuits evaluate, whether each scintillation is likely to have arisen from an annihilation event based on its energy and timing in relationship to scintillations arising on the opposite side of the detector array. If the electronic logic accepts a pair of impulses, their position is recorded. Subsequently, a line connecting respective points of scintillation is created and saved into electronic memory. From numerous such lines of response (LOR), a tomographic image of the distribution of activity within the patient's body can be reconstructed.



*Fig. 1. An example of hybrid PET/CT scanner*



*Fig. 2. An outline of the geometry of positron emission tomography. Annihilations (yellow dots) occur within the cylindrical phantom simulating the body of the patient. Green lines represent pathways of both quanta of annihilation radiation traveling in opposite directions. Multiple blocks of detectors arranged into one ring detect appropriate events.*

There are scanners that are commercially available from a number of manufacturers. They differ with respect to the type, number, size and configuration of crystals. The design characteristics influence the system sensitivity, spatial and contrast resolution and, together with coincidence electronics, also affect performance of the scanner at high count-rates. PET scanners can operate with each ring of detectors operating independently, being separated by high-density septa to provide collimation between planes. This is termed 2-dimensional or 2-D acquisition. Alternatively, the septa can be removed and all the detector blocks become linked allowing detection of LOR across detector rings. This is termed 3-dimensional or 3-D acquisition. Increasing the number of detector rings as well as the possibility to acquire data 3-D both dramatically influences the throughput of the scanner by increasing the sensitivity of photon detection but also potentially increase the coincidental detection of photon events that are temporally-related but have not arisen from annihilation events. These are called ‘randoms’ and opposed to those that arise from annihilation events, which are termed ‘trues’. Scattered photons are also more likely to be collected in larger detector arrays. Randoms and

scattered photons contribute to the ‘noise’ in a PET image and degrade spatial and contrast resolution. Modern iterative reconstruction algorithms apply some correction (e.g. for attenuation and scatter) and can enhance the image quality, but can not easily deal with randoms.

In the past, the most popular material for detectors was bismuth-germanate (BGO). Because of its high density, BGO provides good stopping power of 511 keV photons but is a relatively inefficient scintillator. Recently other detector materials with similar stopping power but higher light output, better energy discrimination and much more efficient rejection of randoms have gained popularity. These include lutetium oxyorthosilicate (LSO), germanium oxyorthosilicate (GSO), and lutetium-yttrium oxyorthosilicate (LYSO). Although there have previously been PET scanners constructed with thallium doped sodium iodide (NaI(Tl)), the detector material used in gamma-cameras, this has significant limitations in relationship to count rate capability. The axial field of view in high performance scanners typically exceeds 15 cm. Accordingly, more than 10,000 crystals are utilized in scanners with at least three rings of detectors. The spatial resolution of scanners is defined as the full width of a point spread function at half the maximum count value (FWHM). This should be better than 5 mm in clinical scanners and it is approaching 2 mm in the state-of-the-art devices.

Stand-alone PET scanners have effectively disappeared from the market. Today, almost all manufacturers only offer PET in combination with CT. Such devices are known as hybrid PET/CT scanners. A PET/CT scanner represents linear arrangement of PET scanner and CT scanner, equipped by one conjoint patient’s couch, enabling stepwise scanning of patients without change of their position. So, these hybrid PET/CT scanners are also known as in-line scanners. They are exclusively constructed from the state-of-the-art PET scanners and multi-detector spiral CT scanners.

*Although superseded stand-alone PET scanners are still available and can often be purchased quite inexpensively, hybrid scanners are highly recommended to Member States because of their diagnostic and efficiency advantages.*

Rapid progress has occurred in the development of both the PET and CT components during the last few years with the aim of increasing spatial resolution and sensitivity, speeding up data acquisition and reducing radiation burden to patients. An example of a promising approach is breath dependent gating of PET scan to reduce loss of spatial resolution caused by breathing motion. Other options to the basic scanner configuration are available to increase scanner quality and productivity including larger detector arrays.

If diagnostic quality CT images are to be acquired, the obvious necessary external complement to PET/CT scanner is an automated injector of intravenous contrast media to guarantee adequate opacity of vascular structures during CT acquisition. A laser beam generator mounted on walls and ceiling to create crosshair on the patient’s body for his/her exact repositioning at PET/CT scanner and radiation planning system represents another valuable external device.

## 1.5. INFORMATION TECHNOLOGIES

There is a strong need for advanced information systems in order to effectively manage the clinical operations of a PET Centre. The console delivered with the scanner fulfills the minimum requirements for viewing and short-term storage of generated images. The number

of consoles required depends on the workload. Approximately one console is recommended for each seven PET/CT investigations performed per day.

Many patients undergo repeated PET/CT investigations as part of therapeutic response assessment and for surveillance after definitive treatment. Therefore, an electronic Picture Archiving and Communication System (PACS) is an important resource. There are clear benefits in being able to easily review previous studies from the archive and compare these with the current study. Efficient storage and retrieval of images is also an essential precondition for research. A backed-up disk array with a magnitude in the order of tens of terabytes (TB) should be installed, depending on the scanner throughput and number of slices produced by scanner. Remote access to the archive by referring physicians is a significant advantage (e.g. for surgery planning).

The efficiency of operation of the PET Centre can be improved when a Radiological Information System (RIS) is used to support the whole process of investigation, i.e. planning the scanner time for particular patients, patients' dosage, collection of important facts during the whole investigation, creation of documents including cover sheets, worksheets, reports and the release of reports to in-house or even extramural referring physicians. The highest benefit can be achieved when RIS, PACS and Hospital Information System (HIS) are well integrated, allowing clinical and demographic information provided by the referring physician to be directly propagated into fields appropriate to scanner operation and later into the text result, thus minimizing the need for data entry while minimizing the number of possible mistakes. Provision of access to images to the referring clinician is an important function of such a system.

*Compliance of HIS, RIS and PACS to common standards like HL7 ([www.hl7.org](http://www.hl7.org)) and DICOM (<http://medical.nema.org/>) are highly desirable.*

## 1.6. METHODOLOGY FOR ONCOLOGICAL PET/CT INVESTIGATION

For a typical oncological PET/CT investigation, the following events typically occur:

- Patient preparation occurs at home, or in the ward, and involves good hydration for all tracer studies. In the particular case of fluorine-18-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG)-PET/CT, fasting is required for six hours and avoidance of excessive physical exertion for one-three days is recommended.
- Immediately after arrival at PET centre, the patient's history is recorded and an intravenous cannula is placed.
- Oral contrast material is administered in split doses to opacify alimentary canal.
- For patients undergoing a study using  $^{18}\text{F}$ -FDG, the blood glucose level is checked.
- Intravenous administration of radiopharmaceutical.
- Depending on the radiopharmaceutical, the scan is commenced at a variable interval after intravenous administration of the tracer. For whole-body imaging the length of delay is chosen to obtain appropriate contrast between tumour and background. In the particular case of  $^{18}\text{F}$ -FDG-PET/CT, the delay is typically 50–120 minutes.

- Placement of the patient on the couch and positioning within the scanner.
- Scout acquisition of CT topogram and definition of the appropriate field of view to encompass known, suspected or potential sites of disease.
- Use of intravenous administration of contrast material depending on clinical situation and question. Optionally contrast CT can be added after PET scan or not used at all.
- Start of CT acquisition.
- Start of PET acquisition.
- Check of images and their transfer to the digital archive.
- Release of the patient from the PET Centre.
- Reporting and releasing the report for referring physician.

## 1.7. RADIATION PROTECTION

Unlike low-energy photons (140 keV) of technetium-99m ( $^{99m}\text{Tc}$ ) used in scintigraphy, annihilations of positrons generate pairs of high-energy photons (511 keV). As the penetration of radiation through the matter dramatically increases with the energy of photons, standard shielding used in scintigraphy is insufficient for shielding of positron emitters. The situation is further complicated by the short physical half-life of most positron emitters, which yields higher occupational dose rates and necessitates that higher initial activities be handled in the daily routine of staff. Therefore, special shielding must be applied to protect personnel as much as possible during the drawing-up and administration of radiopharmaceuticals, since some irradiation will be unavoidable when staff members need to interact with radioactive patients. It is important to recognize that shielding aprons and gloves that are used for medical X ray examinations, are of no value with PET tracers.

A vial containing enough activity for full day's operation of a PET or PET/CT scanner comprises 5–10 GBq. For this activity, 6 cm thick lead shielding is desirable in terms of radiation protection. A thinner and therefore more practical container with the same stopping power can be produced from tungsten or even from depleted uranium but these options are more expensive.

It is important to implement a compatible solution for the complex series of processes involved in the handling of radiotracers. That means shielding for:

- Transportation from the radiopharmaceutical laboratory;
- Temporary storage of radiotracers;
- Safe withdrawal of individual doses into syringes and measurement of their activity;
- Syringes and safe administration of radiotracer to the patient;
- Temporary storage of radioactive waste.

There are custom-designed shielding units and even fully automated systems for filling syringes that are commercially available to aid in reducing occupational exposure to radiation in PET facilities.

Appropriate shielding of walls is also important. However, room layout and size is of higher value because the dose rate decreases with the square of the distance from the radioactive source. It is desirable to separate radioactive patients from the vicinity of personnel as much as possible. When a gamma camera also operates in the PET Centre, it is important to prevent the highly penetrating radiation from PET tracers influencing the sensitive scintigraphic detectors by locating it at an appropriate distance from patients undergoing PET studies and by use of appropriate wall shielding.

Training of personnel is the key issue. Even personnel experienced in the handling of unsealed sources used in conventional nuclear medicine can encounter a significant increase of personal doses after introduction of PET technology. Education regarding shielding techniques and the need to minimize the time of exposure to patients is critical. Most discussion with patients should occur before administration of radiotracer, and subsequent contact should be restricted to procedures needed for safe and professional performance of the scan. As few individuals as possible should be involved in patient contact after tracer administration.

When the PET Centre is appropriately designed with adequate shielding and personnel are well trained, highly productive operation of PET Centre can be achieved safely with whole-body doses to employees not exceeding 5 mSv per year.

## 1.8. LEGAL CONSIDERATION

In different countries, there are varied regulations concerning the handling of pharmaceuticals and radioactive sources and the allowable exposure of humans to ionizing radiation. It is important that staff of PET centres be cognisant of these regulations and implement them. However, compliance issues can arise if the actual legislation in force has been developed for standard nuclear medicine procedures and doesn't consider high-tech operation of a PET Centre. Nevertheless, due to the high risk of irradiation of personnel and patients as a result of inappropriate handling of unsealed sources of ionising radiation, it is highly desirable that the installation of PET and PET/CT scanners should only be considered in those departments where the conditions of safe operation can be met. National regulatory bodies should approve important aspects of the safe operation of PET and PET/CT scanners.

When radiopharmaceuticals are prepared in-house for use in a small number of patients, it is highly desirable that these should be prepared according to principles of Good Laboratory Practice (GLP) which does not require their registration. In this situation, any adverse effects or unexpected biodistribution of a batch of tracer is likely to be rapidly identified and lead to harm minimization by cessation of further scans. On the other hand, when the production is of commercial scale and distributed to a number of facilities simultaneously, thereby potentially being administered simultaneously to many patients, principles of good manufacturing practice (GMP) should be fulfilled and the radiopharmaceutical should be registered. It is known that  $^{18}\text{F}$ -FDG, fluorine-18-fluoride ( $^{18}\text{F}$ -fluoride) and fluorine-18-fluorodihydroxyphenylalanine ( $^{18}\text{F}$ -FDOPA) are currently registered in some countries at least, and are required to be produced under GMP conditions. Other tracers are typically prepared on individual basis.

Initiation of a PET or PET/CT investigation should be based on presence of a suitable clinical indication determined by a referring physician who is informed about the risks and contraindications as well as the possible diagnostic advantages of the procedure in a particular disease condition and patient. At this moment there are diverse opinions as to whether a given indication is acceptable. The final decision regarding execution of the investigation and the way it should be performed is the responsibility of the physician operating at the PET department.

In some countries, nuclear medicine (responsible for PET) and diagnostic radiology (responsible for CT) have developed as completely separate specialties. In such countries, differing national regulations and credentialing for each of these modalities can complicate operation of hybrid PET/CT scanners. In other countries, nuclear medicine represents the subspecialty of diagnostic radiology simplifying introduction of this technology. Nevertheless, hybrid PET/CT is a new and unique modality that requires knowledge that goes beyond that required to operate and interpret PET and CT as stand-alone modalities.

Whenever possible, it is highly desirable for reasons of efficiency and cost that PET/CT investigations are supervised by an imaging specialist crossed-trained in both modalities (whether initially trained as a nuclear physician or as diagnostic radiologist), rather than by two independent specialists. Unfortunately, hybrid imaging is very young and there are major differences in postgraduate training in different countries. Accordingly, it is not possible to provide general recommendations for cross-training of physicians at this time.

## **2. MODELS OF CLINICAL PET FACILITIES**

There are varied models of PET facilities in different countries and places, as the centres reflect the distinct historical development and organizational structures of health care in the region. Some aspects of these differences are considered in this chapter in order to explain advantages and disadvantages of particular models.

### **2.1. LOCATION OF PET/CT SCANNER**

A PET/CT scanner can be easily installed in any room measuring approximately 8x5 m or even less provided it meets the manufacturer's requirements (weight-bearing capacity, temperature stability, and adequate power supply). Access to a PET/CT scanner will strongly influence performance of diagnostic services.

#### **2.1.1. Inside a hospital**

A PET facility localized inside a large hospital has the advantage of concentration of health care at a single location that is convenient for patients. PET/CT scans can be introduced into standardized institutional diagnostic and treatment paradigms. All patients that meet prescribed criteria can thereby rapidly access PET/CT investigations without complex regulatory or eligibility negotiations. The education of referring physicians is easier, as is the communication of results. The logistic services of hospitals act to support the operation of the PET facility, which is usually organized as a separate clinic of the hospital that is licensed for handling of unsealed radioactive sources. A clear advantage is the availability of advanced life support teams capable of resuscitation in event of rare but life-threatening allergic reactions to intravenously administered contrast media.



This model, however, has the risk of possible over-usage of PET/CT due to it being readily available.

#### *Oncologically oriented hospital*

A PET facility localized within a hospital with a large oncologic case-load can operate very efficiently, due to the ease of patient scheduling. When a late cancellation of PET/CT investigation occurs, another patient can easily replace the cancelled one without loss of scanner time or wastage of short-lived radiopharmaceutical.

In an oncologically oriented hospital the need for PET/CT investigation can easily exceed the capacity of a single PET/CT scanner, limiting access for patients from other nearby healthcare facilities. This should be considered at national or regional level, when introducing the first PET facility if equity of access is to be achieved.

#### *Hospital without oncological orientation*

In a hospital that cannot fully utilize a PET/CT scanner with its own patients, it is more difficult to operate the PET/CT scanner as efficiently as there is no pool of patients ready for PET/CT investigation to replace patients who cancel or don't attend their investigation. This is offset by greater potential equity of access to the PET/CT scanner by patients of other healthcare facilities.

### **2.1.2. Stand-alone facility**

PET facilities have also been established as stand-alone centres, i.e. outside any hospital. These PET facilities must make an effort to overcome the disadvantages associated with lack of an intrinsic patient population. This bigamy not present a large problem since the vast majority of patients can undergo PET/CT on an outpatient basis. A necessary requirement for such a facility is access to good transportation for patients.

The communication of such a PET centre with collaborating health care facilities needs to be facilitated as much as possible. Connection of PACS systems for rapid access to reports and images and the possibility of teleconferencing are desirable.

Access to medical emergency facilities is important to prevent deaths from extremely rare but potentially fatal allergic reactions to contrast media.

When establishment of a new stand-alone PET facility is under consideration, the risk of inadequate patient numbers to support efficient operation of the facility should be anticipated. This may be particularly the case when new facilities are established in centres that formerly referred patients to the stand-alone facility.

### **2.1.3. Mobile facility**

Various PET/CT scanners can be mounted on trucks. This mobile unit can operate on a regular or irregular basis in one region. The advantage is that even small health care facilities gain access to PET/CT technology tailored to their demands (e.g. two days a week or once per three weeks). The advantage of this solution is that the patients do not have to travel to a distant PET Centre. The major disadvantage relates to the additional cost of enabling mobility of the scanner. Strenuous efforts are required to achieve smooth organization of operation

including planning the journey, and ensuring availability of personnel and radiopharmaceutical.

When local personnel are employed to report the PET/CT scans, there is the disadvantage of generally lower experience compared with high-throughput facilities and therefore a risk of lower accuracy of some reports. However, better communication with local referring doctors is likely to be achieved compared to when reports are generated by remote specialists using teleradiology.

The advantage of a mobile PET/CT solution is its high flexibility. When one hospital loses the interest in utilising the mobile PET/CT service (e.g. it installs its own PET/CT scanner), the mobile facility can easily move to another region of need.

#### **2.1.4. Non-clinical research institution**

In the past, PET scanners were also installed in some non-clinical facilities where they primarily served a research role. When not being occupied by research studies, these scanners could also be utilized for clinical investigations. This model is no longer viable because specialized animal PET scanners are available on the market and they are more appropriate for research in comparison to clinical PET/CT scanner.

Of the current models of PET/CT facility, efficient use of the scanner, staff, available isotope and other infrastructure requires a high throughput of patients. *Optimal clinical utilization of PET/CT is best achieved in a tertiary healthcare facility.*

## **2.2. LOCATION OF RADIOPHARMACEUTICAL PRODUCTION**

The strategy regarding where to install a PET/CT scanner is highly influenced by the availability of a regular and highly reliable supply of radiopharmaceuticals with short physical half-life. The most popular radionuclide for PET is  $^{18}\text{F}$  with the half-life of around two hours. This means that at two, four, six and eight hours after its production only 1/2, 1/4, 1/8 and 1/16, respectively, of the original activity remains. Therefore, a PET/CT scanner located within four hours from the production unit is acceptable but becomes increasingly impractical if transportation times exceed this.

When considering establishment of a new PET Centre it is important to realize that a PET/CT scanner can operate immediately after its installation however production and distribution of radiopharmaceuticals for human use presents a greater logistic problem and operation often cannot commence as quickly as the scanner. Many tests and validation procedures must be performed to fulfil criteria of national regulatory bodies. The licensing process takes time. The regular preparation or production of radiopharmaceuticals for human usage may take up to one year after installation of all technology. Therefore appropriate timing of installation of PET/CT scanner is crucial.

Radiopharmaceutical production is also typically more frequently affected by down-time in comparison to PET/CT scanners. Accordingly, there are advantages in having some redundancy of licensed suppliers of radiopharmaceuticals. Existence of competitors in the market is of general advantage as well but needs to be balanced with the potential for wastage of resources if insufficient doses are sold by each supplier to amortise production costs.

### **2.2.1. Supply from distance**

It is possible to install a PET/CT scanner up to four hours from a production facility for radiopharmaceuticals. However, before committing to such a model, a feasibility study should be done with tests simulating regular delivery of  $^{18}\text{F}$  based radiopharmaceuticals twice a day. Unexpected complications like a fog at the airport, ground ice, traffic jams, special check-in requirements when handling radioactivity etc. should be taken into consideration and the reliability of transportation within time limit of four hours should be assessed. For air transport, a feasible flying time is generally two hours or less when combined with the time taken for road transportation and goods' clearance. Door to door transportation is often influenced by the traffic conditions at different times of day and by weather. Again, testing this under appropriate situations is vital to ensure practical operation of a remote site.

Supply from distance is valuable in following situations and aspects:

- Temporally, when the PET/CT scanner is already installed, but the local preparation/production of radiopharmaceuticals is under construction or licensing;
- Secondary source backing-up local production;
- Source of complementary radiopharmaceuticals that are not available locally;
- Existence of competitors.

The clear disadvantage of the supply from the distance is the higher cost and inability to access radionuclides with a short half-life. The latter item is not a big disadvantage for clinical PET/CT as the vast majority of investigations is based on transportable  $^{18}\text{F}$ .

### **2.2.2. On-site individual preparation**

On-site individual preparation of radiopharmaceuticals is advantageous since radionuclides with shorter half-life can be utilized as well as complementary radiopharmaceuticals for specific diagnostic tests. The disadvantage of this approach is the higher cost, because the complex facility installed and the personnel serve only one clinical PET Centre.

### **2.2.3. Satellite concept**

The satellite concept merges both previous concepts and represents the most efficient model. It is valuable to create one centrally positioned production unit located in close proximity to several PET/CT scanners and co-located with at least one of these. This means that at least part of production can be utilized directly on site without any losses due to transportation. The higher production capacity enables supply to other scanners within a distance of up to four hours. Thus, the cost of the equipment and personnel can be divided between more investigations. Strategic location of central unit requires good access to traffic arteries.

The satellite system of distribution can be established step-by-step. Production can initially serve one or more local PET/CT scanners. The existence of production unit facilitates the decision of other health care facilities in the proximity to install their own PET/CT scanners, which will subsequently be supplied from the central production unit. *The satellite radiopharmaceutical model is highly recommended.*

### 2.3. NUMBER OF INSTALLED SCANNERS

Utilization of one PET/CT scanner is a standard. Creating a larger facility with more scanners increases its efficacy significantly. To operate more than one scanner in fact doesn't require twice the amount of radiotracer and thereby reduces production and transportation costs for each individual patient dose. Medical, technical, nursing and secretarial personnel can also be allocated more efficiently. In case of planned down-time or unexpected breakdown of one scanner, the other can be utilized for more acute patients or operate for extended hours to prevent patients being cancelled. This is particularly important for patients already injected with radiotracer, thus minimizing undesirable wasteful irradiation of patients. When more scanners are installed, the operation of PET Centre becomes smoother and more robust.

As the number of investigations increases, radiation protection of the staff becomes more important. This can be solved through use of various shielding systems available on the market.

*Planning of more than one PET/CT scanner per facility is highly recommended.*

### 2.4. EXAMPLE OF PET CENTRE

The IAEA supported a project to establish a model PET Centre in the Czech Republic in the late 1990s. At that time the Czech Republic was considered as a post-communist country under development. The aim of the project was to test whether the creation of PET Centre is feasible in countries of a similar level of development. The project was successful and it resulted in the introduction of clinical PET into daily medical practice. Consequently, it stimulated extension of the existing PET Centre with installation of a PET/CT scanner and also installation of four other scanners into three hospitals in different regions of the Czech Republic. The final benefit of the project is reflected by the fact that the availability of PET in the Czech Republic has now reached similar levels to those in all but a few of the most developed European countries (>1500 PET and PET/CT investigations per 1 million of inhabitants in the year 2007). This project will be reported in more detail later in this document. It should be noted that it represents only one successful model among many other different PET facility models that may be more or less successful.

#### 2.4.1. General concept

The first PET facility was established as a core of a future satellite system on the premises of the Na Homolce Hospital in Prague, which is centrally located in Bohemia. The hospital is highly specialized for neurology and cardiology. Oncology represents only a small part of its activity. The relatively low internal demand for oncology studies enabled equal access of PET investigation to all referring physicians in the Czech Republic, based on medical priority.

#### 2.4.2. Building outline and equipment

A building that was ten years old and comprised two-floors (Fig. 3) was completely renovated internally, and a cyclotron vault was constructed adjacent to this. The floor plan of the building occupies 720 m<sup>2</sup> approximately with the adjacent cyclotron vault occupying an additional 90 m<sup>2</sup>. The lower floor houses the laboratory for mass production of radiopharmaceuticals and their dispatch by cars to satellite hospitals and by elevator to upper floor for on-site utilization. On the upper floor there is a nuclear medicine outpatient clinic.



*Fig. 3. The free-standing building of the PET Centre in Prague (Na Homolce Hospital).*

#### *Radiopharmaceutical production and preparation*

Radiopharmaceutical unit consists of cyclotron vault with 2 m thick walls and ceiling designed from concrete of defined quality. A high-capacity production cyclotron is housed inside (energy of protons 18 MeV, capacity up to 500 GBq of  $^{18}\text{F}$ ). The access to the cyclotron is through a labyrinth covered by heavily-shielded, motorized slip doors. Operator and utility rooms are located in close proximity to this.

An 'air-lock' antechamber forms a second compartment. Positive pressure ventilation provides for air of defined quality. Together with a special regime of entrance and dressing of personnel, category C laboratory conditions are achieved. Inside this compartment, there are hot cells with laminar flow of the air filtered through HEPA filters, thus a clean environment of category A is achieved within hot cells. Synthesis modules are housed inside the hot cells and they are fed by radioactive precursors from cyclotrons via a shielded capillary. One of the hot cells serves for dispensing of the radiotracer into vials. Moreover, within the clean room, there is also a laboratory for preparation of radiopharmaceuticals for scintigraphy equipped with laminar flow hoods that house Molybdenum-99/Technetium-99m ( $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ ) generators.

A laboratory for quality control of radiopharmaceuticals represents the next important compartment. This is equipped with various measuring devices. All these three main compartments including passages belong to a controlled zone, which has negative pressure ventilation as a whole. There is a monitored air waste gate with safety valve.

Other important components of this facility include material sluices, elevators, waste storage cabinets, archives, offices, dressing rooms, a hygiene loop, and a room for radiopharmaceutical dispatch.

### *Outpatient clinic*

There are three connected compartments within the outpatient clinic. The first one represents an area for patients, including the reception desk, a waiting room, toilets, and access to the scanner rooms. The waiting room is a long spacious corridor with separate groups of seats in a geometric design which facilitates radiation protection of patients.

On the opposite side of the building there is another compartment comprised of archives, storage, offices for personnel including a meeting room, two reporting rooms, and one common control room with lead glass windows facing three scanner rooms. Both compartments join each other at the reception desk of the clinic, where the archives are readily available to receptionists.

Adjacent to these two compartments there is a controlled zone consisting of a room for withdrawing radiopharmaceuticals from vials into syringes, a room for radioactive waste, a hygiene loop, four rooms for patient preparation and administration of radiopharmaceuticals and three scanner rooms equipped with:

- Double detector general purpose gamma-camera for single photon emission computed tomography (SPECT);
- Dedicated BGO based PET;
- Hybrid LSO based PET/CT (dual slice CT).

#### **2.4.3. Personnel**

The number of personnel has increased since opening in accordance with the growing capacity of the centre. At the time of this report, with  $^{18}\text{F}$ -FDG being produced two-three times per day on five-seven days per week, two cyclotron operators and four radiochemists are required for radiopharmaceutical production and two additional specialists for quality control.

The outpatient clinic operates for 13 hours a day from Monday to Thursday, and for nine hours on Friday. There are seven licensed physicians including the medical director. Currently, these are five nuclear physicians and two radiologists. In addition, there are 10 technologists (seven radiological assistants and three nurses qualified in nuclear medicine), three administrative workers and one general nurse.

#### **2.4.4. Workflow and overall performance of the clinic**

There are three deliveries of  $^{18}\text{F}$ -FDG per working day: at 7:15 a.m., at 11:00 a.m. and at 2:30 p.m. (The late delivery is omitted on Friday). Technologists start at 6:30 a.m. with quality check of systems. The first patients are scheduled for 7:00 a.m., the first administration of  $^{18}\text{F}$ -FDG occurs at 7:20 a.m. and acquisition of the last patient finishes between 7:00–7:30 p.m. (on Friday around 2:30 p.m.).

Approx. 12 patients are scheduled for the older BGO PET scanner (10–11 torso studies and 1–2 brain studies) and 19 patients are scheduled for faster LSO PET/CT scanner daily. The organization of the workflow is apparent from Fig. 4. The total number of investigations and their spectrum is reported in Fig. 5. Such high throughput of patients was not achieved immediately after installation of each scanner, but evolved over a two-year period of fine-tuning of all processes.

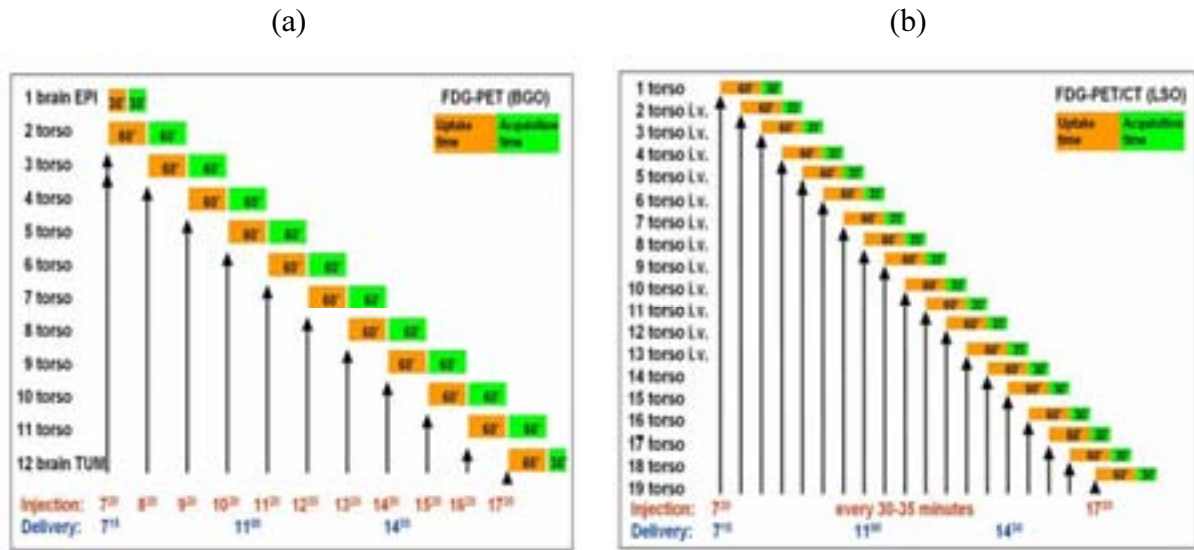


Fig. 4. Schemes of scheduling of  $^{18}\text{F}$ -FDG-PET (a) and  $^{18}\text{F}$ -FDG-PET/CT scanning (b) in a daily clinical routine. Times of  $^{18}\text{F}$ -FDG injection are depicted for particular patients; uptake period (orange) and acquisition (green) follow and overlap with another patient (s).

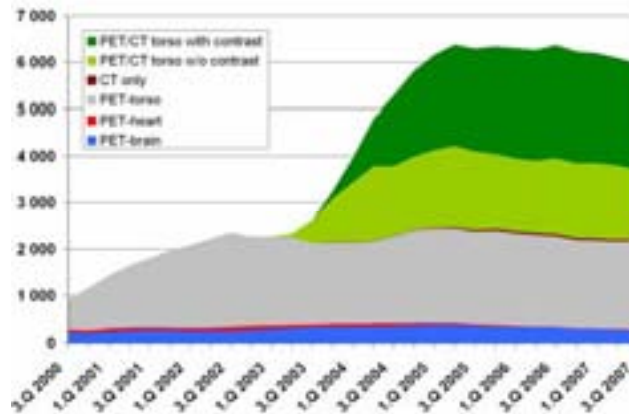


Fig. 5. Evolution of different PET and PET/CT investigations. Total number of investigations within the last 12 months is represented at each time point. The slower slope at the beginning represents introduction of new modality into clinical practice, while the more rapid slope is encountered later, when a clinically more attractive high throughput PET/CT scanner was installed in the period when clinicians had already become familiar with PET.

#### 2.4.5. Radiation protection

At the same beginning of the operation of PET clinic, no compact system of shielding was commercially available and personnel handled  $^{18}\text{F}$ -FDG and PET patients in similar way as with SPECT. Even though the staff were used to handling unsealed sources of  $^{99\text{m}}\text{Tc}$  in routine nuclear medicine practice, the average personnel doses increased significantly despite

the number of PET patients not exceeding five per day in the early years of operation. In this situation there was no potential for a further substantial increase of numbers of PET investigations. Thus, the behaviour of personnel had to be changed and a new generation of shielding had to be developed. This had an excellent effect and was effective until the installation of the next PET/CT scanner (Fig. 6). The significant increase of administered activity that occurred due to this (Fig. 7) resulted in the second peak in personnel doses. Therefore, a more efficient type of shielding was developed and applied again. Despite the high amount of patients investigated and the amount of activity utilized within the facility, the average whole-body personnel doses are at the level of 4 mSv per year, which is acceptable in most regulatory environments.

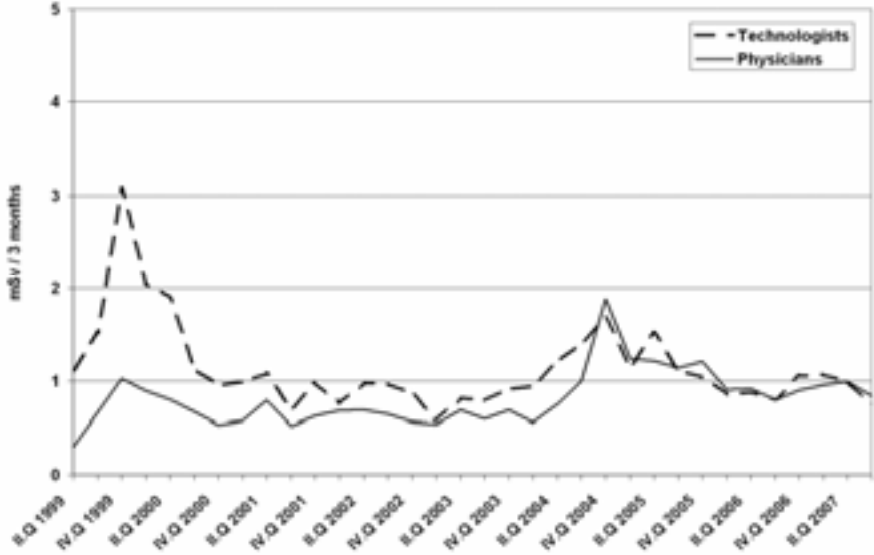


Fig. 6. Evolution of average whole-body doses per quarter of a year are displayed separately for physicians and technologists. There are two apparent peaks just after introduction of new PET, and later, PET/CT scanners. The scale of 5 mSv per quarter of a year represents the aliquot of 5 years occupational limit (100 mSv).

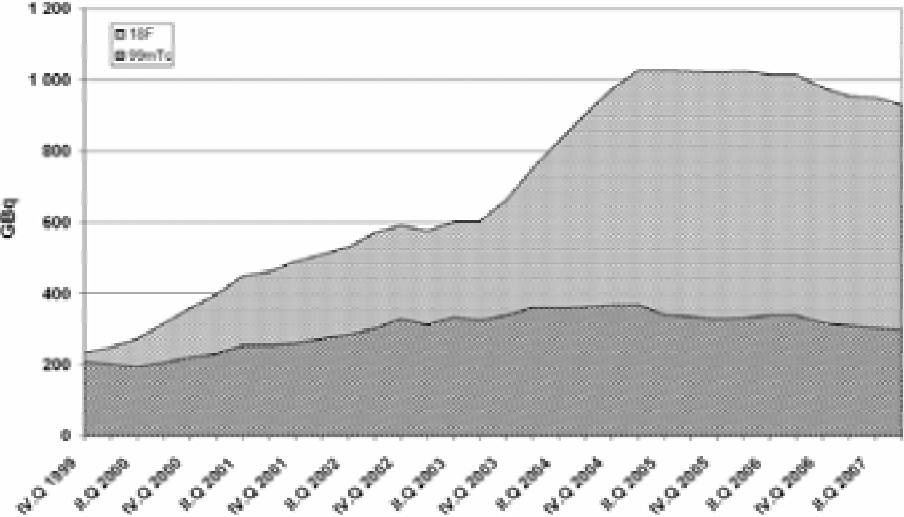


Fig. 7. Evolution of total activity administered to the patients. The total amount of activity within the last 12 months is represented at each time point.



### 3. ADVANTAGES AND DISADVANTAGES OF PET COMPARED TO OTHER DIAGNOSTIC IMAGING MODALITIES

#### 3.1. HISTORICAL OVERVIEW OF DIAGNOSTIC IMAGING

The traditional physical examination that follows medical interview of a patient consists of inspection, palpation, percussion, auscultation and neurological examination. The discovery of X ray by Wilhelm Conrad Roentgen in 1895 and its application to medicine greatly facilitated the accuracy of medical diagnosis. In particular, it expanded the capability of inspection from superficial naked-eye observation to detection of objects inside the body that are opaque to the X ray, such as bones. The development of contrast media that followed made it possible to observe objects such as the gastro-intestinal tract and blood vessels, which are transparent to X rays when contrast media is not used.

In the early 20<sup>th</sup> century, Thomas Edison tried to take X ray photographs (radiographs) of the human brain, which eventually resulted in failure because of the skull that covers the brain and is opaque to the X ray. This dream of Edison's was realized 70 years later when CT was invented by Godfray Hounsefield. As in other radiographs, the CT image reflects variation in the attenuation of X rays in the object imaged. Its ability to discern minute differences in X ray attenuation through multiple projections allows the visualization of structures invisible with conventional X ray images. CT technology revolutionized diagnostic imaging and rapidly became the dominant imaging modality not only for brain imaging but also for whole body imaging. The technology has evolved with faster scanning and image processing as well as better spatial resolution. The recent development of multi-detector CT (MDCT) has even enabled cardiac imaging for the diagnosis of ischemic heart disease.

The discovery of the X ray in Germany was rapidly reported world-wide. Antoine Henri Becquerel, who had devoted himself to the study of fluorescence and phosphorescence in Paris, France accidentally found that uranium salt spontaneously emits a strongly penetrating ray. After serial experiments, he assumed that these fluorescent materials emit X rays. Marie Curie coined the term 'radioactivity' for this phenomenon and devoted the rest of her life to the study of radioactive materials. She found new radioactive elements, polonium and radium in 1898, after tremendous efforts made in cooperation with her husband Pierre. In Cambridge, UK Ernest Rutherford discovered that uranium emits two different types of radiation, which he named alpha and beta rays. The third type of radiation, gamma ray was discovered by Paul Viral. Frederick Soddy, who worked with Rutherford, found that radium D could not be separated chemically from lead. He gave the two elements the nomenclature 'isotopes' to signify that they occupy the same position in the periodic table of elements. George de Hevesy, who also worked with Rutherford, detected the chemical behavior of lead by measuring radioactivity of its isotope radium D. He later used the same technology to study behavior of thorium B in a pea plant and then that of radium D in rabbits. This technique, which is based on the tracer principle, was first applied to humans by Helman Blumgart and Soma Weis in 1927 in the USA. In order to measure the circulation time, Radon was intravenously injected in one arm and appearance of radio-activity in the other was detected using Willson's cloud chamber. Thus, nuclear medicine began as an application of the tracer principle.

Subsequent invention of the cyclotron in 1931 by Ernest Lawrence and discovery of artificially produced radioisotopes in 1934 by Frederic and Irene Joliot-Curie allowed de Hevesy to use phosphorus-32 (<sup>32</sup>P) as a tracer in biological studies. Through his tracer studies Hevesy observed that living organisms are in a constant state of chemical flux, characterized

by a delicate balance between the rate of formation and rate of breakdown of body constituents. This 'dynamic state of body constituents' is an important discovery that resulted from tracer technology.

Another decade or two elapsed before various radio-nuclides and tracer compounds became routinely used in clinical medicine. During World War II, Enrico Fermi and his colleagues developed nuclear reactors as part of the wartime Manhattan Project, which also led to the development of atomic bombs. When the war was over nuclear reactors were used for peaceful objectives, including biomedical research. Reactor-produced radionuclides and tracers started to be shipped all over the world.

The development of the rectilinear scanner in 1951 by Benedict Cassen, in combination with iodine-131 ( $^{131}\text{I}$ ) labeled tracers, made it possible to provide nuclear medicine images (scintigraphy) that could be used for routine clinical diagnosis. The scintillation (gamma) camera developed by Paul Anger in 1956 became the prevailing instrument for the nuclear medicine imaging when Harper developed the  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ -Generator in 1964. When this became commercially available it provided a 'happy marriage' of the capabilities of the Anger camera and  $^{99\text{m}}\text{Tc}$ .

The first tomographic nuclear medicine imaging techniques were developed by David Kuhl in the late 1950s and early 1960s. These included both radioisotopic emission and transmission scans of the body. The emission scanning technique came to be called SPECT but only became widely available in the early 1980s. The use of radionuclide transmission scans actually preceded X ray tomography by several years but didn't enter clinical practice until well after CT, when combined with PET for attenuation correction. Nevertheless, having been stimulated by the great success of CT in diagnostic imaging, gamma cameras were eventually adapted to detect and reconstruct axial tomographic images. PET grew out of the work of David Kuhl and the techniques of back-projection image reconstruction that he developed for nuclear medicine imaging. Michel Ter-Pogossian, in St Louis, and Gordon Brownell, in Boston, pioneered PET scanners in the mid 1970s, utilizing the phenomenon of dual annihilation photons from positron decay to develop the principle of coincidence detection. PET, which had been used primarily for clinical research, gradually became a routine clinical tool from the late 1980's. A significant advance in PET technology was its combination with CT by David Townsend and co-workers in the 1990's. At the present time hybrid PET/CT is the dominant configuration for PET imaging.

Two groups of researchers working independently in the USA, one led by F. Bloch and the other by E.H. Purcell discovered nuclear magnetic resonance (NMR) and reported almost simultaneously in 1946. Since then NMR spectroscopic investigation of matter became a powerful analytic tool in chemistry and physics. Relaxation times ( $T_1$  and  $T_2$ ) can also be measured as NMR parameters that provide information on the mobility and chemical environment of nuclei. It was observed in 1971 by Raymond Damadian that  $T_1$  relaxation time is prolonged in tumour tissues as compared with the values in normal tissues. Subsequently  $T_2$  relaxation time was also found to be prolonged in tumours. These changes in relaxation time were attributed to the increased water content and changes in the intracellular electrolyte composition. Paul Lauterbur was the first to demonstrate, in 1973, that images could be produced by using the interaction of magnetic and radiofrequency (RF) fields. Further methodological improvements followed, which have led to the generation of NMR tomographic images comparable to images obtained by CT. Clinical NMR images, later called Magnetic Resonance Images (MRI), have been primarily obtained by using the signal from hydrogen nuclei (protons), which abundantly exist as water in living tissues. Progress in

technology development has been rapid leading to improvement in image quality and speed of image acquisition and processing. This had led to the widespread clinical use of MRI.

After about 1985, CT and ultrasonography (US) rapidly replaced liver scintigraphy, which had been the most frequently used non-invasive imaging procedure since the 1960s. The technology of US had been developed and improved in relation to military use. After World War II the technology was applied to peaceful uses, particularly in medical diagnosis. US technology has been widely used in various medical specialties as a handy real-time imaging procedure that can be performed at bed-side, just like a modern-age stethoscope. There are several reasons why US is so widely used. It does not use ionizing radiation, limiting regulatory constraints. The cost for US instruments is much less relative to other imaging devices such as CT, Magnetic Resonance Imaging (MRI) and PET. Furthermore, technological advancements in transducer digital signal processing, introduction of color Doppler and contrast agents have resulted in better clinical images in terms of sensitivity and spatial resolution. All these factors have contributed to frequent clinical utilization of US.

## 3.2. ADVANTAGES AND DISADVANTAGES OF EACH IMAGING MODALITY

### 3.2.1. Simple radiography with and without contrast agents

Differences of X ray absorption by the body components when irradiated X rays pass through the body are recorded by X ray film or other recording materials such as imaging plates as two dimension images.

The instrument used is relatively inexpensive as compared with CT, MRI, PET and PET/CT. The spatial resolution of the images is high. The images are useful in the detection of lesions in the bone, because of their radiodensity, and in the chest, because of the contrast provided by air within the lung parenchyma. It is also useful in the abdomen when air-fluid levels exist. With use of contrast agents the stomach and gastro-intestinal tracts, urinary tracts and vessels can be visualized. However, in general, the ability to distinguish soft tissues is poor.

Patients are exposed to ionization radiation, but this has minimal health effects. Elaborate radiographic techniques, such as interventional radiology (IVR), may cause higher radiation exposures but these are usually offset by the diagnostic or sometimes therapeutic benefits of such procedures.

### 3.2.2. CT

The CT image reflects variations in the attenuation of collimated X ray beams that pass through the body and are detected by a scintillation detector. The X ray tube and the detector are connected rigidly and are supported by a gantry. An object to be imaged is scanned by the stepwise rotation of the gantry surrounding the body. The collected data consists of a series of profiles of the attenuation of X rays in the tissues. These radiation transmission profiles acquired by the CT detector system are recorded in a digital form by a computer system. Images of transverse sections of the body are reconstructed using computer algorithms. The method is termed the 'convolution' or 'filtered back projection' method.

The ability to discern minute differences in X ray attenuation allows the visualization of the body structures that are invisible with conventional radiographs. Although contrast resolution is higher than conventional radiograph, spatial resolution is less.

The CT enables the accurate and noninvasive quantitative determination of the X ray absorption of the tissues.

CT examinations are now applied to wide varieties of diseases in the brain, chest, bone, hepato-biliary system, pancreas and genitourinary system. Recent advances in technology have achieved rapid scanning, enabling even examination of the beating heart. It can be applied easily to seriously ill cancer patients and small children without concern regarding motion artefacts. Artefacts caused by bones potentially limit examinations of soft tissues and organs surrounded by bony structures. These include the cerebellum, spinal cord and oral cavity.

Radiation doses to the patient are relatively high. Repeated examinations of small children have to be carefully justified and the possibility of using other examination procedures that do not utilize ionizing radiation should be considered. The rapid increase in the use of CT worldwide has been associated with increased population diagnostic radiation exposure doses and has caused concern with regard to future cancer risk. However, many of these estimates are based on a calculation of radiation risk involving a linear, no threshold model that may over-estimate the true risk of low-dose radiation exposures.

### **3.2.3. Magnetic resonance images (MRI)**

Nuclei with magnetic moment alone can produce NMR signals. Those nuclei have either an odd number of protons or neutrons (or both). Examples are H-1(p:1, n:0), H-2(1,1), C-13(6,7), N-14(7,7). They turn on their axis in the same way that the earth spins. As all nuclei have at least one unit of charge, spinning charged nuclei generate magnetic field or magnetic moment. Nuclear magnetic moments that have random orientation will align in the presence of strong external magnetic field ( $B_0$ ) either with or against the magnetic field. The sum of the excess magnetic moments, or macroscopic magnetization vector  $M$ , will have a size or magnitude related to strength of  $B_0$ . A higher field strength magnet will provide a greater signal to noise ratio that can be translated into NMR images with improved spatial resolution or reduced imaging time. H-1 or proton is regarded as the most suitable nucleus for NMR imaging because of its large natural abundance in the body and the consequently highest signal that it generates due to the degree of intrinsic magnetic field.

Although the equilibrium magnetization vector ( $M$ ) is difficult to measure at rest, this vector exhibits dynamic properties of great importance for NMR detection, when moved off its equilibrium. By applying the second magnetic field using specially designed antennas or radio frequency (RF) coils the  $M$  is deflected or tipped off axis and rotates in conical fashion about the  $B_0$  magnetic field direction. The frequency of this movement, or precession is proportional to magnetic field strength ( $B_0$ ) and its constant, called the gyromagnetic ratio, varies for different nuclei. For example, when 42.6 mega Hertz (MHz) electromagnetic energy is applied by a RF coil using a 1 Tesla (=10,000 gauss) magnetic strength machine only H-1 nucleus in a tissue sample responds and gives signals (resonance). Other nuclei with different gyromagnetic ratios in the sample remain quiet. Such absorption and reemission of radiofrequency electromagnetic energy by certain nuclei placed within strong magnetic field is the essence of NMR. The same coil used to transmit the RF pulse can be used to receive the NMR signal. The strength and duration of the RF pulse determine the angle of tilt of  $M$ . The maximum signal is obtained when the magnetization vector is tipped 90 degrees off axis. After an RF pulse is applied, the magnetization vector  $M$  returns to the equilibrium position along the z-axis parallel to  $B_0$  direction. These processes are characterized by two sample related time constants, that is  $T_1$  (longitudinal or spin-lattice) and  $T_2$  (transverse or spin-spin)

relaxation time. These parameters enable excellent soft tissue contrast and sensitivity for lesion detection with the NMR imaging. The induced NMR signal decays with time, which is called free induction decay (FID). A mathematical manipulation, which is called Fourier transformation, converts signal intensity versus time into signal intensity versus frequency. The resultant frequency spectrum is the typical outcome in NMR spectroscopy.

In order to make body images of NMR signal, localization of where the signals come from is necessary. With this purpose the magnetic field gradient is used. This magnetic gradient represents a 3<sup>rd</sup> magnetic field, in addition to the static field (B<sub>0</sub>) and the radiofrequency domain (B<sub>1</sub>) and is generated by small electromagnets within the larger main magnets and cause small reproducible changes in the magnetic field from one location to the next. By rotating the gradient electronically, projections can be obtained around the body and an image (MRI) can be re-constructed using computer algorithm in a manner analogous to that used in CT.

Unlike CT, where signal intensity is related to the single parameter of X ray attenuation, a number of variables influence the amount of signals on the MRI. These signals include certain characteristics that are intrinsic to the tissues being imaged, such as spin density, relaxation times T<sub>1</sub> and T<sub>2</sub>, and flow or diffusion within the body.

The expression of these parameters is determined by the specific RF-pulse sequence used for data acquisition. The orientation of cross sectional images is not limited to the longitudinal axis of the body but can be chosen freely.

MRI features the high tissue contrast, which gives discrimination between tissues of similar densities such as the grey and white matter in the brain, as well as between cancer and normal tissues. The use of paramagnetic contrast medium enhances tissue contrast, enabling better distinction of pathological from normal tissues. The bone, with little water, content does not make any signal and thus does not interfere with visualization of structures surrounded by the bone. This includes sites such as the posterior cranial fossa, spinal cord, etc.

MRI depends largely on difference of imaging methods such as pulse sequences. In spite of recent progress in technology, imaging takes time and therefore motion artefact is problematic in taking images of the sites where physiological motion is unavoidable.

Ferromagnetic substances have to be removed from vicinity of the MRI instruments, which may limit medical procedures such as image guided biopsy, etc. It is not possible to examine patients who have metallic substances inside their body. Although safety of MRI with less than 2 tesla (T) static magnetic field was regarded safe so far, potential biological effects arising from ultrahigh (>4T) static magnetic fields, rapidly switched magnetic field gradients, and radio-frequency absorption remain to be studied. Although widely considered to be safer than other diagnostic imaging modalities because of lack of ionizing radiation, the health effects of high field strength MRI have not been extensively evaluated but include a risk of significant thermal heating leading to burns and tissue coagulation, potentially leading to death.

#### **3.2.4. Ultrasonography (US)**

Human ears can hear sounds with frequency ranging from 20 to 20,000 Hertz (audio frequency). Sound waves with higher frequency than this range are generally called ultrasound. In US examination high frequency sound waves are transmitted into the human

body and their reflection at the junction of tissues of different acoustic character is detected using the same probe.

By the analysis of the reflection of waves (echo), internal structures and blood flow can be displayed in grey scale images. The time taken for detection of reflection waves reflects the depth of body structures. The transverse position is determined by moving the direction of the US beam being transmitted inside the body. Transmission of US is impeded by gas and bone. In order to transmit US into the body an entrance point (acoustic window) of the US beam has to be found. Generally this is achieved by angling the probe away from gas and bone and using an acoustic gel to improve sound transmission through the skin.

In general US instruments are less expensive than other imaging devices. Because of the small size and portability of scanning devices, US is very convenient and can be used in a wide variety of clinical settings, including at the bedside of very sick patients. As there is no need to be concerned about the hazardous effects of ionizing radiation, regulation of US devices is much more relaxed than for other diagnostic imaging modalities. The images are displayed instantaneously and image interpretation can be made on real time basis. On the other hand the diagnosis is more examiner dependent and therefore potentially less objective than other imaging procedures. Spatial resolution is not as fine as for CT. However, reflection of US occurs at the boundary of tissues of different acoustic characteristics and is not dependent on the thickness of the structure. Therefore, very thin structures, such as the layers of the intestine can be clearly visualized. Quantitative analysis is difficult in general and is one of the limitations of US. Recent adaptation of US to endoscopic use has increased the spectrum of disease that can be evaluated. Endoscopic ultrasound (EUS) and endo-bronchoscopic ultrasound (EBUS) are now important techniques for evaluating primary tumours of the bowel and bronchus, respectively, and of adjacent structures, particularly including regional lymph nodes. Both techniques also allow biopsy.

### **3.2.5. Nuclear medicine imaging including SPECT and PET**

The imaging modalities described above primarily display the structure of the human body and thereby provide anatomical information that can be used for diagnosis of diseases. On the other hand, nuclear medicine imaging is based on tracer principles and primarily gives images of function, including physiology, biochemistry or metabolism, by analyzing the dynamic behaviour of molecules in organs and tissues. After the 1980s, clinical nuclear medicine imaging entered the era of tomography, reflecting the widespread clinical acceptance of the advantages of CT. SPECT and PET are now the dominant imaging procedures in nuclear medicine. Changes in function often precede changes in anatomy in various disease conditions. Therefore, nuclear medicine imaging may be useful for early diagnosis of disease and for evaluation of treatment effects in the early post-therapeutic stage. Recent progress in image processing, particularly in PET, allows easy demonstration of whole body images and interactive display, which allows easy detection of metastases from cancer, etc. Although contrast of a lesion versus surrounding tissues is high when radiotracers accumulate in the lesion, spatial resolution in general is poor compared with radiographs, CT or MRI. The cost of instruments used is also relatively high. The cost of each examination also depends on the cost of radiopharmaceuticals used and the throughput capability of the scanner.

Patients are exposed to ionizing radiation administered to the bodies. The radiation exposures are different from radiographs and CT, which involve external and generally only partial body exposure, whereas radionuclide administered into patients causes internal whole body exposure in a non-uniform manner determined by the biodistribution and clearance kinetics of

that tracer. Another difference from X ray diagnosis is that the exposure is determined by the radioactivity injected and not by the number of images taken. Therefore, detailed examinations can be performed on different sites and at different times after injection to clarify findings without increasing radiation exposure.

### 3.3. CORRELATIVE IMAGING AND IMAGE FUSION

In the 1960s some institutes superimposed rectilinear scans on radiographs taken with remotely placed X ray tubes. Both techniques were performed to avoid magnification of the image, allowing superimposition of the resulting images without further image manipulation. One of the first applications was to cardiac imaging where the superimposed images were used for diagnosis of pericardial effusion. In the early 1980s PET and CT instruments were installed side by side in Gunma University Hospital PET centre of neuroscience (Maebashi, Japan) to provide similar fused images of tomographic images. Patients were moved by an electrically controlled bed from PET to CT for acquisition of images from both systems in the same anatomical position. The two resulting images were superimposed to allow exact localization of brain lesions. An example was the localization of brain tumours, which accumulate radiotracers such as carbon-11-methionine ( $^{11}\text{C}$ -MET) and  $^{18}\text{F}$ -FDG, in reference to brain anatomy obtained from contrast CT.

As shown in those early examples, it is important to compare images from different modalities in order to achieve the correct diagnosis and then to accurately localize sites of disease. Initially, correlation of images was made by direct visual comparison of films obtained under standardized conditions. Later computer-assisted image acquisition and co-registration became possible. These advances increased interest in correlative imaging and spawned hybrid devices for imaging. The resulting fusion images reflected co-registration of images of different modalities facilitated by means of the hardware. The most successful example of such an approach clinically has been rapid global acceptance of fusion images of  $^{18}\text{F}$ -FDG PET with CT using PET/CT instruments. Single photon emission computed tomography/X ray computed tomography (SPET/CT) is now available and magnetic resonance/positron emission tomography (MR/PET) is under development. These modalities add most value to functional imaging techniques that contain little information regarding anatomy due to the specificity and high contrast that they demonstrate between the target and other normal tissues. In such studies, the ability to combine function and detailed anatomical images such as CT and MRI is crucial for diagnostic and treatment planning purposes.

As fusion images of different modalities become common use, the knowledge and skills required for accurate interpretation of images will change and will impact the system of training and education of nuclear medicine physicians and diagnostic radiologists to meet these needs.

## 4. PET APPLICATIONS IN ONCOLOGY

The glucose analogue,  $^{18}\text{F}$ -FDG, is the workhorse for most oncological PET studies and the tracer for which there is the strongest body of evidence. While much of this evidence has been obtained in head-to-head comparisons with conventional imaging techniques, PET is generally used as a complementary technique in clinical cancer imaging. Indeed, the development of hybrid imaging, as represented by combined PET/CT scanners (Beyer, Townsend et al. 2000) means that the distinction between anatomical and functional imaging has become blurred.

Diagnosis, staging, treatment planning, therapeutic monitoring and post-treatment surveillance are the key processes involved in evaluation of cancer patients and to determine the most appropriate management. Imaging, because of its non-invasive nature, plays a key role in all these phases of cancer evaluation and is currently highly dependent upon anatomical imaging techniques such as CT and MRI. However, being based primarily on size criteria, infiltration of normal structures such as lymph nodes can be difficult to detect on radiological techniques. Similarly, benign processes may form lesions that may be mistaken for tumours. In some diseases, including lung and ovarian cancer, the diagnostic performance of CT is sufficiently poor as to make surgical staging a routine diagnostic procedure prior to curative resection but sampling errors can occur. Despite these limitations, staging remains one of the most important prognostic biomarkers in cancer and is generally used to guide treatment.

Based on a combination of characteristics of the primary tumour (T stage), regional lymph nodes (N stage) and distant metastatic sites (M stage), patients are generally grouped into clinical stages from I-IV. Treatments are then selected and delivered on the basis of this stage. Subject to co-morbidities and the type of cancer, patients with stage I-II disease are generally treated surgically, while patients with stage III disease are treated by combined modalities, often including radiotherapy, and patients with stage IV disease are generally treated with chemotherapy or palliative treatments. Thus, the first step in judging the clinical role of PET is to determine its clinical effectiveness in staging cancer.

Since  $^{18}\text{F}$ -FDG imaging was first used for the evaluation of suspected cancer in the 1980s it was clear that high uptake of this tracer was a characteristic of many malignancies. Thus, despite the fact that an  $^{18}\text{F}$ -FDG-PET scan is actually an *in vivo* biodistribution of glucose metabolism, the simplistic assumption that focal accumulation of  $^{18}\text{F}$ -FDG, not related to normal physiological processes, reflects malignancy was associated with quite acceptable diagnostic accuracy in the majority of early validation studies. As discussed in greater detail elsewhere, progressive improvements in instrumentation, particularly the development of PET/CT, have further enhanced the diagnostic performance of PET. Because of this continuing evolution, the clinical effectiveness of PET cannot be necessarily judged from the results obtained in earlier studies nor can that of conventional cancer imaging techniques which have also had ongoing improvements, such as the development of MDCT and higher field strength MRI utilizing new pulse sequences and improved image analysis algorithms. Nevertheless, the performance of PET, like that of any diagnostic test, needs to be defined by certain key parameters including sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy. According to Bayes' theorem, both the NPV and PPV are highly influenced by the prevalence of disease in the test population. Accordingly, sensitivity and specificity are often considered to be the most appropriate parameters to describe the intrinsic diagnostic performance of a test. Clinical validation of diagnostic imaging tests in cancer should be assessed by their ability to deliver meaningful information that can influence patient treatment and outcomes. Given that cancer is a disease that carries a significant likelihood of a decrease in the quality and duration of life, the ability of a test to provide prognostic stratification of groups of patients is important. For individual patients, the accuracy of the staging process is critical. Unfortunately, more accurate diagnosis of cancer may not necessarily improve survival of an individual patient, particularly if no effective treatment is available. Nevertheless, it may prevent futile attempts at locoregional cure, sparing the patient the financial and physiological costs of this therapy.

There is now abundant evidence that whether validated by pathology, or clinical follow-up,  $^{18}\text{F}$ -FDG-PET is more accurate, due to a variable degree of superior sensitivity, specificity or



both, than conventional imaging techniques for both the diagnosis and staging of cancer (Gambhir, Czernin et al. 2001) and the diagnostic performance of molecular imaging with  $^{18}\text{F}$ -FDG has been further enhanced with the advent of PET/CT (Czernin, Allen-Auerbach et al. 2007). Furthermore, there are increasing data indicating that these techniques have a high impact on patient management. Nevertheless, because of cost and availability issues as well as technical performance characteristics, not all patients with cancer are suitable for evaluation with PET. For example, PET is not appropriate for staging very small primary carcinomas, since partial volume effects and a very low likelihood of distant spread conspire to limit both apparent sensitivity and specificity. Similarly PET is probably of limited in disease that is obviously widely metastatic on routine clinical evaluation, unless being used as a baseline for therapeutic response assessment or to detect otherwise occult lesions at risk of complications and that may benefit from palliative intervention.

Accordingly, in considering the clinical role of PET in oncology it is appropriate to consider a problem-based system of indications that can potentially be applied to any cancer provided that it has documented avidity for  $^{18}\text{F}$ -FDG in most cases. 'Indication fragmentation', as applied in many recent institutionalised health technology assessments (HTA), has complicated the evaluation of the clinical efficacy of  $^{18}\text{F}$ -FDG-PET and lacks a clinical orientation. Issues relating to the performance of HTA and cost-effectiveness are discussed elsewhere.

A potential range of clinical scenarios for which  $^{18}\text{F}$ -FDG-PET has shown to be worthwhile includes:

- The non-invasive characterization of the likelihood of malignancy of mass lesions, which are not readily amenable to biopsy, or for which biopsy attempts have already failed.
- The detection of cancer in patients at significantly increased risk of malignancy on basis of elevated tumour markers, clinical symptoms or signs but in whom routine tests have failed to detect a cancer.
- Staging of high-risk malignancy amenable to potentially curative therapy for which disease extent is critical to treatment selection.
- Planning of highly targeted therapy where delineation of disease is critical to efficient and safe treatment delivery and thereby, therapeutic success.
- Assessment of therapeutic response in diseases with a significant likelihood of treatment failure, and for which earlier demonstration of therapeutic failure may benefit the patient.
- Surveillance of high-risk malignancies or evaluation at clinical relapse where salvage therapies exist and for which early intervention may be curative or prolong life.
- For all of these clinical scenarios there are multiple independent examples of  $^{18}\text{F}$ -FDG-PET and, more recently, PET/CT being effective. In each clinical scenario, the superior accuracy of  $^{18}\text{F}$ -FDG-PET/CT is most likely to prevent futile attempts at cure by detecting otherwise occult distant metastatic disease, allowing reduced therapeutic costs and more rational allocation of scarce or expensive therapies. Thus, although the unit cost of PET scans is relatively high compared to conventional evaluation techniques, the superior accuracy and impact on management decisions has the potential to both reduce global cancer costs and improve outcomes.

#### 4.1. $^{18}\text{F}$ -FDG-PET FOR EVALUATING MASS LESIONS

Accurate and timely diagnosis of cancer is a cornerstone of modern oncology. One of the first situations where  $^{18}\text{F}$ -FDG-PET was evaluated as a non-invasive tool in this role was for characterization of solitary pulmonary nodules (SPN). Using a range of imaging devices, studies performed in various countries around the world found that PET had a relatively high accuracy with the majority of  $^{18}\text{F}$ -FDG-avid lesions being malignant and the vast majority of non-avid lesions being benign. The high accuracy of  $^{18}\text{F}$ -FDG-PET for the evaluation of SPN in most published series from North America, Europe and Australia and its adoption into clinical practice has not, however, been mirrored by experience in regions of the world with a higher prevalence of infectious diseases that are associated with enhanced glucose metabolism. Such inflammatory lesions may mimic malignant lesions on both radiological and  $^{18}\text{F}$ -FDG-PET studies. Accordingly, they act to decrease the prevalence of malignant lesions in the target population and therefore, the PPV, and apparent specificity, of  $^{18}\text{F}$ -FDG-PET. Nevertheless, since most of the processes that cause abnormal  $^{18}\text{F}$ -FDG accumulation in the lungs are disease processes that warrant active treatment, a specific pathological diagnosis, or, at least, early review, is required for positive PET results while negative PET results can be managed conservatively. The difference in disease prevalence between different populations mandates different further investigation and management paradigms must be applied depending on local factors.

#### 4.2. $^{18}\text{F}$ -FDG-PET FOR CANCER DETECTION

The use of PET has been advocated as part of screening programs, and has found greatest utilization in Japan. Although, possibly involving individuals at increased risk of malignancy, there are reported rates of previously unidentified malignancies in up to 3% of the screened population using a combination of  $^{18}\text{F}$ -FDG-PET, CT, MRI and a battery of laboratory tests (Ide 2006). In patients being evaluated for known or suspected cancer by  $^{18}\text{F}$ -FDG-PET or PET/CT, incidental confirmed second malignancies have also been described to occur in 1–3% of patients, with colonic and thyroid malignancies appearing to predominate. Nevertheless, even these rates of detection are probably insufficient to justify widespread use of  $^{18}\text{F}$ -FDG-PET/CT as a routine cancer screening modality in view of the cost and resource allocation considerations.

However, with increasing use of other screening tests for cancer, including various blood markers, and wider use of CT and other imaging procedures for diagnosis of various non-specific symptoms, there are a growing number of patients suspected to have cancer but in whom conventional evaluation paradigms fail to confirm a diagnosis or yield false-positive results. The significant anxiety that such results can cause patients needs to be considered. If the rationale for performing such screening is to detect cancer at an earlier and hopefully more easily curable stage, then use of a sensitive imaging technique is logical. The relatively high sensitivity of  $^{18}\text{F}$ -FDG-PET/CT will equate to an excellent NPV in patients with a low prevalence of disease, allowing a high degree of reassurance to be given to patients with a negative scan. Conversely, a positive PET may give a sufficiently high post-test likelihood of malignancy to warrant further histopathological examination to exclude a malignant basis. Evaluation of elevated CA-19.9, CA-15.3, CA-125 or CEA levels are potential situations where  $^{18}\text{F}$ -FDG-PET/CT might find a clinical role but where strong supporting evidence is lacking.

#### 4.3. $^{18}\text{F}$ -FDG-PET FOR STAGING OF CANCER

This process of cancer staging often involves significant time and cost but is vital to correct management choices. If the cancer cannot be cured by currently available techniques, then palliative treatments that maximize quality of life should be employed, avoiding the cost and morbidity of futile curative attempts. Where it can be cured, accurate delineation of disease extent is vital for treatment choice and planning. Across a range of indications, early retrospective studies demonstrated that patient management was altered in a substantial number of cases as a consequence of the stage migration associated with whole-body  $^{18}\text{F}$ -FDG-PET imaging. Furthermore, where biopsy or clinical follow-up was able to ascertain the appropriateness of the resulting stage migration,  $^{18}\text{F}$ -FDG-PET was also shown to be correct an overwhelming percentage of the time compared to conventional investigational paradigms.

Using standardized criteria developed at The Peter MacCallum Cancer Centre, the impact of the PET result on management has been defined as: ‘high’ when, as a result of the PET findings, there is a change in management intent or modality, e.g. curative to palliative, or surgery to medical therapy; ‘medium’ if there is change in delivery of treatment but not intent or modality, e.g. a change in radiation treatment volume; ‘low’ when management planned is still deemed appropriate on the basis of PET information; and ‘no’ if the management planned seems inappropriate but treatment is not altered, i.e. the PET findings are ignored. This methodology was first used to report the impact of  $^{18}\text{F}$ -FDG-PET in a prospective cohort of patients with known or suspected lung cancer at various phases of the diagnostic process including primary staging (Kalff, Hicks et al. 2001). Similar studies were subsequently reported on the impact of  $^{18}\text{F}$ -FDG-PET in many other clinical situations. This methodology has been adopted for a national data collection process in Australia and is similar to that being used in the United States for the National Oncological PET registry (NOPR) (Hillner, Liu et al. 2007). A recent report of the results of the NOPR indicate that PET changes management in over a third of patients, echoing the results of single institutional trials and indicating that the results obtained at academic centres can be generalized.

#### 4.4. $^{18}\text{F}$ -FDG-PET FOR TREATMENT PLANNING

Recent innovations in radiotherapy have seen a move to more highly targeted treatment methods such as three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) that allow use of higher radiation doses to the tumour while sparing adjacent normal tissues. However, applying tight treatment margins means that it is vital that lesions be accurately and precisely defined. Without this accuracy, ‘geographic misses’ may occur. Due to the contrast afforded by differential  $^{18}\text{F}$ -FDG uptake in cancer cells, while still providing the anatomical landmarks and attenuation characteristics required for radiotherapy dose planning and delivery, PET/CT offers the potential for improved differentiation of malignant from benign tissues and, therefore, better definition of the radiotherapy treatment plans.

#### 4.5. $^{18}\text{F}$ -FDG-PET FOR THERAPEUTIC MONITORING

For both localized and widely disseminated cancers, a growing array of therapeutic agents is becoming available. Many of these agents are added to conventional therapies, adding cost and potential new toxicities to existing treatment paradigms. In this context, early and robust identification of non-responders is needed to facilitate earlier termination of ineffective treatment allowing a change to these alternative treatments in the hope that these may be more

efficacious. Additionally, it may allow avoidance of futile side effects that diminish physiological reserves, and compromise quality of life.

Although tumour markers are commonly used to assess treatment response, they are not always available and provide no localizing value. Therefore they cannot be used to guide salvage therapies like surgery or radiotherapy in the event of persisting abnormality. Therapeutic response assessment is therefore generally based on the changes in the measured dimensions of lesions identified on CT or other structural imaging techniques. These changes are recorded and graded according to definitions detailed in the Response Evaluation Criteria in Solid Tumours (RECIST) (Therasse, Eisenhauer et al. 2006), representing a modification of earlier World Health Organization (WHO) response criteria (Miller, Hoogstraten et al. 1981). Unfortunately, changes in lesion size are relatively slow to occur and may be limited by fibrotic healing. This may lead to unnecessary prolongation of treatment, or even institution of more aggressive treatment in the mistaken belief that there has been a poor response to earlier interventions. Conversely, structures such as lymph nodes that return to normal size may still harbour disease. One of the major theoretical advantages of PET compared to structural imaging techniques is that there is usually a more rapid decline in tumour metabolism than in tumour size. Preliminary studies, reported more than 10 years ago, demonstrated that reduced  $^{18}\text{F}$ -FDG uptake generally both precedes and predicts subsequent morphological response. Recommendations on the use of  $^{18}\text{F}$ -FDG-PET for therapeutic response assessment have recently been made in a consensus statement from the National Institutes of Health in the United States (Shankar, Hoffman et al. 2006).

While there is growing enthusiasm that PET can provide early therapeutic response assessment, the preferred methodology for metabolic response assessment remains controversial. Methods vary in complexity from simple visual comparison of baseline and post-treatment scans to complex computational approaches. The most important objective of response assessment is reliable stratification of prognosis and appropriate guidance of further treatment requirements. The term 'metabolic response' is now being widely used to denote the degree of qualitative or semi-quantitative change in  $^{18}\text{F}$ -FDG uptake in target lesions. The simplest method of evaluating metabolic response is visual analysis but its subjectivity has been seen as a limitation. To overcome this there needs to be attention to detail with respect to achieving a consistent display of images. It is also important to use a standardized nomenclature for qualitative reporting of serial  $^{18}\text{F}$ -FDG-PET scans that can be applied to all tumour types and can be consistently applied by different individuals and institutions. In the schema described by Mac Manus et al. (Mac Manus, Hicks et al. 2003), a complete metabolic response (CMR) is defined as a return of  $^{18}\text{F}$ -FDG uptake in previously documented lesions to a level equivalent to, or less than, residual radioactivity in normal tissues within the organ in question. A partial metabolic response (PMR) constitutes a significant visual reduction in  $^{18}\text{F}$ -FDG uptake in tumour sites based on visual inspection of appropriately displayed comparative images. Stable metabolic disease (SMD) and progressive metabolic disease (PMD) are defined respectively by a lack of change, or an increase in the extent of metabolic abnormality in a pattern consistent with tumour growth or development of new sites of disease. For those categories that involve a qualitative change in the intensity of uptake, such as PMR, measurement of tracer uptake could be a useful to validate the qualitative impression.

The semi-quantitative parameter that is currently preferred to assess the change in  $^{18}\text{F}$ -FDG uptake in tumours is the standardized uptake value (SUV). There is not yet consensus regarding what degree of  $^{18}\text{F}$ -FDG signal reduction should constitute a partial or complete metabolic response. While there is a strong rationale for adopting a standardized approach for PET definition of therapeutic response categories, it needs to be recognized that uptake and

retention of molecular tracers is a biological process. As such, it is subject to the mechanism of drug action and the cellular consequences of this.

Despite reservations about the scientific validity of qualitative analysis, multiple studies that have used this methodology have demonstrated its ability to stratify prognosis based on broad categories of metabolic response. Indeed, most studies evaluating the use of PET in lymphoma have used visual analysis to dichotomize responders into complete and incomplete metabolic responses. This methodology was adopted as the most appropriate standard for this role in a recent consensus statement on the use of  $^{18}\text{F}$ -FDG-PET for response evaluation (Juweid, Stroobants et al. 2007), based on its ability to powerfully stratify patient outcome. Qualitative analysis of  $^{18}\text{F}$ -FDG-PET to assess response of solid tumours to treatment has been used in multiple studies and has also demonstrated that PET can provide statistically significant prognostic stratification, particularly when patients are dichotomized between CMR and non-CMR groups. While a CMR and PMD are likely to be fairly consistently interpreted between individual reporting physicians and between institutions, the methodology used to define a PMR is less clearly defined at this time. As opposed to lymphoma, solid tumours rarely respond rapidly to treatment by depopulation of viable cells. Therefore, partial metabolic responses have predominated in 'responders' within most  $^{18}\text{F}$ -FDG-PET therapeutic monitoring trials, particularly those involving chemotherapy. Where abnormal radiotracer uptake remains in a lesion, determination of the degree to which it has reduced may have therapeutic and prognostic implications. There is now increasing evidence for the prognostic value of semi-quantitative measures of  $^{18}\text{F}$ -FDG-PET response in various solid malignancies (Weber and Figlin 2007).

#### 4.6. $^{18}\text{F}$ -FDG-PET FOR RESTAGING

Following definitive treatment of cancer, ongoing symptoms, residual structural imaging abnormalities or elevated tumour markers are not uncommon. There are also many patients at significant risk of relapse even in the absence of any objective evidence of residual disease. The limitations of structural imaging that limit interpretation of staging scans are further augmented by post-treatment changes in the restaging setting. In the setting of post-treatment recurrence, malignant deposits may co-exist with scar tissue, increasing the likelihood of sampling error on biopsy and when disease is absent, providing a considerable and unnecessary source of anxiety for the patient. Clinically, it is important not only to detect residual or recurrent cancer but also to determine whether it is suitable for salvage locoregional therapies, or whether systemic treatment might be more appropriate. Being based on the metabolic characteristics of tissues,  $^{18}\text{F}$ -FDG-PET should be less susceptible to the effects of prior treatment. Many studies throughout the world have demonstrated that  $^{18}\text{F}$ -FDG-PET is more accurate than conventional imaging for detection of residual cancer following definitive treatment of various haematological and non-haematological malignancies.

#### 4.7. USE OF $^{18}\text{F}$ -FDG-PET AS A BIOMARKER

It is important to recognize that the SUV, although having the attraction of apparent scientific rigor through provision of a measure, is a simplistic measure of a complex process and reflects a biological continuum related to tissue glucose metabolism not necessarily to a particular biological characteristic of cancer cells. Studies have failed to demonstrate a convincing diagnostic advantage of SUV-based diagnosis over qualitative interpretation. Nevertheless, whether assessed qualitatively or by SUV, the intensity of  $^{18}\text{F}$ -FDG uptake seems to be an important biomarker of disease aggressiveness in many forms of malignancy.

#### 4.8. ALTERNATIVE TRACERS FOR CANCER EVALUATION

The diversity of factors that contribute to tissue glucose metabolism limits the specificity of  $^{18}\text{F}$ -FDG as a cancer-imaging agent. As discussed elsewhere, new tracers that address the perceived limitations of  $^{18}\text{F}$ -FDG as a cancer tracer are in development and some are finding clinical application. However, the challenge for all these tracers is to match the excellent diagnostic performance of  $^{18}\text{F}$ -FDG across a wide range of cancers and in many disparate clinical situations. That  $^{18}\text{F}$ -FDG was the first tracer to be widely applied in clinical practice has been both a blessing and a curse. The bar has been set very high for any new-comers!

#### 4.9. CONCLUSION

PET/CT has established a central role in clinical oncology practice and is likely to remain so for the foreseeable future. The challenge for the future is to use the complex and often unique information provided by molecular imaging to design new treatment strategies based on more than simply counting lesions. Integration with advances in molecular biology and targeted therapeutics will usher a new age of personalized oncological care and even in the developing world has the opportunity to rationalize treatment delivery, reduce waste and improve outcomes in delivering treatment to cancer patients.

### 5. USE OF TRACERS OTHER THAN $^{18}\text{F}$ -FDG IN ONCOLOGY

Analysis of the literature of PET in oncology clearly reveals the dominance of  $^{18}\text{F}$ -FDG compared to other PET tracers. The biological basis of  $^{18}\text{F}$ -FDG-PET is uptake of the tracer by glucose transporters, followed by a metabolic trapping. Usually cancer cells show an enhanced glucose metabolism and allow high sensitivity PET imaging of cells by virtue of this phenomenon. In addition to this, ready availability of automated radiosynthesis of this radiopharmaceutical allowing efficient commercial distribution, even to nuclear medicine centers distant from the site of production thanks to the advantages of the relatively long life of  $^{18}\text{F}$ , makes  $^{18}\text{F}$ -FDG the most widely used radiochemical to image many kinds of cancer worldwide.

However, it is important to recognize that, being a tracer of glucose metabolism,  $^{18}\text{F}$ -FDG is not a 'specific' radiotracer for imaging malignant disease. There are several benign conditions and many physiological processes that lead to increased uptake of this tracer. These include, but are not limited to, normal wound healing, infection and inflammation, active muscle contraction during the uptake period, and activated brown fat. Normal organs, including the brain, liver, kidneys and bone marrow have relatively high  $^{18}\text{F}$ -FDG uptake, even under fasting conditions, and this provides background activity that may mask small lesions or malignancies with low glucose metabolism. Such malignancies include some neuroendocrine tumours, mucinous tumours, differentiated teratomas, many prostate carcinomas, lobular breast cancer, some renal and hepatocellular carcinomas, and most bronchioloalveolar carcinomas. The relatively poor  $^{18}\text{F}$ -FDG uptake of these tumours compromises the sensitivity of PET for the detection of tumour sites. Considering these issues the interpretation of images with  $^{18}\text{F}$ -FDG sometimes is difficult and, in certain situations, does not provide adequate diagnostic accuracy to appropriately guide patient management. For all these reasons, the role of alternative radiopharmaceuticals is becoming of increased interest. In particular, there has been a search for tracers that might overcome the weaknesses of  $^{18}\text{F}$ -FDG-PET as imaging tracer, especially with respect to ability to visualize tumours with low avidity for  $^{18}\text{F}$ -FDG.

Research in PET radiochemistry has provided access to many alternative tracers for oncology at the present time. Many of these tracers have been evaluated in both pre-clinical and clinical studies. Some have the ability to uniquely characterize specific aspects of tumour biology and, as a result, to offer several diagnostic advantages in comparison with  $^{18}\text{F}$ -FDG in particular types of tumours. A few examples of tracers that are currently of great interest are listed in the following Table 3.

TABLE 3. EXAMPLES OF TRACERS, THEIR PROCESSES AND ACRONYMS

Biochemical/ biological process	Radiopharmaceutical	Acronym	
Proliferation	Carbon-11-thymidine	$^{11}\text{C}$ -Thy	
	Fluorine-18-fluorodeoxythymidine	$^{18}\text{F}$ -FLT	
Amino-acid transport	Carbon-11-methionine	$^{11}\text{C}$ -MET	
	Fluorine-18-fluoroethyltyrosine,	$^{18}\text{F}$ -FET	
	Fluorine-18-fluorometilthyltyrosine	$^{18}\text{F}$ -FMT	
Hypoxia	Fluorine-18-fluoromisonidazole	$^{18}\text{F}$ -FMISO	
	Fluorine-18-fluoroetanidazole	$^{18}\text{F}$ -FETA	
	Fluorine-18-fluoronitroimidazole	$^{18}\text{F}$ -FETNIM	
	Fluorine-18-fluoroazomycin-aribinoside	$^{18}\text{F}$ -FAZA	
	Copper-60- diacetylmethylthiosemicarbazone	$^{60}\text{Cu}$ -ATSM	
	Copper-62- diacetylmethylthiosemicarbazone	$^{62}\text{Cu}$ -ATSM	
	Copper-64- diacetylmethylthiosemicarbazone	$^{64}\text{Cu}$ -ATSM	
Receptors	Fluorine-18-octreotide analogues	$^{18}\text{F}$ -DOTATOC $^{18}\text{F}$ -DOTANOC $^{18}\text{F}$ -DOTATATE	
	Gallium-68-octreotide analogues	$^{68}\text{Ga}$ -DOTATOC $^{68}\text{Ga}$ -DOTANOC $^{68}\text{Ga}$ -DOTATATE	
	Fluorine-18-fluoroestradiol	$^{18}\text{F}$ -FES	
	Fluorine-18-galacto-RGD(Arg-Gly-Asp)	$^{18}\text{F}$ -galactoRGD	
	Dopamine metabolism	Fluorine-18-fluorodihydroxyphenylalanine	$^{18}\text{F}$ -FDOPA
	Lipid and fatty acid metabolism	Carbon-11-choline	$^{11}\text{C}$ -CH
Fluorine-18-fluorocholine		$^{18}\text{F}$ -FCH	
Carbon-11-acetate		$^{11}\text{C}$ -acetate	
Fluorine-18-fluoroacetate		$^{18}\text{F}$ -acetate	

## 5.1. SOME EXAMPLES OF CLINICAL USE OF NON $^{18}\text{F}$ -FDG RADIOPHARMACEUTICALS

### 5.1.1. Brain tumours

$^{18}\text{F}$ -FDG-PET is currently used for brain tumour detection, defining tumour extent and degree of malignancy (grade) in primary evaluation. In the post-treatment setting it is also used for assessment of tumour response and differentiation of viable tumour versus radiation necrosis, especially in cases where radiology can differentiate between these processes. However,  $^{18}\text{F}$ -FDG has high physiological uptake in the normal cortex, sometimes masking small lesions and secondary metastases in this area, and also has limited value in low-grade gliomas, since these tumours tend to have somewhat lower glucose metabolism than high-grade lesions and therefore have poor contrast against background brain uptake.  $^{11}\text{C}$ -MET and other tracers of amino-acid metabolism, such as fluorine-18-fluoroethyl tyrosine ( $^{18}\text{F}$ -FET) and fluorine-18-fluoromethyl tyrosine ( $^{18}\text{F}$ -FMT), are much more sensitive for detecting low-grade brain tumours and for differentiating tumour relapses after treatment. Apart from these tracers, many clinical studies report that other radiopharmaceuticals, including carbon-11-choline ( $^{11}\text{C}$ -CH) and fluorine-18-fluorocholine ( $^{18}\text{F}$ -FCH), seem to also demonstrate a good diagnostic value in depicting brain neoplasias and can overcome the limitations of  $^{18}\text{F}$ -FDG.

### 5.1.2. Lung cancer

It is well known that usually  $^{18}\text{F}$ -FDG-PET misses a number of bronchioloalveolar carcinoma without invasive component. Some clinical trials have investigated the diagnostic value of the alternative radiopharmaceuticals  $^{18}\text{F}$ -FCH or  $^{18}\text{F}$ -acetate and demonstrated their reliability in depicting this cancer type.

### 5.1.3. Liver tumours

$^{18}\text{F}$ -FDG has proved very useful in the evaluation of liver metastases from a variety of primary malignancies (mainly colorectal, gastric and oesophageal cancer). Cholangiocarcinomas are also generally very  $^{18}\text{F}$ -FDG-avid, although clinical findings report that the  $^{18}\text{F}$ -FDG uptake is somewhat higher in the intra-hepatic localizations than in the hilar and extra-hepatic variety. On the contrary  $^{18}\text{F}$ -FDG-PET shows a relatively low sensitivity in detecting primary hepatocellular carcinoma (HCC). This appears to be due to expression of glucose-6-phosphatase within the malignant cells, leading to washout of  $^{18}\text{F}$ -FDG and decreased tumour to background ratios compared to other tumours that have very low or no expression of this enzyme. Reduced Glut-1 expression might also play a role in other HCC. The sensitivity increases somewhat in patients with moderately or poorly differentiated HCC and in large tumours. Radiolabelled choline and acetate have been validated as alternative tracers for HCC, and appear to be more reliable since genes involved in lipid metabolism are up-regulated in those cases with low  $^{18}\text{F}$ -FDG-avidity.

### 5.1.4. Neuroendocrine tumours

Only the clinically most aggressive neuroendocrine tumours show intense  $^{18}\text{F}$ -FDG uptake. Consequently,  $^{18}\text{F}$ -FDG-PET is not ideally suited for staging of neuroendocrine tumours, due to their generally low glycolytic metabolism. Radiochemistry developments have made some alternative radiopharmaceuticals available. Specifically, these include positron-emitting molecules belonging to the group of dopamine metabolites, such as fluorine-18-fluorodihydroxyphenylalanine ( $^{18}\text{F}$ -FDOPA), or small peptides that bind somatostatin receptors, such as several octreotide analogues. Many similar compounds of this family have



been developed by chemical substitution in their structure in order to obtain tracers with high affinity for the somatostatin receptor sub-types that are differentially expressed by each tumour. Recently, a radiolabelling procedure has been developed for  $^{68}\text{Ga}$ , a radioisotope with a half-life of 68.3 minutes. This radionuclide is produced from a  $^{68}\text{Ge}/^{68}\text{Ga}$  generator that is now commercially available and practical due to the long half life of the parent radionuclide. The most frequently reported  $^{68}\text{Ga}$ -tracer currently is  $^{68}\text{Ga}$ -DOTANOC (a conjugate of the somatostatin analogue 1-Nal 3-octreotide (NOC) and  $^{68}\text{Ga}$  labelled 1,4,7,10-tetra azacyalododecane-N, N, N, N-tetraacetic acid (DOTA)). In different series of patients with neuroendocrine tumours, this tracer has been demonstrated to be superior to indium-111- ( $^{111}\text{In}$ )-pentetretotide in detecting small lesions and cancers bearing a low density of somatostatin receptors. In particular it offers excellent quality of imaging and very high tumour to background ratios. Other tracers might be more suitable for selecting patients for radionuclide therapy due to the differing somatostatin receptor subtype affinities of the different octreotide analogues. For example,  $^{68}\text{Ga}$ -DOTATATE (DOTA- $^{\text{D}}$ Phe $^1$ , Tyr $^3$ -octreotate) may be the most suitable agent if treatment with Lutetium-177 ( $^{177}\text{Lu}$ )-DOTATATE is planned.

### 5.1.5. Prostate cancer and urological malignancies

Fluorine-18-FDG is not the best tracer to image and stage primary prostate cancer since the radiopharmaceutical is excreted through the urinary tract, affecting visualization of lesions in the pelvic area due to masking by the physiological concentrations. Beside this,  $^{18}\text{F}$ -FDG uptake may be intrinsically low or affected by androgen ablation. The latter is a critical issue for patients under hormone therapy.  $^{18}\text{F}$ -FDG-PET has shown also a limited role also in local re-staging and recurrence detection.  $^{11}\text{C}$ -CH may be of higher value for staging, detecting pelvic recurrences and monitoring prostatic cancer. In particular, it seems useful for restaging cases after prostatectomy that are associated with increasing levels of PSA. The fluorinated analogue,  $^{18}\text{F}$ -FCH is more suitable for clinical use, due to the longer half life of  $^{18}\text{F}$  and has revealed better accuracy for detecting local recurrences and lymph node metastases. Also  $^{11}\text{C}$ -MET and  $^{11}\text{C}$ -acetate have been evaluated for the diagnosis of intraprostatic nodules by short dynamic scanning and validation with multi-core biopsies. They have shown a high detection rate in patients with increased PSA levels and repeated US-guided negative biopsies. However their appropriate clinical role remains to be evaluated.

For bladder cancer,  $^{18}\text{F}$ -FDG-PET is useful for identifying distant metastases but has limitations for detecting primary tumour due to the urinary excretion of  $^{18}\text{F}$ -FDG. The  $^{18}\text{F}$ -FDG-PET is often negative for renal cell carcinoma because the low accumulation of the tracer within cancer cells. Promising results have been shown by  $^{11}\text{C}$ -CH,  $^{18}\text{F}$ -FLT,  $^{18}\text{F}$ -acetate and  $^{18}\text{F}$ -FCH. More clinical data are needed to define the clinical value of these imaging methods for urological malignancies.

### 5.1.6. Breast cancer

Breast cancer is currently imaged by  $^{18}\text{F}$ -FDG. This technique provides important information in staging, re-staging and monitoring therapy. However, lobular breast cancer sometimes does not accumulate  $^{18}\text{F}$ -FDG. Therefore different tracers are under study in order to find those with a higher sensitivity or able to better characterize tumour biology.  $^{18}\text{F}$ -FCH and  $^{18}\text{F}$ -FLT can provide information on cell proliferation and predict therapy response to neoadjuvant or definitive chemotherapy.

Various fluorinated oestrogen analogues have been suggested as diagnostic probes for evaluating receptor status of breast cancer. A high rate of breast cancer patients do not respond to hormone therapy; fluorine-18-fluoroestradiol ( $^{18}\text{F}$ -FES) binds oestrogen receptors and can select patients who might be suitable candidates for endocrine therapy. The integrin  $\alpha(v)\beta(3)$  is a key player in angiogenesis and metastasis. The tracer fluorine-18-galacto-RGD (Arg-Gly-Asp) ( $^{18}\text{F}$ -galactoRGD) demonstrated generally elevated and highly variable expression of these receptors in breast cancer and other malignancies (lung cancer, renal cell carcinoma, rectal cancer etc.) Even though  $^{18}\text{F}$ -FDG-PET has been demonstrated in preliminary studies to be more sensitive for tumour staging,  $^{18}\text{F}$ -galacto-RGD-PET warrants further evaluation for treatment selection and response evaluation of targeted molecular therapies with antiangiogenic drugs.

### 5.1.7. Hypoxia studies

A characteristic feature of solid tumours is their tendency to become hypoxic. This is a clinically important phenomenon since hypoxic tumours typically show radiation resistance and may also be more resistant to chemotherapy. For example, this has been shown for Mitomycin C. In addition, cellular response to hypoxia includes the expression of growth factor genes leading to increased tumour cell vascularization and other genes associated with increased metastatic potential. Accordingly, tumour hypoxia has been shown to be associated with poor prognosis in several cancer types. For these reasons various tracers have been developed as markers of hypoxic tissue. The radiosynthesis of fluorine-18-fluoromisonidazole ( $^{18}\text{F}$ -FMISO) has been improved and automated. Images of hypoxic tissues have been obtained mainly in non small cell lung cancer and in head and neck cancer. A recent  $^{18}\text{F}$ -FMISO derivative, the fluorine-18-fluoroetamidazole ( $^{18}\text{F}$ -FETA) has proved to be more stable, with lower levels of circulating and urinary metabolites. Another analogue with similar characteristics is fluorine-18-fluoroazomycin-arabinozide ( $^{18}\text{F}$ -FAZA). Among these hypoxia markers it should be mentioned the bioreductive metal complex copper-60-diacetyl methyl thiosemicarbazone ( $^{60}\text{Cu}$ -ATSM), that is trapped only in hypoxic tissues, showing higher tumour uptake and more rapid tissue clearance than  $^{18}\text{F}$ -FMISO. This compound can be labelled with the positron emitting radionuclide copper-62 ( $^{62}\text{Cu}$ ), produced by a small generator avoiding the use of the cyclotron; the resulting tracer is  $^{62}\text{Cu}$ -ATSM.

### 5.1.8. Cell proliferation studies

Specific proliferation tracers could have enormous potential for PET oncology to predict/monitor treatment response. Brain tumours were first imaged with carbon-11-thymidine ( $^{11}\text{C}$ -Thy). This agent showed better uptake than  $^{18}\text{F}$ -FDG in recurrent tumours after therapy. Carbon-11-thymidine was then applied to study chemotherapy response in small cell lung cancer. The response was demonstrated with  $^{11}\text{C}$ -Thy but not with  $^{18}\text{F}$ -FDG.  $^{18}\text{F}$ -FLT benefits from the longer half-life of  $^{18}\text{F}$  and its straightforward radiosynthesis. In addition, its biodistribution shows several advantages over  $^{11}\text{C}$ -Thy. Several clinical studies have now been performed assessing visualization of breast cancer, head and neck tumours and lymphomas. However, except in some isolated reports,  $^{18}\text{F}$ -FLT today is considered to be a tool to investigate the correlation with cell proliferation and prognosis rather than a radiopharmaceutical for routine tumour imaging and differential diagnosis.

## 5.2. CONCLUSIONS

The future of clinical PET in oncology is moving in two main directions: technological improvement (more efficient detectors, hybrid systems, hardware and software implementation) and the development of non- $^{18}\text{F}$ -FDG-PET tracers. These tracers will be labelled primarily with  $^{18}\text{F}$  but, where appropriate, also with  $^{11}\text{C}$ ,  $^{68}\text{Ga}$ , the copper isotopes,  $^{60}\text{Cu}$ ,  $^{62}\text{Cu}$  and copper-64 ( $^{64}\text{Cu}$ ), and other positron emitting radionuclides. These will be complexed to various amino-acids, substrates of fatty acid metabolism, protein and nuclear acid synthesis, hypoxia markers, and some specific receptor ligands. Some of these have already shown promising results in the detection and management of various cancers where  $^{18}\text{F}$ -FDG has a limited role. These radiotracers will have more specific mechanisms of uptake. A few of them are already used in the clinical practice in several PET centers, while the majority are still under investigation. Their clinical use will often require a cyclotron facility on site and a radiochemistry laboratory with a good team of skilled radiochemists but some tracers will lend themselves to production at commercial distribution sites or can be made from generators, thereby removing the requirement of a cyclotron at all PET facilities. It goes without saying that use of these 'niche' PET radiopharmaceuticals should currently be reserved for only those PET centers with radiochemistry research capability and the necessary resources for radiopharmaceutical production and quality assurance.

## 6. PRINCIPLES OF COST-BENEFIT ANALYSIS AS APPLIED TO PET/CT

### 6.1. PET/CT- A RAPIDLY EVOLVING TECHNOLOGY

Since its introduction into diagnostic oncology in around 2000, PET/CT has had an impressive technological evolution. Over a few short years, spiral CT scanners have evolved from 2-slice to 64-slice devices while the PET component has been enhanced by new types of crystals and modification to electronics that improve spatial and temporal resolution, sensitivity and contrast. The impact of 2-dimensional (D) versus 3-D whole body imaging has decreased the scanning time required to achieve the same statistical quality using an unchanged administered dose, or allows a reduced dose to be given to the patient while maintaining current acquisition characteristics. A new generation of scanners has been designed based on time-of-flight utilising avalanche photodiode detectors that will further improve technical performance. As a consequence of the great improvement in PET/CT technology and increasing evidence of its clear diagnostic superiority over either stand-alone PET or side-by-side interpretation of separately acquired PET and CT scans, there has been rapid penetration of PET/CT into clinical practice. This can be explained by the many advantages of hybrid imaging compared to conventional imaging using stand-alone devices. These advantages include faster patient throughput (around 30% greater than with PET), higher patient compliance due to shorter scanning times, routine and near-instantaneous image fusion made possible by contemporaneous imaging at a single examination performed on the same scanning bed. The significantly improved precision of co-registration of anatomy and function has been shown to result in greater diagnostic confidence and accuracy in localization of lesions compared to physiological uptake (specificity) and increased lesion detection (sensitivity).

There has already been a great many publications in oncology literature comparing the diagnostic efficacy of PET/CT with that of PET or CT alone, and also with other diagnostic modalities. The generally excellent results that have been published have encouraged rapid introduction of this new hybrid diagnostic system into routine oncological practice. General

acceptance by oncologists has been very high throughout the world, reflecting its excellent technical performance, clinical utility and scientific potential. At present, none of the major imaging instrumentation manufacturers produces stand-alone PET scanners. Consequently, only PET/CT machines are now sold new into the market. There is, however, a market for reconditioned PET scanners as existing facilities upgrade older scanners to new PET/CT devices.

## 6.2. IS PET/CT TOO EXPENSIVE FOR THE DEVELOPING WORLD?

There is no doubt that the costs of PET/CT are relatively high when compared with those of other diagnostic imaging procedures. A general evaluation of the costs of the different diagnostic imaging procedures should include not only the equipment costs, but also the siting costs involved in accommodating the equipment in a new location, which also contribute to capital costs. Operational costs involved with employing the staff required to perform the diagnostic examination and the consumables utilised must be added to these costs. The amortisation of capital costs and the direct operational costs contribute to the final cost per scan. Accordingly, higher throughput offers cost efficiency advantages. The annual fixed costs can be calculated on the basis of the equipment, siting and technical staffing. Capital costs are generally written off over seven years. These figures listed in Table 4 are the mean values reported by the source Medical Options. These figures may not necessarily be relevant to the developing world.

TABLE 4. EVALUATION OF COSTS OF VARIOUS DIAGNOSTIC IMAGING PROCEDURES

Imaging	Equipment € ×1000	Staff	Siting cost €×1000	Annual €×1000	Consumable €	Annual Throughput	Cost/scan €
PET/CT	2,200	2	750	1,177	400	2,000	996
Scintigraphy	490	2	60	419	50	2,000	262
MR	975	2	250	720	40	3,000	234
CT	750	2	100	572	30	5,000	103
US	135	1	-	144	40	2,000	91

Reduction in annual costs can be obtained by extending the life of the equipment, reduced expenditure on siting or amortisation of siting costs over a longer period, and increasing scan volume. Nevertheless, from these data, PET/CT is currently the most expensive imaging modality on the list with respect to unit scan costs. This is primarily driven by the need to utilise the PET radiopharmaceuticals that are quite expensive. Again, economies of scale can operate to reduce this component of the scan cost. Centralised cyclotron facilities which distribute to a number of scanners operating in parallel can act to reduce the cost per dose.

However, beyond the direct costs of a diagnostic scan are its ability to accurately perform its role in selecting and planning appropriate treatment. The cost of many therapeutic

interventions, both directly and related to their morbidity, are substantially greater than those associated with diagnostic imaging procedures. Accordingly, more accurate and appropriate allocation of therapeutic resources can substantially offset the cost of a more expensive diagnostic procedure and may even be cost-saving.

### 6.3. THE BASIS OF ECONOMIC EVALUATION

Escalating health-care costs and increasingly strict limitations on financial resources over recent decades, have strengthened the concept that decisions regarding implementation of a new diagnostic test should be based not only on technical and scientific considerations, but also on the evaluation of economic factors. The economics of diagnostic imaging is part of a process now known as 'health technology assessment'. Cost-effectiveness analysis is essential for a complete evaluation of a diagnostic modality. A diagnostic procedure can be considered cost-effective when the same outcome is achieved at a lower cost or when its benefits are great enough to justify its additional cost. In other words, cost effective does not always mean cheaper. However, if more expensive, it must also have an additional benefit that justifies the additional costs.

Three economic evaluation methodologies can be used for assessing imaging studies: a) cost-effectiveness analysis; b) cost-utility analysis, and; c) cost-benefit analysis.

- Cost-effectiveness analysis is performed through a cost minimization study or evaluating the cost-effective ratio. The minimization study can be adopted when it is known that the clinical effectiveness of two diagnostic tests is equivalent. In this case the only parameter to be considered is the total cost of each strategy, and the final choice will select the procedure with the lowest cost.
- The cost-effective ratio is another way to compare the strategy under investigation and either the current standard of care or no intervention, or between two competing alternative strategies. Thus, the ratio represents the incremental price of reaching a health unit effect from a given intervention when compared with an alternative.
- The cost-utility analysis is considered a form of the cost-effectiveness analysis where adjustments are done for the 'value attached to the benefits'. One of the most widely used measures of the health outcome is 'the quality adjusted life year' or QALY. This sets out the change in resource use and the number of quality-adjusted life years. QALYs estimate the effect on survival and the changes in quality of life stemming from the introduction of the modality under investigation.
- The cost-benefit analysis may be regarded as an extension of the cost-utility study where all the measurements of the effectiveness, including quality adjusted life, pain and other negative effects can be expressed as financial value. There are different proposals to calculate the monetary value of 'life', for example through earning or 'willingness to pay', but all these methods have significant limitations.

All the above mentioned economic evaluations require an accurate study of different parameters through clinical trials. These can be carried out as: a) retrospective economic evaluation of previously performed clinical trials; b) prospective randomized controlled trials of costs and effectiveness simultaneously; c) expert consensus; d) computer modelling methods including meta-analysis and sensitivity analysis. The intrinsic value of these clinical trial methods depends on the study design, including different aspect such as randomization, k

statistics for inter- intra-observers variations, final diagnosis defined by histological control, blind-read procedure, etc. Up to now several studies on economic evaluation of  $^{18}\text{F}$ -FDG-PET have been performed in oncology, but there have been very few randomized studies and only few robust meta-analyses are available. All these studies have provided evidence that  $^{18}\text{F}$ -FDG -PET in different situations is cost-effective, and therefore preferable to CT and, where appropriate to other diagnostic modalities. An example of such a study was a retrospective analysis carried out in Italy on the cost-effectiveness of  $^{18}\text{F}$ -FDG-PET in patients with known or suspected lung cancer. This evaluation compared three different diagnostic strategies including  $^{18}\text{F}$ -FDG-PET. The introduction of PET in the clinical management of all patients with known or suspected lung cancer previously evaluated only with CT, resulted cost-effective and this modality can allow to gain 2.64 life years at an annual cost of about €415.

Regarding PET/CT, since this hybrid system represents the most recent introduction in the diagnostic work-up of cancer patients, at present there are relatively few papers on economic evaluations. Heinrich et al. studied the cost/benefit analysis of PET/CT on the management of resectable pancreatic cancer, based on the charged cost of PET/CT and pancreatic resection and included the time frame of staging and surgery. PET/CT findings changed the management in 16% of patients with pancreatic cancer deemed resectable after routine staging ( $P = 0.031$ ) and resulted in cost saving. Strobel et al. studied the usefulness of performing two PET/CT scans in Hodgkin lymphoma patients, after two cycles of therapy and after completion of the first-line treatment. Cost saving was calculated for the potentially superfluous PET/CT examinations. The conclusion was that end-treatment PET/CT is unnecessary if the diagnostic imaging during the treatment shows a complete response and the clinical course is uncomplicated. Therefore an imaging cost reduction of 27% in the study population can be achieved by omitting end of treatment PET/CT in interim complete responders. Fleming et al. evaluated 286 consecutive PET/CT scans in previously untreated head and neck cancer patients. Predictive positive value, sensitivity, specificity, accuracy, diagnostic upstaging and treatment management changes were determined from a subset analysis of 123 patients. The statistics were verified by comparing PET/CT results with surgical specimens histopathology. Treatment was altered in 30.9% of these patients because of PET/CT findings, including up-staging, diagnosing distant and unresectable disease, and detecting secondary primary malignancies. These observations have a clear economic impact by enabling the most effective treatment choices.

In summary, even though not yet firmly established by a large number of published papers, daily experience demonstrates that PET/CT has a substantial impact on patient management because it can assist (better than PET and/or CT alone) in defining potential candidates for curative surgery, in planning the appropriate surgery or radiotherapy, and redirecting patients with unresectable disease to other therapeutic options. Looking at the role of PET/CT on staging disease, it is easy to understand how correct staging can avoid futile operations for cancers that could never have been cured by surgery. In addition, in the case of restaging and follow-up, the correct imaging of the presence or absence of disease is critical for the subsequent treatment selection. In particular, the ability to avoid unnecessary intervention in patients with false-positive structural imaging results due to residual scar tissue represents a clear economic and patient benefit. In therapy planning, PET/CT can better define the target and the strategy of the treatment and can provide earlier and more reliable identification of non-responders than conventional non-invasive imaging approaches. This means that it is possible to avoid ineffective and toxic treatments and optimize the therapy. Obviously all these issues have an economic impact on the health system in general but also on the socio-economic background, because the individual health has a great impact on the family, on the workplace, and extends to involve wider relationship networks and other life activities.

#### 6.4. HEALTH TECHNOLOGY ASSESSMENT (HTA) ON PET/CT

The health technology assessment is a methodology used to evaluate new technologies proposed for introduction into medical practice and is often performed by those responsible for healthcare financing. It focuses attention to the following issues: a) the technology itself; b) patients; c) the economy and d) the organisation. The aim of HTA exercise is to study the utility of a diagnostic test described on one or more levels of a hierarchy, with higher levels relating more closely to the social impact. The hierarchies of the diagnostic efficacy of PET/CT are listed in Table 5.

TABLE 5. HIERARCHIES OF THE DIAGNOSTIC EFFICACY OF PET/CT

Hierarchy	Issue	Parameter under investigation
1	Technical	Technical imaging quality
2	Diagnostic accuracy	Sensitivity, specificity, negative and positive predictive value
3	Diagnostic thinking	Likelihood ratio
4	Therapeutic	Changes in therapeutic choices (patient management)
5	Patient outcome	Improvement in morbidity/mortality
6	Societal	Cost-benefit analysis

Before the PET era, diagnostic imaging modalities were previously introduced into clinical routine well before sufficient published data on their diagnostic efficacy were available. This happened for conventional radiology, US, MRI, CT and also conventional nuclear medicine. As new diagnostic imaging tests were developed they were merely introduced into routine practice when they became the preferred test of referring physicians. Often they were simply added to old tests in order to increase diagnostic confidence and without evidence that this positively influenced patient outcomes. HTA programmes were set up by many Institutions, Health Agencies and Governments around the early 1990s in response to increasingly limited economic resources in the health care and the high cost of many new technologies. They produced research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in National Health Systems. Several HTA reports on PET were carried and published in different countries from the year 2000 onwards (Australia, Canada, France, Germany, Spain and UK). These used different methods and addressed different issues and were mixed in their findings. However, some of them led to approval of the clinical use of PET for a range of oncological indications, some of which were subject to confirmation of clinical effectiveness by further data collection. This was the basis for extension of access to PET in both Australia and the USA. PET has been the first of many technologies to be subjected to such intense economic scrutiny. Many of the institutionalised health technology assessment groups are members of the International Network of Agencies for Health Technology Assessment (INAHTA). In spite of the use of the similar approaches and methodology, the INHATA reports have often arrived at rather

different views with respect to clinical value of PET. A few of the earlier reports negated the clinical value of PET, while others recommended the use of PET for different indications from one country to another. The observed lack of reproducibility regarding PET in INAHTA reports has led to questions regarding the reliability of such reports and the potential for conflict of interest when the body funding the evaluation also has a vested interest in financing healthcare. In spite of these criticisms, HTA does have theoretical benefits for evaluating the role of PET in cancer management by studying technologic aspects, measuring diagnostic efficiency and identifying the role of this diagnostic modality in comparison with other current options by using established, transparent and consistent methods established within evidence-based medicine (EBM). Comprehensive analysis must also include patient outcome and societal aspects, and consider cost-benefit analysis.

HTA reports ideally start from a study of the typical patient pathway for each given disease in a certain jurisdiction and estimate all the benefits and resources used on that pathway, with and without access to the new technology, in order to determine the strategies by which new diagnostic tests might be used beneficially for both patients and society. In the case of the use of PET in oncology, such modelling varies for every individual cancer and for each stage of cancer, and is also influenced by the availability, performance and cost of both diagnostic and therapeutic procedures in different healthcare settings. It is therefore very complex to construct. Consequently, a pragmatic approach has generally been to choose a particular cancer and generic question to investigate. In the first instance, this has usually been a cancer, or group of clinical indications, for which the use of PET has been suggested to be supported by the strongest evidence base. The assumption is that if a strong economic case cannot be made for the utility of PET in this situation, then it is unlikely to be worthwhile in other indications with even less robust evidence. Although there is often an assumption that the value of new technologies must be reflected in an ability to improve patient outcomes, of course this is influenced by the potential for successful therapy. Historically, the ability of improved diagnosis to provide better prognostic stratification has spawned the development of new therapies that can successfully alter outcomes of the patients in differing groups as defined by the new diagnostic paradigm. An example was the development of cholesterol lowering drugs following demonstration that cholesterol levels were the most important contributor to the poor prognosis associated with elevated fatty acid levels in blood. Lack of currently effective therapies and limited capacity for immediately improving patient outcomes should therefore not necessarily justify withholding access to new diagnostic technologies like PET. Furthermore, withholding futile or likely ineffective and morbid treatments may provide benefits not measurable by improvement in duration of life.

By searching on the International Network for Agencies of Technological Assessment web site (<http://inahta.org/>) for the HTA reports it is possible to currently find 23 publications on the subject of PET or PET/CT (HTA records or NHS-EED economic evaluations) that discuss the clinical role of this diagnostic modality in Oncology.

As example of the above mentioned studies, some HTA reports will be briefly summarized. The Adelaide Health Technology Assessment in 2004 published a report on 'Combined CT and PET Scanner' having the intended purpose to evaluate the need for PET/CT examinations in the health system, considering not only the already established oncological indications but also the cardiovascular and neurological diseases. This report analyzes the local clinical need and burden of disease, the treatment alternatives and the existing diagnostic comparators. Two issues were taken as clinical outcomes: the diagnostic effectiveness (PET/CT vs. PET, PET/CT vs. CT and PET/CT vs. conventional diagnostic work-up) and the safety. The cost-analysis was performed on the existing cost-effectiveness evidence, on the cost of the



management of cancer and on the management of neurological and cardiovascular disorders. The conclusions of this study were in favour of the potential use of PET/CT also in the diagnosis and the management of non-oncological indications (cardiovascular and neurological disease). The use of PET/CT scan in oncology during the course of the treatments and the development of new indications was considered an unavoidable trend that in the future will contribute to increase the number of PET scans. The conclusions were that PET/CT was able to improve diagnostic capabilities when compared to PET or CT alone, depending on the type, the stage of tumour and whether analysed on a lesion-by-lesion basis or by patient. This study confirmed also that PET/CT improves the localisation of lesions and decreases the number of equivocal lesions, when compared to PET alone. Figures of merit about its diagnostic sensitivity and specificity in different conditions have been reported. The economic analysis was carried out based on the capital cost of purchasing a PET/CT scanner and the estimated cost to the health system in case of utilization of at least one scan for all patients with newly diagnosed cancer.

A systematic review published by the Agencia de Evaluation de Tecnologia Sanitaria (AETS) in 2004 has investigated the relative contribution of PET/CT to the clinical management of oncology patients. The report aimed to assess whether this technology is able to provide a higher diagnostic accuracy compared with other available technologies, if it can influence the patient's management and, finally, if its use can further benefit cancer patients. The authors' conclusion was that PET/CT is a useful technique for detection of malignancy, with a significant reduction of inconclusive lesions. Other worthwhile indications were felt to include radiotherapy planning, guidance of biopsy and therapeutic monitoring. The diagnostic accuracy of PET/CT for tumour re-staging (loco-regional and distant metastasis) was shown to be even a little better than for staging cancer. The authors' conclusion was that PET/CT could be cost-effective through reduction of unnecessary diagnostic methods or treatments, including surgery. Some other advantages of PET/CT that were recognised were that it is less time consuming compared with PET alone, allows higher throughput of patients and the fact that the simultaneous acquisition of PET and CT images limit the alignment problems.

A review by the French National Authority for Health (HAS), published in 2005, assessed different aspects regarding the use of PET/CT in France (technical, legislative, medical, economic and organisational) in order to establish equipment selection criteria and organisational implications. The results stressed the technical advantages of PET/CT over PET (faster attenuation correction and better localization). The rules for installing combined PET/CT in healthcare organisation were established to be the same as for installing a PET machine alone. The clinical studies tended to show that PET/CT had improved sensitivity and especially specificity, compared with PET alone. However the potentially significant clinical impact and the potential for replacing diagnostic CT with PET/CT could not be assessed. For the organisational aspect this report recommended that the PET/CT system has to be integrated into an imaging network. The estimated capital outlay for a PET/CT system in 2.5 millions € compared with 1.7 millions € for a PET system. The estimated operating budget was 2–2.2 million € for 2000 examinations per year.

A more recent overview published on the clinical effectiveness of PET published by Facey et al. in 2007 aimed to evaluate the clinical effectiveness of FDG-PET in breast, colorectal, head and neck, lung, oesophageal and thyroid cancer and in lymphoma and melanoma. For each cancer, the use of <sup>18</sup>F-FDG-PET to aid management decisions relating to diagnosis, staging, restaging of recurrence, treatment response monitoring, and radiotherapy planning was evaluated. The conclusions of the authors were that the strongest evidence for the clinical effectiveness of PET was in staging of NSCLC, restaging of lymphoma, staging and restaging

of colorectal cancer and characterisation of solitary pulmonary nodules. PET/CT was evaluated only in six cancer types (excluding breast and melanoma). Most studies combined different groups of patients to assess primary and recurrent tumours for staging and restaging respectively. These showed that PET/CT generally improved accuracy by 10–15% over PET, resolving some equivocal PET findings in such cancers. The conclusions of the report regarding PET/CT is that there is likely to be new capital investment required in the newer PET/CT technology, despite at present there still being less evidence of utility than there is for PET. However, PET clinical effectiveness results can be extrapolated to cover PET/CT.

Many technology assessment projects have been recently approved and commenced by Agencies for Health Technology Assessment throughout the world, with the goal of comparing the cost-effectiveness of PET/CT technology with other diagnostic technologies financed from public sources in diagnostic oncology. This because the economic analysis of PET/CT scanning identified from the literature are still very limited and conclusive evidences are considered to be lacking. Data on quality of life and patient outcomes using the combined technology are almost absent, despite the enormous growth in the clinical use of PET/CT. The methodology of these evaluations is hampered by the fact that HTA studies take a lot of time to be carried out, the approaches are not yet fully standardized and are often not able to follow the rapid technical developments occurring in the modality. Scientific papers confined to the diagnostic efficacy of new tests are often considered sufficient by the clinical community to justify their clinical use. However, these considerations do not diminish the importance of economic analysis as a means to provide a more reliable basis on which implementation decisions can be taken, even though it should be stressed that any economic analysis of diagnostic technologies will never be able to negate the individual benefits of improved diagnosis to individual patient care. Clinicians reading HTA reports should be aware that they are often performed by non-clinicians with little or no involvement in the care of cancer patients, nor knowledge of the diagnostic and therapeutic implications of the data that they are reviewing. Further, it is important to recognise that the reports that are generated are often funded and published by Governments or private insurance groups with a vested interest in constraining costs without being rigorously subjected to expert review. Therefore, caution should be applied when considering application of the recommendations of these reports to patient care and particularly in advising individual patients regarding the utility of PET and PET/CT in the diagnostic process related to their own specific disease clinical situation. In particular, the conclusions of several INAHTA reviews have been challenged by experts in PET actually involved in those reviews and have also been completely at odds with expert clinical opinion of the utility of PET in oncology.



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