
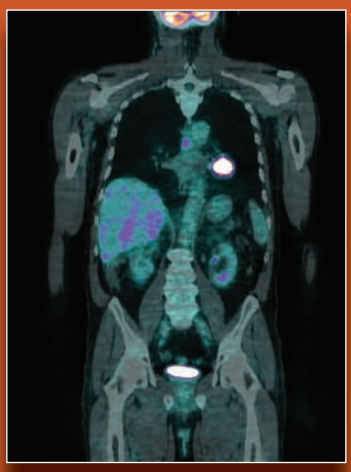


IAEA HUMAN HEALTH SERIES

No. 11

Planning a Clinical PET Centre

IAEA
International Atomic Energy Agency

IAEA HUMAN HEALTH SERIES PUBLICATIONS

The mandate of the IAEA human health programme originates from Article II of its Statute, which states that the "Agency shall seek to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world". The main objective of the human health programme is to enhance the capabilities of IAEA Member States in addressing issues related to the prevention, diagnosis and treatment of health problems through the development and application of nuclear techniques, within a framework of quality assurance.

Publications in the IAEA Human Health Series provide information in the areas of: radiation medicine, including diagnostic radiology, diagnostic and therapeutic nuclear medicine, and radiation therapy; dosimetry and medical radiation physics; and stable isotope techniques and other nuclear applications in nutrition. The publications have a broad readership and are aimed at medical practitioners, researchers and other professionals. International experts assist the IAEA Secretariat in drafting and reviewing these publications. Some of the publications in this series may also be endorsed or co-sponsored by international organizations and professional societies active in the relevant fields.

There are two categories of publications in this series:

IAEA HUMAN HEALTH SERIES

Publications in this category present analyses or provide information of an advisory nature, for example guidelines, codes and standards of practice, and quality assurance manuals. Monographs and high level educational material, such as graduate texts, are also published in this series.

IAEA HUMAN HEALTH REPORTS

Human Health Reports complement information published in the IAEA Human Health Series in areas of radiation medicine, dosimetry and medical radiation physics, and nutrition. These publications include reports of technical meetings, the results of IAEA coordinated research projects, interim reports on IAEA projects, and educational material compiled for IAEA training courses dealing with human health related subjects. In some cases, these reports may provide supporting material relating to publications issued in the IAEA Human Health Series.

All of these publications can be downloaded cost free from the IAEA web site:
http://www.iaea.org/Publications/index.html

Further information is available from:

Marketing and Sales Unit
International Atomic Energy Agency
Vienna International Centre
PO Box 100
1400 Vienna, Austria

Readers are invited to provide their impressions on these publications. Information may be provided via the IAEA web site, by mail at the address given above, or by email to:

Official.Mail@iaea.org.

PLANNING A CLINICAL PET CENTRE

The following States are Members of the International Atomic Energy Agency:

AFGHANISTAN
ALBANIA
ALGERIA
ANGOLA
ARGENTINA
ARMENIA
AUSTRALIA
AUSTRIA
AZERBAIJAN
BAHRAIN
BANGLADESH
BELARUS
BELGIUM
BELIZE
BENIN
BOLIVIA
BOSNIA AND HERZEGOVINA
BOTSWANA
BRAZIL
BULGARIA
BURKINA FASO
BURUNDI
CAMBODIA
CAMEROON
CANADA
CENTRAL AFRICAN REPUBLIC
CHAD
CHILE
CHINA
COLOMBIA
CONGO
COSTA RICA
CÔTE D'IVOIRE
CROATIA
CUBA
CYPRUS
CZECH REPUBLIC
DEMOCRATIC REPUBLIC OF THE CONGO
DENMARK
DOMINICAN REPUBLIC
ECUADOR
EGYPT
EL SALVADOR
ERITREA
ESTONIA
ETHIOPIA
FINLAND
FRANCE
GABON
GEORGIA
GERMANY
GHANA
GREECE
GUATEMALA
HAITI
HOLY SEE
HONDURAS
HUNGARY
ICELAND
INDIA
INDONESIA
IRAN, ISLAMIC REPUBLIC OF
IRAQ
IRELAND
ISRAEL
ITALY
JAMAICA
JAPAN
JORDAN
KAZAKHSTAN
KENYA
KOREA, REPUBLIC OF
KUWAIT
KYRGYZSTAN
LATVIA
LEBANON
LESOTHO
LIBERIA
LIBYAN ARAB JAMAHIRIYA
LIECHTENSTEIN
LITHUANIA
LUXEMBOURG
MADAGASCAR
MALAWI
MALAYSIA
MALI
MALTA
MARSHALL ISLANDS
MAURITANIA
MAURITIUS
MEXICO
MONACO
MONGOLIA
MONTENEGRO
MOROCCO
MOZAMBIQUE
MYANMAR
NAMIBIA
NEPAL
NETHERLANDS
NEW ZEALAND
NICARAGUA
NIGER
NIGERIA
NORWAY
OMAN
PAKISTAN
PALAU
PANAMA
PARAGUAY
PERU
PHILIPPINES
POLAND
PORTUGAL
QATAR
REPUBLIC OF MOLDOVA
ROMANIA
RUSSIAN FEDERATION
SAUDI ARABIA
SENEGAL
SERBIA
SEYCHELLES
SIERRA LEONE
SINGAPORE
SLOVAKIA
SLOVENIA
SOUTH AFRICA
SPAIN
SRI LANKA
SUDAN
SWEDEN
SWITZERLAND
SYRIAN ARAB REPUBLIC
TAJIKISTAN
THAILAND
THE FORMER YUGOSLAV REPUBLIC OF MACEDONIA
TUNISIA
TURKEY
UGANDA
UKRAINE
UNITED ARAB EMIRATES
UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND
UNITED REPUBLIC OF TANZANIA
UNITED STATES OF AMERICA
URUGUAY
UZBEKISTAN
VENEZUELA
VIETNAM
YEMEN
ZAMBIA
ZIMBABWE

The Agency's Statute was approved on 23 October 1956 by the Conference on the Statute of the IAEA held at United Nations Headquarters, New York; it entered into force on 29 July 1957. The Headquarters of the Agency are situated in Vienna. Its principal objective is "to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world".

IAEA HUMAN HEALTH SERIES No. 11

PLANNING A CLINICAL PET CENTRE

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2010

COPYRIGHT NOTICE

Marketing and Sales Unit, Publishing Section
International Atomic Energy Agency
Vienna International Centre
PO Box 100
1400 Vienna, Austria
fax: +43 1 2600 29302
tel.: +43 1 2600 22417
email: sales.publications@iaea.org
http://www.iaea.org/books

Printed by the IAEA in Austria
April 2010
STI/PUB/1457

IAEA Library Cataloguing in Publication Data

Planning a clinical PET centre. — Vienna : International Atomic Energy Agency, 2010.
p. ; 24 cm. — (IAEA human health series, ISSN 2075-3772 ; no. 11)
STI/PUB/1457
ISBN 978–92–0–104610–9
Includes bibliographical references.

1. Tomography, Emission — Methodology. 2. Nuclear medicine. 3. Positrons — Emission. I. International Atomic Energy Agency. II. Series.

IAEAL 10–00630

FOREWORD

Establishing a positron emission tomography (PET) centre is a large scale process that requires careful planning, inputs from multiple stakeholders, the support and approval of relevant authorities, secure funding, and a detailed implementation strategy. The need for a carefully planned strategy is even more essential in the conditions prevailing in a developing country, where the introduction of PET may be impeded by a scarcity of financial resources and, in many cases, an inadequate understanding of the potential roles and contributions PET imaging can play in a health care system.

Different imaging techniques are based upon different underlying physiological and physical principles and, accordingly, provide unique clinical insights. The recent introduction of hybrid PET/computed tomography (CT) equipment has had a major impact on the imaging field, as the co-registration of PET and CT data couples functional and anatomical information, thus optimizing the clinical utility of the images. PET/CT, used with [^{18}F]-FDG as a radiotracer, has had such an impact on patient management that it has reformed many traditional diagnostic approaches, and offers a new tool to be used in the development of protocols and strategies in oncology.

The use of clinical PET, as well as the installation of new PET/CT systems, has been growing exponentially all over the world. Clinical PET is currently viewed as the most significant diagnostic tool in its field.

In a large project of this type, a strategy should be developed to address the major issues as spelled out in the framework of governmental policies and strategies for the improvement of health care services in a country. The design of a successful strategy should include the participation of several stakeholders, such as the Ministries of Health or Education or Science, potential beneficiaries such as universities, representatives of the oncology, radiology and nuclear medicine communities and medical societies, scientists, and engineers specializing in accelerator or cyclotron technology, nuclear and medical physics, radiochemistry or radiopharmacy.

This publication addresses the issues discussed above in a systematic manner, with the aim of setting out a well defined pathway for establishing a cyclotron/PET centre capable of providing advanced PET/CT imaging services to the general population. The focus of this strategy is to acquire approval for the project and the necessary resources from the authorities through the systematic preparation of the required information and justifying arguments.

Issues related to the cost effectiveness of clinical PET in oncology are discussed. The information is intended to be useful in decision making when allocating resources. This is a critical issue for the development of both clinical oncology and nuclear medicine in IAEA Member States.

This publication presents a comprehensive overview of the steps involved in the establishment of a clinical PET facility, from strategy formulation to cyclotron implementation, radiopharmaceutical production and clinical applications. Also covered are staff requirements and radiation protection issues. It is intended for health care administrators, project and site planners, as well as all professionals involved in providing PET services.

The IAEA officers responsible for this publication were M. Dondi and S. Palm of the Division of Human Health and M. Haji-Saied of the Division of Physical and Chemical Sciences.

CONTENTS

1. INTRODUCTION

1.1. BACKGROUND

The initial applications of positron emission tomography (PET) began almost five decades ago, but were initially limited to the research setting. In the mid-1990s, PET began to be used in clinical practice in the more developed countries of the world — with proven impact, especially in oncology. In particular, the rapid developments in PET imaging over the last ten years are due to significant achievements in several fields. Among them, the general acceptance of the value of FDG–PET in clinical oncology was a major step, as it led to the widespread use of the technique and an increasing demand for this type of examination. In parallel with this and no less relevant, there have been important technological improvements such as the introduction of hybrid systems which couple PET with X ray computed tomography (PET/CT).

1.2. OBJECTIVE

Establishing a PET centre is a large scale process that requires careful planning, inputs from multiple stakeholders, the support and approval of the authorities, secure funding, and a detailed implementation strategy. The need for a carefully planned strategy is even more essential in the conditions prevailing in a developing country, where the introduction of PET may be impeded by a scarcity of financial resources and, in many cases, an inadequate understanding of the potential roles and contributions PET imaging can play in a health care system.

The issues discussed above are addressed in this publication. The aim is to set out a well defined pathway for establishing a cyclotron/PET centre capable of providing advanced PET/CT imaging services to the general population. The focus of this strategy is to acquire approval for the project and the necessary resources from the authorities through the systematic preparation of the required information and justifying arguments.

1.3. SCOPE

This publication presents a comprehensive overview of the steps involved in the establishment of a clinical PET facility, from formulation of a strategy to cyclotron implementation, radiopharmaceutical production and clinical

applications. Also covered are staff requirements and radiation protection issues. It is intended for health care administrators, project and site planners, as well as professionals involved in providing PET services.

1.4. STRUCTURE

There are nine sections and six appendices in this publication.

Section 2 discusses the use of PET in clinical practice, including the rationale for its application; the constraints; strategies for use; and practical approaches for its application. Section 3 describes the epidemiology and provides a definition of needs for a clinical PET centre. Section 4 provides a cost–benefit analysis of PET/CT. Section 5 describes the major pieces of equipment needed for the establishment of a PET centre. Section 6 focuses on the design of a PET centre and provides a number of models of clinical PET facilities. Section 7 gives details of the design of a cyclotron facility, while Section 8 details staffing requirements in setting up a PET centre. Finally, Section 9 looks at a number of radiation protection issues that need to be considered in setting up a clinical PET centre.

The appendices focus on clinical indications of PET in oncology, in neurology, in cardiology, and inflammation and infection. They also address production needs and implementation of a quality management system to help PET practitioners maintain or improve the quality of service for their patients.

2. INTRODUCTION OF PET IN CLINICAL PRACTICE

2.1. GENERAL CONSIDERATIONS

2.1.1. Rationale

PET has been in use in a research setting for more than three decades now and has been implemented in clinical practice in the more developed countries of the world for more than a decade, with proven impact on clinical outcome [2.1–2.3]. A keen interest in establishing a PET centre is a much needed initial condition, but planners, medical doctors and scientists must be able to justify their ideas in a convincing project proposal and obtain the support and financing of the relevant authorities.

The initial investment in a PET centre is in the range of at least several million dollars, which is quite often contrasted unfavourably with the much lower initial investment required for other imaging modalities, such as magnetic resonance imaging (MRI) or computed tomography (CT). In addition, governments tend to view medical imaging as just one of a battery of medical imaging modalities, and may not properly appreciate its unique capabilities.

Planning for the introduction of PET to a country where it is not already well established should address local high priority health issues and be driven by demonstrable medical needs. That is to say, priorities should be demand oriented rather than technology or prestige driven, and be compatible with the national government's long term health care policies and strategies, in order to improve and strengthen existing diagnostic and therapeutic infrastructure. It is worth noting that governments are increasingly formulating five to ten year development plans and demanding that the formulation and approval of project proposals be carried out within a larger national framework if they are to be considered for funding.

Similarly, the IAEA regards both financial commitment from the national government and evidence that the project complies with national health priorities and development strategies, as prerequisites for its support of a project.

2.1.2. Constraints

There are a number of constraints that may be encountered during the establishment of a cyclotron/PET project. Some can be counteracted fairly easily. For example, to ease doubts about PET being an expensive technology, epidemiological data can be used to demonstrate that PET is an efficient and cost effective means of addressing health issues of relevance for the population at large, and not only for a limited segment of it as it is perceived in some cases.

In developing nations other major constraints are:

— *Financial.* The initial capital investment required is high, up to $6 million or more. In addition, planners should consider operational and maintenance costs, which are typically 10% of the capital costs per annum, and the need to employ qualified professionals to run the centre. The financial resources required often come as a shock to government officials, particularly if the benefits of PET technology are not well understood.
— *Structural.* PET has become a routine diagnostic procedure in many industrialized countries largely because of the availability in those countries of a reimbursement scheme, which is typically implemented after a demonstration of a positive cost–benefit ratio for several medical indications. Unfortunately, national medical reimbursement schemes are not widespread in developing nations and limited, weak or non-existent reimbursement schemes for health care services are an impediment to the adoption of PET. Private schemes, however, might also be taken into account.
— *Political.* It is often necessary to compete with other priorities in the health sector. In a developing country it is not uncommon to encounter the opinion that PET is too expensive and that there are other more pressing health priorities, which may require a bigger share of the scarce funding available. Similarly, it is often argued that MRI and CT are less expensive and sufficient for local needs. It is important in these cases to point out the unique clinical value of the information that PET can provide.
— *Conceptual.* There is often a lack of awareness within the local medical community of the complexity and cost of implementing a cyclotron/PET programme. It is important to devise ways of informing planners and the local medical community that this is a complex and sophisticated technology that can be successfully implemented and exploited only by a properly qualified and educated multidisciplinary team.
— *Organizational.* Lack of a culture or tradition of careful planning. In most cases, medical technologies are purchased on a turnkey basis and are ready to be operated immediately. Establishing a cyclotron/PET facility, however, is far more complex and detailed planning is essential.
— *Human resources.* Lack of professionals in numbers and experience. Planning should provide for advanced training of key professionals (including medical, scientific, technical and nursing staff) at an early stage, preferably at well established international facilities.

2.2. STRATEGIES

2.2.1. The starting point

The path from project conception to a full fledged operational cyclotron/PET centre may take a considerable amount of time, typically between three and five years. However, there are instances when this process may take even longer. A dedicated, multidisciplinary group of professionals, committed to the project, will help to reduce the duration of the project.

As a first step, it is recommended that a Task Force (TF) be established at the outset to act as a think tank to elaborate the conceptual and technical aspects of the proposed project. This group will develop the necessary justifications, liaise with and lobby the national health authorities, and be the engine that moves the project forward in all its dimensions and stages. The TF should have a clear line of command and well defined responsibilities and schedules with the corresponding authority to make decisions and take the corresponding actions. As much as possible, the composition of the TF team should be multidisciplinary and include representatives of all the major stakeholders.

2.2.2. Building alliances

Most of the time the TF, as a core organization, will not by itself be capable of mounting a sufficiently convincing case to ensure the support of the national authorities for a project that requires such a large investment. Seeking and building alliances and synergies with other interested groups is therefore of paramount importance. These strategic alliances should be established with identified selected groups of the public sector and, possibly with the private sector as well. Health care providers, universities, research institutes, and medical specialists are ideal stakeholders who might be interested in having access to a cyclotron/PET facility. Additionally, as has happened in many cases, private nuclear medicine services would also benefit from the availability of PET radiopharmaceuticals, and therefore may also contribute to the justification to the government for investment, or may even be willing to set up a joint facility under an appropriate scheme. Building strategic alliances with identified stakeholders from the outset of the project will contribute to the formulation of a more relevant and balanced project proposal with enhanced chances of government and international support.

2.2.3. Strengths and weaknesses

It should be remembered that PET and its potential impacts are still not well known and fully appreciated in many developing countries. Understandably then, national health authorities tend to more readily perceive other pressing priorities in the health care system with respect to local epidemiology and social demands. This aspect should be kept in mind when devising a strategy for the establishment of a cyclotron/PET centre. Therefore, a productive strategy may be to include steps or actions to transform an apparent barrier such as the one just mentioned into a positive issue, for example, by demonstrating that PET can very effectively address, in a cost effective manner, and along with existing diagnostic modalities, important national and social health care priorities such as cancer. PET should be seen as an invaluable and unique technique in its own right, and as one that can complement the diagnostic power of other modalities, rather than as an expensive competing technology beyond the reach of most of the population.

A large part of the medical community is also not fully aware of the potential impact of PET on their own clinical specialties. Such individuals may not be supportive of the project, and may construct barriers that can delay the implementation of the project, as has been observed on many occasions. Here again, an intensive and well designed information and educational campaign will help to overcome this problem.

2.3. A PRACTICAL APPROACH

The role of the TF is to produce, first, a well balanced, technically sound and comprehensive project proposal document (PD), and then, if approval is granted from the national health authorities, a full feasibility study (FS). In all these actions the TF is called upon to play a decisive role in identifying strengths and weaknesses and to introduce corrective measures when necessary. Indeed, with initial modest resources at hand, the first practical objective is to prepare documentation and material to demonstrate the value of PET in the context of the national health care policies.

The following is a ‘two step’ approach that has proved to be effective in situations where there was only an embryonic idea to set up a PET centre.

2.3.1. Step 1: The project document

The PD should clearly outline the mission of the PET centre within the context of national health care policies and strategies. It should include: an account of the major justifications for the project, an outline of the problems that

may be faced during implementation and the strategies for solving them, the need for more advanced clinical diagnostic tools, an estimate of the total cost of the project and the time for its implementation, identification of potential financial sources, guidelines for project implementation, and identification of interested stakeholders.

The PD is addressed principally to decision makers in the government and seeks the official endorsement of the relevant government authorities to proceed to a more advanced phase of the project, namely, the preparation of a comprehensive feasibility study (FS). It can also be utilized for the preparation of a comprehensive project proposal (PP) to the IAEA and/or other potential financing sources within as well as outside the country.

It is not always necessary to follow this suggested two step approach, depending on the circumstances. If there is already a well informed understanding and the authorities have already decided that the PET technology is to be established, a feasibility study alone may be sufficient.

2.3.2. Step 2: The feasibility study

Essentially, the FS should be designed to provide a clear, comprehensive, and quantitative picture of what exactly is required for a cyclotron/PET centre in terms of financial resources and otherwise. This document should elucidate the 'whys and hows' of the project, in the framework of national health policies. It should give the relevant authorities a well informed understanding of the project, to help them consider its short and long term political, and financial implications. It should contain a clear set of concrete recommendations so that they can make the necessary decisions.

The FS expands the conceptual and policy aspects of the PD and should provide: documented and quantitative evidence to justify the investment; definitions of the technological components needed — including the site, staff and training requirements — approximate estimates of the financial requirements; and legal, regulatory, and environmental issues. The FS will define the scope, phases and priorities of the utilization programme, and propose a management and operational structure as well as a realistic business plan. The short and long term financial implications of the project, from the initial investment to the routine operation of the facility, are a critical part of the FS, and should include the identification of potential financial sources and schemes, and propose strategies to secure the funding.

The advantage of this two-step approach is that it avoids entanglement in an involved, time consuming, and in many cases costly feasibility study process, sometimes without any assurance from the national authorities that a

cyclotron/PET project proposal will be supported. Such assurances are best obtained in writing.

2.3.3. Project schedule

Managing a project to implement a clinical PET centre is a demanding task that is long and time consuming. Figure 2.1 depicts a Gantt chart of a typical project when the centre must be built from the scratch.

REFERENCES TO SECTION 2

[2.1] FACEY, K., BRADBURY, I., LAKING, G., PAYNE, E., Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers, Health Technol. Assess. **44** Oct. 11 (2007) iii–iv, xi–267.

[2.2] PODOLOFF, D.A., et al., NCCN Task Force Report: Positron emission tomography (PET)/computed tomography (CT) scanning in cancer, J. Natl Compr. Cancer Network **5** (2007) Suppl 1:S1–S22.

[2.3] HILLNER, B.E., et al., Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: Initial results from the National Oncologic PET Registry, J. Clin. Oncol. **26** 13 (2008) 2155–2161.

FIG. 2.1. Gantt chart of a PET project from inception (N.M.: nuclear medicine).

3. EPIDEMIOLOGY AND DEFINITION OF NEEDS

3.1. BACKGROUND

Planning a new PET programme for a country or geographical area is a complex task, requiring multidisciplinary competence and knowledge. In order to properly define clinical needs, and prepare an effective plan for the introduction of PET into a designated health care system (whether national or regional), it is advisable that a composite panel of experts covering all relevant major disciplines (nuclear medicine, clinical oncology, haematology, radiation oncology, medical physics, health technology assessment, epidemiology, health care administration, etc.) be set up as early as possible in the development phase to identify clinical needs.

The scope of the activities of this panel should be clearly defined to avoid duplication and confusion with other entities involved in the project. The goals of this panel should be quite distinct from those of the work group responsible for site planning and the selection and installation of equipment.

This section will address the criteria for appropriate use of PET in clinical practice, the national/regional needs in terms of number of examinations per year in a specified time frame (i.e. the next five years), the number of scanners needed to fulfil the expected workload, and advice regarding reimbursement policies.

Although PET has applications in oncology, cardiology, neurology and other fields, in the following paragraphs explicit reference is made only to its use in oncology as this is by far the most common application at the present time and is thus the best guide to health technology assessment (HTA) and health economic considerations.

Health technology assessment (see Section 4.4) is defined as a policy research approach that examines the short and long term social consequences of the application or use of technology and may be considered as a bridge between science and policy, requiring a balance between the ideals of scientific rigour and the realities of policy making [3.1].

3.2. GLOSSARY

The key terms used in this publication are defined below.

incidence. The number of new cases of a specific disease arising in a specified population in a given period of time. Several countries/regions have cancer registries dedicated to the collection and statistical evaluation of this kind of information. Incidence is usually expressed as the total number of cases per year, or as the rate per 100 000 persons per year. The latter provides an estimate of the average risk of developing a cancer.

prevalence. With reference to a specific type of cancer, or to an ensemble of cancers of different types, prevalence is defined as the number of living persons in a given population who have been diagnosed with that type of cancer (or cancers). Complete prevalence is the proportion of the population at any time that has been diagnosed with a cancer, regardless of when the diagnosis occurred and whether or not the patient is still under treatment or is considered cured. Partial (or limited) prevalence is the number of patients diagnosed within a specified time interval. Patients who survive for five years after diagnosis are usually considered cured; nevertheless, depending on the type of disease, they may still require follow up and diagnostic procedures.

mortality. The number of deaths occurring in a specified period of time in a given population. It can be expressed as an absolute number of deaths per year, or as a rate per 100 000 persons per year.

survival. The probability of surviving for a given period of time with a specific type of malignant cancer, expressed as time elapsed since diagnosis (e.g. survival rate at five years). The probability of survival is influenced by mortality due to the cancer of primary interest and from other causes.

relative survival is then defined as the ratio of the observed survival in the group of patients to the survival expected in a group of people in the general population who are similar to the patients with respect to all possible factors affecting survival at the beginning of the follow-up period, except for the disease of interest.

indication. A clinical condition, risk factor, or circumstance for which the use of a particular intervention would be appropriate as determined or specified by, for example, a clinical practice guideline, standard of care, regulatory body, or other authoritative source.

clinical guideline. A systematically developed statement to assist practitioner and patient decisions about appropriate health care for one or more specific clinical circumstances. The development of clinical PET practice guidelines can be considered a particular type of HTA; or, it can be considered to be one of the types of policy making that is informed or supported by HTA.

appropriateness. A measure of the manner of use and outcomes of a health technology. For a diagnostic technique, its use is considered appropriate when studies available in the scientific peer review literature fulfil all of the following conditions:

— There is evidence of a higher diagnostic performance (higher sensitivity and specificity), compared with other current techniques;
— The information obtained from the technique of interest has an influence on clinical practice;
— The information supplied by the technique has a positive impact on the patient's outcome by allowing the adoption of effective practice or the non-adoption of ineffective or harmful practice.

peer review. The process by which manuscripts submitted to health, biomedical, and other scientifically oriented journals and other publications are evaluated by experts in appropriate fields (usually anonymously to the authors) to determine if the manuscripts are of adequate quality for publication.

3.3. PET IN ONCOLOGY: ROLE OF EPIDEMIOLOGY INDICATORS

PET (and PET/CT) finds its major applications in oncology, in the diagnosis, staging and restaging of several types of cancers [3.2], monitoring the response to therapy, and in contributing functional information useful for the planning of radiotherapy treatment. As a first step towards defining the need for PET within a health care system, it is therefore useful to define the population that could potentially benefit from this technology.

Since patients can be referred for a PET scan at any time during the progression of their disease (i.e. at initial diagnosis, staging, restaging, during treatment or follow up), prevalence is the most useful indicator to identify the population of patients for which PET is potentially indicated. However, incidence should also be carefully considered, particularly in the case of lung cancer, for which, due to the relatively limited survival, prevalence tends to incidence.

The prevalence of cancer is influenced by a complex variety of factors, including but not limited to, sex, age and diet, working and living habits, and so on. Prevalence is then an indicator that can vary within a country or geographical region. The first approach for a local health authority or a team planning a PET programme in oncology is then to acquire data on the local prevalence of cancer.

Cancer registries are present in many countries, but unfortunately, even in developed countries, they do not cover the entire population. Information on prevalence, incidence and mortality can be obtained from local cancer registries or institutions involved in cancer diagnosis, treatment or epidemiology.

When up to date statistics on cancer prevalence are not available, information may be obtainable from international institutions and projects, such as the World Health Organization (WHO) [3.3] the Cancer Mondial and Globocan projects [3.4] or, in Europe, the Eurocare project [3.5]. If no local information is available, published data on neighbouring countries or regional data can be used.

Cancers are classified according the international classification of diseases (ICD) scheme; the current version of the classification is ICD-10, but it should be noted that most data published in recent years are based on the previous ICD-9 codes.Further information and the on-line database of classifications can be accessed at the web site of WHO [3.6].

Ideally, prevalence data for each of the most important ICD-9 codes (see Table 3.1) should be obtained. If detailed data are not easily available, statistics on lung, breast, colorectal, lymphoma, and possibly prostate and stomach cancers, should be included in the analysis.

Significant variations in prevalence are common, even in different areas of the same country. Nevertheless, a careful evaluation of available data can supply useful information for planning the installation and distribution of diagnostic and therapeutic technologies.

Finally, epidemiology indicators such as incidence and prevalence change continuously with time. In very general terms, cancer prevalence is increasing slightly with time due to factors related not only to changes in life style, ageing, increased exposure to risk factors, and to improvements in the quality of treatment, but also to better diagnosis and data collection. This tendency to increase needs special consideration by health authorities in the planning of diagnostic and therapeutic technologies.

TABLE 3.1. ICD-9 CODING FOR THE MOST COMMON NEOPLASMS

Cancer site	ICD-9
Oral cavity	140.0–145.9, 149.0–149.9
Nasopharynx	147.0–147.9
Other pharynx	146.0–146.9, 148.0–148.9
Oesophagus	150.0–150.9
Stomach	151.0–151.9
Colon and rectum	153.0–154.0, 159.0
Liver	155.0–155.1
Pancreas	157.0–157.9
Larynx	161.0–161.9
Lung	162.0–162.9
Melanoma of skin	172.0–172.9
Prostate	185.0–185.9
Testis	186.0–186.9
Kidney, etc.	189.0–189.9
Bladder	188.0–188.9
Brain, nervous system	191.0–191.9
Thyroid	1930 – 1939
Non-Hodgkin lymphoma	200.0–200.9, 202.0–202.9
Hodgkin lymphoma	201.0–201.9
Multiple myeloma	203.0
Leukaemia	204.0–208.9
Breast	174.0–175.9
Uteri	179.0–180.9, 182.0–182.9
Ovary	183.0–183.9
All sites but non-melanoma skin	140–208

3.4. PET IN ONCOLOGY: ROLE OF ACCEPTED INDICATIONS

The manner in which a medical technology is exploited in practice is greatly influenced by available evidence of its usefulness and efficacy for particular indications, and the indications for which reimbursement is available.

Two factors are in continuous evolution and are somewhat conflicting: demonstration of evidence for a given indication, and its recognition and reimbursement by health care systems and insurances or refunding agencies, are processes travelling on different pathways, with different speeds. The strict application of economic analysis on a cost–benefit basis can obviously slow investment in a new technology [3.7].

This process is still ongoing with regard to PET and PET/CT, and at present it is possible to see how specific indications are recognized as being evident, and thus reimbursed, in some countries, while they still are not reimbursed in other countries, not only because of considerations of health economics, but also due to peculiarities in the organization of the health care system and local conditions.

Information on these subjects is widely available in current scientific literature and several HTA reports have been published. A representative list of references is given at the end of this chapter.

Clearly, the wider the accepted indications, the greater the number of requests for PET examinations. The population selected (i.e. on the basis of prevalence or other factors) and the level of evidence that is requested (i.e. number and type of recognized indications) are critical parameters in the hands of policy makers and health administrators when determining the level of investment a country or region is willing to commit to these costly technologies. Table 3.2 summarizes the currently recognized PET indications worldwide according to the following definitions:

appropriate. All of the following conditions must be met:

- Evidence of improved diagnostic performance (higher sensitivity and specificity) compared with other current techniques;
- The information derived from the PET scan influences clinical practice;
- The information from PET has a plausible impact on the patient's outcome, either through adoption of more effective therapeutic strategies or non-adoption of ineffective or harmful practices.

potentially appropriate (potentially useful). Evidence of improved diagnostic performance (higher sensitivity and specificity) compared with other current techniques, but lacking evidence of an impact on treatment and outcome.

inappropriate. Clinical situations for which improved accuracy of tumour stage will not alter management, or for which the performance of PET is poorer than that of other current techniques.

It should, however, be considered that in a continuously evolving context, FDG–PET is a rapidly evolving technology. Table 3.2 will require periodic update and readers are advised to seek the most recent reports pertinent to this particular area of studies.

Overall, the indications for the use of PET in oncology that are recognized almost worldwide are for the following cancer types:

— Lung cancer;
— Colorectal cancer;
— Lymphoma.

TABLE 3.2. INDICATIONS FOR FDG–PET ON ONCOLOGY ACCORDING TO FOUR DIFFERENT CATEGORIES. **A**: WIDELY ACCEPTED AS APPROPRIATE; **B**: ACCEPTED AS APPROPRIATE IN SEVERAL COUNTRIES; **C**: UNDER INVESTIGATION AS POTENTIALLY USEFUL; **D**: GENERALLY CONSIDERED AS INAPPROPRIATE

Cancer site	ICD-9	Diagnosis	Staging	Restaging	Treatment monitoring/ planning
Oral cavity	140.0–145.9, 149.0–149.9	D	C	B	C
Nasopharynx	147.0–147.9	C	B	B	C
Other pharynx	146.0–146.9, 148.0–148.9	C	B	B	C
Oesophagus	150.0–150.9	C	A	B	B
Stomach	151.0–151.9	C	C	C	C
Colon and rectum	153.0–154.0, 159.0	C	B	A	B
Liver	155.0–155.1	D	D	C	D
Pancreas	157.0–157.9	C	C	B	C
Larynx	161.0–161.9	C	B	B	C
Lung	162.0–162.9	A	A	A	B

TABLE 3.2. INDICATIONS FOR FDG–PET ON ONCOLOGY ACCORDING TO FOUR DIFFERENT CATEGORIES. **A**: WIDELY ACCEPTED AS APPROPRIATE; **B**: ACCEPTED AS APPROPRIATE IN SEVERAL COUNTRIES; **C**: UNDER INVESTIGATION AS POTENTIALLY USEFUL; **D**: GENERALLY CONSIDERED AS INAPPROPRIATE (cont.)

Cancer site	ICD-9	Diagnosis	Staging	Restaging	Treatment monitoring/ planning
Melanoma of skin	172.0–172.9	C	A	A	C
Prostate	185.0–185.9	D	C	C	D
Testis	186.0–186.9	C	C	C	C
Kidney, etc.	189.0–189.9	D	D	C	C
Bladder	188.0–188.9	C	C	C	C
Brain, nervous system	191.0–191.9	C	B	B	C
Thyroid	1930–1939	C	C	B	C
Non-Hodgkin lymphoma	200.0–200.9, 202.0–202.9	B	A	A	A
Hodgkin lymphoma	201.0–201.9	B	A	A	A
Multiple myeloma	203	C	C	C	C
Leukaemia	204.0–208.9	D	D	D	D
Breast	174.0–175.9	D	B	B	B
Uterus	179.0–180.9, 182.0–182.9	C	B	B	C
Ovary	183.0–183.9	C	B	B	C

REFERENCES TO SECTION 3

[3.1] DRABORG, E., GYRD-HANSEN, D., POULSEN, P.B., HORDER, M., International comparison of the definition and the practical application of health technology assessment, Int. J. Technol. Assess. Health Care **21** 1 (2005) 89–95.

[3.2] MITTRA, E., QUON A., Positron emission tomography/computed tomography: The current technology and applications, Radiol. Clin. North Am. **47** 1 (2009) 147–60.

[3.3] http://www.who.int/topics/cancer

[3.4] http://www-dep.iarc.fr

[3.5] http://www.eurocare.it

[3.6] http://www.who.int/classifications/icd

[3.7] WILLIAMS, I., McIVER, S., MOORE, D., BRYAN, S., The use of economic evaluations in NHS decision-making: A review and empirical investigation, Health Technol. Assess. **12** 7 (2008) iii, ix–x, 1–175.

4. COST–BENEFIT ANALYSIS OF PET/CT

4.1. THE RAPID GROWTH OF PET/CT

Since its introduction in diagnostic oncology in the 1990s [4.1, 4.2], PET/CT has undergone 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 modifications to electronics and reconstruction algorithms that improve spatial and temporal resolution, sensitivity and contrast. The move from 2-D to 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 (TOF) utilizing avalanche photodiode detectors that will further improve technical performance. As a consequence of the great improvements in technology and increasing evidence of its 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 with 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 with physiological uptake (specificity) and increased lesion detection (sensitivity).

There have already been a great many publications in the oncology literature comparing the diagnostic efficacy of PET/CT with that of PET or CT [4.3, 44] 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 systems are now being marketed.

4.2. 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 in employing the staff required to perform the diagnostic examination and the consumables utilized must be added to these costs. The amortization 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. The figures listed in Table 4.1 are the mean values reported by the source Medical Options [4.5]. These figures were derived from data on developed countries and may not be valid for all Member States.

A reduction in annual costs can be obtained by extending the life of the equipment, reducing the expenditure on siting, amortizing the siting costs over a longer period, or increasing patient numbers. Nevertheless, from these data, it can be seen that 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 utilize PET radiopharmaceuticals, which are quite expensive. Again, economies of scale can operate to reduce this component of the scan cost. Centralized cyclotron facilities which distribute to a number of scanners operating in parallel can act to reduce the cost per dose.

TABLE 4.1. EVALUATION OF COSTS OF VARIOUS DIAGNOSTIC IMAGING PROCEDURES

Imaging	Equipment cost (€ × 1000)	Siting cost (€ × 1000)	Annual cost (€ × 1000)	Consumables (€)	Annual throughput	Cost/scan (€)
PET/CT	2200	750	1177	400	2000	996
Scintigraphy	490	60	419	50	2000	262
MRI	975	250	720	40	3000	234
CT	750	100	572	30	5000	103
Ultrasound	135	—	144	40	2000	91

However, perhaps, more important than the direct cost of a diagnostic scan is its ability to accurately influence the selection and planning of 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 save costs.

4.3. THE BASIS OF ECONOMIC EVALUATION

Escalating healthcare 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' [4.6]. 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, being 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: cost effectiveness analysis; cost–utility analysis; and cost–benefit analysis:

— **Cost effectiveness analysis** is performed through a cost minimization study or by 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 compare two competing alternative strategies. Thus, the ratio represents the incremental price of achieving a unit health effect from a given intervention when compared with an alternative.
— The **cost–utility analysis** is a form of cost effectiveness analysis in which adjustments are made on the basis of 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 in financial terms. There are various ways to calculate the monetary value of 'life', for example through earnings or 'willingness to pay', but all these methods have significant limitations.

All of the economic evaluations mentioned above require thorough clinical trials. These can be carried out as:

— Retrospective economic evaluation of previously performed clinical trials;
— Simultaneous prospective randomized controlled trials of costs and effectiveness;
— Expert consensus;
— Computer modelling methods including meta-analysis and sensitivity analysis.

The intrinsic value of the clinical trial depends on the study design, including randomization, k statistics for inter intra-observer variations, final diagnosis confirmed by histological control, blind-read procedure, and so on. Several studies of the economic value of FDG–PET have been performed in oncology, but there have been very few randomized studies and only a few robust meta-analyses are available. All of these studies have provided evidence that FDG–PET in different situations is more cost effective than CT and, where appropriate, other diagnostic modalities. An example of such a study was a retrospective analysis carried out in Italy on the cost effectiveness of FDG–PET in patients with known or suspected lung cancer. This evaluation compared three different diagnostic strategies including FDG–PET. The inclusion of PET in the clinical management of all patients with known or suspected lung cancer previously evaluated only with CT, was shown to be cost effective, with a gain of 2.64 life years on average at an annual cost of about €415 [4.7].

Since PET/CT is a recent introduction to the diagnostic work-up of cancer patients, there are relatively few papers on economic evaluations. Heinrich et al. [4.8] performed a cost–benefit analysis of PET/CT in the management of resectable pancreatic cancer, based on the cost of PET/CT and pancreatic resection and 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 savings. Strobel et al. [4.9]

studied the usefulness of performing two PET/CT scans in Hodgkin lymphoma patients, one after two cycles of therapy and another after completion of the first-line treatment. A cost saving was calculated for the potentially superfluous PET/CT examinations. The conclusion was that the end treatment PET/CT is unnecessary if the diagnostic imaging during 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 treatment PET/CT in interim complete responders. Fleming et al. [4.10] 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 analysis of a subset of 123 patients. PET/CT results were compared with the histopathology of surgical specimens. Treatment was altered in 30.9% of patients on the basis of PET/CT findings, including upstaging, 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 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 in staging disease, it is easy to understand how correct staging can avoid futile operations for cancers that could never have been cured by surgery [4.11]. In addition, in the case of restaging and follow-up, the accurate determination of the presence or absence of disease is critical for 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 [4.12].

In therapy planning, PET/CT can better define the target volume and treatment strategy, and can provide earlier and more reliable identification of non-responders than conventional non-invasive imaging approaches. Thus, 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 socioeconomic background, because the health of an individual has a great impact on the family, on the workplace, and extends to involve wider relationship networks and other life activities.

4.4. HEALTH TECHNOLOGY ASSESSMENT OF PET/CT

As already mentioned, the aim of HTA 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 4.2.

Until recently, diagnostic imaging modalities were introduced into clinical routine well before sufficient published data on their diagnostic efficacy were available. This happened for conventional radiology, ultrasound, 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 for 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.

HTA reports on PET were published in several countries from the year 2000 onwards (Australia, Canada, France, Germany, Spain and the United Kingdom). These used various methods and addressed different issues and were mixed in their findings. However, some 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.

TABLE 4.2. HIERARCHIES OF THE DIAGNOSTIC EFFICACY OF PET/CT

Hierarchy	Issue	Parameter under investigation
1	Technical	Technical image 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

Many of the institutionalized HTA groups are members of the International Network of Agencies for Health Technology Assessment (INAHTA). In spite of the use of similar approaches and methodology, the INHATA reports have often arrived at rather different views with respect to the 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 health care.

In spite of these criticisms, HTA does have theoretical benefits for evaluating the role of PET in cancer management by studying technological aspects, measuring diagnostic efficiency and identifying the role of the 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 with 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, this is of course 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.

4.4.1. Examples of PET/CT HTA

As an example of the abovementioned studies, the Adelaide Health Technology Assessment in 2004 published a report on 'Combined CT and PET Scanner' [4.13] evaluating the need for PET/CT examinations in the health system, considering not only already established oncological indications but also cardiovascular and neurological diseases. This report analyses the local clinical need and burden of disease, the treatment alternatives and the existing diagnostic comparators. Clinical outcomes considered were the diagnostic effectiveness (PET/CT versus PET, PET/CT versus CT and PET/CT versus conventional diagnostic workup) and safety. The cost analysis was performed based on the existing cost effectiveness evidence, 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 for diagnosis and the management of non-oncological indications (cardiovascular and neurological disease).

An increase in the number of PET/CT scans in oncology was considered to be unavoidable due to the development of new indications and a growing use to evaluate treatment. The conclusions were that PET/CT was able to improve diagnostic capabilities when compared with PET or CT alone, depending on the type and stage of the tumour, and whether the data were analysed on a lesion by lesion basis or by patient. This study also found that PET/CT improves lesion localization and decreases the number of equivocal lesions when compared when PET alone. The sensitivity and specificity of PET/CT in different conditions were reported. The economic analysis was based on the capital cost of purchasing a PET/CT scanner and the estimated cost to the health system of performing at least one scan for all patients with newly diagnosed cancer.

Systematic reviews published by the Agencia de Evaluation de Tecnologia Sanitaria (AETS) in 2004 and 2005 [4.14, 4.15] investigated the relative contribution of PET/CT to the clinical management of oncological patients. The report aimed to assess whether this technology is able to provide higher diagnostic accuracy than 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 findings. Other worthwhile indications were felt to include radiotherapy planning, guidance of biopsy and therapeutic monitoring. The accuracy of PET/CT in tumour restaging (locoregional and distant metastasis) was shown to be even a little better than for staging cancer [4.16]. It was also concluded that PET/CT could be cost effective through reduction of unnecessary diagnostic procedures or treatments, including surgery. Some other advantages of PET/CT that were recognized were that it is less time consuming than PET alone, allows higher throughput of patients and that the near simultaneous acquisition of PET and CT images limits alignment problems.

A review by the French National Authority for Health, published in 2005 [4.17], assessed several aspects regarding the use of PET/CT in France (technical, legislative, medical, economic and organizational) to establish equipment selection criteria and organizational 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 a health care organization were established to be the same as for installing a PET machine alone. Clinical studies tended to show that PET/CT improved sensitivity and especially specificity, compared with PET alone. However, the potential clinical impact of replacing diagnostic CT with PET/CT could not be assessed. The report recommended that the PET/CT system should be integrated into an imaging network. The estimated capital outlay for a PET/CT system was €2.5 million compared with €1.7 million for a PET system. The operating budget was estimated to be within the range €2.0–2.2 million for 2000 examinations per year.

A more recent overview on the clinical effectiveness of PET was published by Facey et al. in 2007 [4.18]. Their paper evaluated 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 FDG–PET to aid management decisions relating to diagnosis, staging, restaging of recurrence, treatment response monitoring, and radiotherapy planning was evaluated. The conclusions of this report was that the strongest evidence for the clinical effectiveness of PET was in the staging of NSCLC, the restaging of lymphoma, the staging and restaging of colorectal cancer and the characterization of solitary pulmonary nodules. PET/CT was evaluated in only 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 were that there was likely to be a need for new capital

investment for PET/CT, despite there still being less evidence of utility than there was for PET. However, PET clinical effectiveness findings can be extrapolated to cover PET/CT.

Many technology assessment projects are under way throughout the world, with the goal of comparing the cost effectiveness of PET/CT with other diagnostic technologies financed from public sources in diagnostic oncology. This is because economic analyses of PET/CT scanning in the literature are very limited and conclusive evidence is still 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 HTAs are time consuming, and 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 no economic analysis of diagnostic technologies will ever be able to negate the individual benefits of improved diagnosis to individual patient care.

Clinicians reading HTA reports should be aware that the assessments 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 recognize 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 subjecting them to rigorous expert review.

Therefore, caution should be used when considering the recommendations of these reports, and particularly in advising individual patients regarding the utility of PET and PET/CT in the diagnostic process related to their own specific disease or clinical situation. In particular, the conclusions of several INAHTA reviews have been challenged by experts in PET actually involved in those reviews and are completely at odds with expert clinical opinion on the utility of PET in oncology.

REFERENCES TO SECTION 4

[4.1] CHARRON, M., et al., Image analysis in patients with cancer studied with a combined PET and CT scanner, Clin. Nucl. Med. **11** (2000) 905–910.

[4.2] BEYER, T., et al., A combined PET/CT scanner for clinical oncology, J. Nucl. Med. **41** 8 (2000) 1369–1379.

[4.3] VON SCHULTHESS, G.K., Positron emission tomography versus positron emission tomography/computed tomography: From "unclear" to "new-clear" medicine, Mol. Imaging Biol. **6** 4 (2004) 183–187.

[4.4] ANTOCH, G., et al., Accuracy of whole-body dual-modality fluorine-18–2-fluoro-2-deoxy-d-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: Comparison with CT and PET, JCO **1** (2004) 4357–4368.

[4.5] http://www.medicaloptions.co.uk/reports.html

[4.6] INTERNATIONAL NETWORK OF AGENCIES FOR HEALTH TECHNOLOGY ASSESSMENT, Health Technology Assessment (HTA) Glossary, 1st edn, 5 July (2006).

[4.7] MANSUETO, M., et al., Cost-effectiveness analysis in the clinical management of patients with know or suspected lung cancer: [^{18}F]fluorodeoxyglucose PET and CT comparison, Q. J. Nucl. Med. Mol. Imaging, **51** 3 (2007) 224–234; Epub: 2007 June 1.

[4.8] HEINRICH, S., et al., Neoadjuvant chemotherapy generates a significant tumor response in resectable pancreatic cance without increasing morbidity: Results of a prospective phase II trial, Ann, Surg. **248** 6 (2008)1014–1022.

[4.9] STROBEL, K., et al., Cost-effective therapy remission assessment in lymphoma patients using 2-[fluorine-18]fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography: Is an end of treatment exam necessary in all patients? Ann. Oncol. **18** 4 (2007) 658–664.

[4.10] FLEMING, A.J., Jr., JOHANSEN, M.E., The clinician's expectations from the use of positron emission tomography/computed tomography scanning in untreated and treated head and neck cancer patients, Curr. Opin. Otolaryngol. Head Neck Surg. **16** 2 (2008) 127–134.

[4.11] REED, C.E., et al., Results of the American College of Surgeons Oncology Group Z0050 trial: The utility of positron emission tomography in staging potentially operable non-small cell lung cancer, J. Thoracic Cardiovasc. Surg. **126** (2003) 1943–1951.

[4.12] HILLNER, B.E., et al., Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: Initial results from the national oncologic PET registry, J. Clin. Oncol. **10** 1200/JCO 2007.14.5631 (2008).

[4.13] MUNDY, L., MERLIN, T., HODGKINSON, B., BRAUNACK-MAYER, A., HILLER, J.E., Combined CT and PET scanner. Australia and New Zealand Horizon Scanning Network, Horizon Scanning Report, ACT, Canberra (2004).

[4.14] http://www.isciii.es/htdocs/investigacion/publicaciones_agencia/41PET-TAC.pdf

[4.15] IPE 05/46 Uso tutelado de la Tomografía por Emisión de Positrones (PET) con ^{18}FDG.

[4.16] GUGIATTI, A., et al., Economic analyses on the use of positron emission tomography for the work-up of solitary pulmonary nodules and for staging patients with non-small-cell-lung-cancer in Italy, Quar. J. Nucl. Med. Mol. Imaging, **48** 1 (2004) 49–61.

[4.17] http://www.has-sante.fr/portail/upload/docs/application/pdf/TEP_TDM_rap.pdf
[4.18] FACEY, K., BRADBURY, I., LAKING, G., PAYNE, E., Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers, Health Technol. Assess. **11** 44 (2007) iii–iv, xi–267.

5. EQUIPMENT

Several major pieces of equipment need to be considered in the establishment of a PET centre. The two most expensive are the cyclotron and the PET/CT scanner. In addition to these items, the choice of the synthesis module, the radionuclide calibrator and the hot cells also need consideration. Detailed information on the equipment needed to produce and qualify the radiopharmaceutical can be found in an IAEA report entitled Cyclotron Produced Radionuclides: Guidelines for Setting up a PET Facility [5.1].

5.1. CYCLOTRON

5.1.1. Methodology of decision making

The choice of a cyclotron will depend entirely on the programme in place at a new facility. In order to choose a cyclotron, a methodology should be followed which takes into consideration the requirements of the facility and the environment in which the accelerator will be placed. A procedure that has proven to be very useful is as follows:

— Interview all the users to define the proposed programme;
— Generate a list of radioisotopes which will be needed from these users;
— Develop priorities for the programme;
— Evaluate the space allotted to this project;
— Evaluate the potential cyclotrons with respect to this programme and space;
— Examine construction obstacles and chemistry requirements;
— Evaluate all alternatives.

The most important considerations in the choice of a cyclotron are the particle beam energy and the beam current. Almost all commercially available cyclotrons are negative ion machines. This means the beam coming out of the ion source is H^-. The beam is extracted by stripping the electrons off the H^- ion and creating an H^+ ion which curves in the opposite direction in a magnetic field and is therefore pushed out of the machine. This type of extraction is very efficient and therefore there is little residual activation of the interior of the machine when compared with the older positive ion machines. With this type of cyclotron the targets are usually the main source of radiation dose in cyclotron operations.

5.1.2. Radionuclide production fundamentals

The reason the particle energy and the beam current are the most important parameters for the choice of a cyclotron is shown in Eq. (5.1) for the production of radionuclides:

$$dn = I_0 N_A \, ds \sigma_{ab} \tag{5.1}$$

where

dn is the number of reactions occurring in 1 s;
I_0 is the number of particles incident on the target in 1 s;
N_A is the number of target nuclei per gram;
ds is the thickness of the material, in grams per cm^2;
σ_{ab} is the cross-section, expressed in units of cm^2.

The amount of radionuclide that can be produced will depend directly on the beam current (I_0) and the cross-section (σ_{ab}), which is a function of the beam energy. The energy of several commercial cyclotrons is given in Table 5.1. The energy of the cyclotron will determine which nuclear reactions may be used to produce radionuclides with each cyclotron.

TABLE 5.1. CYCLOTRON PARTICLE ENERGIES

Cyclotron model	Proton energy (MeV)	Deuteron energy (MeV)
IBA C10SS	10	
Siemens Eclipse	11.2	
Sumitomo HM10	10	
Kotron 13	13	
GE PETtrace	16.5	8.4
IBA 18/9	18	9
ACSI TR19	13–19	9
Sumitomo HM18	18	9

5.1.3. Deuteron operation for the cyclotron

Deuterons are an option on most of the cyclotrons designed for the production of PET radionuclides. There are some advantages and disadvantages with deuterons. The advantages are that it is possible to use alternative routes to some PET radionuclides such as oxygen-15. The disadvantages of the deuteron option are the increased cost, increased complexity of the machine and the increased space required for the machine. Most routine users rarely, if ever, use deuterons. The recommendation is that deuterons are not required for all the routine PET radionuclides and most of the radionuclides that show some promise in the future.

5.1.4. Cyclotron beam current

The beam current of the cyclotron determines how much radioisotope can be produced at a given energy. In theory the production yield is directly proportional to the beam current. In practice, the beam current that may be used on any target is determined by the ability to remove the heat produced in the target by the beam. For the three higher energy cyclotrons being considered here, the rated beam currents are given in Table 5.2.

The gas and liquid targets are not usually run above 100 μA (and 30–40 are more typical) since significant density reduction will occur resulting in lower yields. Therefore, production of the four common PET radioisotopes will be limited by the targetry and not the beam current on any of the higher energy cyclotrons.

TABLE 5.2. CYCLOTRON BEAM CURRENTS

Cyclotron	Proton beam current (μA)	Deuteron beam current (μA)
Siemens RDS	100	—
Sumitomo HM10	100	—
Kotron 13	100	—
GE PETtrace	100	60
IBA Cyclone 18/9	150	60
ACSI TR19	200	50
Sumitomo HM18	200	50

5.1.5. Targets and modules

All of the cyclotrons have the capability of dual beam irradiation, although there are some limitations on which targets may be used. The Siemens RDS has a maximum of 14 targets mounted, the Sumitomo HM10 has five target positions and the IBS Cyclone 10 has six target positions. The IBA Cyclone 18/9, the Sumitomo HM 12 and the ASCI TR19 cyclotron can have a maximum of eight targets mounted at the same time (Fig. 5.1). The GE PETtrace cyclotron has six target ports. In the case of the IBA machines, any two targets may be irradiated simultaneously and therefore this is the most flexible of the cyclotrons. In the ACSI and Sumitomo machines, there are four targets on each side of the machine and any one of the four targets on one side may be irradiated with any one of the four targets on the other side of the machine; therefore, this gives good flexibility in irradiation choice. The GE PET trace can irradiate any two targets as long as they are at least two targets away from each other (target 1 can be run with targets 4, 5 and 6, target 2 can be run with targets 5 and 6, etc.). This decreases flexibility somewhat, but should not result in serious problems if care is taken in target arrangement.

Satisfactory gas and liquid targets for producing isotopes of carbon nitrogen, oxygen and fluorine are available from all manufacturers. Automated synthesis systems are available for many radiopharmaceuticals of clinical interest, both from cyclotron manufacturers and from other companies, and target systems are also being developed by manufacturers other than GE Healthcare, Siemens, IBA, and ACSI.

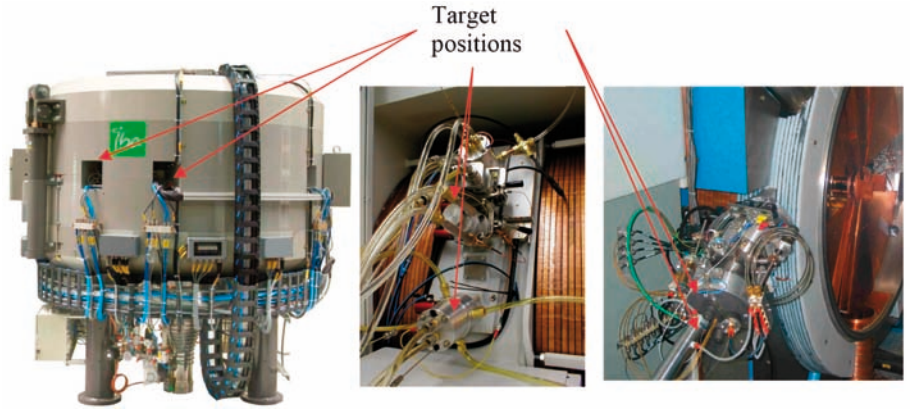

FIG. 5.1. Target arrangement for the three higher energy cyclotrons. At left is the IBA Cyclone 18/9, in the centre is the GE PETtrace, and at right is the ACSI TR19.

The nuclear reaction products arising from the irradiation of gas and liquid targets are easily transported to the synthesis or processing equipment using shielded tubes. While minimum distances from the target to the processor are desirable because of possible line loss, transport distances of well over 30 m have been successful in routine production.

There is considerable interest in some PET radionuclides that have not been in routine use. These include some of the metal radionuclides, such as ^{64}Cu and ^{86}Y. These radionuclides must be made using a solid target system. Although there is research interest in these radionuclides, there is no clinical use for them at the moment. It is suggested that a solid target system not be installed until such time as radiotracers using these radionuclides have been proven to be clinically useful. If these radionuclides are being considered, then a beam line is a valuable addition to the radionuclide production capability.

5.1.6. Maintenance and service agreements

Service on the cyclotron is one of the most important aspects of the facility maintenance. If the cyclotron is not in operation, no radionuclides can be produced. For this reason, the maintenance and service should be considered from the beginning of the process. A maintenance contract can be negotiated with the vendor if facility personnel cannot take care of routine maintenance either for reasons of technical expertise or of time constraints. Service agreement details and costs should be obtained in writing during the purchase of the cyclotron.

Modern cyclotrons are almost totally automated (depending on the model and manufacturer) and require very little expertise to operate. On the other hand, it is advisable to have at least one or two people on the staff capable of cyclotron maintenance and repair.

An array of spare parts should be on hand in the facility to quickly replace parts which may fail more frequently. A list of recommended spare parts can be obtained from the cyclotron vendor.

5.2. PET/CT SCANNERS

5.2.1. Basic components of a PET system

The basic components of a PET system are shown in Fig. 5.2. These include the scintillator, detector, photomultiplier tubes (PMT), electronics, and reconstruction software.

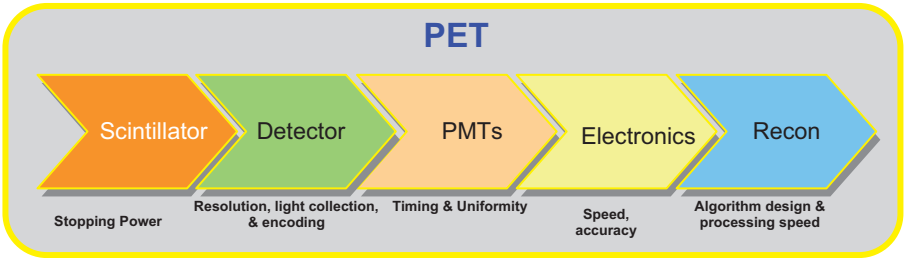

FIG. 5.2. Basic components of a PET system.

Each of the PET system components shown in Fig. 5.1 makes an important contribution to the overall performance of the PET system. Each component has desired characteristics which need to work in harmony with the other components. The scintillator crystal, for example, stops gamma photons emitted from the patient and relay the signal in a form of light that the detector can distinguish. Scintillators can be made from different crystals that have slightly different properties in terms of stopping power, decay time, light output, emission of light, etc. The properties of interest for crystals which can be used in PET are given in Table 5.3.

TABLE 5.3. CHARACTERISTICS OF THE MOST IMPORTANT SCINTILLATOR CRYSTALS USED IN PET (FROM REF. [5.2])

Crystal material	Light yield (photons/MeV)	Emitted light wave length (nm)	Light emission decay time (ns)	Density (g/cm^3)	Effective atomic number	Refractive index	Energy resolution at 511 keV (%)
NaI(Tl)	38 000	415	230	3.7	51	1.85	10
BGO ($Bi_4Ge_3O_{12}$)	9 000	480	300	7.1	75	2.15	20
LSO (Lu_2SiO_5)	26 000	420	40	7.4	66	1.82	15
LYSO $(Lu_{1-y}Y_y)_{2(1-x)}SiO_5$	32 000	430	40	7.1	66	1.82	12
GSO (Gd_2SiO_5)	13 000	440	50	6.7	59	1.85	15
$LaBr_3$ (5% Ce)	60 000	370	25	5.3	47	1.9	10
LuAP (0.4% Ce) ($LuAlO_3$)	12 000	365	18	8.3	65	1.94	7

The NaI(Tl) crystal has mostly been used in the past, and BGO and GSO have been more common up to very recently. However, today practically all manufacturers have chosen LSO or LYSO as the scintillator for state of the art PET systems. The reasons are that LSO and LYSO have relatively high linear attenuation coefficients, and they have the shortest decay time (40 ns) among the crystals listed above. This short decay time allows the application of time of flight (TOF) methodology in the reconstruction process of images, which significantly reduces the noise in the images and improves contrast. Short decay time also allows scanning with higher count rates, which is important in 3-D mode PET, and leads to shorter acquisition times.

The design of the detector, which includes the size and shape of the crystals, and the packing and positioning of PMT tubes, is also very important. Different PMT tubes have different properties with regard to timing and uniformity. The electronics behind the PMT tubes determine the speed and accuracy of processing. Finally, the reconstruction algorithms sort the acquired data into readable images, and are frequently being improved by vendors.

5.2.2. Recent developments of PET/CT systems

All new PET systems are manufactured in combination with CT and these are the considered state of the art technology (shown in Fig. 5.3).

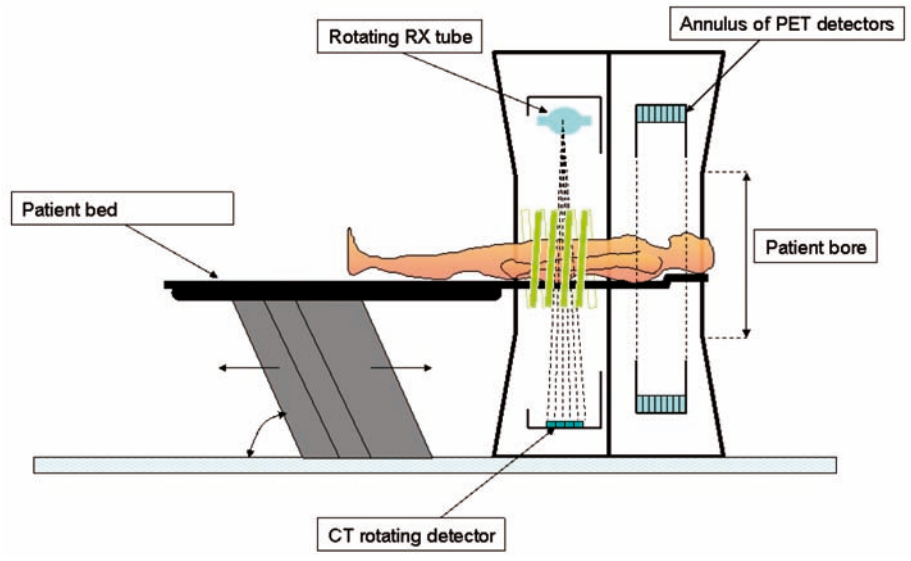

FIG. 5.3. Schematic view of a typical PET/CT scanner.

A more recent development, TOF, can significantly reduce the signal to noise ratio and improve the contrast in clinical images, which leads to better detection of lesions, especially small ones and those in large patients [5.3]. TOF is based on measuring the difference in arrival time of the two coincidence photons at the detectors in order to better locate the annihilation position of the emitted positron (Fig. 5.4). TOF PET/CT systems require all the components of a PET system (as shown in Fig. 5.2) to be state of the art. It must include fast crystals (e.g. LSO or LYSO), appropriate detectors, very fast PMT tubes, electronics, and processing computers. TOF reconstruction algorithms require significantly more computing power and time because it is necessary to perform TOF calculations for each line of response (LOR).

Other recent advances in PET technology are depth of interaction (DOI) correction, utilizing new detectors, either fast ceramic or other inorganic scintillators, or detectors with higher quantum efficiency, i.e. avalanche photodiodes (APDs). Also, new reconstruction algorithms, mostly 3-D algorithms, have been developed with the inclusion of the TOF information.

Recent developments also include the creation of PET/MRI (magnetic resonance imaging) systems, which is made possible by using APDs instead of magnetically susceptible PMTs. These developments have already been achieved in microPET/CT systems and are being studied in larger prototypes. One approach is to use PET and MRI as two separate devices that are close together (Fig. 5.5).

A second approach, which allows true simultaneous PET/MRI, was technologically developed with PET scanner as an insert within a whole body MRI. After inauguration of preclinical PET/MRI scanners, dedicated for small animal imaging [5.5], the first clinical PET/MRI was introduced in 2007 (Fig. 5.6). The magnetic field insensitive PET scanner is inserted into a 3 T

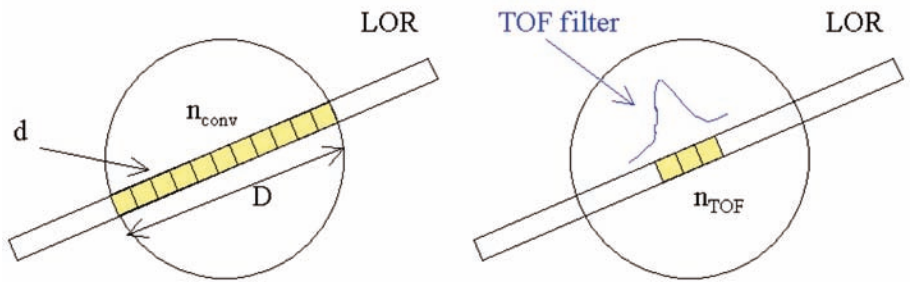

FIG. 5.4. Illustration of the TOF concept. Image elements contributing to an LOR for conventional PET (left) and TOF PET (right) [5.4].

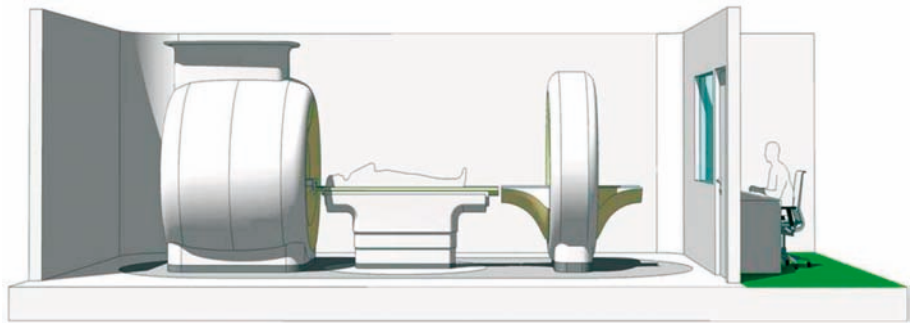

FIG. 5.5. A prototype whole body PET/MRI system. The system provides the full clinical spectrum of applications in a whole body solution. The device is intended for use as a research tool only and has not been released for commercial sale, nor does it have 510K(FDA) approval. (Courtesy of Philips Healthcare, USA.)

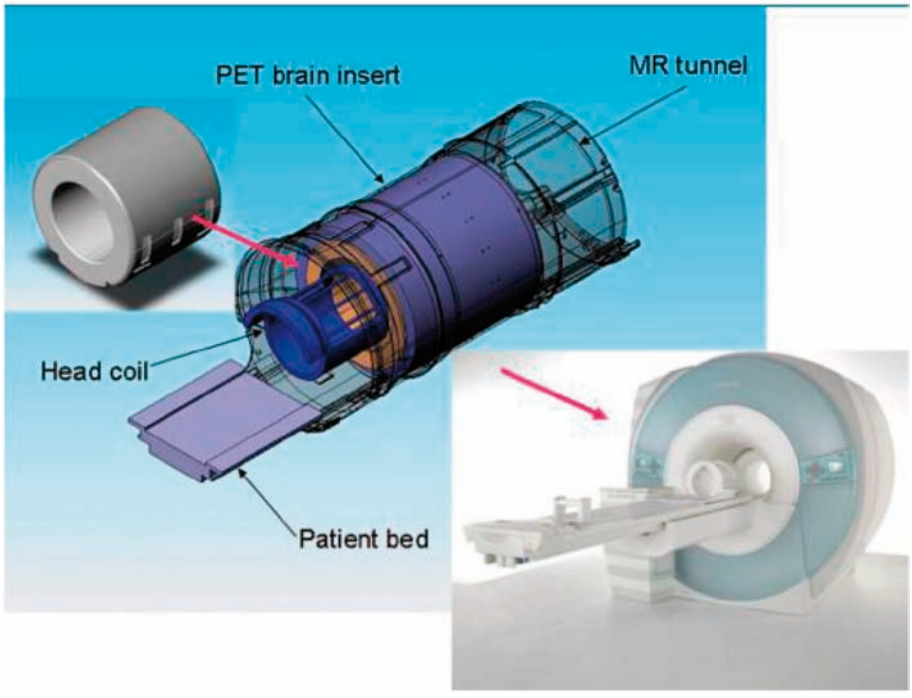

FIG. 5.6. Drawing and photograph of an integrated PET/MRI design showing isocentric layering of MR head coil, detector ring, and tunnel of MR magnet (from [5.5], modified; courtesy of Siemens).

clinical MRI system and allows simultaneous data acquisition from both PET and MRI. First clinical results were very encouraging and proved the feasibility of integrated PET/MRI technology based on APDs [5.6].

5.3. RADIONUCLIDE ACTIVITY CALIBRATOR[1]

The radionuclide activity calibrator is a fundamental requirement for the operation of a PET centre. It allows accurately measured radiopharmaceutical doses to be administered to patients, and is also used for other laboratory tasks like measuring time–activity curves. A PET centre will thus be equipped with one or more radionuclide activity calibrators, depending on the type of installation. The dose calibrator has to be calibrated at a standards dosimetry laboratory; alternatively, a set of calibration sources (traceable to a primary standard) should be available on site. In routine practice, a minimum of one check source traceable to a primary standard is required.

A radionuclide activity calibrator is in essence a well type, gas filled ionization chamber into which a radioactive material is introduced for measurement. A typical radionuclide activity calibrator is depicted schematically in Fig. 5.7.

The activity of a sample is measured in terms of the ionization current produced by the emitted radiations that interact within the gas of an ionization chamber. The chamber is usually sealed and under pressure, and has two coaxial cylindrical electrodes maintained at a voltage difference from a suitable supply.

In the associated electrometer, the ionization current is measured and displayed, usually in digital form, in units of activity (e.g. becquerel). The measurement involves the application of a calibration coefficient that corresponds to the ionization current produced by unit activity of the radionuclide being assayed. The calibration coefficient for an individual radionuclide depends on the volume and physical nature of the sample as well as the container construction and its position within the well of the ionization chamber. For use in PET, the dose calibrator must be calibrated against a traceable source in a similar geometry to that being used in the clinical dose in order to ensure accuracy. A check against this traceable source should be done routinely (daily is preferable).

[1] Most of the material in this section has been taken from the IAEA publication Quality Assurance for Radioactivity Measurement in Nuclear Medicine, Technical Reports Series No. 454, IAEA, Vienna (2006).

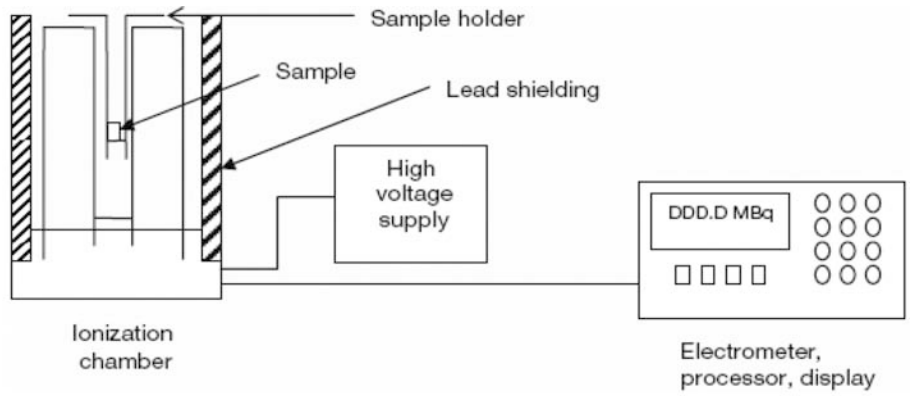

FIG. 5.7. Schematic of a radionuclide activity calibrator.

Lead shielding around the ionization chamber provides protection to personnel against radiation hazards and reduces the effect of environmental radiation (background). A sample holder and a removable liner that can be easily cleaned in the event of radioactive contamination of the chamber well are usually provided.

Further information regarding these types of equipment, including their usage, calibration and quality assurance (QA)/quality control (QC) can be found in IAEA Technical Reports Series No. 454. For activity calibrators used in PET, particular care should given to selecting appropriate equipment, particularly with regard to linearity for activities greater than about 20 GBq.

5.4. AUTOMATED RADIOPHARMACEUTICAL MODULES

5.4.1. Nucleophilic fluorination

Syntheses of radiopharmaceuticals are performed in automated modules that are usually placed in lead shielded hot cells for radiation protection purposes. The modules use radiochemical syntheses for which the reaction parameters have been determined in detail. For well known compounds such as FDG, modules are commercially available. For other compounds, modules can be purchased which can be programmed to perform a wide variety of synthetic procedures. That additionally opens the possibility of changing synthetic procedures and parameters in order to optimize the labelling reaction during automatic operation.

Except in the case of F-DOPA, all fluorination reaction modules use nucleophilic substitution reactions with ^{18}F-fluoride. This type of labelling procedure typically implies a sequence of reaction steps:

— ^{18}F-fluoride is produced in ^{18}O enriched water. It can be extracted from the ^{18}O water or used directly. It is mixed with a weak base and transferred into a solvent such as acetonitrile or DMSO for evaporation to dryness. The reason for this is that the fluoride ion is not reactive at all in aqueous solution, so a careful evaporation of all traces of water is mandatory to use ^{18}F-fluoride in the labelling reaction described in the next item.
— The fluoride is brought into solution either with a cryptand complexing agent such as kryptofix 222 or with a tetraalkylammonium salt.
— Within the 'reactor' (which can be cooled or heated according to the reaction conditions), the reaction is carried out and then the cleavage of any protecting groups ('hydrolysis') is performed.
— Some modules use cartridges to isolate the intermediate product before hydrolysis or to remove the product from the reaction solution if the labelling reaction is almost quantitative. Conditions for elution of the final product off the column are usually chosen so that the result is an injectable solution.
— If undesired products are also obtained in the reaction, a separation step is necessary which is usually done with semi-preparative high pressure liquid chromatography (HPLC).

For the synthesis of FDG, modules are available with fixed programmes using switching valves or systems with disposable cassettes or similar disposal set-ups.

An advantage of modules with disposable cartridges is that the cartridge may be removed quickly and another put in its place so that a second synthesis may be performed immediately after the first without the necessity of cleaning the system in between syntheses. In case of failure, the production can easily be repeated. This is not the case in a system that does not use cartridges since there contamination remaining in the system. In this case, twin systems are recommended so that a second production may be performed quickly. As a back-up, a module capable of a wide variety of fluorinations can also be used to synthesize FDG.

For ^{18}F-O-fluoroethyl–tyrosine or ^{18}F-ethyl-choline, the modules are extended so that the coupling reaction is included as a second reaction step. These modules do not markedly differ from those described above. The valves and fittings used in these modules are commonly available all over the world.

5.4.2. Electrophilic fluorination

For most compounds containing benzene, and other compounds which do not undergo nucleophilic fluorination readily, electrophilic fluorination (a reaction involving a positively charged F-atom) may be possible. The most common example is the synthesis of [^{18}F] FDOPA. The particularly high electron density at the benzene ring gives rise to repulsion of the negatively charged ^{18}F-fluoride-ion and no bond formation is possible. For this type of ^{18}F labelling, [^{18}F]F_2 is produced at the cyclotron with gas phase target systems. Because of the high reactivity of molecular fluorine with traces of air or water, it must usually be bubbled through the reaction solution as a gas. The labelling reaction is carried out in modules with valves as discussed above which are available from several commercial vendors.

5.4.3. Labelling with carbon-11

The established method for production of methyl iodide starts with the catalytic reduction of $^{11}CO_2$ or a mixture of ^{11}CO and $^{11}CO_2$ (which is the chemical form of the carbon-11 obtained directly from the target after irradiation) to [^{11}C]methane. The ^{11}C-methane is circulated through iodine at 700°C and methyl iodide is then trapped from the circulating ^{11}C-methane by adsorption on a Porapak column.

5.4.3.1. Methyliodide module

The most widely used synthetic method for the production of methyl iodide is the catalytic reduction of $^{11}CO_2$ or a mixture of 1^{11}CO and $^{11}CO_2$ to [^{11}C]methane. This is due to the fact that $^{11}CO_2$ is the primary chemical form of carbon-11 produced in the nitrogen gas target. After conversion, the ^{11}C-methane is circulated through iodine at 700°C and methyl iodide is then trapped adsorptively from the circulating 11C-methane on a Porapak column.

In the methylation reaction, the methyl iodide is desorbed. It may also be used for the on-line formation of ^{11}C-methyltriflate with the advantage of higher labelling yields due to the higher reactivity of ^{11}C-methyltriflate in comparison to ^{11}C-methyliodide.

5.4.3.2. Methylation reaction

Modules for labelling with ^{11}C contain a unit for the formation of ^{11}C-methyliodide or ^{11}C-methyltriflate. The ^{11}C precursor is transferred from the separate module by helium gas to the reaction vessel. The reaction vessel is

usually cooled to trap the methyl iodide and then heated afterwards to carry out the reaction. The isolation of the intermediate or final product may be possible by adsorption on a cartridge (solid state extraction) or in the case where there are methylated side products, the product must be purified by HPLC.

5.4.3.3. Maintenance and repair — Service contract

Vendors can provide service contracts for the maintenance of the synthesis modules. However, good training of the facility personnel is important because an understanding of the reaction details and module parameters enables facility staff to make simple repairs or process changes quickly. Production failures can often be avoided if there is a general understanding of the process and parameters and rapid action is taken. Valves and fittings should be checked frequently. Simple repairs such as replacing a malfunctioning valve can be easily carried out by well trained personnel. A good supply of spare parts at the facility is also good practice so that parts are readily available. The vendor may also supply telephone support either free of charge or as part of a service contract. This support should be delineated in writing during the purchase negotiations with the vendor.

If the products are to be distributed, there should be a separate room for the packaging and shipping of radiopharmaceuticals. Licensing and/or registration of the facility with the appropriate authorities is required before commercial distribution. This will depend entirely on the local regulations.

5.5. HOT CELLS

One of the key pieces of equipment in the radiopharmacy is the hot cell. The hot cell provides a shielded enclosure for handling highly radioactive materials and serves as an isolator providing clean environment for the preparation of radiopharmaceuticals. The choice of hot cell will depend on whether one wants two independent modules or two modules in the same hot cell. This will depend on the type of facility and the production schedule. Having the ability to carry out a second synthesis is very advantageous in a clinical programme when patients are waiting for the radiopharmaceutical. The key issue is radiation protection in case of synthesis failure. If the synthesis modules are in two separate shielded enclosures, there will be a lower radiation dose than if the hot cell must be opened in order to load the second module or to clean and prepare the same module for a second synthesis. The thickness of lead shielding is determined by the quantity of FDG being processed; 75 mm of lead or equivalent is typical. For radiation safety reasons, the air pressure inside the hot cells should be maintained well below the pressure of the room where the hot cell

is situated. Furthermore, the hot cells should be equipped with an appropriate air handling system (inlet and outlet air filters as a minimum). Lead glass windows or TV monitors should be provided with the hot cells.

Hot cells are commercially available from several manufacturers. Shielded enclosures for synthesis modules are usually smaller and more compact and come in designs that may include the ability to stack synthesis modules or to place two or more side by side in the same module. Redundancy in FDG synthesis modules is recommended in case mechanical or chemical problems result in a failed production.

5.6. RADIOANALYTICAL EQUIPMENT

As safety of drugs has become a particularly important issue in the last years, it is of great importance that the appropriate quality management systems for validation and the appropriate radionalytical equipment for radioanalytical testing are duly considered [5.7].

The modules applied for performing the syntheses mainly include HPLC systems for isolating the product out of the reaction solution. At any rate, careful analysis of each batch is necessary for ensuring the chemical and radiochemical purity and identity of the product.

HPLC and thin layer chromatography (TLC) are generally used in parallel. There were misleading discussions denying the need for such an approach. Yet, while its high resolution allows HPLC to ensure the identity of the compound and exclude impurities, TLC permits the correct activity balance of the product related to the total activity of the solution.

5.6.1. High pressure liquid chromatography

Two HPLC systems are considered to be the core of the radioanalytical equipment, one with a gradient system and a UV array detector and one with a refractive index detector (RI) in parallel to a UV detector with multiple wavelengths. The systems should be equipped with column switching valves for fast changing between different columns.

Depending on the programme of radiopharmaceuticals to be produced, two to four isocratic HPLC systems with UV detector are necessary in addition. All systems have a shielded NaI(Tl)-scintillation detectors in line with the other detectors for simultaneous registration of radioactivity and mass.

5.6.2. Thin layer chromatography

TLC plates are developed in chambers. For detection of the spots, a UV lamp (two wavelengths) is used, and radioactivity is recorded by a Phosphor-Imager or a TLC NaI(Tl) radioscanner.

5.6.3. Gamma spectroscopy:

The purity of the radionuclides produced at a cyclotron is controlled by gamma spectroscopy for which usually a Ge semiconductor crystal is used. Interestingly, for that purpose a low cost NaI(Tl) crystal can be used since resolution is sufficiently good for controlling the PET radionuclides, but the efficiency for long term purity control is advantageously high. As some of the important radionuclides can only be differentiated by their half-life, a programme for automated determination of the half-lives is particularly useful. The impurity of ^{13}N in ^{18}F can only be determined in this way.

5.7. MISCELLANEOUS LABORATORY EQUIPMENT

As in any chemical laboratory, equipment is needed such as a pH meter, osmometer, melting point apparatus, balances, microevaporator with vacuum pump, distillation unit, glassware for simple organic chemical work, a small IR spectrometer and an ultrasound bath. These are all small pieces of equipment which financially come to an amount which cannot just be added if not planned from the beginning. This is an example why some centres may experience difficulties in getting started.

REFERENCES TO SECTION 5

[5.1] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Guidelines for Setting up a PET Facility, Techncial Reports Series No. 471, IAEA, Vienna (2009).

[5.2] INTERNATIONAL ATOMIC ENERGY AGENCY, Quality Assurance for PET and PET/CT Systems, IAEA Human Health Series No. 1, IAEA, Vienna (2009).

[5.3] KARP, J.S., SURTI, S., DAUBE-WITHERSPOON, M.E., MUEHLLEHNER, G., Benefit of Time-of-Flight in PET: Experimental and Clinical Results, J. Nucl. Med. 49 (2008) 462–470.

[5.4] CONTI, M., et al., First experimental results of time-of-flight reconstruction on an LSO PET scanner, Phys. Med. Biol. **7** 50 19 (2005) 4507–26.

[5.5] JUDENHOFER, M.S., et al., Simultaneous PET-MRI: A new approach for functional and morphological imaging, Nat. Med. **14** 4 (2008) 459–465; epub 2008 Mar. 23.
[5.6] SCHLEMMER, H.P., et al., Simultaneous MR/PET imaging of the human brain: Feasibility study, Radiology **248** 3 (2008) 1028–1035.
[5.7] INTERNATIONAL ATOMIC ENERGY AGENCY, Strategies for Clinical Implementation and Quality Management of PET Tracers, IAEA, Vienna (2009).

6. PET FACILITY DESIGN

6.1. MODELS OF CLINICAL PET FACILITIES

A PET/CT scanner can be installed in any room measuring approximately 8 m × 5 m, or even less, that meets requirements from the manufacturer (such as weight bearing capacity, temperature stability, and adequate power supply), as well as issues concerning radiation safety (e.g. shielding). Access to a PET/CT scanner will strongly influence performance of diagnostic services. Hence, there are various models for setting up PET facilities in different countries, as they will reflect the different developments and organizational structures of different health care systems.

6.1.1. Location inside a hospital

Locating a PET facility within a large hospital has the advantage of concentrating health care at a single location that is convenient for patients. PET/CT scans can be introduced into standardized institutional diagnostic protocols and all patients that meet prescribed criteria can thereby rapidly access PET/CT investigations. Education of referring physicians is easier, as is the communication of results. The logistic services of hospital will support the operation of the PET facility, which is usually organized as a separate clinic of the hospital that must be licensed for the handling of unsealed radioactive sources. A hospital setting offers the clear advantage of the availability of a resuscitation team in the event of rare but life threatening events.

6.1.1.1. Oncology oriented hospitals

A PET facility situated within a hospital with a large oncologic case load, such as a cancer centre, can operate very efficiently due to the ease of patient scheduling. When a late cancellation of a PET/CT investigation occurs, another patient can easily replace the cancelled one without loss of scanner time or wastage of expensive radiopharmaceuticals.

It should be kept in mind that in an oncology 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 health care facilities.

6.1.1.2. Hospitals without a specific oncological orientation

Although a general hospital may not fully utilize a PET/CT scanner with its own patients, this potential drawback is offset by a greater potential of access offered to out patients or to patients and referring clinicians from other health care facilities. This should be considered at a national or regional level when introducing the first PET facility, if equity of access is to be achieved.

6.1.2. Stand alone PET facility

There are also PET facilities that are established as a stand alone centre, i.e. outside a hospital. These facilities are set up as out patient clinics as the vast majority of patients can undergo PET/CT on an out patient basis. A necessary requirement for such a facility is access to good transportation for patients. There is also a need for good communication between such a PET centre and referring health care providers. Connection through picture archiving computerized systems (PACS) for rapid access to reports and images, and the possibility of teleconferencing, are desirable.

With regard to hospitals, access to medical emergency facilities is important to prevent extremely rare but potentially fatal allergic reactions to radiological contrast media used for the CT component of the procedures.

6.1.3. Mobile PET

PET/CT scanners can be mounted on a truck and a mobile unit can operate on a regular basis in a specific region. The advantage is that even small health care facilities gain access to PET/CT services tailored to their demands (e.g. two days a week or even less) and patients do not have to travel to a distant PET centre.

The major disadvantage is that the logistics required to achieve smooth operation of such a facility, including planning transportation, and ensuring availability of personnel and radiopharmaceutical, requires extra efforts.

When local personnel are employed to report the PET/CT scans, there is the disadvantage of generally lower experience compared with that available in high throughput facilities, with the risk of lower accuracy of some reports. However, the level of interaction with local referring doctors will be definitely better than what could be achieved when reports are generated by remote specialists using teleradiology.

Mobile PET/CT units are becoming increasingly widespread. They must be held to the same standards of quality as fixed units. Therefore, all procedures stated in this publication are required also for mobile imaging systems [6.1].

6.1.4. Research oriented non-clinical institution

In the past, PET scanners were often installed in non-clinical facilities where they were utilized for research purposes. When scanner time was not occupied by research studies, those scanners could also be utilized for clinical investigations. This model is no longer viable because specialized pre-clinical PET scanners are available on the market and they are more appropriate for research in comparison to clinical PET/CT scanners.

Overall, in all current models in PET/CT facilities, efficient use of the scanner, staff, available isotopes and other infrastructure require a high throughput of patients. Optimal clinical utilization of PET/CT is best achieved in a tertiary health care facility.

6.1.5. Number of installed scanners

Most PET/CT facilities have only one scanner. Creating a larger facility with more scanners increases its efficiency significantly. Operating two scanners requires less than twice the amount of radiopharmaceuticals and thereby reduces production and transportation costs for each individual patient dose. Medical, technical, nursing and secretarial personnel can also be used more efficiently. In case of planned downtime or unexpected breakdowns of one scanner, the other can be utilized for high priority procedures or operate for extended hours to prevent cancellation of scheduled studies. This is particularly important for patients already injected with radiotracer, thus avoiding unnecessary irradiation resulting from administration without being scanned. Indeed, when more than one scanner is installed, the operation of a PET centre becomes smoother and more robust.

As the number of investigations increases, radiation protection of the staff becomes more important, but this is manageable with a proper usage of the various shielding systems available on the market. Planning for more than one PET/CT scanner per facility is highly recommended.

6.2. LAYOUT OF A PET/CT IMAGING FACILITY

6.2.1. General considerations

The facility can be divided into two parts. These are the PET/CT imaging facility and the cyclotron–radiopharmacy. The cyclotron facility is discussed in Section 7. The layout of a PET/CT imaging facility should obviously reflect the aims of the project. It should facilitate the production of the final diagnostic

product (i.e. the report) in a reliable, easy, efficient and safe way for the patient and for the staff.

The rapid developments in PET imaging over the last ten years are due to significant achievements in several fields. Among them, the general acceptance of the value of FDG-PET in clinical oncology was a major step as it led to the widespread use of the technique and an increasing demand for this examination. In parallel with this and no less relevant, there were important technological improvements.

Among the revolutionary technological changes that took place during this period, the first is the introduction of more efficient detectors, like LSO and BGO, followed by the introduction of the PET/CT hybrid scanner, which had a highly significant impact on the diagnostic value of the PET images and of diagnostic imaging in general [6.2]. All of these technological improvements happened before a 'plateau' had been reached in the use of PET with the previous technology, and where its usage was still increasing due to the burgeoning use of FDG in oncology and the increasing number of clinical indications approved for reimbursement. So, the fast evolution of PET, the increased acceptance of FDG-PET in oncology and technological developments, make it difficult for facilities to keep the layout in tune with changes in clinical framework and imaging context, unless the changes were foreseen and taken into account before the layout was implemented. This is especially relevant in the case of PET/CT technology, as the peculiarities and characteristics of the equipment have an effect on the design and hence on lay out.

Therefore, the layout is influenced by the distribution and size of the rooms required to meet the functional needs, and the radiation protection requirements, which depend on the amount and kind of work to be carried out in the facility. The layout design process is lengthy and involves several phases, each of which depends upon the context, scope and aims of the project. These phases are briefly outlined in what follows.

6.2.2. Choice of location

The location of the facility is also a very important issue as it may affect the flow of patients, materials, and radiation protection. Easy access for both outpatients and inpatients, as well as an independent exit for the patient after the scan that avoids mixing with other patients or the public in the building, is desirable. The same applies to FDG, which should be delivered as promptly as possible either to the hot lab of the facility in case individual doses are going to be dispensed from a vial or to the preparation rooms in case they are delivered as monodose. Radiation protection issues in relation to the kind of work carried out in the adjacent rooms around the facility and above and below should be

considered to avoid unnecessary exposure of the public as well as potential interference with sensitive instrumentation.

Setting up the PET/CT facility in place of a pre-existing PET only facility may require significant renovation work. Consideration must be given to the size of the scanning room, the number of preparation rooms (a larger number of preparation rooms permitting a higher throughput of patients) and the need to meet with additional radiation protection requirements. Nevertheless, provided the space available is large enough to meet all the needs, a total renovation can provide a satisfactory installation consistent with the mission of the facility and radiation protection regulations.

Overall, the construction of a new building is the most favourable choice since it offers better choices in terms of the most appropriate site design, distribution of activities and size of the whole facility.

Locating the facility in a nuclear medicine department deserves special consideration as it offers many advantages. First, considerable space can be saved since many rooms can be of common use (see the next section on design). Second, the staff members are already trained in the use of radiotracers and are familiar with radiation protection issues. Moreover, a larger number of staff will allow more frequent rotation and hence the minimization of radiation exposure.

A vision for the future is a must when dealing with a technique like PET/CT: there is increasing demand, and indications are very likely to increase considerably. Space must therefore be allotted for future growth. Whatever the decision concerning the location, the total space allocated to the facility must be consistent with the functional programme, which defines the number and variety of activities to be performed within the PET/CT facility.

6.3. DESIGN OF THE FACILITY

The design of the facility has to suit the functional programme, which defines the activities of the facility and will be reflected in the layout. It is crucial for the success of the facility to organize a design team that can work in a coordinated way. That includes the facility director, physicians, architects, engineers, radiation protection experts, and equipment vendors.

The next step is to develop a floor plan taking into account how the rooms and the space will be distributed according to functions to be performed in each area the flows and radiation protection measures. A suggested layout is described below.

According to the risk and level of radiation exposure, in the following, different functions will be allocated to areas with either a low risk (Section 6.3.1) of significant radiation exposure (so called ‘cold’ or ‘uncontrolled areas’), or with

high risk (Section 6.3.2) of radiation exposure (so called 'hot' or 'controlled areas'). Activities listed under Section 6.3.1 could be shared with other facilities (e.g. if the PET centre is set up in an already existing nuclear medicine and/or diagnostic imaging department).

6.3.1. Low risk areas

Reception. As patients arrive they are received and logged in by the administrative staff. Brochures and leaflets with general information about the PET/CT technique and any specific recommendations that apply to their particular scan should be provided and available to read while waiting. Typically, the reception is located at the front of the facility, normally with the *secretarial room* to its rear. Both areas need between 10–20 square meters, depending on the workload.

Waiting room. The appointment schedule should allow for a waiting time of no more than 30 minutes and if any delay is likely patients should be informed. It should be taken into account that oncological outpatients frequently come with an accompanying person, and so the waiting room should be constructed accordingly. An area of no less than 16 square metres is advised for a department with a single scanner. A location close to the reception is recommended.

Consulting room. In this room the request and clinical records are analysed and the patient is interviewed and physically examined, if necessary. The patient is informed about the nature of the specific examination he/she is undergoing. This room should be close to the waiting room and adequately equipped. A supply of oxygen gas for medical use and vacuum for aspiration and all other services as per local regulations should be provided. An area of not less than 12 square metres is necessary.

Cleaning utilities room and store. A small room or cabinet should be available for the storage of QC phantoms, supplies and other materials. There should also be a dedicated space allocated to the cleaning utilities. Those can be located at one end of the facility and 5 square metres each would be sufficient.

Offices. In addition to the reporting room, a certain number of rooms should be available for clinical, scientific and technical staff, and for meetings and teaching activities, the number depending on the size and aims of the unit.

6.3.2. High risk areas

Small hot lab. Normally, PET radiopharmaceuticals can be delivered to the injecting room in two ways: either in a monodose syringe or in a vial. When it is in a vial, the radioactivity may be very high, depending on the number of patients, and each dose has to be dispensed from the vial; in this case, a small room,

designed as a basic hot lab with shielding for positron emitters and near the injecting room, is needed. The IAEA's Operational Guidance on Hospital Radiopharmacy: A Safe and Effective Approach [6.3] should be consulted for proper guidance on setting up this laboratory.

The most favourable situation applies when the PET imaging facility is part of a PET/CT centre with its own production unit (cyclotron and radiochemistry lab). This allows for mono-dose syringes to be delivered to each injecting room in lead containers.

Preparation, injection and uptake room. When procedures start, patients are asked to lie on a bed or to sit on a reclining chair. They might be medicated or otherwise treated according to the protocols followed in the unit before being injected with the FDG dose. If there is no specific changing room, a locker or small wardrobe should be provided in the preparation room for safekeeping of patient belongings. Position and size are crucial for smooth operations in a busy PET centre. These rooms should be located close to the scanners room; an adequate work place/station should be available for the nursing personnel. Injection/preparation rooms should be available to host three to four patients (not less then roughly 12–16 square metres) for each PET/CT scanner installed. Patients after injection are a relatively intense source of radiation (of the order of 30–50 μSv/h per patient at 100 cm just after the administration). The assembly of several patients in the uptake room areas is a radiation protection problem that should not be overlooked; proper positioning and shielding of the uptake rooms need particular attention [6.4].

Toilet. After injection and an uptake period dependent on the protocol, before starting the actual PET scan procedure, patients are asked to void their bladder. The toilet must be located adjacent to the preparation rooms so that it can be easily accessed from any one of them. Within the facility, the toilet and preparation rooms are like an independent block that accomplishes specific functional and radiation protection requirements. About 30 square metres is sufficient for the entire block.

Control and scanning room. This is the core of the facility. The scanning room must be easily reached from the preparation rooms and the toilet. The door is normally just in front of the preparation block.

Although the area needed for proper installation of a PET/CT scanner can be as small as 7 m × 5 m, some extra space will ease diagnostic as well as maintenance operations. Vendors' prerequisites and installation guidelines should be considered in the planning phase. Also, careful consideration should be given to the fact that PET/CT scanners are somewhat demanding in terms of site prerequisites: the gantry of a multi-modality scanner could weigh in excess of 3000 kg. The corridors and angles should allow the biggest single package to be moved until its final position. Most parts of the scanners are air cooled; since the

power consumption can reach 30 kW·h, proper air conditioning is mandatory. For scanners that are water cooled, some extra space may be necessary for the water chiller.

Post-examination waiting room. Patients should wait in the post-scan waiting room while their scans are checked. They will also need to change clothes if they are wearing a hospital gown. This allows faster patient throughput. Patients are released from the post-scan waiting room and leave the facility.

Reporting room. When the scan is finished the examination is checked and the images transferred for reporting. There should be space for at least one processing and fusion workstation, one for visualization, a desktop, and the typical furniture for diagnostic imaging. The area should be not less than 10 square meters and it should be located in the same area as the offices. Since studies could be transferred through the PACS system, this room does not necessarily need to be in the 'controlled area'.

Waste disposal room. The materials used for the dispensing of the FDG and anything which could be contaminated (clothes, linen, etc.) should be stored in a dedicated area to let the radioactivity decay before being disposed. The whole space required for a facility adhering to the above description is about 170–200 square meters, of which about half will be 'controlled/restricted' areas, including the PET/CT block and the tracer administration block, while the other half will host activities which do not imply the use of any radioactivity, such as offices and the reception block. Therefore, should the facility be located in a nuclear medicine department, about 40% of the space required could be considered as being for common use, which would account for a considerable saving in the budget allocated for construction.

REFERENCES TO SECTION 6

[6.1] INTERNATIONAL ATOMIC ENERGY AGENCY, Quality Assurance for PET and PET/CT systems. IAEA Human Health Series No. 1, IAEA, Vienna (2009).

[6.2] BEYER, T., et al., Combined PET/CT Scanner for Clinical Oncology, J. Nucl. Med. **41** (2000) 1369–1379.

[6.3] INTERNATIONAL ATOMIC ENERGY AGENCY, Operational Guidance on Hospital Radiopharmacy: A Safe and Effective Approach, IAEA, Vienna (2008).

[6.4] INTERNATIONAL ATOMIC ENERGY AGENCY, Radiation Protection in Newer Medical Imaging Techniques: PET/CT, Safety Reports Series No. 58, IAEA, Vienna (2009).

7. CYCLOTRON FACILITY DESIGN

7.1. RADIOPHARMACEUTICAL SUPPLY

A reliable and uninterrupted source of positron emitting radiotracers is a basic prerequisite for the successful establishment of a clinical PET facility. The radiotracer production model may include the provision of PET radiopharmaceuticals only for in-house use as well as the operation of a centralized radiopharmacy for local or regional distribution to other PET satellite centres. Excess production of radiotracers of ^{18}F and ^{11}C may also be used to supply R&D programmes in universities or pharmaceutical companies that utilize conventional PET or pre-clinical (small animal) PET scanners.

The strategy regarding where to install a PET/CT scanner is strongly influenced by the availability of a reliable supply of PET radiopharmaceuticals. The most popular radionuclide for PET is [^{18}F]-fluorine, with a half-life of around 2 h. This means that at 2, 4, 6 and 8 h after its production only 1/2, 1/4, 1/8 and 1/16, respectively, of the original activity remains. Locating a PET/CT scanner within 4 h of the production unit is acceptable but becomes increasingly impractical if transportation times exceed this.

When the establishment of a new PET centre is under consideration one must realize that a PET/CT scanner can operate immediately after its installation, and after passing all acceptance tests, but the production or distribution of radiopharmaceuticals for human use is a greater logistical problem and often cannot be established as quickly as the scanner. Many tests and validation procedures must be performed to meet the requirements of national regulatory bodies. The licensing process takes time. The regular production of radiopharmaceuticals for human use may take up to one year after installation of all technology. Therefore, timing the installation of the PET/CT scanner appropriately is crucial.

Radiopharmaceutical production is also typically more frequently affected by downtime than PET/CT scanners. Accordingly, there are advantages in having some redundancy of licensed suppliers of radiopharmaceuticals. The 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 amortize production costs.

7.1.1. Supply from a distance

As discussed above, it is possible to install a PET/CT scanner up to 4 h away from a cyclotron facility. However, before committing to such a model, a

feasibility study should be carried out with tests simulating regular delivery of [^{18}F]-fluorine based radiopharmaceuticals twice a day. Unexpected complications like fog at the airport, icy roads, traffic jams, customs and special check-in requirements when handling radioactivity should be taken into account and the reliability of transportation within a time limit of 4 h should be assessed. By air, a feasible flying time is generally 2 h 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 the practical operation of a remote site.

Supply from a distance is valuable in the following situations:

— Temporarily, when the PET/CT scanner has been installed, but the local radiopharmaceutical facility is still under construction or being licensed;
— As a secondary backup source;
— As a source of complementary radiopharmaceuticals that are not available locally;
— As a potential alternate source of supply, thus increasing competition between suppliers.

The clear disadvantage of the supply from a distance model is the higher cost of individual doses, and the inability to access radionuclides with shorter half-lives such as ^{11}C. However, this might not be a major disadvantage in clinical practice, since the vast majority of PET investigations is based on [^{18}F]-fluorine which may be transported over reasonable distances.

7.1.2. On-site individual preparation

On-site individual preparation of radiopharmaceuticals is advantageous since radionuclides with shorter half-life (such as ^{11}C, ^{13}N and ^{15}O) 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.

7.1.3. Satellite concept

The satellite concept merges both previous concepts and identifies the most efficient model where one or more peripheral PET scanners are supplied with radiopharmaceuticals from a remote cyclotron. 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. This means that at least part of

production can be utilized directly on-site without any transportation losses. The higher production capacity enables supply to be provided to other scanners within a distance of up to 4 h travel time. Thus, the cost of the equipment and personnel can be divided between more investigations. Ideally, the satellite unit should be located so as to ensure good access to traffic arteries.

The satellite system of distribution can be established step by step. At first the production may supply one or more local PET/CT scanners. The existence of the production unit then facilitates decisions by other health care facilities in the vicinity to install their own PET/CT scanners, which will be supplied by the central production unit.

The satellite radiopharmaceutical production model is strongly recommended.

7.2. LAYOUT OF THE CYCLOTRON FACILITY

In drafting this report, consideration has been limited to the following three types of facilities. A great deal of information on the planning and operation of a cyclotron radiopharmacy may be found in Ref. [7.1].

7.2.1. Type 1 facility: radionuclide generator or facility with an external supply of radiotracer

The simplest type of PET centre is one where radionuclides are supplied by generators, or are purchased from a local distribution centre either in the form of radiochemicals or as finished radiopharmaceuticals. Typical examples of the isotopes that could be produced from generators are $^{62}Zn/^{62}Cu$ and $^{82}Sr/^{82}Rb$. ^{18}F can be delivered from a regional centre, either as FDG or as a fluoride ion. ^{18}F in the form of fluoride ion can be processed into a radiopharmaceutical on-site.

This situation does not require an accelerator, but does require the allocation of some laboratory space. In most cases, the radionuclides will not be in the form of the desired radiopharmaceutical and, therefore, must be processed either with a commercial kit, with more extensive simple chemistry, or in an automated synthesis module. This implies that there must be shielded space somewhere near the PET/CT scanner suite to do the processing. The more extensive the chemistry required, the more elaborate are the facilities that will be needed. This will be separate from the space required to do the blood analysis, which will be in or near the PET suite. The bare minimum will be a space to process, and a separate space with the facilities to do QA on the final product before injection. A set of guidelines for the areas needed for these activities is given in Table 7.1 and in the following tables. These are representative values and may vary with the scope of the facility.

TABLE 7.1. SPACE REQUIREMENTS FOR A TYPE 1 FACILITY

Function	Classification	Area (m^2)	No. of air changes (h^{-1})	Room pressure (Pa)
Entrance for personnel	Uncontrolled area	4	—	—
Offices for staff	Uncontrolled area	50	—	—
Quarantine storage room	Uncontrolled area	5	—	—
Material entrance	Uncontrolled area	3	—	—
Corridor	Uncontrolled area	24	—	—
Janitorial room	Uncontrolled area	2	—	—
Kitchen	Uncontrolled area	9	—	—
Data centre (archive)	Uncontrolled area	7	—	—
Toilets	Uncontrolled area	12	—	—
Storage room for released raw materials	Uncontrolled area	12	—	—
Storage room for technical gases	Uncontrolled area	2	—	—
Personnel airlock for entering the controlled area	Controlled area	9	5–10	–5
Corridor	Controlled area	34	5–10	–10
Preparatory laboratory	Controlled area	7	5–10	–10
Radiopharmaceutical handling	Controlled area, GMP class ‘C’	16	10–20	+20
Storage for radioactive waste, recalled products andretention samples	Controlled area	3	5–10	–25
Janitorial room	Controlled area	2	5–10	–10
QC laboratory	Controlled area	25	5–10	–10
Material airlock/emergency exit	Controlled area	4	5–10	–5

7.2.2. Type 2 facility: Cyclotron production for in-house use

In this type of PET centre, a small accelerator is used to generate some, or all, of the commonly used positron emitting radionuclides (^{15}O, ^{13}N, ^{11}C and ^{18}F). In addition to these radionuclides, some commercially purchased generators may be used.

QA testing must be done on representative samples to verify that the pH, radiochemical purity, pyrogens and radionuclidic purity are within QA limits. These samples can then be sent out for sterility testing. The space required for the QA testing will be the same as for a Type I facility, or about 30 m^2 (300 ft^2). The processing space requirements will also be about the same as the Type I facility and, of course, the testing and processing areas should be separated.

With an accelerator on-site, the spectrum of radiopharmaceuticals which may be produced is much wider. This type of accelerator will require additional shielding, as well as space for electronics, water cooling, a heat exchanger, and a control room. There is a wide choice of accelerators available from manufacturers. The choice will depend on the specific situation, but some guidelines are given in Ref. [7.1].

There will almost certainly be some synthesis modules in use, which may be supplied by the manufacturer of the accelerator or purchased separately. This type of facility has the potential for expansion in the future. New radiopharmaceuticals may be developed which offer better diagnostic tools for the physician. However, this facility will rely on the manufacturer to produce a commercial unit for the production of these radiopharmaceuticals, since the facility personnel will not be developing any chemical syntheses or designing automated synthesis modules.

Facilities for the synthesis modules should be situated near the cyclotron and PET/CT areas (to minimize transfer losses), and be well shielded to prevent undue radiation exposure to personnel. The ideal situation would be a small shielded room where the synthesis modules are easily accessible. The more usual situation will be that the synthesis modules are inside small shielded enclosures (mini hot cells), where access is somewhat more restricted. A consideration in this arrangement is to be sure that a module that must be loaded with fresh reagents for the next synthesis is shielded from another module that still has a substantial amount of radioactivity from the last synthesis. There should also be sufficient space around each module that it is possible to access it, and perform maintenance and repairs easily.

Another possibility is to have the synthesis modules in the cyclotron vault or other shielded area. This has two disadvantages. If the cyclotron is not completely self-shielding, then reagents cannot be added while the accelerator is running. The second disadvantage is that some types of electronics are particularly susceptible to radiation damage (specifically from neutrons), and storage in a high radiation environment will require frequent replacement of parts. An alternative is to use a substantial amount of shielding around each module, but this usually restricts access and increases the space occupied by each module. The minimum amount of space required for this facility is listed in Table 7.2.

TABLE 7.2. SPACE REQUIREMENTS FOR A TYPE 2 FACILITY

Function	Classification	Area (m^2)	No. of air changes (h^{-1})	Room pressure (Pa)
Entrance for personnel	Uncontrolled area	4	—	—
Offices for staff	Uncontrolled area	50	—	—
Quarantine storage room	Uncontrolled area	5	—	—
Material entrance	Uncontrolled area	3	—	—
Corridor	Uncontrolled area	25	—	—
Janitorial room	Uncontrolled area	2	—	—
Kitchen	Uncontrolled area	10	—	—
Data centre (archive)	Uncontrolled area	7	—	—
Toilets	Uncontrolled area	12	—	—
Storage room for transport containers	Uncontrolled area	7	—	—
Storage room for released raw materials	Uncontrolled area	12	—	—
Storage room for technical gases	Uncontrolled area	2	—	—
Personnel airlock for entering the controlled area	Controlled area	10	5–10	–5
Corridor	Controlled area	40	5–10	–10
Preparatory laboratory	Controlled area	7	5–10	–10
Packing room	Controlled area	10	5–10	–10
Personnel airlock for entering the clean room	Controlled area, GMP class ‘C’	5	10–20	+5
Radiopharmaceutical production laboratory	Controlled area, GMP class ‘C’	20	10–20	+20
Storage for radioactive waste, recalled products and retention samples	Controlled area	3	5–10	–25
Service corridor for hot cells	Controlled area	5	5–10	–25
Shielding vault for the cyclotron	Controlled area	80 (20 internal)	10–20	–60

TABLE 7.2. SPACE REQUIREMENTS FOR A TYPE 2 FACILITY (cont.)

Function	Classification	Area (m^2)	No. of air changes (h^{-1})	Room pressure (Pa)
Service room	Controlled area	20	10–20	–30
Power supply room	Controlled area	10	10–20	–30
Control room for the cyclotron	Controlled area	10	5–10	–10
Janitorial room	Controlled area	2	5–10	–10
QC laboratory	Controlled area	25	5–10	–10
Material airlock/emergency exit	Controlled area	4	5–10	–5

7.2.3. Type 3 facility: Cyclotron production for distribution

A type 3 facility will be somewhat similar in requirements to the type 2 facility. The main difference will be in the requirement for a space associated with the distribution function and the more extensive quality control procedures will be required. Radioisotope distribution centres have long been associated with large operations, which include radioisotope production. A more recent development is the distribution centre for a single product such as FDG. The QA and laboratory requirements are significantly greater for a distributed product than for the one being used in-house. Office space for staff and records management is also necessary.

7.2.4. Solid targets: Beam lines

Provision should be made in the vault and radiochemistry laboratory to install a beam line on the cyclotron and have an area for processing these targets.

7.2.5. Radiochemistry space requirements

The laboratory should be planned as a suite of rooms, the complexity depending on the extent of the proposed work and the number of workers. In many countries there are certain requirements for the design and construction of adequate radioisotope laboratories. Conformance with these regulations will be required from any applicant for a license to manipulate unsealed radioactive material. A more complete description of the radiochemistry laboratories can be found in Ref. [7.1].

7.2.5.1. Hot cell type

The choice of hot cell will depend on whether one wants two independent modules or two modules in the same hot cell. This will depend on the type of facility and the production schedule. Having the ability to carry out a second synthesis is very advantageous in a clinical programme when patients are waiting for the radiopharmaceutical.

7.2.6. Timeline to distribution for new facilities

The amount of time from moving the equipment into the radiochemistry laboratory and the time the first delivery of FDG goes out the door is expected to be six months to one year. The number of documents that must be created and procedures which must be established will define the time line and not the time to get the synthesis modules operational.

7.2.7. Facility expansion planning

At some point after the facility has been established, new tracers and a larger programme will likely be required. There are several steps which should be followed in order to facilitate this expansion. One of the simplest is to set up the cyclotron as the central core of the facility and radiate out from there. More detail on building design methodology can be found in Ref. [7.1].

7.2.8. Research in pre-clinical research

Depending on the type of facility, animal studies may play a significant role in pre-clinical research. If this is the case, provision must be made for the production of radiotracers for animal studies. The QC standards are not as high for the animal studies as for human studies and, therefore, the production schedule can be increased for these types of tracers.

REFERENCE TO SECTION 7

[7.1] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Guidelines for Setting Up a Facility, Technical Reports Series No. 471, IAEA, Vienna (2009).

8. STAFF REQUIREMENTS: ORGANIZATION FOR A PET FACILITY

8.1. INTRODUCTION

When a PET centre is to be set up, certain issues have to be dealt with during the planning stage before the vendors are called to submit their proposals. There are also significant economic implications and consequences arising from the purchase as well as operation of the centre. The design of the centre should essentially reflect the objectives of the individual facility. This decision will in turn decide the type of equipment and infrastructure needed as well as the related personnel, quality control and safety issues. Also, the overall size of this facility will depend on whether it is integrated into an established nuclear medicine service or is a separate PET facility.

Currently, the most common type of PET examination in clinical practice is an FDG whole body scan for oncological studies. Whole body scans may truly image the whole body or may image the body from the base of the skull to mid-thigh, depending on the clinical indications.

The number of staff, their qualifications and experience are a very important, if not the most important, issue for the efficient running of the PET facility. Many a times, while designing a PET facility, the availability of adequate number of staff might be limited due to various reasons. It is very important that the staff be identified early and be sent for training in their area of responsibilities.

The functions involved in the workflow process are listed in Table 8.1. The key staff involved and venue are listed in Table 8.2. It must be emphasized that the staff members are qualified personnel with specialized training.

8.2. PHYSICIANS

To run the clinical activities of a PET/CT scanner, there is a need for continuous presence of at least one fully qualified medical doctor. His/her qualifications must be in accordance with national rules and the guidelines of national scientific medical societies. The number of physicians required for running of one PET/CT scanner depends on the number and clinical conditions of the patients investigated, on the different types of PET/CT investigations, and on the organization of the work at the department (basically the number of daily shifts (one or two) as well as the amount of time dedicated to clinical meetings with referring physicians). At least one physician should be present for each shift.

TABLE 8.1. PROCESS OF CLINICAL PET SCAN EXAMINATION

Prior to scan	
Clinical request.	Multidisciplinary evaluation of patient; Decision on PET scanning.
Giving appointment date.	Date, time of appointment.
Instructions to patients.	Preparatory instructions.
Scan day	
Administrative admission.	Registration of patient; Charging of patient.
Interview with physician.	History taking and physical examination; Final decision on scanning.
Preparation of radiotracer.	Amount of radionuclide activity prepared and measured as unit dose in syringe; Dosage checked with dose calibrator; Syringed dose kept in shielded container.
Preparation of patient prior to injection.	Change of clothing; Height and Weight measurement; Removal of possible artefacts; Checking of glucose level; Insertion of IV line/bladder catheter; Medication; Oral contrast.
Injection of radiotracer.	Injection of radiotracer into the patient;
Waiting (radioactive).	Waiting (radioactive) to be scanned. Empty bladder.
Preparation of scanner prior to scanning.	Setting of acquisition parameters.
Patient positioning of patient in scanner.	Achieving immobilization of patient in gantry.
Scanning procedures.	Transmission and emission scanning; IV constrast administration.
Completion of scan	Quality checking of scan image; Transmission/exporting of scanned image/data for archiving and reading; Removal of IV canula/bladder catheter; Allowing patient to leave the department.
Reporting of scan	Reporting of scan
Dispatch of scan result	Dispatch of scan report to requesting doctor.

Interpretation of PET studies and clinical qualification of responsible physicians have been considerably debated, particularly after the introduction of hybrid PET/CT scanners [8.1, 8.2]. There are two models of PET/CT interpretation:

(1) The PET component of the PET/CT investigation should be interpreted by a licensed nuclear medicine physician with experience in PET, and the CT component by a licensed diagnostic radiologist with expertise in CT. Strong opinions have been expressed that a single report should be issued to avoid inconsistencies, confusion and redundancy. However, this model of combined interpretation by two different imaging experts is time consuming and its economic efficiency should be taken into consideration.

TABLE 8.2. KEY STAFF FUNCTION AND VENUE IN CLINICAL PET EXAMINATION

Prior to scan	Staff involved	Venue
Clinical request	Referring physician	Referring site/clinic
Giving appointment date	Administrative staff, nurse	Reception
Instructions to patient	Administrative staff, nurse	Reception
Scan day		
Administrative admission	Administrative staff, nurse	Reception
Interview with physician	Physician	Consultation room
Receiving of adioisotope	Medical physicist	Radiotracer receiving room
Preparation of radiotracer	Radiopharmacist	Hot lab
Preparation of patient prior to injection	Nurse	Changing room Waiting room
Injection of radiotracer	Technologist/nurse	Injection room
Preparation of scanner prior to scanning	Technologist	Console and scanning room
Patient positioning of patient in scanner	Technologist	Scanning room
Scanning procedures	Technologist	Console room
Completion of scan	Technologist	Console room
Reporting of scan	Physician	Reporting room
Dispatch of scan result	Dispatch clerk	Reception

(2) When a single imaging expert has to interpret PET/CT images, there is a need to define the training requirements for physicians who can interpret and integrate both components of the PET/CT scan. This is an ongoing matter of discussion inside the international and national societies of nuclear medicine and radiology. Independent reporting of PET/CT should be done by a licensed physician who has executed and reported under experienced supervision a number of PET, CT and/or PET/CT studies according to the recommendations of local academic and professional authorities.

8.2.1. Training options

High quality image interpretation with hybrid systems requires high level training in both nuclear medicine and radiology. There are several ways to achieve such training; the choice will differ between countries owing to differences in infrastructure and legislation. Training should be properly structured and comprehensive and should be conducted in accredited training centres. It should incorporate the principles and all modalities of both specialties to allow the trainee to acquire a full understanding of the possibilities and difficulties of each technique and its medical background, and provide the basis for participating in the necessary and inevitable evolution of multimodality imaging. Refresher type courses can prepare for specific training or refresh knowledge, but cannot replace appropriate on-site training. It is not acceptable for training to be focused on a single technique.

8.3. MEDICAL PHYSICISTS

Medical physicists practising in nuclear medicine must be qualified as physicists with academic studies in medical physics (typically at the postgraduate level) and clinical training in nuclear medicine physics. For the CT component of the PET/CT system, a medical physicist specialized in diagnostic radiology should also be consulted. Medical physicists specialized in nuclear medicine physics are referred to as ‘clinically qualified nuclear medicine physicists’. Senior nuclear medicine physicists are clinically qualified nuclear medicine physicists with at least six years of practical experience after qualifying in clinical nuclear medicine physics.

A clinically qualified nuclear medicine physicist should have at least:

(a) A university degree in physics, engineering or an equivalent physical science.
(b) At least one year of academic postgraduate studies leading to a Master's degree in medical physics (or an equivalent). This requires studies in several areas of medicine (e.g. radiodiagnostics, nuclear medicine and radiotherapy).
(c) The equivalent of at least two years of full time comprehensive clinical in-service training in nuclear medicine physics undertaken in a hospital. This nuclear medicine physics residence training will be under the supervision of an experienced or senior nuclear medicine physicist.

In addition:

— In the case that the academic studies include a considerable clinical training component, this should be taken into account in the fulfilment of the time requirement;
— This training should preferably be approved by a suitable professional body, i.e. a board that will issue a clinical certification.

It should be emphasized that the holder of a university degree in medical physics without the required hospital training cannot be considered to be clinically qualified.

The responsibilities of nuclear medicine physicists cover five major areas:

(1) Specification, acceptance testing, and calibration of nuclear medicine equipment;
(2) Measurement and calculation of activity and dose;
(3) Quality assurance and radiation safety;
(4) Training of allied health professionals in nuclear medicine physics;
(5) Education of health professionals and the public in nuclear medicine physics and radation effects.

An extensive description of the clinical training required of nuclear medicine physics staff is given in Ref. [8.3].

Radiation safety requires the establishment and maintenance of a radiation protection programme designed to ensure the safety of staff and the public. There is also a need to design and certify all radiation shielding for the facilities. These duties are the responsibility of the medical physicist specialized in nuclear medicine and/or of the radiation protection officer, who may or may not be the

same person. The administrative structure will vary depending on the country, the facility and the resources; what is important is that the necessary authority be available.

For quality control, the nuclear medicine physicist will be involved in establishing and operating an ongoing quality control programme for the facility. The nuclear medicine physicist, in association with the nuclear medicine physician, determines the equipment needs of the facility. In general, this includes the involvement of the nuclear medicine physicist in preparing bid specifications and evaluating vendor quotations with respect to both technical requirements and cost effectiveness.

Together with the physician, the medical physicist will design and implement all the elements of the nuclear medicine programme that are described in this report. These include equipment selection, facility design, quality control of radiation sources and imaging devices, tracer studies and internal dose calculation, maintenance, training of ancillary staff, and radiation protection. It should be understood that the practice of nuclear medicine will benefit from having clinically qualified medical physicists on its staff. The specific number of qualified medical physics staff required will depend on the number of patients treated, whether therapy is undertaken, the type of treatment performed, and many other factors.

8.4. PERSONNEL FOR RADIOPHARMACY

The facility for the production of PET radioisotopes and radiopharmaceuticals/radiotracers requires staff representing a wide range of qualifications. The number as well as the qualification level of personnel that will be needed in order to maintain smooth operation of the facility will be determined by the size and scope of the facility. In general, the staff should have the formal education, training and experience that are relevant to the assigned tasks. Table 8.3 represents the primary production personnel and Table 8.4 summarize the support personnel that should be considered depending upon the size of the facility. While most of these employees would be required to be regular employees, some may be contracted from outside sources (e.g. radiation safety officer and pharmacist).

TABLE 8.3. SUMMARY OF PRIMARY PRODUCTION PERSONNEL TYPE AND TYPICAL QUALIFICATIONS

Primary job function	Minimum education	Specialized training
Cyclotron operator(s)	Two year technical degree or equivalent	Specialized training, which may include: — Factory training; — On the job training; — Supervised training; — Extensive mechanical and electrical repairs; — Radionuclide production; — Targetry; — Radiation safety.
Production chemist(s) (radiochemists)	Diploma or degree in chemistry or equivalent	— Experience in GMP; — Synthesis of radiotracers; — Courses in laboratory operations; — Radiation safety; — Board certified or as required by local regulations.
QC chemist	Diploma or degree in chemistry, pharmacy or biological sciences	— Analytical chemistry and instrumentation; — Quality assurance and management; — Experience in GMP; — Synthesis of radiotracers; — Courses in laboratory operations; — Radiation safety.
Qualified person[a]	Formal training in GMP	— Formal training in GMP; — Two years of practical experience working in an authorized GMP licensed facility to release radiopharmaceuticals[a]

[a] May require a certified nuclear radiopharmacist or pharmacist depending on location and regulations.

8.5. TECHNOLOGISTS AND NURSES

In various countries there are different regulations and definitions of the contents of these occupations. The difference between nurses specialized in nuclear medicine and technologists specialized in nuclear medicine may be unclear. Nurses are involved in PET/CT investigation whereas technologists are

not allowed to place intravenous cannula or to administer pharmaceuticals. The total number of nurses and technologists can be estimated as the number of physicians multiplied by a factor of 2–3.

8.6. SUPPORT STAFF

Other support personnel are required for managerial, administrative and logistics functions (Table 8.4).

Individuals may (and often do) perform multiple functions in this list of job responsibilities. The only restriction is that the QC person should be independent of the production operations or must have independent oversight of these duties. The product cannot be released by the production chemist without additional oversight except in extraordinary circumstances. More information can be found in Refs [8.4, 8.5].

TABLE 8.4. SUMMARY OF SUPPORT PERSONNEL TYPE AND TYPICAL QUALIFICATIONS

Primary job function	Minimum education	Specialized training
Radiation protection officer	Degree in medical physics, health physics or radiation physics	— Supervised training; — Radiation safety.
Engineer	Experience in electronics, electromechanical engineering, or equivalent	— Experience in electronic diagnosis and repair, — Laboratory operations, — Radiation safety.
Manager	Advanced degree in physical or biological sciences	— Quality management; — Supervision and management; — Experience in GMP; — Experience in laboratory operations; — Radiation safety.

REFERENCES TO SECTION 8

[8.1] BISCHOF-DELALOYE, A., et al., White Paper of the European Association of Nuclear Medicine (EANM) and the European Society of Radiology (ESR) on Multimodality Imaging, Eur. J. Nucl. Med. Mol. Imaging **34** (2007) 1147–1151.

[8.2] COLEMAN, R.A., et al., Concurrent PET/CT with integrated imaging system: Intersociety dialogue from the Joint Working Group of the American College of Radiology, the Society of Nuclear Medicine, and the Society of Computed Body Tomography and Magnetic Resonance, J. Nucl. Med. **46** (2005) 1225–1239.

[8.3] AMERICAN ASSOCIATION OF MEDICAL PHYSICISTS, Essentials and Guidelines for Hospital-Based Medical Physics Residency Training Programs, Report of the Subcommittee on Residency Training and Promotion, AAPM Report No. 90, AAPM, College Park, MD (2006).

[8.4] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Principles and Practice, Technical Reports Series No. 465, IAEA, Vienna (2008).

[8.5] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Physical Characteristics and Production methods, Technical Reports Series No. 468, IAEA, Vienna (2008).

9. RADIATION PROTECTION

9.1. BACKGROUND

This section provides guidelines for a PET/CT and cyclotron facility for achieving the radiation safety of staff, patients, caregivers and members of the public. The principles of radiation protection must be well established and emphasized from the outset of the project. The International Commission on Radiological Protection (ICRP) is responsible for establishing these principles and are addressed in their two main publications [9.1, 9.2]. The operational aspects of the principles include: justification for eliminating unnecessary examinations; optimization through use of ALARA (as low as reasonably achievable, taking into account other factors such as image quality or clinical purpose and cost) and dose limitation. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) works to compile data on ionizing radiation and assesses its impact on humans and the environment.

Based on the work of these two international organizations, the IAEA has developed a set of standards for radiation safety. The existing standards (International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources (BSS)) are currently being revised; however, the changes are not expected to be very significant. The national organizations use the international standards (BSS) to frame their own regulations. The BSS and associated guidance documents [9.3–9.6] help users achieve a good standard of protection and a consistent national approach to licensing and inspection. Some countries develop practice specific regulatory guidance, while others develop practice specific regulations. Since PET/CT is a relatively new area, most countries do not yet have specific national guidance. This report, along with another publication from the IAEA [9.6], is expected to play an important role. The internationally harmonized guidance from the IAEA regarding radiation protection is recognized as being important by Member States.

In PET/CT facilities, situations in which there is a potential for radiation exposure are reasonably well known. The level of radiation doses that can be encountered by staff and patients has been estimated in a number of publications and are reviewed in this section as well as measures to reduce radiation exposure.

9.2. RADIATION EFFECTS AND THE PHILOSOPHY OF RADIATION PROTECTION

The effects of radiation are classified into two groups: deterministic effects (tissue reactions) and stochastic effects (cancer and heritable).

Deterministic effects are predictable and dose related, having a threshold below which the effect does not occur. This threshold is variable depending on the nature and condition of the exposed tissue. Above the threshold dose, the severity of the injury, including impairment of the capacity for tissue recovery, increases with dose, e.g. skin injury. The main effects in this category are: cataract, infertility, skin injury and epilation. In the case of PET/CT, there is a risk of skin injuries to fingers of the staff handling high activities whereas other effects remain a remote possibility with good radiation protection.

Stochastic effects are probabilistic and their severity has no relationship to dose. Although the likelihood (probability) of inducing a stochastic effect increases with dose, there is no identifiable threshold for producing the effect. There are two effects in this category: carcinogenesis and genetic. Genetic effects have been observed in non-human species but have not yet been documented in humans. Based on data from many decades of observations and research, the ICRP has recently reduced the tissue weighing factor for gonads [9.2]. In the past, it has been common practice to focus serious attention on the risk of genetic effects, something which needs to be rationalized. Carcinogenic effects cannot be eliminated and have been documented in human populations, primarily among survivors of the Hiroshima and Nagasaki atomic bombings. There have been frequent reports of carcinogenic risks to patients undergoing multiple CT procedures. Further details are given in the following sections.

Based upon the above classifications, the philosophy of radiation protection has been:

— Prevention of deterministic injuries;
— Limiting the probability of stochastic harm.

9.3. PROTECTION OF STAFF

The continued emphasis on occupational protection spanning over a century has resulted in significant protection of staff in many areas of application of radiation with few exceptions. For example, in most nuclear medicine departments in the world, the radiation exposure of the staff is one-tenth or one-twentieth of the annual dose limit. The current dose limits as given by the ICRP, in terms of effective dose for staff, are 20 mSv/year (a) based on averaging

of a five year dose limit of 100 mSv. A significant part of the radiation exposure to staff accrues from the handling of radiopharmaceuticals and, in particular, the syringes containing the injections. For an injection syringe with 10–15 mCi (370–560 MBq) of ^{18}F-FDG, for example, the resulting finger doses can be as high as 30 μSv or higher per patient procedure [9.7, 9.8]. Talking about effective dose alone may be misleading since localized exposure to hands and fingers (with low weighting factors in the effective dose calculation) may be significant. The effective dose is not useful for estimating the deterministic risk to fingers as it is primarily an index developed for stochastic risk estimation. The exposure to hands and fingers can result in deterministic risk to skin. For this reason, dose limits are also specified for hands (500 mSv/a), and are based on deterministic risk relative to a threshold for erythema. Similar dose limits have also been specified for the lens of eye (cataract) and for the thyroid (based on stochastic risk of thyroid cancer). The main sources of radiation exposure for staff in the PET/CT facility include:

— Unshielded radiopharmaceuticals (present during preparation and dispensing).
— Patients injected with PET radiopharmaceuticals.
— The patient toilet.
— Sealed calibration sources, quality assurance phantoms.
— The CT scanner, as staff in nuclear medicine may have difficulty in realizing that they need to be away (at a distance/outside the room) when the CT is being taken. For the PET part, there is no difference in staff exposure when PET scanning is 'ON' or 'OFF' (e.g. during the patient's adjustments), whereas for the CT part, the radiation appears only when the scan is being taken (X ray tube ON).

A number of factors affect the radiation exposure to staff, e.g. the number of patients imaged, type and amount of radiopharmaceutical administered per patient, length of time spent by the patient in each area of the PET/CT facility, and the facilities physical layout.

Functions that lead to the highest staff exposures include:

— Assaying the amount of radiopharmaceutical;
— Administering the radiopharmaceutical;
— Performing tasks near the patient (post-injection) during the radiopharmaceutical uptake period;
— Escorting the patient to and from the scanner;
— Positioning the patient on the scanner bed;
— Calibration and quality control of the PET scanner using sealed sources.

These exposures can be minimized through good design, good practice, patient instruction/cooperation and attention to the importance of the basic approaches including distance, time and shielding. Radiochemists and radiopharmacists also receive significant exposure in facilities that manufacture and prepare their own radiopharmaceuticals.

A very important aspect of staff protection traditionally has been the facility design. While this is crucial in radiopharmacy laboratories, radiotherapy and diagnostic radiology facilities, it becomes relatively less important when the staff member has to be in the room where radiation sources are present, for example the interventional rooms and, to some extent, in PET/CT facilities.

9.4. SHIELDING OF CYCLOTRON AND PET/CT FACILITY

A number of technical and operational advances, including composite shielding materials, automated transfer of radioactive material, automated radiosynthesis and purification, and robotics, have contributed to a generally excellent record of radiation safety in cyclotron production of radiopharmaceuticals. Radiation doses to personnel working in a cyclotron facility are typically well below the regulatory exposure limits (annual effective dose of about 1–3 mSv and hand dose of 25–50 mSv), with approximately half of the hand dose accruing in filling and handling of radiopharmaceutical filled syringes and half while opening the radiochemistry module. For persons working outside the facility but adjacent to the cyclotron facility, with proper shielding, public dose limits of 1 mSv/a can be maintained [9.9, 9.10]. The shielding, of up to 1.3 cm of lead for PET/CT scanner rooms and up to about 2 cm of lead for uptake rooms (versus only 0.318 cm of lead or less for a CT scanner alone) has been estimated by Zanzonico et al. [9.10]. This might take the form of interlocking lead blocks sandwiched between layers of plywood for structural support. Due to cost and weight considerations, it is worth exploring the possibility of varying the thickness of the shielding material in each boundary. A useful framework for shielding calculations is provided by the NCRP [9.11]. SPECT–CT facilities will generally not require shielding beyond that dictated by the CT scanner.

An additional consideration in the design of PET or PET/CT facilities is possible ‘cross-talk’ with nearby counting and imaging systems. Reasonable efforts should be made to locate the PET or PET/CT scanner and uptake rooms as far away from sensitive counting and imaging equipment as possible. Otherwise, additional shielding up to 2 cm of lead may be required (e.g. in the form of portable shields) to reduce the background count rates for such equipment to acceptably low values [9.12]. However, it should be stated that not all countries

accept the NCRP guidelines. Several, with an emphasis on optimization, set more demanding goals. For example, 1 mSv and 0.3 mSv are used in some countries as the design goals for areas occupied by workers and the general public, respectively. It needs to be stressed, however, that the above mentioned shielding figures are provided for illustrative purposes only. A qualified health or medical physicist should perform actual shielding calculations on a case by case basis.

The layout of the facility in terms of siting of uptake rooms is challenging because space is often limited and the distances to adjoining, occupied areas are often small. As a result, shielding is almost always required for such rooms in order to maintain doses to the staff and general public below their respective limits. For further details about layout of patient facilities (interview/consultation room, uptake room, waiting room, scan room, post-scan patient changing room), readers are referred to an IAEA publication [9.6].

9.5. PROTECTION OF PATIENTS

Unlike staff and members of the public, there are no dose limits prescribed by any international or national organizations for patients. This does not mean that any amount of radiation dose can be delivered to patients in medical examinations and procedures. There are very clear requirements on justification, optimization and reference levels. In addition to generic justification of the use of PET/CT for defined clinical conditions, justification at an individual level is recommended. Individual justification assesses the need of the PET/CT examination for the particular patient. If the justification principle is suitably applied, many unnecessary examinations can be avoided. Unfortunately, in practice, there is substantial need to improve situation with regard to justification.

Optimization requires that once an examination is justified, the exposure should be kept as low as reasonably achievable for the required image quality [9.2]. There has been lot of emphasis on this and has resulted in a significant reduction of patient doses through the process of optimization as evidenced by a large number of publications.

The concept of diagnostic reference level (DRL) is a powerful tool for optimization in patient protection as it helps in evaluating whether the patient dose (with respect to stochastic effects) is unusually high or low for a particular medical imaging procedure. DRLs are not dose limits as they are established based on contemporary technology and practice. In Publication 60 of the ICRP [9.1], diagnostic reference levels were described as values of measured quantities above which some specified action or decision should be taken. They should be applied with flexibility, to allow higher doses where indicated by sound clinical judgment.

The most suitable measured quantity in nuclear medicine is the injected radioactivity and, in the case of CT, a computed tomography dose index (CTDI) has been the accepted quantity. Very often, the non-measurable quantity of 'effective dose' is used to indicate patient dose. The ICRP and UNSCEAR have cautioned against the use of effective dose to estimate detriment (to individual or specific populations). Such estimates suffer from uncertainties arising from potential demographic differences (in terms of health status, age and sex) between a specific population of patients and the general populations for whom the ICRP derived the risk coefficient. It has been suggested, for example, that effective dose could broadly underestimate the detriment from diagnostic exposure of younger patients by a factor of about 2 and, conversely, could overestimate the detriment from the exposure of older patients by a factor of at least 5. Thus, rigorous analysis of radiation risk from diagnostic medical exposure requires detailed knowledge of organ doses and the age and sex of patients.

Despite these limitations, both the ICRP and UNSCEAR have used effective dose as the quantity to represent risk in the absence of a better quantity, but with an understanding of its limitations. This report follows this approach.

9.5.1. Internal exposure

The effective dose E_{int} resulting from intravenous administration of an activity A can be estimated from:

$$E_{int} = \Gamma \cdot A \tag{9.1}$$

where Γ is a dose coefficient computed for the adult hermaphrodite MIRD phantom. For ^{18}F labelled FDG and ^{82}Rb, the dose coefficients are 19 and 3.4 μSv/MBq, respectively [9.13]. These dose coefficients hold for standard patients with a body weight of about 70 kg and are generic rather than patient specific since age, gender of patients and individual pharmacokinetics are not taken into account. In fact, the radiation risk is somewhat higher for females and for younger patients when compared to male and older patients. Age and gender specific dose coefficients can be found in the ICRP report.

9.5.2. External exposure (CT)

Dose assessment in CT is challenging and depends not only on the body region exposed but also on a variety of scan-specific parameters (tube potential (kVp), tube current multiplied by exposure time (mAs), slice collimation, pitch factor) and technical features of the scanner (e.g. beam filtration, beam shaping

filter, geometry and acquisition algorithm used) [9.14,9.15]. Thus, values for patient dose vary considerably between centres and machines. Oversimplified approaches have correlated mAs with patient dose, assuming that kVp and other parameters in a particular CT scanner are kept constant. This has also led to the unsatisfactory practice of using mAs as dose indicator when comparing different scanners.

Various software packages have been developed to address these problems. For example, with whole body CT scans, Brix et al. [9.16] present a simple approach to providing a rough estimate of organ doses and effective dose. The organ dose, D_T, can be roughly estimated as:

$$D_T = \Gamma_T^{CT} \cdot CTDI_{vol} \tag{9.2}$$

where Γ_T^{CT} is an organ specific dose coefficient that relates the volume CT dose index, $CTDI_{vol}$, to organ dose [9.16]. The organ doses can be combined with weighting factors in the normal way, to give effective dose. For a whole body CT (thyroid to the symphysis), Brix et al. use 1.47 dose coefficient together with the $CTDI_{vol}$ to calculate an effective dose in mSv [9.16].

9.5.3. Combined exposure in PET/CT

The effective dose from a combined PET/CT examination is the sum of the effective doses arising from all scan components, and thus depends on the range of acquisition parameters mentioned above. The total effective dose for the whole body FDG-PET/CT depends upon protocol, but can be around 25 mSv [9.16]. Up to 70% of this is contributed by the CT scan elements; and 85% of the CT contribution (two-thirds of the total) may arise from the final diagnostic scan (8.6), while the remaining 15% comes from the scout and CT acquisition done for attenuation correction purposes. An alternative approach, which is commonly used, is to perform the PET/CT only from cerebellum to mid-thigh. The dose in this case would be approximately in the range 15–20 mSv.

Patient dose management in PET is less complex than in CT, provided one has a well designed facility, and one has control of the radioactivity that is administered. On the other hand, dose management in CT has continued to be a challenge. A significant part of this challenge arises from the fact that overexposure in CT is frequently not detected. In contrast to film based radiography where overexposure is evident in a dark images, increasing dose in CT and in other digital imaging techniques results in images with less noise (improved visual appearance) and fewer streak artefacts, although not necessarily with greater diagnostic information. It is widely believed that image quality in CT often exceeds the clinical requirements for diagnosis [9.17].

The ICRP has noted that technical and clinical developments in CT have not necessarily led to a reduction in patient dose per examination, and that there is a clear need for optimization of doses [9.14, 9.15]. In recent years, many papers have shown that adequate diagnostic information can be obtained with CT studies using lower doses [33–35]. All manufacturers have incorporated automated exposure control (AEC) into their systems. Further details about patient dose management are available in Refs [9.6, 9.14, 9.15].

9.6. AUTHORIZATION OF PRACTICE

A person with 'legal training' should be involved with the project, who obtains authorization for a practice involving a source of radiation and who should bear the primary responsibility for protection and safety.

The BSS require that 'legal persons', who are responsible for protection and safety, apply to the regulatory body for authorization of radiation use. This authorization should take the form of a registration or a license. The BSS further clarify that:

> "Typical practices that are amenable to registration are those for which: (a) safety can largely be ensured by the design of the facilities and equipment; (b) the operating procedures are simple to follow; (c) the safety training requirements are minimal; and (d) there is a history of few problems with safety in operations. Registration is best suited to those practices for which operations do not vary significantly." [9.3]

Given the complexity of a PET/CT facility, particularly when there is a cyclotron, the risks involved in the use of large quantities of radiopharmaceuticals, the substantial training required, and the fact that the safety of the facility depends largely on human performance, the demonstration of safety requires an assessment for each facility. Therefore, its authorization should take the form of a licence rather than a registration. The process of authorization can be simplified, however, by establishing standardized training programmes, by a relatively standardized QA programme in modular form to take account of different levels of complexity, equipment and sources for each facility, and by establishing a simple mechanism to provide evidence that both training and QA are met [9.5].

A PET/CT facility, once constructed, is difficult to later modify. Regulatory bodies may choose a two stage process of authorization, i.e. to require initial application when construction is about to begin, especially for facilities that include therapeutic applications of radionuclides. A good way to implement the

two stage process is by providing the regulatory body with a picture of the intended applications and the facility design. Allowance for evolving new procedures should be made, provided that they fit into the shielding and facility design.

Substantial modifications of a PET/CT facility, sources, or procedures may have safety implications which need verification of compliance with regulations. The regulatory bodies may also require an application for this. The same is true for partial or total decommissioning of a nuclear medicine facility. The legal person applying for an authorization should refrain from carrying out any of the actions of the practice until the registration or license, as appropriate, has been granted.

Regulatory bodies may require that the authorization be renewed periodically. Periods of renewal are based on safety criteria[1]. The factors include the inspection frequency, the safety record of the facility, and the stability of the user's operation. Considering these factors, a suitable period for renewal of nuclear medicine authorization may be of the order of five years. Consultation between the regulatory and health authority in this respect may be advisable.

9.6.1. Inspection

The BSS require that the:

"...principal parties shall permit duly authorized representatives of the [regulatory body]…to inspect their protection and safety records and to carry out appropriate inspections of their authorized activities". [9.3]

9.6.2. Personnel accreditation[2]

The BSS require that:
"(a) all personnel on whom protection and safety depend be appropriately trained and qualified so that they understand their responsibilities and perform their duties with appropriate judgement and according to defined procedures." (para. 2.30 [9.3])

[1] The frequency of revalidation is influenced by several factors, as described in Ref. [9.5], in view of which a reasonable period for the renewal of a nuclear medicine authorization is five years.

[2] Regulations in a number of countries require a personal authorization as formal recognition of the holder's competency to carry out a job safely.

In nuclear medicine practice, and also in a PET/CT facility, the following individuals carry responsibility for protection and safety, by virtue of tasks involving decisions, operation or handling of sources or equipment, which could lead to an accidental exposure:

— Medical practitioners working with radionuclides (e.g. nuclear medicine physicians[3], and other appropriately trained clinical specialists);
— Medical physicists in nuclear medicine (qualified experts in nuclear medicine physics);
— Other health professionals involved in the clinical use of radionuclides (e.g. radiopharmacists, nuclear medicine technologists[4]);
— Radiation protection officer (RPO);
— Staff performing special tasks (e.g. contamination tests, some of the QC tests).

To comply with the BSS requirements for the above mentioned staff, evidence of their education and training relative to protection and safety should be demonstrated. Training in radiation protection is necessary, but by no means sufficient, to practice. As a precondition, qualifications and certification in each respective profession are indispensable. This is not usually defined by radiation protection regulations or granted by a regulatory body, but rather by academic institutions and boards or societies. In the case of qualified experts the BSS defines them as:

> "An individual who, by virtue of certification by appropriate boards or societies, professional licences or academic qualifications and experience, is duly recognized as having expertise in a relevant field of specialization, e.g. medical physics, …". [9.3]

[3] The medical practitioner responsible for using radionuclides for diagnosis or therapy, depending on the objectives of the procedure. He/she decides the course to be followed in the case of each patient in order to best meet the needs specified by the referring physician, taking into account the possibilities associated with the various techniques of diagnosis and treatment with radiopharmaceuticals and the doses involved. The nuclear medicine specialist holds a nationally accepted medical degree who, in addition, has completed a nationally prescribed programme of training in the discipline of radiology and who has been credentialed by a national medical speciality certifying agency.

[4] Specialized staff responsible, under medical supervision, for the preparation, administration and measurement of radiopharmaceuticals; patient identification and patient information and to help ensure radiation protection. Under the supervision of the qualified expert in nuclear medicine physics, he/she carries out basic QC tests.

For nuclear medicine specialists, radiopharmacists, medical physicists, nuclear medicine technologists, and radiation protection officers, the typical documentary evidence indicated above, i.e. qualification credentials, should consist of:

(a) A degree relevant to the profession, issued by the competent education and examining authorities as required in the country and accreditation required in the country to exercise the profession, granted by the competent authorities or other institutions;
(b) A course on radiation protection for which the contents, methodology and teaching institution are recognized or approved by the regulatory body. This course may be integrated into the curricula of the professional education provided that it meets the training criteria for radiation protection specified by the regulatory body;
(c) On the job training supervised by accredited professionals with experience before working without supervision, as required in the country.

Evidence of competence for maintenance and servicing of medical equipment may consist of the following:

— Certification, ideally by the manufacturer, of having completed a training programme on the type of authorized equipment;
— Course on radiation protection for which the contents, methodology and teaching institution are approved by the regulatory body.

Personal accreditation or authorization may need to be renewed periodically. The regulatory body may provide guidance on qualification requirements for each category of job found in particular practices.

The courses and syllabuses used in professional education and training are generally defined by the departments of health and/or education authorities in a country in cooperation with the professional bodies. A suitable approach is for the training criteria for radiation protection for medical exposure, specified by the regulatory body in consultation with relevant professional bodies[5] (BSS, para. II.1 (f)) [9.3], to be incorporated into the professional education and training.

[5] In countries in which a national professional body does not exist, a regional body or international professonal organizations may be consulted for advice.

It may be appropriate and convenient for the regulatory body to recognize certain training centres and courses for their quality and suitability in connection with the radiation protection requirements. For example, they can identify: (a) departments which have been accredited as training centres for the profession (if any) and facilities; (b) syllabuses and qualifying bodies that are responsible for training and accreditation in nuclear medicine and recognizing them for training in radiation protection as well. Such recognition can be formally conferred by a process of accreditation based on the training criteria referred to above. The evaluation for accreditation should involve training facilities, teaching staff, content and methods for training, examination procedures, and training records.

The following staff members do not require personal accreditation on radiation protection but do require instruction on radiation protection:

— Nurses handling patients with therapeutic amounts of radioactivity and nurses in a nuclear medicine department;
— Maintenance, engineering and cleaning staff working in nuclear medicine laboratories.

REFERENCES TO SECTION 9

[9.1] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, 1990 Recommendations of the International Commission on Radiological Protection, Publication 60, Annals of the ICRP **21** (1991) 1–3.

[9.2] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Recommendations of the International Commission on Radiological Protection, Publication 103, Annals of the ICRP **37** (2008) 2–4.

[9.3] FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS, INTERNATIONAL ATOMIC ENERGY AGENCY, INTERNATIONAL LABOUR ORGANIZATION, OECD NUCLEAR ENERGY AGENCY, PAN AMERICAN HEALTH ORGANIZATION, WORLD HEALTH ORGANIZATION, International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources, Safety Series No. 115, IAEA, Vienna (1996).

[9.4] INTERNATIONAL ATOMIC ENERGY AGENCY, Radiological Protection for Medical Exposure to Ionizing Radiation, IAEA Safety Standards Series No. RS-G-1.5, IAEA, Vienna (2002).

[9.5] INTERNATIONAL ATOMIC ENERGY AGENCY, INTERNATIONAL LABOUR OFFICE, INTERNATIONAL ORGANIZATION FOR MEDICAL PHYSICS, PAN AMERICAN HEALTH ORGANIZATION, WORLD FEDERATION OF NUCLEAR MEDICINE AND BIOLOGY, WORLD HEALTH ORGANIZATION, Applying Radiation Safety Standards in Nuclear Medicine, Safety Reports Series No. 40, IAEA, Vienna (2005).

[9.6] INTERNATIONAL ATOMIC ENERGY AGENCY, Radiation Protection in Newer Imaging Techniques.: PET/CT, Safety Reports Series No. 58, IAEA, Vienna (2008).

[9.7] GUILLET, B., et al., Technologist radiation exposure in routine clinical practice with ^{18}F-FDG PET, J. Nucl. Med. Technol. **33** (2005) 175–179.
[9.8] TANDON, P., VENKATESH, M., BHATT, B.C., Extremity dosimetry for radiation workers handling unsealed radionuclides in nuclear medicine departments in India, Health Phys. **92** (2007) 112–118.
[9.9] GONZALEZ, L., VANO, E., CORDEIRO, C.A., CARRERAS, J.L., Preliminary safety evaluation of a cyclotron facility for positron emission tomography imaging, Eur. J. Nucl. Med. **26** (1999) 894–899.
[9.10] ZANZONICO, P., DAUER, L., ST GERMAIN, J., Operational radiation safety for PET-CT, SPECT-CT, and cyclotron facilities, Health Phys. **95** 5 (2008) 554–70.
[9.11] NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS, Structural Shielding Design for Medical X-Ray Imaging Facilities, Report No. 147, NCRP, Bethesda, MD (2004).
[9.12] MADSEN, M.T., et al., AAPM Task Group 108: PET and PET/CT shielding requirements, Med. Phys. **33** (2006) 4–15.
[9.13] BEYER, T., ANTOCH, G., BOCKISCH, A., STATTAUS, J., Optimized intravenous contrast administration for diagnostic whole-body ^{18}F-FDG PET/CT, J. Nucl. Med. **46** (2005) 429–35.
[9.14] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Managing Patient Dose in Computed Tomography, Publication 87, Annals of the ICRP **30** (2001) 4.
[9.15] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Managing Patient Dose in Multi-Detector Computed Tomography (MDCT), Publication 102, Annals of the ICRP **37** (2007) 1.
[9.16] BRIX, G., et al., Radiation exposure of patients undergoing whole-body dual-modality ^{18}F-FDG PET/CT examinations, J. Nucl. Med. **46** (2005) 608–613.
[9.17] REHANI, M., BERRY, M., Radiation doses in computed tomography (Editorial), Br. Med. J. **320** (2000) 593–594.

Appendix I

CLINICAL INDICATIONS

I.1. ONCOLOGY

There has been an extraordinary increase in the number of PET examinations worldwide over the years. Initially, PET studies were mainly focused on brain metabolism and function, but since the impressive technological development of scanners and the advent of whole body PET the main application of clinical PET has been in oncology. At present up to 95% of the clinical activity of a PET centre consists of oncological PET studies. The range of non-oncological indications is expected to increase, albeit to a lesser extent. The main reason why PET is successful in oncology is that it provides a considerable amount of diagnostic information that is very useful for the clinical management of patients. Neoplastic cells show certain metabolic characteristics that coincide with the availability of the glucose analogue ^{18}F-FDG, which today is the most suitable radiopharmaceutical for PET [I.1]. Malignant cells have a higher glycolitic activity than normal cells, and an increased expression of glucose transporters (GLUT) has been described, leading to a favourable tumour/background ratio. PET imaging is based primarily on metabolic activity of the lesions, while conventional modalities such ultrasound, CT and MRI better describe morphology. The oncologists require both a good detectability of cancer lesions and also biological parameters capable of describing the cancer process in terms of metabolism, proliferation and aggressiveness. Because of these characteristics, PET has been compared with conventional imaging, and the diagnostic accuracy often was more successful than that of radiological tests in several conditions [I.2]. Thus, PET is generally used as a complementary technique in clinical cancer imaging. The recent development of image fusion methods and the availability of hybrid systems, as represented by combined PET/CT scanners, is going to make less evident the distinction between the anatomical imaging that are typical of radiological tests and functional imaging typical of PET [I.3, I.4].

The crucial steps that the physician dealing with a cancer patient has to face in order to choose the most effective and appropriate management are: diagnosis, staging, treatment planning, therapy monitoring and post-treatment surveillance. Also, in the diagnostic process the prognostic evaluation has to be included since it identifies the subgroups of patients that should be addressed by a less or more aggressive therapy. The success of the treatment depends strongly on the capability to detect cancer at the earliest stages to define its extension, to know its

biology and to establish the most effective treatment, if it exists. The final results can be measured in different ways. Two of them are particularly relevant: the complete disappearance of the tumour and the survival of the patients. Diagnostic imaging, because of its non-invasive nature, has a fundamental role in all the steps of cancer evaluation and is currently based on radiological imaging such as ultrasound, CT and MRI. These techniques describe mainly morphology and are based on the size of the tumour mass. Sometimes, when the limits of cancer are not well defined or cancer cells infiltrate normal organs or soft tissues, the radiological modalities fail to depict malignancy. Similarly, anatomical distortion after therapy or benign processes may form alterations that may be mistaken for malignant tumours. In some anatomical districts, the diagnostic performance of conventional radiological modalities is very limited, and this makes necessary surgical staging prior to curative resection, though sampling errors can occur. Despite these limitations, staging remains one of the most important prognostic methods in cancer detection and is generally used to guide treatment. The TNM system that describes the characteristics of the primary tumour (T-stage), regional lymph nodes (N-stage) and distant metastatic sites (M-stage), permits the grouping of patients into four clinical stages, from I to IV. Treatments are then selected and delivered on the basis of this system: patients with stage I–II disease are generally treated surgically with radical intent, 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 other palliative treatments.

Since FDG imaging was first used for the diagnosis of suspected cancer in the 1980s, it was clear that high uptake of this radiopharmaceutical was a characteristic of many malignancies, even if FDG is not a ‘specific tracer’ for cancer. Technological improvements in instrumentation, particularly the development of hybrid system PET/CT, have enhanced the diagnostic performance of PET. The same situation occurred with conventional radiology, which has also recorded impressive improvements, such as the development of multidetector CT and higher field strength MRI utilizing new pulse sequences and improved image analysis algorithms. The performance of PET, like that of any diagnostic test, needs to be represented by measurable parameters, including sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy. Both the NPV and PPV are greatly affected by the prevalence of disease in the test population. Therefore, sensitivity and specificity are often considered 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 useful information that can influence the treatment and the outcomes of patients. Given that cancer 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 very 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.

At present, there is abundant evidence that, whether validated by pathology or clinical follow-up, FDG–PET is more accurate under many conditions due to the variable degree of superior sensitivity, specificity, or both, than conventional imaging techniques for both the diagnosis and staging of cancer. The advent of PET/CT has further enhanced the diagnostic performance of PET [I.5, I.6]. 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 malignancies, because of the resolution limits of the instruments. Similarly, PET is probably of limited importance 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. Again, PET with FDG is not reliable in tumours with low metabolic activity due to the poor uptake of FDG.

It is very difficult to list the cancer type that can be studied by PET, since the data from the literature report results in lung cancer, colorectal cancer, head and neck cancer, breast cancer, gynaecological cancer, prostatic cancer, testicular cancer, pancreatic cancer, oesophageal cancer, renal cancer, thyroid cancer, hepatocellular cancer, brain tumours, melanoma, lymphoma, and any other cancer provided that they have documented avidity for FDG [I.7]. It should be mentioned that FDG is not the only possible tracer for PET, but there are other radiopharmaceuticals capable of exploring different pathways (amino acid uptake, cell proliferation, DNA synthesis, membrane lipid metabolism and hypoxia markers). These options can enlarge the clinical indication of PET since they are more reliable in visualizing certain tumours (such as neuroendocrine tumours), or can add specific information to pure cancer imaging [I.8].

The clinical situations under which the usefulness of PET has been generally recognized and accepted include [I.9]:

— The non-invasive characterization of tumour masses suspected of malignancy, not defined by other diagnostic imaging modalities and 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 the basis of clinical symptoms or signs or elevated tumour markers, but in whom routine imaging and laboratory 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 may prolong life.

For all of these clinical scenarios there are multiple independent examples of FDG–PET and, more recently, PET/CT being effective. In each clinical scenario, the superior accuracy of 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 with conventional evaluation techniques, the superior accuracy and impact on management decisions has the potential to both reduce global cancer costs and improve outcomes.

I.1.1. FDG–PET for cancer screening or detection

Japan has experienced in the use of PET in screening programmes [I.10]. In a population involving individuals at increased risk of malignancy, the reported rate of previously unidentified malignancies accounts for up to 3% of the screened population using a combination of FDG–PET, CT, MRI and a battery of various laboratory tests. In addition, studies with FDG–PET or PET/CT on patients with known or suspected colon, and thyroid cancer using FDG–PET or PET/CT, describe a rate of incidental second malignancies in 1–3% of patients, with histological confirmation. There is agreement that the rates of detection are probably insufficient to justify widespread use of FDG–PET/CT as a routine cancer screening modality considering the costs and the availability of the instrumentation. However, the relatively high sensitivity of FDG–PET/CT and the excellent NPV in patients with a low prevalence of disease support the possibility that FDG–PET/CT might find a clinical role in the presence of situations of elevated levels of circulating tumors markers (CA-19.9, CA-15.3,

CA-125, or CEA) and conventional diagnostic evaluation fail to confirm a diagnosis or yield doubtful or false–positive results.

I.1.2. FDG–PET for evaluating mass lesions

Accurate and timely diagnosis of cancer is a key issue in modern oncology. One of the first situations where FDG–PET was evaluated as a non-invasive tool in this role was for the characterization of solitary pulmonary nodules (SPN) [I.11]. Using a range of imaging devices, multi-institutional prospective studies came to the conclusion that FDG–PET can differentiate between individual pulmonary nodules as regards etiology (benign/malignant) with a high degree of diagnostic accuracy and that by this means unnecessary invasive surgery can be avoided. The majority of FDG avid lesions are malignant and the vast majority of non-avid lesions are benign. The high level of accuracy of FDG–PET for the evaluation of SPN in most published information from Australia, Europe and North America, 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 in both radiological and 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 FDG–PET [I.12]. Nevertheless, since most of the processes that cause abnormal 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.

With reference to other mass lesions in the different anatomical districts, the capability of FDG–PET to differentiate malignancy from benign processes depends also on the metabolic activity of the tissue, since hyperplasia plays a role in FDG uptake. A good example is the benign colorectal polyps, where high FDG uptake was observed more in adenomatous polyps than hyperplastic polyps. These can be considered as false-positive results. However, since it is thought that adenomatous polyps are premalignant lesions, their discovery, sometimes incidental during a whole body PET study, leads to a beneficial surgical diagnosis with resection. Of course the diagnostic performance of FDG–PET is clearly influenced by the size of the lesion. Masses smaller than 5–6 mm in diameter are not visualized with PET, and this is a limit of this diagnostic approach when compared with radiological modalities. Another problem is represented by the topographical location of the lesion mass. For instance, the evaluation of pelvic abnormalities close to the bladder or urethral structures can cause problems using

FDG due to the fact that the tracer is eliminated through urine and the physiological uptake can mask the presence of FDG avid lesions.

I.1.3. FDG–PET for staging of cancer

The most used indication of FDG–PET is cancer staging since clinical evidence shows that PET often is able to depict lesions not detected by conventional methods (CT, ultrasound, MRI). PET/CT has generally demonstrated a clinical performance superior than PET and/or CT alone. In principle, CT in hybrid systems was used for attenuation correction and cancer location was not the first issue. The recent increased availability of scanners combining 32–64 detectors suggest that the diagnostic CT studied during contrast material injection can be combined with the highest quality PET studies. A discussion is ongoing about the real need to perform contrast enhanced CT and when to do it. In any case, with reference to the PET/CT scanner, the hybrid system in several institutions has been replaced by separately acquired PET and CT tests for many oncological indications [I.13]. Some clinical guidelines of international scientific societies have included PET/CT in the current work-up of cancer patients (i.e. lymphoma, colon cancer, lung cancer). The 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 therapies, palliative treatments that maximize quality of life should be adopted, avoiding the cost and morbidity of futile curative attempts. When cancer 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 FDG–PET imaging. Furthermore, where biopsy or clinical follow-up was able to ascertain the appropriateness of the resulting stage migration, FDG–PET was also shown to be correct for an overwhelming percentage of the time compared with 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. The term ‘medium’ is used if there is a change in delivery of treatment but not of intent or modality, e.g. a change in radiation treatment volume. ‘Low’ is used when the management planned is still deemed appropriate on the basis of PET information. Finally, ‘No’ is used 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 FDG–PET in a prospective cohort of patients

with known or suspected lung cancer at various phases of the diagnostic process, including primary staging [I.14]. Similar studies were subsequently reported on the impact of 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 USA for the National Oncological PET registry (NOPR) [I.15]. 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.

I.1.4. FDG–PET for radiotherapy treatment planning

Recent innovations in radiotherapy have seen a move to more highly targeted treatment methods such as three dimensional conformal radiation therapy (3-D–CRT) and intensitymodulated radiotherapy (IMRT) that allow use of higher radiation doses to the tumour while sparing adjacent normal tissues. 3-D–CRT is a high definition technique that conforms the spatial dose distribution to 3-D target volume by modulating the intensity of the radiation beam to focus a higher dose to the tumour while reducing exposure of healthy tissues at minimum. IMRT is an advanced form of 3-D–CRT in which the beam intensity of each field is modulated through computer controlled X ray accelerators delivering precise radiation doses to the tumour or specific area within the tumour. The integration of PET imaging in radiotherapy increases the accuracy of staging and brings the concept of biological target volume (BTV). Due to the contrast afforded by differential 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 [I.16]. The recent clinical experiences in this area have demonstrated that the use of PET leads to changes in treatment intent or avoiding treatment, even changes in treatment strategy and better definition of the gross tumour volume (GTV) of the primary and lymph nodes [I.17]. In addition, there is a clear decrease in the risk of geographically missing the tumour, a better chance of sparing healthy tissue and a reduced risk of interoperator variability in target delineation. In conclusion, PET fulfills the main needs of radiation oncologists.

I.1.5. FDG–PET for monitoring therapy response

For both localized and widely disseminated cancers, a growing variety of therapeutic agents is becoming available. Many of these agents are being combined with conventional therapies, adding cost and potentially new toxicities to existing treatment paradigms. In this context, early identification of non-responders is needed to facilitate earlier termination of ineffective treatment so that these alternative treatments can be changed in the hope that they may be more efficacious. Additionally, side effects that diminish physiological reserves and compromise quality of life may be avoided.

Although tumour markers are commonly used to assess treatment response, they are not always available s and provide no localizing value. Therefore, they cannot be used to guide salvage therapies like surgery or radiotherapy in the event of persistent abnormality. Therapeutic response assessment is thus generally based on changes in the measured dimensions of lesions identified on CT scan or other structural imaging techniques. These changes are recorded and graded according to definitions detailed in the Response Evaluation Criteria in Solid Tumours (RECIST) [I.18], representing a modification of earlier WHO response criteria [I.19]. 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 with structural imaging techniques is that there is usually a more rapid decline in tumour metabolism than in tumour size. Preliminary studies, reported more than ten years ago, demonstrated that reduced FDG uptake generally both precedes and predicts subsequent morphological response. Recommendations on the use of FDG–PET for therapeutic response assessment have recently been made in a consensus statement from the National Institutes of Health in the USA [I.20].

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 [I.21]. 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 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 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 MacManus et al. [I.22], a complete metabolic response (CMR) is defined as a return of 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 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 FDG uptake in tumours is the standardized uptake value (SUV). There is not yet consensus regarding what degree of 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 [I.23]. 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 FDG–PET for response evaluation, based on its ability to powerfully stratify patient outcome [I.24]. Qualitative analysis of 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 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 FDG PET response in various solid malignancies [I.25].

I.1.6. 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, FDG–PET should be less susceptible to the effects of prior treatment. Many studies throughout the world have demonstrated that FDG–PET is more accurate than conventional imaging for the detection of residual cancer following definitive treatment of various haematological and non-haematological malignancies.

I.1.7. Use of FDG–PET as a prognostic 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 FDG uptake seems to be an important biomarker of disease aggressiveness in many forms of malignancy [I.26, I.27].

I.1.8. Alternative tracers for cancer evaluation

It is important to recognize that, being a tracer of glucose metabolism, 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 FDG uptake, even under fasting conditions, and this provides background activity that may mask small lesions or malignancies with low glucose metabolism. Such malignancies such as 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 FDG uptake of these tumours compromises the sensitivity of PET for the detection of tumour sites. Considering these issues the interpretation of images with 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 [I.28]. In particular, there has been a search for tracers that might overcome the weaknesses of FDG–PET as imaging tracer, especially with respect to ability to visualize tumours with low avidity for FDG.

Research in PET radiochemistry has provided access to alternative tracers for oncology at the present time. Some tracers have been evaluated in both pre-clinical and clinical studies others are still under evaluation. In general, they have the ability to uniquely characterize specific aspects of tumour biology and, as a result, to offer several diagnostic advantages in comparison with FDG in particular types of tumours [I.29–I.35]. A few examples of PET radiopharmaceuticals that are today of great interest are: tracers for cell proliferation ^{11}C-thymidine and ^{18}-Ffluorodeoxythymidine; tracers for amino-acid transport ^{11}C-methionine, ^{18}F-fluoroethyltyrosine,^{18}F-fluorometilthyltyrosine; tracers for hypoxia ^{18}F-fluorometilthyltyrosine, ^{18}F-fluoroetanidazole, ^{18}F-fluoronitroimidazole, ^{18}F-fluoroazomycinaribinoside; tracers for receptors: ^{18}F-octreotide analogues, ^{68}Ga-octreotide analogues, ^{18}F-fluoroestradiol, ^{18}F-galacto-RGD(Arg-Gly-Asp), tracers for dopamine metabolism, ^{18}F-fluorodihydroxyphenylalanine, tracers for fatty acid and lipid metabolism ^{11}C-choline, ^{18}F-fluorocholine, ^{11}C-acetate; ^{18}F-fluoroacetate. It should be mentioned that these new tracers that address the perceived limitations of FDG, are not still registered and are not everywhere available. However in many institutions they play a clinical role in particular cancer types such as ^{11}C-methionine, ^{18}F-fluoroethyltyrosine, ^{18}F-fluorometilthyltyrosine in brain

tumours, or ^{11}C-choline, ^{18}F-fluorocholine in prostate cancer, or ^{68}Ga-octreotide analogues in neuroendocrine tumours.

REFERENCES TO APPENDIX I

[I.1] PAUWELS, E.K., STURM, E.J., BOMBARDIERI, E., CLETON, F.J., STOKKEL, M.P., Positron-emission tomography with ^{18}F fluorodeoxyglucose. Party I. Biochemical uptake mechanism and its implication for clinical studies, J. Cancer Res. Clin. Oncol. **126** (2000) 549–559.

[I.2] LUCIGNANI, G., BOMBARDIERI, E., Molecular imaging: Seeing the invisible beyond the "hot spot", Q. J. Nucl. Med. Mol. Imaging **48** (2004) 1–3.

[I.3] BEYER, T., et al., A combined PET/CT scanner for clinical oncology, J. Nucl. Med. **41** (2000) 1369–1379.

[I.4] BOMBARDIERI, E., et al., FDG–PET procedure guidelines for tumour imaging, Eur. J. Nucl. Med. Mol. Imag. **30** (2003) 115–124.

[I.5] POEPPEL, T.D., et al., PET/CT for the staging and follow-up of patients with malignancies, Eur. J. Radiol. **70** (2009) 382–392.

[I.6] CZERNIN, J., ALLEN-AUERBACH, M., SCHELBERT, H.L., Improvements in cancer staging with PET/CT: Literature based evidence as of September 2006, J. Nucl. Med. Suppl 1 (2007) 78–88.

[I.7] MITTRA, E., QUON, A. Positron emission tomography/computed tomography: The current technology and applications, Radiol. Clin. North Am. **47** (2009) 147–160.

[I.8] VALLABHAJOSULA, S., ^{18}F-labeled positron tomographic radiopharmaceuticals in oncology: An overview of radiochemistry and mechanisms of tumour localization, Sem. Nucl. Med. **37** (2007) 400–419.

[I.9] INTERNATIONAL ATOMIC ENERGY AGENCY, A Guide to Clinical PET in Oncology: Improving Clinical Management of Cancer Patients, IAEA-TECDOC-1605, IAEA, Vienna (2008).

[I.10] IDE, M., Cancer screening with FDG–PET, Q. J. Nucl. Med. Mol. Imag. **50** (2006) 23–27.

[I.11] BAR-SHALOM, R., KAGNA, O., ISTRAEL, O., GURANLIK, L., Noninvasive diagnosis of solitary pulmonary lesions in cancer patients based on FDG avidity on PET/CT, Cancer **113** (2008) 3213–3221.

[I.12] KAGNA, O., et al., Eur. J. Nucl. Med. Mol. Imag. **36** (2009) 997–1004.

[I.13] ELL, P., The contribution of PET/CT to improved patient management, Br. J. Radiol. **79** (2006) 32–36.

[I.14] KALFF, V., et al., Clinical impact of ^{18}F-fluorodeoxyglucose positron emission tomography in patients with non-small-cell lung cancer: A prospective study, J. Clin. Oncol. **19** (2001) 111–118.

[I.15] HILLNER, B.E., et al., The National Oncology PET Registry (NOPR): Design and analysis plan, J. Nucl. Med. **48** (2007) 1901–1908.

[I.16] PAN, T., MAWLAWI, O., PET/CT in radiation oncology, Med. Phys. **35** (2008) 4955–4966.

[I.17] KRUSER, T.J., et al., The impact of hybrid PET/CT scan on overall oncologic management, with a focus on radiotherapy planning: A prospective blind study, Technol. Cancer Res. Treat. **8** (2009) 149–158.
[I.18] THERASSE, P., EISENHAUER, E.A., VERWEIJ, J., RECIST revisited: A review of validation studies on tumour assessment, Eur. J. Cancer **42** (2006) 1031–1039.
[I.19] MOLLER, A.B., HOOGSTRATEN, B., STAQUET, M., WINKLER, A., Reporting results of cancer treatment, Cancer **47** (1981) 207–214.
[I.20] SHANKAR, L.K., et al., Consensus recommendations for the use of ^{18}F-FDG–PET as an indicator of theraoeutic response in patients in National Cancer Institute Trials, J. Nucl. Med. **47** (2006) 1059–1066.
[I.21] WEBER, W.A., Assessing tumour response to therapy, J. Nucl. Med. **50** Suppl 1 (2009) 1–10.
[I.22] MACMANUS, M.P., et al., PET is superior to CT scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small cell lung cancer, J. Clin. Oncol. **21** (2003) 1285–1292.
[I.23] KRAK, N.C., et al., Effects of ROI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial, Eur. J. Nucl. Med. Mol. Imag. **32** (2005) 294–301.
[I.24] JUWEID, M.E., et al., Use of positron emission tomography for response assessment of lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma, J. Clin. Oncol. **25** (2007) 571–578.
[I.25] WEBER, W.W.A., FIGLIN, R., Monitoring cancer treatment with PET/CT: Does it make a difference? J. Nucl. Med. **48** (2007) 36–44.
[I.26] DE GEUS-OEI, L.F., et al., FDG–PET prediction of survival of patients with metastatic colorectal carcinoma, Ann. Oncol. **17** (2006) 1650–1655.
[I.27] BERRIOLO, G., et al., [^{18}F]-FDG–PET predicts complete pathological response of breast cancer to neoadjuvant chemotherapy, Eur. J. Nucl. Med. Mol. Imag. **34** (2007) 1915–1924.
[I.28] KUMAR, R., et al., Oncologic PET tracers beyond [^{18}F]-FDG and the novel quantitative approaches in PET imaging, Q. J. Nucl. Med. Mol. Imag. **52** (2007) 50–65.
[I.29] NANNI, C., CASTELLUCCI, P., FARSAD, M., RUBELLO, D., FANTI, S., [^{11}C/^{18}F]-choline PET or [^{11}C/^{18}F]acetate PET in prostate cancer: May a choice be recommended? Eur. J. Nucl. Med. Mol. Imag. **34** (2007) 1704–1705.
[I.30] GROSU, A.L., et al., Hypoxia imaging with FAZA–PET and theoretical considerations with regard to case painting for individualization of radiotherapy in patients with head and neck cancer, Int. J. Radiat. Oncol. Biol. Phys. **69** (2007) 541–551.
[I.31] NANNI, C., FANTI, S., RUBELLO, D., ^{18}F-DOPA PET and PET/CT, J. Nucl. Med. **48** (2007) 1577–1579.
[I.32] BUCK, A.K., et al., Molecular imaging of proliferation in vivo: Positron emission tomography with ^{18}F fluorothymidine, Methods **48** (2009) 205–215.
[I.33] POPPERL, G., KRETH, F.W., MERHRKENS, J.H., HERMS, J., SEELOS, K., FET–PET for the evaluation of untreated gliomas: Correlation of FET uptake and uptake kinetics with tumour grading, Eur. J. Nucl. Med. Mol. Imag. **34** (2007) 1933–1942.

[I.34] VEES, H., BUCHEGGER, F., ALBRECHT, S., KHAN, H., HUSARIK, D., [^{18}F]-choline and [^{11}C]acetate PET: Detection of residual or progressive subclinical disease at very low PSA values after radical prostatectomy, Br. J. Urol. **99** (2007) 1415–1420.

[I.35] LIU, S., Radiolabeled multimeric cyclic RGD-peptides as integrin alphaVbeta3 targeted radiotracers for tumor imaging, Mol. Pharma **3** (2006) 472–487.

Appendix II

NEUROLOGY

II.1. INTRODUCTION

The recent improvement and advances in SPECT technology, the introduction of new radiotracers, and the generalization of PET have set a new scenario for functional imaging. The role of these techniques is being enhanced by the introduction of new pharmaceutical treatments which demand data about its effect on the functional parameters involved in the particular pathology, in the evolution of the disease, and in the outcome.

With regard to brain imaging studies, it is remarkable that the brain was the first organ to be studied by computed tomography (CT), either emission tomography (SPECT and PET) or CT, as an alternative to the EEG and the invasive techniques only available almost 40 years ago. It did not happen by chance as, in fact, in addition to the clinical need of a technique to meet the non-invasive diagnostic requirement, the lack of movement of the brain and its symmetric morphology provided an artefact-free image that was easy to read. Although the reconstructive techniques were applied first in emission tomography, CT gained rapid clinical acceptance and became very soon of generalized use, PET remaining mostly as a research tool for a long time. In some ways, such general acceptance of CT was due to the impact of the detailed anatomical information provided by the images obtained due to the high resolution of the technique. To a certain extent it was assumed that from high quality images of the normal brain would derive a definitive diagnosis of the brain pathology. The initial potential of the technique evolved to the unchallenged first choice technique for imaging of the brain in the clinical arena until the introduction of MRI. Yet, the functional information provided by PET continued to show great potential and future due the underlying principles of the radiotracer techniques. Further improvements and advances in PET technology, along with more ready availability, led to the technique playing a role in the clinical diagnosis of brain pathology. Therefore, PET is currently the functional imaging technique of choice in some clinical contexts although still lacking the detailed structural information of the whole brain.

The introduction of PET/CT potentially overcomes the PET anatomical limitation, but its outstanding contribution in general oncology was not paralleled in neurology and reports in that sense are still scarce; therefore, most of the available data derive from the PET stand alone contribution.

II.2. PET RADIOTRACERS IN NEUROLOGY

As in nuclear medicine in general, specificity is the most ambitious aim when designing a radiotracer for the study or detection of a particular brain pathology; that means synthesizing a molecule which would incorporate actively and exclusively to the components, mechanisms or functions which characterize such pathology. Normally, this aim is only partially achieved, either because the tracer is not exclusively taken up actively by such pathology but by some other pathology, or because, in any case, there is always the physiological uptake corresponding to the biokinetics of the radiotracer. It can be said that the techniques based on the use of this kind of radiotracers although with those limitations, provide direct or specific information on the pathology being studied so that diagnosis is made by the active uptake of the tracer. Such radiotracers are only available for some pathologies, for example the brain, for the study of dopamine synthesis, amino acid metabolism and others.

Traditionally, the more widely available techniques use radiotracers which incorporate into physiological mechanisms rather than into pathological, so that diagnosis is made by the detection of decreased or increased uptake of the tracer which otherwise is taken up by the normal tissues at a certain rate. Therefore, diagnosis is made by the effect of the pathology on the function of the normal tissue or organ as seen in the final image, i.e. the information provided by the image about the pathology being studied is obtained indirectly. These would be indirect techniques and in the case of PET brain imaging are well represented by FDG–PET.

Therefore, according to the nature of the radiotracers used, the PET techniques in neurology could be classified as direct when the radiotracers incorporate into a specific pathological mechanism, or indirect if incorporates to the physiology. This approach should be applied when considering the current role of PET in the main neurological pathologies.

II.2.1. Degenerative dementias

Among the different causes of cognitive deterioration, the neurodegenerative dementias deserve special attention, not only because of their increasing incidence but also, and as relevant, by the difficulty of providing early diagnosis which would allow an early treatment. Among the four main groups of this kind of dementia, Alzheimer's disease (AD), vascular dementia, dementia with Lewis bodies and fronto-temporal dementia, the first is the most common, accounting for about 60% of the total. This is why the diagnosis of AD is the focus of extensive research so as to allow an early differential diagnosis from the

other causes of dementia due to the limitations of the clinical approach in those settings.

The limitations of the clinical evaluation for the diagnosis of AD at the early stage and for its differential diagnosis from other causes of memory decline including normal ageing are well known [II.1, II.2]. In fact, by the time the clinical diagnosis is made, the disease has fully developed, preventing the implementation of any of the available pharmaceutical treatments. In this sense, the introduction of new treatments based on the use of cholinesterase inhibitors and the positive results achieved to delay the progression of the disease when applied at the early stages, has made early diagnosis crucial for the success of treatment.

The unique contribution of functional imaging and its potential in the diagnosis of AD explains the current efforts in developing new radiotracers for the early diagnosis of a disease which otherwise can only be definitely diagnosed by histopathology of the brain tissue. Most of the work done in this field with nuclear medicine techniques is based on the use of radiotracers which inform on the effect of the pathology on functional parameters like brain perfusion and glucose metabolism, either using SPECT and PET technologies in the first case, or PET in the second. That means the use of non-specific tracers whose distribution can be altered by conditions other than AD, and might just reflect the existing neuronal loss even before anatomical changes are shown by the structural techniques. Nevertheless, the effect caused by AD on both functions has proved to be successful, not only contributing to the diagnosis of AD but also to the more challenging early and differential diagnosis with other conditions. Until recently, in the clinical setting, perfusion imaging was studied with SPECT due to its availability, being replaced currently by FDG-PET as it is increasingly available.

FDG–PET provides images of glucose metabolism by the injection of a glucose analogue molecule, 2-{^{18}F}-fluoro-2-deoxy-D-glucose (FDG) which is the tracer most commonly used for the study of the brain. It is assumed that the glucose metabolic changes in the brain parallel those of the blood flow so that, with certain exceptions, like vascular related pathologies, the perfusion techniques (HMPAO-SPECT or $H_2{}^{15}O$-PET) and the FDG–PET provide similar information [II.3]. On the other hand, FDG–PET has been applied since many years ago for the study of the brain metabolism measuring the glucose metabolism regional rates following the method described by Sokoloff et al. [II.4]. Since then, the technique has spread and is applied routinely in the study of AD.

In AD, the characteristic pattern of FDG corresponds to a hypometabolism of tempoparietal regions and posterior cingulated cortex at the first stages of the disease and also frontal hypometabolisn in the late, remaining normal the

metabolism of cerebellum and basal ganglia. Using this pattern, sensitivity and specificity higher than 93% have been reported when clinically established AD was compared with a control group [II.5]. FDG–PET also was superior to MRI and HMPAO SPECT to differentiate AD from other causes of dementias [II.6, II.7]. However, looking for the success of treatment, more challenging is de identification non-demented patients with some kind of cognitive decline since they are more likely to develop AD later [II.3, II.8].

As the metabolic changes due to normal ageing are minimal, some conditions showing some degree of mild cognitive abilities and functional deterioration ranging from very mild decline in cognition, MCD [II.8] to the known mild cognitive impairment (MCI) have been investigated with FDG-PET as potential predictors of AD. MCI is considered as a condition, which develops between normal ageing and the initial stages of AD although the outcome could be other types of dementia, remain stable or revert to normal.

Early work [II.9] showed the potential of FDG–PET to identify MCI patients who could develop AD later. Further work on MCI patients reported metabolic changes in temporal, parietal and cingulate areas which predict the conversion to probable Alzheimer's disease. Moreover, before MCI is established, a much earlier category has been evaluated with FGD–PET, the MCD [II.8], which would precede MCI in several years in non-dementia patients [II.10, II.11]. Hypometabolism patterns in the posterior cingulate area and the associative cortex have been reported in these patients to predict cognitive decline [II.12, II.13]. Also, some investigators have recently reported decreased metabolism in the hippocampus using co-registered FDG–PET and NMR [II.14], and others [II.15] studied the relationship between the genetic risk factors of AD and glucose metabolism. Thus, Drzezga et al. [II.15] reported that glucose metabolism was lower in AD patients with epsilon4 allele than in those patients without.

The direct techniques based on the use of radiotracers which incorporate into specific physiopathological mechanisms of AD have focused attention and hope for some time as the ideal tracers. The amyloid plaque and the neurofibrillary tangles, which presence allows the post-mortem diagnosis of AD and are involved in the origin of AD, have been for many years the target to be identified in vivo by PET imaging tracers as it precedes by decades the clinical diagnosis. Large experience has been already achieved and many data collected with the ^{11}C-PIB which is a thioflavin T derivative and binds to the β-amyloid plaques. When comparing with a control population, Klunk et al. in an early work [II.16], reported that ^{11}C-PIB uptake was twice as high in associative cortical areas of the brain in AD patients. More recently Edison et al. [II.17] found a relationship between the high ^{11}C-PIB uptake and low of ^{18}F-FDG in addition to an increase of ^{11}C-PIB in 98% of the patients in whom AD was clinically

probable. Also, an inverse relationship of ^{11}C-PIB uptake was found when compared with its concentration in CSF [II.18] and with loss of parenchyma in the parietal lobe and posterior cingulated in NMR.

Working in the same line of research on specific tracers, Barrio et al. [II.19] developed the ^{18}F-FDDNP radiotracer which binds to plaques and tangles. This group demonstrated that uptake of the molecule by temporal, parietal and frontal regions of AD patients was significantly higher than in an aging control population without cognitive decline. They also reported a comparison of ^{18}F-FDDNP and ^{18}F-FDG in 83 subjects classified into EA (23 points), MCI (28 points), and no cognitive decline (30 points). The results showed a significant difference of ^{18}F-FDDNP uptake between the normal and MCI groups, and the MCI and the AD groups ($p<0.001$) with an increasing intensity of the uptake from the normal to AD. They also found that FDDNP separated the groups better than ^{18}F-FDG [II.20]. One obvious advantage for ^{18}F-FDDNP compared with ^{11}C-PIB would be its wide availability for general use as it derives from the longer half-life of ^{18}F compared with ^{11}C.

The approach to AD diagnosis by using this type of specific tracers has led to the investigation of some other tracers which incorporate to different brain functions. The Barrio group also tries to evaluate molecules which bind to serotonine receptors showing that in the hippocampus there is a higher density of receptors AD patients [II.21]. Other groups have published recent experience with probes to study the cholinergic receptors reporting promising but contradictory results [II.39, II.40].

II.2.2. Evaluation of movement disorders

The limitations of the clinical evaluation for the diagnosis of movement disorders of which Parkinson´s disease is the most common, are well known. The diagnosis of PD at the early stage and its differentiation from other diseases which show common clinical features explain why functional imaging, SPECT and PET has focused since many years ago on this area of neurology [II.24–II.26].

The potential of nuclear medicine techniques for the study of movement disorders has been based on the findings in post-mortem studies of the loss of nigra substance neurons and the changes undergone by the nigra-striatal dopamine network. Therefore, the dopamine system attracted the attention of nuclear medicine research to design and develop radiolabelled molecules which could identify the abnormal functioning of the dopamine system and thus, allow an early and differential diagnosis of PD for its better treatment management [II.27].

A new scenario for the role of functional imaging is related with the development of new treatments well represented by the introduction of new pharmaceuticals. From this new framework stems a new application of PET techniques for the monitoring the response to drugs used clinically like, in addition to L-DOPA, dopamine agonists or anticholinergics agents [II.28, II.29]. Some other treatments, like cell transplantation or neuroprotective drugs with potential clinical value might increase further the contribution of functional imaging particularly PET/CT imaging.

^{18}F-DOPA has been applied for many years for the study, diagnosis and assessment of PD. This molecule, by tracing the presynaptic dopamine, shows the highest uptake in the striatum in the normal brain. The mechanism underlying the application of ^{18}F-DOPA is that it targets the synthesis of dopamine in presynaptic neurons with high density targets in the striatum. In the early stages of the disease there is a reduction of the targets, and hence of the synthesis of dopamine with an increasing reduction as the disease progresses. The specific uptake pattern found in PD resembles very accurately the pathological findings showing low uptake in the striatum and within this, much lower in the posterior putamen. This pattern is common to all presynaptic tracers, both for SPECT and PET although targeting different functions [II.30, II.31].

In the clinical context, until recently, functional imaging of the presynaptic functions has been based on the use of dopamine transporter molecules (DAT) which bind to a transporter and displays the transporter density. This tracer is labelled with a single photon emitter, ^{123}I. SPECT technology is applied widely and used extensively clinically in the diagnosis and monitoring of PD [II.32]. However, the increasing use and availability of the PET technique due to its exclusive and relevant role in oncology, also explains the increasing use of ^{18}F-DOPA-PET/CT, as the image quality is superior to that obtained by SPECT despite the improvements of this technique in the last years.

In the above context, in addition to early diagnosis, the introduction and development of new drugs for the treatment of PD will increase the demand for ^{18}F-DOPA-PET/CT for monitoring response. Moreover, the research on the development of new radiotracers which bind to other targets involved in the pathophysiology of PD, like serotonin and nor-epineprine transporters [II.33, II.34], offer new challenges for the clinical application of the technique in the study of PD.

II.2.3. Brain tumours

Imaging of the normal brain and of brain tumours were the first clinical application of PET using ^{18}F-FDG as a radiotracer. Since then, the technological progress of PET equipment has been impressive and, regarding brain tumour

applications the technique moved from the research level to the clinical level it is currently the technique of choice in some specific indications.

According to the normal biokinetics of ^{18}F-FDG, it is taken up avidly by the normal brain parenchyma, especially the grey matter. Although this physiological uptake limits the value of FDG-PET for the detection of small tumours, it provides a good reference for comparison with the tumour uptake.

Very early, Patronas et al. [II.35] demonstrated that FDG–PET provided more accurate information on tumour grade than contrast enhanced CT. They also reported a relationship between the grade of malignancy and the intensity of uptake, based on a qualitative image reading. These qualitative results were much later confirmed by Delbeke et al. [II.36], who tried to determine quantitatively the optimal cut-offs to differentiate between low and high grade brain tumours by FDG–PET. They reported a cut–off of 1.5 for tumour to white matter and 0.6 for tumour to grey matter. These cut-offs resulted in a 94% sensitivity and a 77% specificity for diagnosing a high grade tumour. Also, the prognostic contribution of FDG–PET has been assessed by several groups. Patronas et al. [II.37] also confirmed the results obtained by previous work by Alavi et al. [II.38], showing the relationship between increased uptake and short survival and normal or decreased uptake and long survival.

After treatment, FDG–PET has also proved of great value to evaluate the response. After quimiotherapy it has been reported that a decrease of 15–25% of the uptake after the first cycle corresponds to a partial response while an uptake like the surrounding normal parenchyma would correspond to a complete response [II.39]. However, to be reliable FDG–PET examination must be carried out at least two weeks after the end of quimiotherapy so that false positives due to an early transitory uptake can be avoided [II.40]. In addition, an outstanding indication of the technique is the differentiation between residual tumour and post-radiotheraphy necrosis [II.41, II.42]. Similar results were reported for the differentiation between post-surgical changes and residual tumour [II.43]. Normally, in many of these clinical situations, FDG–PET is applied in the context of a previous NMR which shows areas of abnormal enhancement. In these cases, the need of further differentiation and clarification makes co-registration of both images necessary for an optimum result.

In addition to measuring the glucose metabolism by using FDG for the assessment of brain tumours, other functional parameters of brain function can be applied for more specific information. Among other amino acids, methionine labelled with C-11 has been used for many years because of the increased metabolism of this molecule in brain tumours. Just as relevant, unlike FDG, it is not taken up by inflammatory changes. Several mechanisms are involved in the increase uptake of this amino acid by brain tumours: (1) increased transport; (2) increased protein synthesis; (3) breakdown of the blood brain barrier;

(4) methyl group transfer in lipid synthesis; and (5) methionine is the first amino acid incorporated in the synthesis of all proteins [II.44].The increased uptake of ^{11}C-methionine has been reported as being indicative of high grade malignancy and shortest survival [II.45]. In a recent work, Kato et al. [II.46] investigated whether ^{11}C-methionine could provide evidence of malignant transformation of low grade gliomas in 49 consecutive patients before surgical resection by comparing the uptake with proliferative activity. They found a significant correlation of the uptake and the proliferative activity and concluded that diffuse astrocytomas showing high uptake of ^{11}C-methionine may act more aggressively, and those with lower uptake are more quiescent lesions. For defining tumour margins, methinonine has been demonstrated to be superior to FDG [II.47].

^{11}C-methionine has been also applied for the differentiation of recurrence disease and post-treatment changes. A sensitivity of 80% and a specificity of 100% [II.48] have been reported, although some false positive were also found by other groups [II.49, II.50]. From the large body of experience collected, the combined use of ^{11}C-methionine and ^{18}F-FDG has been demonstrated as the best approach for differentiating recurrence and post-radiotheraphy changes [II.44, II.51] so that a high FDG uptake would confirm a high grade tumour, while a low uptake would be consistent with a low grade tumour, post-therapy changes, infarct, benign lesion and, more rarely, a high grade lesion. According to this protocol, the low FDG uptake group would then be followed by a ^{11}C-methionine-PET to differentiate the low and intermediate grade tumours from the rest of the possible causes associated with such low uptake [II.44].

There are many other tracers which have been or still are investigated as they are involved in some mechanisms of tumour biology. ^{18}F-DOPA, in addition to its role in the study of movement disorders, has been reported to be more accurate than FDG–PET for imaging low grade tumours, for evaluating tumour recurrence, and for distinguishing tumour recurrence from radiation necrosis [II.52]. Thymidine, which in a tritiated form is the gold standard to study cell proliferation in vitro labelled with C-11 allows PET imaging of brain tumours [II.53]. The same metabolic parameter, cell proliferation, is evaluated by PET imaging using a radiotracer of thymidine labelled with ^{18}F (^{18}F-FLT) [II.54]. Other tracers representing different aspects of function and metabolism, such as hypoxia with ^{18}F-MISO, or lipid synthesis with ^{11}C-choline are still under evaluation for its clinical application in the study of brain tumours [II.55, II.56].

II.2.4. Epilepsy

Epilepsy is a disorder that is treated successfully with pharmacological treatment in about 70% of the cases, the rest being potential candidates for resection of the epileptogenic zone. Therefore, localizing such zones before surgery is carried out, and is a requirement so that the patient renders seizure free after surgery

The generally accepted approach to the pre-surgical evaluation after the basic clinical examination and scalp EEG, is to carry out anatomical techniques like CT or NMR as the first imaging modalities to exclude structural abnormalities. Once these were excluded, video EEG, interictal and ictal EEG, ictal and interictal SPECT and interictal FDG–PET are done to find out whether there is one or more epileptic sites and to localize the epiletogenic zone. FDG–PET has been successfully applied and a large body of experience has been published. The FDG metabolic pattern associated with the site of the epileptic focus corresponds to hypometabolism in an interictal FDG–PET. Although FDG–PET is usually assessed visually, the automated analysis using an age matched database for comparison is more reliable [II.57].

In a study evaluating FDG–PET for the localization of the site of seizure onset in a selected population of patients with refractory epilepsy partial epilepsy, 44% sensitivity was reported with a better accuracy for temporal lobe epilepsy [II.58]. This is in accordance with the findings of other authors who reported that between 60 and 90% of such of patient groups show an interictal temporal lobe hypometabolism ipsilateral to the side of the seizure focus [II.59, II.60]. When dealing with extratemporal epilepsy, the hypometabolic pattern was reported in 67% of patients.

Prediction of seizure outcome has been also assessed in depth. Lee et al. [II.58] reported the significant correlation between the lobar localization of the ictal focus and the seizure free surgical outcome either by FDG–PET or the concordance of 2 or more pre-surgical evaluations. Regarding the correlation between the extend of hypometabolism and seizure free outcome, Choi et al. [II.61] confirmed that hypometabolism at the ipsilateral temporal lobe was associated with a much higher seizure free outcome (75%) than when it was extratemporal, but in the ipsilateral cerebral hemisphere (45%) or in the contralateral cortex (20%).

Some other mechanisms of brain function have been evaluated for the radionuclide study of epilepsy, in particular PET imaging. PET radiotracers have been developed to bind the receptors of γ-amino-butyric-acid (GABA) which is the main inhibitory neurotransmitter. Thus, ^{11}C- or ^{18}F-flumazenil were applied clinically with very promising results [II.62]. However, a general drawback of these two tracers is that the flumazenil binding to the GABA receptors can be

interfered by antiepileptic drugs. On the other hand, most of the experience achieved is based on the use of ^{11}C, so that a nearby cyclotron is required due to the short $T_{1/2}$. However, this limitation is overcome by the use of ^{18}F-FMZ [II.63]. In this context, interictal FDG–PET, along with interictal and ictal HMPAO SPECT, remain the techniques of choice in the clinical pre-surgical localization of the epileptic zone.

REFERENCES TO APPENDIX II

[II.1] McDANIEL, L.D., LUKOVITS, T., McDANIEL, K.D., AD: The problem of incorrect diagnosis, J. Geriatr. Psychiatry Neurol. **6** (1993) 230–234.

[II.2] KNOPMAN, D.S., et al., Practice parameter: Diagnosis of dementia (an evidence based evidence). Report of the Quality Standards Subcommitee of the American Academy of Neurology, Neurology **56** (2001) 1143–1153.

[II.3] VAN HEERTUM, R.L., TIKOFSKY, R.S., Positron emission tomography and single-photon emission computed tomography brain imaging in the evaluation of dementia, Sem. Nucl. Med. **XXXIII** 1 (2003) 77–85.

[II.4] SOKOLOFF, L., et al., The [^{14}C] deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure and normal values in the conscious and anesthesized albino rat. J Neurochem 28: 897–916, 1977.

[II.5] HENHOLZ, K., PET studies in dementia, Ann. Nucl. Med. **17** (2003) 79–89.

[II.6] DOBERT, N., et al., Diagnostic value of FDG–PET and HMPAO–SPECT in patients with dementia and mild cognitive impairment: Metabolic index and perfusion index, Dement. Geriatr. Cogn. Disord. **20** (2001) 63–70.

[II.7] MIELKE, R., et al., Direct comparison of spatially normalized PET and SPECT scans in Alzheimer's disease, J. Nucl. Med. **43** (2002) 21–26.

[II.8] SILVERMAN, D., MOSCONI, L., ERCOLI, L., CHEN, W., SMALL, G., Positron emission tomography scans for the evaluation of cognitive dysfunction, Sem. Nucl. Med. **38** (2008) 251–261.

[II.9] DE SANTI, S., et al., Hippocampal formation glucose metabolism and volumen losses in MCI and AD, Neurobiol. Aging **22** (2001) 529–539.

[II.10] SILVERMAN, D.H.S., et al., Positron emission tomography in evaluation of dementia: regional brain metabolism and long term outcome, JAMA **286** (2005) 2120–2127.

[II.11] MINOSHIMA, S., et al., Metabolic reduction in the posterior cingulated cortex in very early Alzheimer's disease, Ann. Neurol. **42** (1997) 85–94.

[II.12] HERHOLZ, K., et al., Impairment of neocortical metabolism predicts progression in Alzheimer's disease, Dement. Geriatr. Cogn. Disord. **10** (1999) 494–504.

[II.13] SILVERMAN, D.H.S., et al., Prognostic value of regional cerebral glucose metabolism in patients undergoing dementia evaluation: Comparison to a quantitative parameter of subsequent cognitive performance and to prognostic assessment without PET, Mol. Genet. Metabol. **80** (2003) 350–355.

[II.14] MOSCONI, M., Metabolic interaction between ApoE genotype and onset age in Alzheimer's disease: Implications for brain reserve, J. Neurol. Neurosurg. Psychiatry **76** (2005) 15–23.

[II.15] DRZEZGA, A., et al., Cerebral glucose metabolism in patients with AD and different ApoE genotypes, Neurology **64** (2005) 102–107.
[II.16] KLUNKK, W.E., ENGLER, L.M., NORDBERG, A., Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound B, Ann. Neurol. **55** (2004) 306–319.
[II.17] EDISON, P., et al., Amyloid hypometabolism and cognition in Alzheimer's disease: [11C]PIB and [18F]FDG–PET study, Neurology **68** (2007) 501–508.
[II.18] ARCHER, H.A., EDISON, P., BROOKS, D.J., Amyloid load and cerebral atrophy in Alzheimer's disease: An 11C-PIB positron emission tomography study, Ann. Neurol. **60** (2006) 145–147.
[II.19] AHOGHI-JADID, K., et al., Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer's disease, Am. J. Geriatr. Psychiatry **10** (2002) 24–35.
[II.20] SMALL, G.W., et al., PET of brain amyloid and tau in mild cognitive impairment, New Eng. J. Med. **355** (2006) 2652–2663.
[II.21] KEPE, V., et al., Serotonin 1ª receptors in the living brain of Alzheimer's disease patients, Proc. Natl Acad. Sci. USA **103** (2006) 702–707
[II.22] JUL, D.E., et al., In vivo mapping of cerebral acetylcholinsterase activity in aging and Alzheimer's disease, Neurology **9** (1999) 9–16
[II.23] KUL D.E., et al., In vivo butyrylcholinsterase. Activity is not increased in Alzheimer's disease synapses, Ann. Neurol. **59** (2006) 13–20
[II.24] BECKER, G., et al., Early diagnosis of Parkinson's disease, J. Neurol. **249** Suppl 3 (2002) III40–III48.)
[II.25] GELDMACHER, D.S. Differential diagnosis of dementia syndromes, Clin. Geriartr. Med. **20** (2004) 27–43.
[II.26] ADLER, C.H., Differential diagnosis of Parkinson's disease, Med. Clin. North Am. **83** (1999) 349–367.
[II.27] SEIBYL, J.P., Imaging studies in movement disorders, Sem. Nucl. Med. **33** (2003) 105–113.
[II.28] TUITE, P., RISS, J., Recent developments in the pharmacological treatment of Parkinson's disease, Expert Opin. Invest. Drugs **12** (2003) 1355.
[II.29] JOHNSTON, T.H., BORTCHIE, J.M., Drugs in development for Parkinson´s disease, Curr. Opinion Invest. Drugs. **5** (2004) 720–726.
[II.30] BRUCKE, T., et al. SPECT and PET imaging of the dopaminergic system in Parkinson's disease, J. Neurol. **247** (2000) IV/2–7.
[II.31] ANTONINI, A., DeNOTARIS, R. PET and SPECT functional imaging in Parkinson´s disease. Sep. Med. **5** (2004) 201–206.
[II.32] SEIBYL, J.P., Single photon emission computed tomography and positron emission tomography evaluations of patients with central motor disorders, Sem. Nucl.Med. **38** (2008) 274–286.
[II.33] GUTTMAN, M., et al., Brain serotonine transporter binding in non-depressed patients with Parkinson's disease, Eur. J. Neurol. **14** (2007) 523–528.
[II.34] SCHOU, M., et al., Synthesis and positron emission tomography evaluation of three norepinephrine transporter radioligands: [C-11]-desipramine, [C-11]-talopram, [C-11]-talsupram, Mol. Imaging Biol. **8**(2006) 1–8.
[II.35] PATRONAS, N.J., et al., Glycolitic rate (PET) and contrast enhancement (CT) in human cerebral gliomas, Am. J. Neuroradiol. **4** (1983) 533–535.

[II.36] DELBEKE, D., et al., Optimal cutoff levels of F-18 fluorodeoxyglucose uptake in the differentiation of low grade from high grade brain tumors with PET, Radiology **195** (1995) 47–52.
[II.37] PATRONAS, N.J., et al., Prediction of survival in glioma patients by means of positron emission tomography, J. Neurosurg. **62** (1985) 816–822.
[II.38] ALAVI, J.B., et al., Positron emission tomography in patients with glioma. A predictor of prognosis, Cancer **62** (2005) 1074–1078.
[II.39] YOUNG, H., et al., Measurement of clinical and subclinical tumour response using ^{18}F-fluorodeoxyglucose and positron emission tomography: Review and 1999 recommendations, EORTC PET study group, Eur. J. Cancer **35** (1999) 1771–17782.
[II.40] ROZENTAL, J.M., LEVINE, R.L., NICKLES, R.J., DOBKIN, J.A., Glucose uptake by gliomas after treatment. A positron emission tomographic study, Arch. Neurol. **46** (1989) 1302–1397.
[II.41] CHAO, S.T., et al., The sensitivity and specificity of FDG in distinguishing recurrent brain tumour from radionecrosis in patients with stereotactic radiosurgery, Int. J. Cancer **96** (2003) 191–197.
[II.42] DI CHIRO, G., et al., Cerebral necrosis after radiotherapy and/or intra-arterial chimiotherapy for brain tumors: PET and neuropathological studies, Am. J. Roentgenol. **150** (2001) 189–197.
[II.43] HANSON, M.W., et al., FDG PET in the early postoperative evaluation of patients with brain tumor, **17** (1990) 509–561.
[II.44] FIRSCHMAN, A.J., PET imaging of brain tumors, Cancer Treat. Res. **143** (2008) 67–92.
[II.45] DE WITTE, O., et al., Positron emission tomography with injection of methionine as a prognostic factor in glioma, J. Neurosurg. **95** (2002) 746–750.
[II.46] KATO, T., et al., Analysis of 11C-methionine uptake in low grade gliomas and correlation with proliferative activity, Am. J. Neuroradiol. (2008).
[II.47] ERICKSON, K., et al., Positron emision tomography with ^{11}C-methionine, ^{18}F-glucose, and ^{68}Ga-EDTA in supratentorial tumors, J. Comput. Assist. Tomography **9** 683–689.
[II.48] TSUYUGUCHI, N., et al., Methionine positron emission tomography of recurrent metastatic brain tumor and radiation necrosis after stereotactic radiosurgery: Is a differential diagnosis possible? J. Neurosurg. **98** 1056–1064.
[II.49] DETHY, S., et al., Carbon-11-methionine and fluorine-18-FDG PET study in brain hematoma, J. Nucl. Med. **35 (1994)** 1162–1166.
[II.50] CONTI, P.S., Introduction to brain imaging tumor metabolism with positron emission tomography (PET), Cancer Invest. **13** (1995) 244–259.
[II.51] HUSTINGS, R., POURDEHAND, M., KASCHTEN, B., ALAVI, A., PET imaging from differentiating recurrent brain tumour from radiation necrosis, Radiol. Clin. North Am. **43** (2005) 35–47.
[II.52] CHEN, W., et al., ^{18}F-DOPA PET imaging of brain tumours: Comparison with FDG PET and evaluation of diagnostic accuracy, J. Nucl. Med. **47** 904–911.
[II.53] EARY, J.F., et al., 2-[C-11]-thymidine imaging of malignant tumours, Cancer Res. **59** 615–621.
[II.54] CHEN, W., et al., Imaging proliferation in brain tumours with ^{18}F-FLT PET: Comparison with ^{18}FDG, J. Nucl. Med. **46** (2005) 945–952.

[II.55] DE GRADO, T.R., et al., Synthesis and evaluation of ^{18}F-labeled choline analogs as oncologic PET tracers, J. Nucl. Med. **42** (2001) 1805–1814.
[II.56] DUBOIS, L., et al., Evaluation of hypoxia in an experimental rat tumor model by ^{18}F-fluoromisonidazole PET and inmunohistochemistry, Br. J. Cancer **91** (2004) 1947–1954.
[II.57] LIN, T.W., et al., Predicting seizure free status for temporal lobe epilepsy patients undergoing surgery: Prognostic value of quantifying maximal metabolic asymmetry extending over a specified proportion of the temporal lobe, J. Nucl. Med. **48** (2007) 776–782.
[II.58] LEE, S.K., et al., Surgical outcome and prognostic factors of cryptogenic neocortical epilepsy, Ann. Neurol. **58** (2005) 525–532.
[II.59] DRZEZGA, A., et al., ^{18}F-FDG PET studies in patients with extratemporal and temporal epilepsy: Evaluation of an observer-independent analysis, J. Nucl. Med. **40** (1999) 737–746.
[II.60] CASSE, R., et al., Positron emission tomography and epilepsy, Mol. Imaging Biol. **4** (2002) 338–351.
[II.61] CHOI, J.Y., et al., Extratemporal hypometabolism on FDG PET in temporal lobe epilepsy as a predictor of seizure outcome after temporal lobe lobectomy, Eur. J. Nucl. Med. Mol. Imaging **30** (2003) 581–587.
[II.62] HAMMERS, A., et al., Grey and white matter flumazenil binding in neocortical epilepsy with normal MRI. A PET study of 44 patients, Brain **126** (2003) 1300–1318.
[II.63] CHANG, Y.S., et al., Biological properties of 2[^{18}F] fluoroflumazenil for central benzodiazepine receptor imaging, Nucl. Med. Biol. **32** (2005) 263–268.

Appendix III

CARDIOLOGY

III.1. INTRODUCTION

Coronary artery disease (CAD) is the main cause of death in the developed world and is rapidly becoming such in the developing one. In the last three decades, imaging of CAD has been successfully performed through, myocardial perfusion imaging (MPI) which has become the non-invasive diagnostic test most often applied in the USA, its success being based on the functional characterization of CAD after Gould et al. first described the importance of coronary flow reserve measurements in the clinical evaluation of CAD in the 1970s [III.1]. In the 1980s, the introduction of SPECT made it possible to assess quantitatively the extent and severity of perfusion abnormalities [III.2]. PET has also been developed as a clinical imaging tool for the quantitative assessment of myocardial perfusion and for the characterization of tissue viability in patients with advanced CAD, because of its high sensitivity, homogeneous spatial resolution, and potential for quantitation of tissue tracer concentration. The most recent technical innovation, which has been available for only the last few years, is the integration of PET and CT systems. These dual modality systems offer an advantage over dedicated PET in that they can concurrently provide both metabolic and structural or anatomical images that are automatically fused and overcome some limitations of dedicated PET. Because PET is currently experiencing rapid growth as an imaging modality in oncology, the availability of PET instrumentation in many imaging departments is opening new opportunities for its application to cardiology. Hybrid PET/CT scanners, the current standard of PET imaging, are now increasingly available with high end CT systems that are capable of high resolution cardiac imaging. Those enable a routine combined assessment of anatomy and function/biology, which will increase acceptance of PET among morphology oriented clinical cardiologists. Emerging issues, such as microvascular disease, which precedes the development of overt clinical CAD and represents a prognostic factor in many cardiac pathologies, have been brought up based on PET and its unique strength to measure myocardial perfusion in absolute terms.

A rising concern is the radiation exposure of patients undergoing PET/CT scans. Indeed, radiation exposure from a PET/CT study is the sum of the effective dose from the incorporated radiotracer and the dose from external X ray irradiation during the selected CT acquisition protocol. For a 370 MBq ^{18}F-FDG injection, the effective dose is 7 mSv. For rest–stress ^{13}N-ammonia

(2 × 550 MBq) or ^{82}Rb (2 × 1500 MBq), the effective doses are 2.2 mSv and 5.0 mSv, respectively [III.3, III.4]. The effective dose per CT examination depends on the acquisition parameters chosen (kV, mAs) and the body region being scanned. Measurements of radiation exposure in oncologic whole body ^{18}F-FDG PET/CT examinations showed an effective dose of 14–18 mSv from the contrast enhanced diagnostic CT scan covering the whole body. Reducing radiation exposure by limiting the axial field of view or changing the CT tube current according to anatomy has been proposed to reduce radiation exposure by up to 30–40% [III.5].

III.2. CLINICAL CARDIAC PET TRACERS

III.2.1. Myocardial perfusion

Basically, there are three main tracers suitable for myocardial perfusion imaging with PET. One is $^{13}NH_3$ with a first pass extraction of 80% and linear uptake over a wide range of myocardial blood flow except at very high flow rates. Imaging with $^{13}NH_3$ requires either an on-site cyclotron or proximity to a regional positron radiopharmaceutical source centre. Images are of high quality and resolution. A second tracer is ^{82}Rb, a potassium analogue that has a first-pass extraction of 65% and requires active transport via Na/K-ATPase, which is dependent on coronary flow. Also, with ^{82}Rb, the extraction fraction decreases in a nonlinear manner with increasing blood flow, and this effect is more pronounced when compared to ammonia, although still superior when compared to ^{99m}Tc labelled SPECT compounds [III.6, III.7]. An advantage of ^{82}Rb over $^{13}NH_3$ is that it is produced by a ^{82}Sr/^{82}Rb generator without the need for a costly cyclotron. In the USA, ^{82}Rb is the most frequently employed cardiac PET tracer and has experienced exponential growth in recent years.

III.2.1.1. Myocardial viability

^{18}F-2-deoxy-2-fluoro-D-glucose (^{18}F-FDG) is widely available due to its success as a metabolic imaging tracer in clinical oncology. It is known for decades that the tracer is of high value to determine myocardial glucose utilization as an indicator of myocardial viability. Increased ^{18}F-FDG uptake can be observed in ischaemic tissue, whereas markedly reduced or absent uptake indicates scar formation. ^{18}F-FDG uptake is heterogeneous in normal myocardium in the fasting state and, therefore, oral glucose loading, nicotinic acid derivatives, or infusion of insulin and glucose have been used to enhance myocardial ^{18}F-FDG uptake [III.8]. Images obtained in non-diabetic patients and

in patients with non-insulin-dependent diabetes, after insulin infusion, are of higher quality than those obtained after oral glucose loading [III.9]. Also, bolus injections of insulin have been suggested as possible alternatives and when such protocols for patient preparation are being followed, cardiac ^{18}F-FDG is generally of high diagnostic quality [III.10].

III.2.2. Clinical applications

III.2.2.1. Diagnosis of CAD

With the changing pathophysiological understanding about CAD, it is becoming increasingly difficult to define the gold standard for disease detection. Conventionally, the presence of 50–75% coronary stenosis is considered indicative of obstructive CAD. However, evidence is increasing that although the degree of stenosis may be related to the presence or absence of symptoms, the prognosis of patients cannot be predicted on the basis of angiographic criteria [III.11]. A study has shown that a large subset of patients with acute myocardial infarction has coronary culprit lesions of less than 50% narrowing, limiting the use of the degree of stenosis as a predictor for acute ischaemic syndromes [III.12].

A consensus exists that indications for revascularization in patients with stable coronary disease should be based on evidence of myocardial ischaemia [III.13]. In symptomatic and asymptomatic patients with CAD, a large body of data indicates that the prognosis depends on the extent and severity of perfusion abnormalities during stress interventions. On the other hand, in non-invasive tests such as MPI, the demonstration of normal results during maximal physical or pharmacological stress is associated with a very low risk of cardiovascular complications [III.14].

Therefore, the therapeutic management of patients with known CAD is based on functional characterization of the disease process. The combination of scintigraphic measurement of perfusion and CT depiction of coronary morphology may increase the accuracy of linking functional and morphologic data. This combination is expected to decrease the need for diagnostic cardiac catheterization and prove to be the method of choice for selecting patients for therapeutic intervention.

III.2.2.2. Non-invasive coronary angiography by CT angiography

A large number of studies have recently been published demonstrating the increasing accuracy of multislice-CT angiography for the detection of CAD. With the availability of 16 and 64 slice scanners, the sensitivity and specificity for detection of significant coronary artery stenosis are exceeding 90%

[III.15–III.17]. Most studies were a single centre evaluation and involved patient populations with a high prevalence of CAD. Further prospective multicentre studies are needed to confirm the high diagnostic value of multislice CT imaging for the detection of CAD [III.18]. Multislice CT technology is expected to stabilize, resulting in longer product cycles and thus allowing for more in-depth validation of this technology. However, there is little question that non-invasive coronary angiography will become a clinical reality, changing the workup of patients suspected of having obstructive CAD and the follow-up after surgical and percutaneous revascularization [III.19]. A drawback of CT angiography is its limited ability to correctly assess regional coronary stenosis in the presence of severe coronary calcification [III.20]. Again, the use of MPI at the time of CT angiography may help to reduce the number of false positive results, because normal perfusion reserve in segments distal to a coronary calcification may rule out a high grade lesion [III.21].

III.2.2.3. Identifying plaque burden

Coronary calcification is one of the first biomarkers identifying atherosclerotic coronary lesions. However, several studies indicate that even in the absence of coronary calcification, plaques can be detected by CT, MRI, or ultrasound measurements [III.22–III.24]. A recent study comparing CT with intravascular ultrasound revealed a 19% incidence of noncalcified lesions. With the advent of molecular imaging, there may be an opportunity to enhance contrast in plaque imaging by combining scintigraphic data with CT characterization of individual plaques [III.25]. Those data suggest that it may be possible to identify the inflammatory component of atherosclerotic plaques in vivo, thereby allowing the biologic activity within plaques to be studied. However, ^{18}F-FDG represents a relatively non-specific marker for molecular processes. New radiopharmaceuticals that target the extracellular matrix proteinases or proteins that are upregulated during the inflammatory process may be of interest [III.26, III.27]. There is no question that PET/CT images will improve the evaluation of molecular signals, because targeted tracer signals require anatomical information. Future studies will have to show, however, whether PET/CT can show biological signals in the beating heart and provide incremental prognostic information.

III.2.2.4. Assessment of heart failure

The results of multicentre trials on patients with heart failure indicate that up to 50% of patients with impaired left ventricular function have CAD [III.28]. Because the treatment strategies for patients with CAD are different from those

for patients with primary myocardial disease, such as dilated cardiomyopathy, accurate differentiation of ischaemic and nonischaemic heart disease is important. Again, with the advent of non-invasive coronary angiography by CT, the combination of PET and CT may help not only to separate patients with and without CAD, but also to define the extent of reversible and irreversible ventricular dysfunction based on metabolic evaluation of the left ventricular myocardium. There are relatively few data available demonstrating the accuracy of CT angiography in patients with impaired left ventricular function. The quality of the contrast bolus in patients with low cardiac output may impair image quality. However, because of the reduced cardiac function, motion artifacts may be less prevalent in this population. Therefore, the newer generation of multislice CT scanners is expected to make possible the accurate detection of CAD in patients with impaired left ventricular function.

PET has been validated extensively in the assessment of tissue viability using the combination of metabolic imaging with ^{18}F-FDG and evaluation of myocardial blood flow. The extent of tissue viability predicts recovery of left ventricular function after revascularization [III-29]. Based on coronary angiographic data provided by CT angiography and by the assessment of tissue viability, a non-invasive diagnostic workup may be possible. This possibility may be especially important for patients being considered for cardiac transplantation, when information about the viability of residual tissue and the extent of CAD, as defined by CT angiography, helps with the decision making process. The presence of a mismatch between flow and metabolism is of high prognostic value [III-30]. Several studies have indicated that the presence of metabolic activity in segments with severe dysfunction is associated with higher risk if these segments are not revascularized [III.31]. A study has also shown that residual viability in dysfunctional myocardium is associated with less perioperative risk from the revascularization [III.32]. Therefore, the combination of PET/CT in patients with severe left ventricular dysfunction may improve the diagnostic process and help avoid unnecessary invasive procedures.

This comprehensive cardiac evaluation with PET/CT includes not only the CT angiography data and the myocardial tissue characterization, but also the assessment of regional function through left ventricular ejection fraction [III.33]. Therefore, with a single, non-invasive imaging procedure, the extent and severity of left ventricular dysfunction, the extent of tissue viability, and the overall extent of CAD can be characterized and used to risk stratify the patient.

REFERENCES TO APPENDIX III

[III.1] GOULD, K.L., SCHELBERT, H.R., PHELPS, M.E., HOFFMANN, E.J., Noninvasive assessment of coronary stenoses with myocardial perfusion imaging during pharmacologic coronary vasodilatation. V. Detection of 47 percent diameter coronary stenosis with intravenous nitrogen-13 ammonia and emission-computed tomography in intact dogs, Am. J. Cardiol. **43** (1979) 200–208.

[III.2] SCHWAIGER, M., MELIN, J., Cardiological applications of nuclear medicine, Lancet **354** (1999) 661– 666.

[III.3] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Annals of the ICRP, Publication 80, ICRP, Pergamon Press, London (1998).

[III.4] BRIX, G., et al., Radiation exposure of patients undergoing whole-body dual-modality ^{18}F-FDG PET/CT examinations, J. Nucl. Med. **46** (2005) 608–613.

[III.5] KALENDER, W.A., WOLF, H., SUESS, C., Dose reduction in CT by anatomically adapted tube current modulation. II. Phantom measurements, Med. Phys. **26** (1999) 2248–2253.

[III.6] SELWYN, A.P., et al., Relation between regional myocardial uptake of rubidium-82 and perfusion: absolute reduction of cation uptake in ischemia, Am. J. Cardiol. **50** (1982) 112–21.

[III.7] GOLDSTEIN, R.A., et al., Myocardial perfusion with rubidium-82. II. Effects of metabolic and pharmacologic interventions, J. Nucl. Med. **24** (1983) 907–15.

[III.8] KNUUTI, J., SSCHELBERT, H.R., BAX, J.J., The need for standardisation of cardiac FDG PET imaging in the evaluation of myocardial viability in patients with chronic ischaemic left ventricular dysfunction, Eur. J. Nucl. Med. Mol. Imag. **29** (2002) 1257–66.

[III.9] KNUUTI, M.J., et al., Euglycemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography, J. Nucl. Med. **33** (1992) 1255–62.

[III.10] BACHARACH, S.L., et al., PET myocardial glucose metabolism and perfusion imaging: Part 1—Guidelines for data acquisition and patient preparation, J. Nucl. Cardiol. **10** (2003) 543–56.

[III.11] HACHAMOVITCH, R., HAYES, S.W., FRIEDMAN, J.D., COHEN, I., BERMAN, D.S., Stress myocardial perfusion single-photon emission computed tomography is clinically effective and cost effective in risk stratification of patients with a high likelihood of coronary artery disease (CAD) but no known CAD, J. Am. Coll. Cardiol. **43** (2004) 200–208.

[III.12] LIBBY, P. Current concepts of the pathogenesis of the acute coronary syndromes, Circulation **104** (2001) 365–372.

[III.13] SMITH, Jr., S.C., et al., ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines): Executive summary of the American College of Cardiology/American Heart Association task force on practice guidelines, Circulation **103** (2001) 3019–3041.

[III.14] ISKANDRIAN, A.S., et al., Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease, J. Am. Coll. Cardiol. **22** (1993) 665– 670.

[III.15] PANNU, H.K., FLOHR, T.G., CORL, F.M., FISHMAN, E.K. Current concepts in multi-detector row CT evaluation of the coronary arteries: Principles, techniques, and anatomy, Radiographics **23** (Suppl.) (2003) S111–S125.
[III.16] CHOI, H.S., et al., Pitfalls, artifacts, and remedies in multidetector row CT coronary angiography, Radiographics **24** (2004) 787–800.
[III.17] LAU, G.T., et al., Coronary artery stenoses: Detection with calcium scoring, CT angiography, and both methods combined, Radiology **235** (2005) 415– 422.
[III.18] ACHENBACH, S., DANIEL, W.G., Computed tomography of the coronary arteries: More than meets the (angiographic) eye, J. Am. Coll. Cardiol. **46** (2005) 155–157.
[III.19] CHIURLIA, E., MENOZZI, M., RATTI, C., ROMAGNOLI, R., MODENA, M.G., Follow-up of coronary artery bypass graft patency by multislice computed tomography, Am. J. Cardiol. **95** (2005) 1094–1097.
[III.20] LESCHKA, S., et al., Accuracy of MSCT coronary angiography with 64-slice technology: First experience, Eur. Heart J. **26** (2005) 1482–1487.
[III.21] BERMAN, D.S., et al., Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography, J. Am. Coll. Cardiol. **44** (2004) 923–930.
[III.22] ACHENBACH, S., et al., Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound, Circulation **109** (2004) 14–17.
[III.23] RUTT, C.D., COLEMAN, K.J., Examining the relationships among built environment, physical activity, and body mass index in El Paso, TX, Prev. Med. **40** (2005) 831–841.
[III.24] PATEL, N.A., STAMPER, D.L., BREZINSKI, M.E., Review of the ability of optical coherence tomography to characterize plaque, including a comparison with intravascular ultrasound, Cardiovasc. Intervent. Radiol. **28** (2005) 1–9.
[III.25] RUDD, J.H., et al., Imaging atherosclerotic plaque inflammation with [^{18}F]-fluorodeoxyglucose positron emission tomography, Circulation **105** (2002) 2708–2711.
[III.26] SCHAFERS, M., et al., Myocardial presynaptic and postsynaptic autonomic dysfunction in hypertrophic cardiomyopathy, Circ. Res. **82** (1998) 57– 62.
[III.27] STRAUSS, H.W., GREWAL, R.K., PANDIT-TASKAR, N., Molecular imaging in nuclear cardiology, Sem. Nucl. Med. **34** (2004) 47–55.
[III.28] PICCINI, J.P., KLEIN, L., GHEORGHIADE, M., BONOW, R.O., New insights into diastolic heart failure: Role of diabetes mellitus, Am. J. Med. **116** Suppl. 5A (2004) 64S–75S.
[III.29] DI CARLI, M.F., et al., Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy, Circulation **92** (1995) 3436–3444.
[III.30] DI CARLI, M.F., et al., Long-term survival of patients with coronary artery disease and left ventricular dysfunction: implications for the role of myocardial viability assessment in management decisions, J. Thorac. Cardiovasc. Surg. **116** (1998) 997–1004.

[III.31] EITZMAN, D., et al., Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography, J. Am. Coll. Cardiol. **20** (1992) 559–565.
[III.32] HAAS, F., et al., Preoperative positron emission tomographic viability assessment and perioperative and postoperative risk in patients with advanced ischemic heart disease, J. Am. Coll. Cardiol. **30** (1997) 1693–1700.

Appendix IV

INFLAMMATION, INFECTION AND OTHER PET/CT APPLICATIONS

IV.1. INTRODUCTION

The term inflammation represents a non-specific immune response which can be provoked by a sterile stimulate such as post-surgical healing, tissue reaction to foreign bodies like endoprostheses, or modified cancer cells. Autoimmune diseases constitute a special subgroup of sterile inflammation. In these cases, an inflammation is provoked by the formation of antibodies to antigens present on the surface of tissue cells. They comprise a heterogeneous group of conditions that include: rheumatoid arthritis, inflammatory bowel disease, vasculitis and systemic connective tissue diseases like systemic lupus erythematosus. The most common cause of inflammation is infection caused by microorganisms. Some infections, such as pneumonia, may be naturally acquired. Others may occur as a result of complications following surgery.

Imaging plays an important role in detecting and evaluating suspected infections. CT and MRI both provide excellent spatial resolution and help in diagnosis and planning surgery or other interventions. Standard anatomical modalities are sometimes ineffective in accurate assessment of disease activity, especially when the anatomical structure or the sites of suspected infection are distorted by previous surgery, scar tissue or the presence of an orthopaedic prosthesis. Some diseases are coupled with no or minimal anatomical changes (vasculitis), some pathological foci can mimic normal structure, resulting in false negativity of anatomical modalities. In these settings, functional or metabolic imaging plays a complementary role.

Although FDG–PET/CT has been used successfully in the evaluation of a variety of malignant disorders, FDG is not a tumour specific radiotracer. Increased accumulation of FDG has been demonstrated in sites of inflammation or infection. This presents an issue in the evaluation of patients with solitary pulmonary nodules. A positive finding may represent malignancy, but granulomatous inflammations such as tuberculosis or brucellosis can also be present. In cancer patients with complications following surgery, FDG–PET/CT alone is unable to differentiate between infection or inflammation at the operative site and recurrent tumor.

Fever of unknown origin (FUO) represents a clinical condition that can be addressed by FDG–PET/CT with success. FDG–PET/CT can localize the source of FUO in inflammatory connective tissue disease, vasculitis, systemic lupus

erythematosis, inflammatory bowel disease, neoplasm, infected pseudoaneurysm or non-diagnosed AIDS or syphilis [IV.1].

FDG–PET/CT can be used for the diagnosis of infection of vascular or joint prosthesis, as well as of the stabilization of vertebral column, or for confirmation of clinical suspection of spondylodiscitis.

FDG–PET/CT is an effective imaging modality in the assessment of patients with a variety of infectious and inflammatory processes. The non-specific nature of the tracer remains a limitation. Since the majority of patients are referred when all other diagnostic options are exhausted, the interpreting physician is obligated to indicate any possible source of fever which increases the number of false positive findings. This results in high sensitivity at the expense of specificity. Although FDG–PET/CT is not able to specifically identify the underlying disease state, it can aid the clinician in choosing the next round of targeted, confirmatory tests.

In conclusion, FDG–PET and PET/CT represent a sensitive diagnostic tool which may be helpful in the evaluation of patients with suspected inflammation or infection when other modalities have failed. We need to keep in mind the limitations of spatial resolution, the inability to evaluate areas with high physiological background levels of FDG and the overall lack of specificity. FDG–PET and PET/CT may have the potential to replace other nuclear medicine procedures such as gallium imaging or labelled white blood cells. Because FDG–PET and PET/CT imaging does not require handling of blood products and provides ‘same day’ results, the benefits may outweigh the higher procedural cost in selected patients.

Other clinical applications of PET/CT apart from oncology, neurology, cardiology and infection/inflammation imaging are extremely rare and wait for clinical evaluation. An example of one promising application of PET/CT using fluoride might be assessment of bone and joint benign pathologies [IV.2].

REFERENCES TO APPENDIX IV

[IV.1] JARUSKOVA, M., BELOHLAVEK, O., Role of FDG-PET and PET/CT in the diagnosis of prolonged febrile states, Eur. J. Nucl. Med. Mol. Imag. **33** 8 (2006) 913–918.

[IV.2] GRANT, F.D., et al., SKELETAL PET with ^{18}F-fluoride: Applying new technology to an old tracer, J. Nucl. Med. **49** 1 (2008) 68–78.

Appendix V

PRODUCTION NEEDS

V.1. DEFINITION OF THE POPULATION OF INTEREST

Once the epidemiology data have been collected and approved indications have been selected, it is possible to define the population of interest for the clinical application of PET in oncology.

The first step is an overall estimate of the number of people in a population (*limit population*) for whom the use of a particular test (PET in our case) would be deemed appropriate, given the number of inhabitants in a region, the total prevalence of all types of cancer and the indications approved. This estimate is given by:

$$P_{\text{lim}} = P_T \cdot p \cdot f_a$$

where P_T is the total number of inhabitants (of both sexes) in the region, p is the prevalence for all types of cancer (averaged on both sexes), and f_a is the fraction of all oncological applications for which it is recognized that use of PET is appropriate, at least in a certain phase of the natural history of the disease.

Consider an example in which the calculation is performed for a population of 1 000 000 inhabitants, and assume that the total prevalence of all types of cancers is (on average among sexes) 2.2 %. This means that a total of 22 000 patients are living with cancer at some level of stage and treatment in that region.

On the basis of prevalence data for each type of tumour and of the accepted indications, it is possible to evaluate the fraction for which appropriateness is recognized. Consider that appropriate indications are lung cancer, colorectal cancer and Hodgkin and non-Hodgkin lymphomas, and that these pathologies account for 25 % of all tumours.

The limit population will then be:

$$P_{\text{lim}} = 22000 \times 0.25 = 5500 \text{ cases}$$

It should be clear that this limit population represents the ensemble of patients including all those eligible for a PET scan, but it is not yet the actual number of scans that will be potentially necessary.

Note that not all patients bearing a clinical condition for which PET scanning could be indicated will actually need it. Indeed, sufficient diagnostic information could be obtained using conventional imaging. Also, referral may be conditioned by external factors such as the availability of PET or the confidence of referring physicians on the value of the technique. Specific clinical conditions may also require referring physicians to take decisions which may differ from accepted Guidelines and/or recommendations.

V.2. EVALUATION OF THE EXPECTED NUMBER OF PET SCANS PER YEAR

Several approaches to estimating the number of PET scan requests expected from a designated population have been published. For example, an accurate clinical algorithm has been developed for the most relevant indication, the classification of solitary pulmonary nodules, staging and evaluation of recurrence of lung cancer [V.1]. After estimating the needs in lung cancer, they extrapolate to the needs for all types of cancer, based on the ratio of the workload observed for lung cancer relative to other indications in their PET centre.

This approach has limitations, being based on the workload statistics of a single PET centre in a given country; its strength is that it is not based merely on a theoretical evaluation of the expectations, but on a sound practical experience, even if relative to the first years of this decade and to the relatively limited spectrum of indications approved at that time.

Another interesting approach has been developed by the Regional Health Authority and monitored in the Emilia Romagna Region (Italy); in this region, an assessment of appropriateness and an estimate of the technological needs have been continuously re-evaluated using a consistent approach.

Local data for complete prevalence have been collected, and stratified prevalence data for the main tumours (broad ICD-9 codes) have been evaluated on the basis of limited time prevalence (at five years) gathered from the GLOBOCAN project.

The minimum and maximum number of PET scans expected per year was estimated, as from Eqs (V.1) and (V.2):

$$N_{S\min} = \sum_j P_{Mj} \cdot I_{aj} \cdot w_{\min j} + \sum_j P_{Fj} \cdot I_{aj} \cdot w_{\min j} \quad \text{(V.1)}$$

$$N_{S\max} = \sum_j P_{Mj} \cdot I_{aj} \cdot w_{\max j} + \sum_j P_{Fj} \cdot I_{aj} \cdot w_{\max j} \quad \text{(V.2)}$$

where P_{Mj} and P_{Fj} are the complete prevalence (number of living people with the tumour) for males and females of all ages for tumour j; I_{aj} is an index whose value is set = 1 if a given indication is recognized for tumour j, and 0 otherwise; $w_{min\,j}$ and $w_{max\,j}$ are weighting factors, whose values are assigned as follows.

A panel of professionals (nuclear medicine physicians, oncologists, surgeons, haematologists, biostatisticians, …) reviewed the scientific literature to assess appropriate indications; at the same time, panel members were asked to express their opinion on the minimum and maximum percentage of patients affected by neoplasms, grouped in each of the broad ICD-9 codes, that would be referred for a PET scan during the natural history of their disease, as summarized in Table V.1.

This approach is thus based on 'weighting' current and future trends of the clinical use of PET by professionals well informed about the technique and HTA issues.

The panel reported that the likelihood of a PET scan request was from $w_{min\,j} = 0.3$ to $w_{max\,j} = 0.6$ in patients affected by lung cancer (ICD-9 codes 162.0 – 162.9), and from $w_{min\,j} = 0.05$ to $w_{max\,j} = 0.2$ in patients with colorectal cancer (ICD-9 153.0–154.0, 159.0).

This weighting produces a relatively high degree of variability for each type of tumour; nevertheless, on average consistent evaluations are formulated.

The average number of PET scans expected per year is then simply obtained as the arithmetic mean of N_{Smin} and N_{Smax}.

These indications are based on valuable experience in the field, and have been updated over time, as the approved indications of PET increase. They have also been compared with the effective workload of PET centres whose adherence to approved indications has been audited.

V.3. AN EXAMPLE OF A CALCULATION

Consider a population of four million inhabitants, 48.5% males, 51.5% females, with prevalence for all types of cancer of approximately 2.50% for males and 2.45% for females. The distribution of prevalence for the most common types of tumours is reported in Table V.2.

TABLE V.1. MINIMUM AND MAXIMUM PERCENTAGE OF PATIENTS AFFECTED BY NEOPLASMS, GROUPED IN EACH OF THE BROAD ICD-9 CODES, LIKELY TO BE REFERRED FOR A PET SCAN DURING THE NATURAL HISTORY OF THEIR DISEASE

CANCER SITE	Appropriateness index	Minimum weighting factor	Maximum weighting factor
	I_{aj}	$w_{min\ j}$	$w_{max\ j}$
Oral cavity	1	0.01	0.1
Nasopharynx	1	0.1	0.2
Other pharynx	1	0.1	0.2
Oesophagus	1	0.1	0.3
Stomach	1	0.01	0.1
Colon and rectum	1	0.1	0.3
Liver	0	0	0
Pancreas	1	0.01	0.05
Larynx	1	0.1	0.2
Lung	1	0.5	0.8
Melanoma of skin	1	0.1	0.2
Prostate	1	0.01	0.05
Testis	1	0.05	0.2
Breast	1	0.05	0.15
Cervix uteri	1	0.05	0.15
Corpus uteri	1	0.05	0.1
Ovary, etc.	1	0.1	0.2
Kidney, etc.	0	0	0
Bladder	1	0.01	0.05
Brain, nervous system	1	0.01	0.05
Thyroid	1	0.01	0.03
Non-Hodgkin lymphoma	1	0.8	1
Hodgkin lymphoma	1	0.8	1
Multiple myeloma	1	0.1	0.2
Leukaemia	0	0	0

TABLE V.2. PREVALENCE FOR THE MOST COMMON TYPES OF TUMOURS

CANCER SITE	Prevalence M	Prevalence F
	complete	complete
Oral cavity	1137	451
Nasopharynx	137	72
Other pharynx	521	90
Oesophagus	259	74
Stomach	2043	1545
Colon and rectum	7392	6438
Liver	896	399
Pancreas	297	300
Larynx	2276	160
Lung	4183	994
Melanoma of skin	1491	1540
Prostate	9787	0
Testis	479	0
Breast	0	20380
Cervix uteri	0	1653
Corpus uteri	0	3671
Ovary, etc.	0	1596
Kidney, etc.	2234	1095
Bladder	7056	1444
Brain, nervous system	403	301
Thyroid	316	1344
Non-Hodgkin lymphoma	2173	1819
Hodgkin lymphoma	309	282
Multiple myeloma	717	705
Leukaemia	1309	931
All sites but non-melanoma skin	48463	50385

The total prevalence within the population is thus approximately 93 000 cases. Therefore, given the data in the tables, the equations cited and:

— Considering the prevalence for each sex;
— The appropriateness index and the minimum or maximum weighting factor;
— Finally summing over all types of tumour

it is possible to obtain the following results, for example using a spreadsheet, as shown in Table V.3.

Note that the above is just an example and does not make reference to any specific country or geographical area. Local data or estimates should be used for the prevalence; judgments on the appropriateness of the indications and weighting factors should be based on evidence from updated scientific evidence and knowledge of the local health care system.

V.4. EVALUATION OF THE NUMBER OF PET SCANNERS

Once an estimate of the expected number of PET scans per year has been made, it is possible to address the issue of the number of PET (or PET/CT) scanners required. The determination of the number of scanners required should be based on the estimated average throughput per scanner, rather than maximum possible values.

Forecasts of the yearly workload based on an assumption of 250 working days per year, with the maximum number of scans performed every working day, and neglecting downtime due to maintenance, equipment problems, and decreases in workload at specific times of the year (holidays, festivities), lead to unrealistic estimates. Therefore, although patient throughputs of 2500 scans per

TABLE V.3. MINIMUM, MAXIMUM AND AVERGAE NUMBER OF PET SCANS BASED ON PREVALENCE AND LIKELIHOOD OF UNDERGOING THE TEST

	Minimum	Maximum	Average
Total number of expected scans, M	5591	10 453	8022
Total number of expected scans, F	4584	9697	7140
Total number of expected scans	10 175	20 149	15 162

year or more are reported at some institutions with well tuned operating environments, a more realistic estimate of the effective patient throughput should be considered. Assuming an average workload of 2000 scans per scanner per year is considered adequate in most cases in order to plan adequately the needs for PET scanners in a country or geographical area.

As pointed out previously, changes in the number of PET scans requested should be expected over time, due to:

— Increased knowledge and confidence of the clinicians in the potential of the technology.
— Increases in the number of approved indications.
— Increased access to examinations; the greater the capacity, and the more timely the response, the greater the demand.
— Increased prevalence of cancer with time.

The algorithm described in the previous paragraphs for estimating the expected number of scans produces a range of values instead of a single figure. This allows for scaling the provision of scanners over time, in accordance with the 'growth curve' of the above factors.

Initial provisions can be based on the minimum values of the estimated number of the necessary scans; as the use of PET increases, progressing on the growth curve, the number of scanners can be increased to meet demand, tending towards a number of scanners necessary to perform the number of scans that were forecast. This process will take a few years, and during this time review and adjustment of the epidemiological data can be done, and compared with the effective workload observed.

Recalling the example developed in the previous section, and assuming an average workload per scanner of 2000 scans/year, if we consider the maximum number of scans expected (about 16 000, according to the data used in the example), an installed base of eight scanners would be necessary. Clearly, if all the scanners were installed at 'time 0', the observed number of scans would not be immediately equal to the limit, but would instead show a slow growth, tending to that value. It is then suggested that initial planning allows for the minimum number of scans, about 7000 in the example, requiring an initial installed base of three scanners. However, it is important to keep it clearly in mind that the expected workload will increase progressively towards the average and then the maximum number.

As pointed out, up to date local epidemiological data and appropriateness indicators should be used in modelling the needs. On the basis of a generic assessment that takes into account global, non-specific data, it is suggested that the initial number of scanners is planned on the basis of approximately one

scanner per million inhabitants. In a well developed context, it is expected that this figure will rise to 2.0 up to 2.5 scanners per million inhabitants.

REFERENCES TO APPENDIX V

[V.1] BEDFORD, M., MAISEY, M.N., Requirements for clinical PET: Comparison within Europe, Eur. J. Nucl. Med. Mol. Imag. **31** (2004) 208–221.

Appendix VI

QUALITY MANAGEMENT SYSTEM

VI.1. QUALITY SYSTEM DOCUMENTATION

The aim of a quality management (QM) process in PET is to assist PET/nuclear medicine departments/facilities in maintaining or improving the quality of service for their patients. The QM programmes should review and evaluate the quality of all elements involved, including staff, equipment and procedures, patient protection and safety, the overall performance of the nuclear medicine department as well as its interaction with external service providers.

Ensuring proper patient care needs a continuous process of improving operating procedures, equipment usage and clinical practices in order to maintain all aspect of operation 'under control'.

A quality management system is useful:

— To help fulfil regulatory needs;
— To optimize the effectiveness of patient care;
— To demonstrate that equipment is safe and in the proper operating condition to ensure optimal results;
— To allow reliable performance of quantitative procedures.

In order to set up a quality management system, a PET or nuclear medicine department should prepare an extensive series of written documents, describing operations and the QA programme.

A not exhaustive list of the documents needed include:

— Responsibilities and authorities;
— Job descriptions;
— Standard operating procedures (e.g. patient's referral, patient's reception and management, examination and scanning, equipment calibration and QC, sources safety, on job training, internal auditing);
— Management of deficiencies and non-conforming situations;
— Data and reference values tables;
— Reports;
— Documentation management (including formal procedures for changing/updating and distributing documents).

Preparing and maintaining documentation is a time consuming task. A solution, frequently adopted to save time, consists in preparing flow charts of the processes, including comments, rather than full texts.

The formal documentation for a quality system can very seldom be prepared 'at once'. A gradual approach, by drafting, reviewing and improving documents, is a practical solution; this is frequently referred to as 'document maintenance'.

The ISO 9000 family of documents addresses in full detail the structure of a QM system, regardless of what the user organization does. It is to be noted that such a system can be set up independent of the final goal to achieve certification from an authorized body.

VI.1.1. Quality system and justification issues

All medical exposures should be justified by weighing the diagnostic or therapeutic benefits they produce against the radiation detriment they might cause, taking into account the benefits and risks of available alternative techniques that do not involve medical exposure.

Making specific reference to the clinical use of PET, the overall justification of the practice should be carried out by the health authority, in conjunction with appropriate professional bodies. This process is generally accomplished through health technology assessment studies aimed at assessing appropriate indications.

Once general justification/appropriateness has been established, when an individual patient is considered, no examination should be programmed unless it has been requested by a referring medical practitioner. The practitioner should provide information on the clinical context, or whether it is part of an approved research programme.

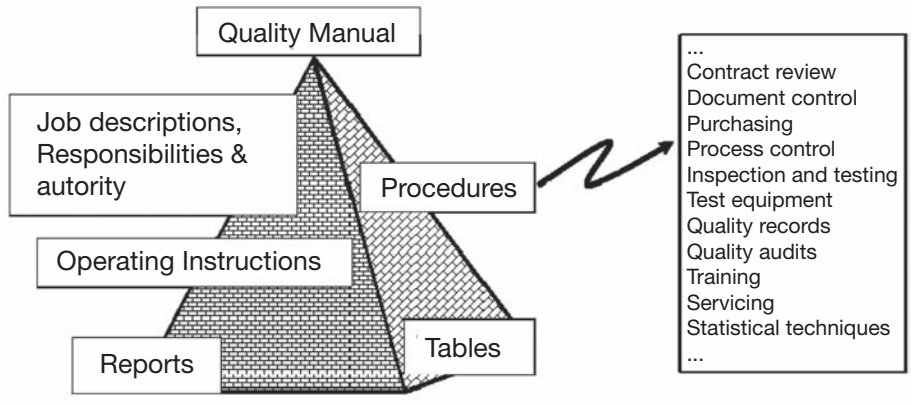

FIG. VI.1. Hierarchical structure of the document system for quality management.

Justification of the medical exposure in every individual case should be carried out by the nuclear medicine specialist, in consultation, as appropriate, with the referring medical practitioner, taking into account the appropriateness of the request, the characteristics of the individual patient and relevant information from other radiological and non-radiological procedures

Documented procedures should be issued to address the previous points; particular attention and specific procedures should be adopted in the case the patient could be pregnant, is breast feeding or is a child.

In justifying the exposure of an individual patient for a PET (PET/CT) examination, relevant national or international guidelines should be taken into account.

VI.1.2. Patient management and clinical protocols

The QM system should include not only technical aspects of the operation of a PET/nuclear medicine departments, but all the components of the process that may have an influence on the quality of the result as perceived by the patient.

The terminology used in QM systems can be misleading. It is therefore useful to clarify the difference between different terms, like ‘guideline’, ‘clinical protocol’ and ‘standard operating procedure’:

— Procedure guidelines are a part of the process of evidence based medicine; personnel collect current opinions from relevant scientists and associations and give a definition of the ‘state of the art’ in a certain matter. That is, there may be a guideline on the use of FDG–PET in oncology. Guidelines may be issued by different bodies/organizations and may have different levels of recognition by law in different countries.
— The term ‘protocol’ is used in several different contexts. One of the most frequent uses is in research protocols or in multicentre trials. In this context, it represents an agreement on how to perform a detailed series of operations. It does not necessarily have any legal recognition and it is not a common base for the definition of the ‘state of the art’, but simply an agreed work programme. Another use of ‘protocol’ is in referring to the operating procedure that it is adopted inside a department to perform a given task, i.e. FDG–PET scans. In this sense, an internal protocol reflects only a convention inside a department.
— A standard operating procedure (SOP) is a formal document whose format, content, revision and distribution are kept under control. An SOP is used to define how a task or series of operations is performed inside an organization (a department). In this sense, an SOP has (at least superficially) the same function as an ‘internal protocol’, as discussed previously. But a SOP is

intended as a formal document and thus needs to be traceable to reference documents (i.e. guidelines from professional bodies) and in relation to the full set of SOPs dealing with other related subjects inside the organization.

SOPs should be in place for all relevant components of the operation of a department, not only as regards the performance of a specific type of diagnostic examination.

Reception and management modalities have a strong impact on a patient's experience in a health structure. Detailed instructions and operating procedures should be prepared in order to grant that these relevant part of the process are 'under control' and are managed in a reliable way by all the components of the staff. For example, the waiting time inside the department prior to the effective start of the procedure (e.g. the administration of the radiopharmaceutical), should be monitored, as well as the time that an in-patient has to wait after the conclusion of the examination to be accompanied back to his/her ward.

Informative material for patient's instructions should be available in local languages. Standardized clinical protocols should be formally documented on the basis of national or international guidelines. They should be made accessible to all the relevant members of the staff, e.g. written in the local language. The protocols should be periodically reviewed and audited [VI.1, VI.2].

VI.1.3. Roles and responsibilities

An exhaustive description of the competencies, skills and training needed by the different professionals involved in the operation of a PET is given elsewhere in this publication (see Section 8).

Here reference is made only to the specific roles and responsibilities for a quality system:

— Nuclear medicine physicians. A specialized physician whose responsibility for quality encompasses the general services of the centre. In particular, he/she supervises all patient care and management procedures and all clinical protocols. In addition, he/she supports and enforces the QA/QC of equipment, establish clinical review and auditing.
— Medical physicists specialized in nuclear medicine. These people are responsible for the performance of acceptance testing and organization/ supervision of routine calibration and QC of imaging and radiation measurement equipment, including radiation protection instrumentation.

— Radiochemists/radiopharmacists. Responsible for the performance of acceptance testing and organization/supervision of routine calibration and QC of all radiopharmacy equipment; QC of chemicals, enriched materials, precursors material and kits; QC of radiopharmaceuticals products and batch release.
— Nuclear medicine technologists. These people are needed to contribute to the preparation of clinical examination protocols and the performance of patient examinations according to established protocols. Technologists are involved in the performance of routine calibration and QC of scanners.
— Cyclotron operators. They are in charge of the daily operations. In addition, they take part in the acceptance test of the cyclotron and related equipment and are responsible for calibration and QC procedures for equipment.
— Nurses and other staff involved in caring for the patient. These people play a key role in the management and care of the patient and they are instrumental in the patient's positive perception of the centre operation. They collaborate in preparing protocols of patient management and information material as well as in checking the operation of other institutional services (i.e. hospital transportation service).
— Administrative staff. These people represent the first encounter a patient has with the centre. They receive the patients according to the established protocols. In collaboration with the medical and technical staff, they are responsible of the application of the procedures for scheduling studies.

All the staff of the PET centre, according to their specific role and responsibilities, should actively participate in auditing and reviewing the overall operation.

VI.1.4. Audits

The aim of a QM process is to assist nuclear medicine departments/ laboratories in maintaining or improving the quality of service for its patients.

The QM programmes should review and evaluate the quality of all elements involved, including staff, equipment and procedures, patient protection and safety, the overall performance of the nuclear medicine department as well as its interaction with external service providers.

According to this view, audits are a powerful instrument to help implementation and tuning of a QM system. Several options are possible with regard to audits:

— Internal audit. Members of the staff of a department/institution can be trained and qualified as quality system evaluator; they can perform regular audits of the QMS.
— External (at the department). The audit is performed by other members of the hospital staff, or by means of peer reviews by professionals from other institutions.
— External. Evaluators from a certifying body.

Further details on the options and the auditing modality, can be found in Ref. [VI.1].

VI.1.5. Radiopharmaceuticals preparations: Guidelines for implementation of GMP

The use of a poor quality PET radiotracer may prevent correct diagnosis. It may even pose a health hazard. The welfare of the patient undergoing a procedure demands that radiopharmaceuticals conform to the required specifications for identity, purity, efficacy and safety.

VI.1.6. Regulation of in-house versus distribution

Regulations governing the testing of a radiopharmaceutical vary. If the product is to be used locally, the requirements may differ from those that apply when it is to be distributed to other PET centres. Regulations differ throughout the world and in different Member States. Assuming that regulations will be harmonized in the future, the wisest course of action is to design facilities that will satisfy the present requirements in most countries. Guidance in setting up and operating a GMP compliant facility may be found in Refs [VI.3, VI.4].

VI.1.7. Approved and licensed dispensing unit

Two questions need to be answered:

— Timeline for getting approvals;
— Can the commercial supplier help with getting permissions?

The FDG may be dispensed into multi-injection vials or as a single dose in a syringe. The multi-injection vial allows more flexibility in dosing and is more secure in transport. The single dose in the syringe allows better control of the maximum administered dose and in the radiation dose to the medical personnel administering the dose.

A laboratory with a clean room of Class C or D is to be considered to be sufficient for the radiopharmaceutical production. This assumes that critical steps with sterile solutions are performed in a carefully controlled environment with respect to the number of particles. A Class A enclosure is needed for dispensing FDG if it is dispensed into open vials. If the FDG is placed into a multi-injection vial through a sterilizing filter, the GMP regulations state that it must be done is a Class A environment, but GMP regulations for PET drugs as described in the United States Food and Drug Administration guidance states that this final filtration may be done in a Class C environment. The difference in cost between these two options is significant. In all cases, the local regulations take precedence.

Quality control of raw materials is an important aspect of the GMP controls. Storage protocol and space must be provided to separate raw materials received in the facility from those which have been inspected and accepted for use in preparation of radiopharmaceuticals for human use. Most facilities will not perform acceptance testing on all the materials and rather will accept a certificate of analysis (COA) from the manufacturer that the material meets the specifications outlined in the acceptance criteria listed in the facility documents.

One the material has been accepted, it should receive a label with the expiration date and some indication that this material is ready for use in the preparation of radiopharmaceuticals for human use. Typically, this is done by attaching a label of a specific colour which can be readily recognized.

The movement of personnel and materials is one of the most critical aspects in the design of the facility. More information about this can be obtained in Ref. [VI.3]. This book contains ideal flow diagrams for all personnel and components.

Equipment should be chosen to be able to meet GMP requirements for [^{18}F]-FDG radiopharmaceutical manufacturing, but it is not necessary to purchase more elaborate and expensive equipment which goes far beyond these requirements. FDG is usually prepared in a synthesizer contained in a hot cell, with laminar flow enclosures meeting the specifications required for aseptic preparation of the final product. More detailed information can be obtained in Ref. [VI.3].

The following analytical equipment for ensuring the identity and purity of each synthesis is mandatory for chromatography in synthesis modules:

— Chromatography equipment:
  • HPLC;
  • Gas chromatograph;
  • TLC scanner.

— Radiation measuring equipment:
  • Gamma spectrometer;
  • Gamma counter;
  • Dose calibrators.
— Analytical instruments:
  • Balances;
  • pH meters or paper;
  • Incubators.

More information on these instruments can be found in Ref. [VI.3].

VI.2. QUALITY ASSURANCE OF PET/CT SYSTEMS

A proper QM system will also ensure that QC tests of PET and PET/CT scanners are effective. Therefore, the QM system should include several basic components:

— A clear definition of responsibilities for the defined actions regarding QA;
— Documents illustrating the correct use of the imaging equipment, of test objects, phantoms and sources, detailing test modalities and procedures to follow in the case of abnormal results that do not correspond to what is expected, or in case of malfunction;
— Records of all tests, calibrations, and corrective actions performed;
— Proper training of all staff involved in the correct and safe use of the equipment, its QC procedures and all aspects pertaining to QA.

The QMS control life cycle regarding medical imaging equipment is described in Fig. VI.2, which is based on the IEC 1223-1 standard [VI.5]. On this basis, it should be clear that QA/QC does not merely consist of performing routine tests during the operation of the equipment. A proper QMS should also include the specification and acquisition phases, and thus starts well before the actual installation and operation of the equipment [VI.6.].

The specification document for any new system should include information regarding acceptance and end of warranty testing so that the vendor understands the requirements and schedule. In addition, the manufacturer should ensure that a service engineer is present during acceptance and end of warranty testing to correct any problems encountered by the medical physicists doing the testing. Once the equipment has been adequately specified, identified and purchased, the

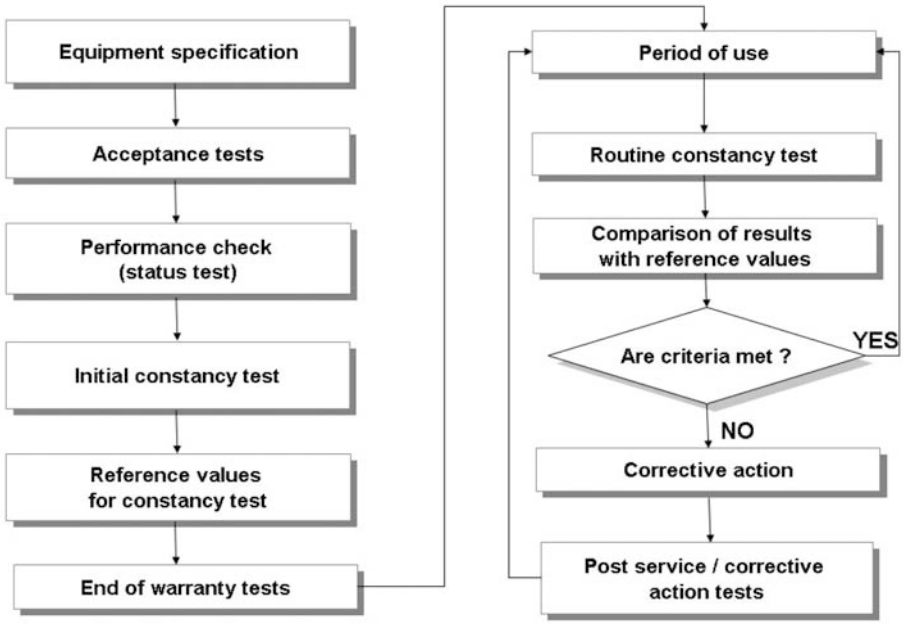

FIG. VI.2. QA/QC cycle for a medical imaging device (based on Ref. [VI.4]).

equipment must be properly installed. Acceptance tests should then be performed, preferably by a qualified independent medical physicist, in order to verify that the scanner meets all requirements in terms of performance and operational parameters.

Some confusion exists about the differences between QA and QC. However, QA refers in general to the concept of taking actions to ensure that delivered products or services meet performance requirements. The QMS is the programme that controls how quality is maintained and ensured throughout an organization. Quality assurance may encompass various aspects such as quality of medical care based on specific indicators, e.g. the infection rate in a hospital; the satisfaction of patients with their care; credentialling of the medical staff; and continuing education of the hospital staff. The QMS defines what steps will be taken to ensure that the desired level of care is maintained and how that will be documented. Quality control for PET/CT applies to a specific set of measurements focused on monitoring the performance of installed imaging equipment relative to image quality and dose on a periodic basis, e.g. monthly.

An IAEA publication assists with the process of acceptance testing and QC of PET scanners [VI.6]. It supplements the material found in international and national standards, such as IEC and NEMA publications and other relevant

documents referenced in that publication. To establish reference values and action levels to compare with the results of routine tests, an initial series of QC tests must be performed immediately after completion of the acceptance procedures. During the operational life cycle of the equipment, regular QC tests should be performed, as described in the referenced publications.

REFERENCES TO APPENDIX VI

[VI.1] INTERNATIONAL ATOMIC ENERGY AGENCY, Quality Management Audits in Nuclear Medicine Practices, IAEA,Vienna (2008).

[VI.2] INTERNATIONAL ATOMIC ENERGY AGENCY, Nuclear Medicine Resources Manual, IAEA, Vienna (2006).

[VI.3] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Guidelines for Setting Up a Facility, Technical Reports Series No. 471, IAEA, Vienna (2009).

[VI.4] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Production and Quality Control of FDG, Technical Reports Series No. XXX, IAEA, Vienna (in publication).

[VI.5] PUSCHERT, W., IEC projects and achievements in the field of quality assurance in diagnostic radiology, Radiat. Prot. Dosim. **57** (1995) 91–94.

[VI.6] Quality Assurance for PET and PET/CT Systems, IAEA Human Health Series No. 1, IAEA, Vienna (2009).

CONTRIBUTORS TO DRAFTING AND REVIEW

Drafting

Abdul Khader, M.A.	Penang Hospital, Malaysia
Amaral, H.	Oncological Clinical Institute, Santiago, Chile
Belholavek, O.	Homolce Hospital, Prague, Czech Republic
Bombardieri, E.	Istituto Nazionale Tumori, Milan, Italy
Carril Carril, J.M.	Hospital Universitario, Santander, Spain
Chanachai, R.	Mahidol University, Bangkok, Thailand
Dondi, M.	International Atomic Energy Agency
Fulton, R.	Westmead Hospital, Sydney, Australia
Haji-Saeid, M.	International Atomic Energy Agency
Knesaurek, K.	Mount Sinai Medical Center, New York, USA
Marengo, M.	S.Orsola-Malpighi University Hospital, Bologna, Italy
Machulla, H.-J.	PET Center, Tubingen, Germany
Mut Bastos, F.	International Atomic Energy Agency
Palm, S.	International Atomic Energy Agency
Rehani, M.	International Atomic Energy Agency
Schlyer, D.	Brookhaven National Laboratory, New York, USA
Vera Ruiz, H.	Advanced Technical Solutions Ltd, La Paz, Bolivia

Review

Fulton, R.,	Westmead Hospital, Sydney, Australia
Dondi, M.	International Atomic Energy Agency

IAEA
International Atomic Energy Agency

Where to order IAEA publications

In the following countries IAEA publications may be purchased from the sources listed below, or from major local booksellers. Payment may be made in local currency or with UNESCO coupons.

AUSTRALIA
DA Information Services, 648 Whitehorse Road, MITCHAM 3132
Telephone: +61 3 9210 7777 • Fax: +61 3 9210 7788
Email: service@dadirect.com.au • Web site: http://www.dadirect.com.au

BELGIUM
Jean de Lannoy, avenue du Roi 202, B-1190 Brussels
Telephone: +32 2 538 43 08 • Fax: +32 2 538 08 41
Email: jean.de.lannoy@infoboard.be • Web site: http://www.jean-de-lannoy.be

CANADA
Bernan Associates, 4501 Forbes Blvd, Suite 200, Lanham, MD 20706-4346, USA
Telephone: 1-800-865-3457 • Fax: 1-800-865-3450
Email: customercare@bernan.com • Web site: http://www.bernan.com

Renouf Publishing Company Ltd., 1-5369 Canotek Rd., Ottawa, Ontario, K1J 9J3
Telephone: +613 745 2665 • Fax: +613 745 7660
Email: order.dept@renoufbooks.com • Web site: http://www.renoufbooks.com

CHINA
IAEA Publications in Chinese: China Nuclear Energy Industry Corporation, Translation Section, P.O. Box 2103, Beijing

CZECH REPUBLIC
Suweco CZ, S.R.O., Klecakova 347, 180 21 Praha 9
Telephone: +420 26603 5364 • Fax: +420 28482 1646
Email: nakup@suweco.cz • Web site: http://www.suweco.cz

FINLAND
Akateeminen Kirjakauppa, PO BOX 128 (Keskuskatu 1), FIN-00101 Helsinki
Telephone: +358 9 121 41 • Fax: +358 9 121 4450
Email: akatilaus@akateeminen.com • Web site: http://www.akateeminen.com

FRANCE
Form-Edit, 5, rue Janssen, P.O. Box 25, F-75921 Paris Cedex 19
Telephone: +33 1 42 01 49 49 • Fax: +33 1 42 01 90 90
Email: formedit@formedit.fr • Web site: http://www. formedit.fr

Lavoisier SAS, 145 rue de Provigny, 94236 Cachan Cedex
Telephone: + 33 1 47 40 67 02 • Fax +33 1 47 40 67 02
Email: romuald.verrier@lavoisier.fr • Web site: http://www.lavoisier.fr

GERMANY
UNO-Verlag, Vertriebs- und Verlags GmbH, Am Hofgarten 10, D-53113 Bonn
Telephone: + 49 228 94 90 20 • Fax: +49 228 94 90 20 or +49 228 94 90 222
Email: bestellung@uno-verlag.de • Web site: http://www.uno-verlag.de

HUNGARY
Librotrade Ltd., Book Import, P.O. Box 126, H-1656 Budapest
Telephone: +36 1 257 7777 • Fax: +36 1 257 7472 • Email: books@librotrade.hu

INDIA
Allied Publishers Group, 1st Floor, Dubash House, 15, J. N. Heredia Marg, Ballard Estate, Mumbai 400 001,
Telephone: +91 22 22617926/27 • Fax: +91 22 22617928
Email: alliedpl@vsnl.com • Web site: http://www.alliedpublishers.com

Bookwell, 2/72, Nirankari Colony, Delhi 110009
Telephone: +91 11 23268786, +91 11 23257264 • Fax: +91 11 23281315
Email: bookwell@vsnl.net

ITALY
Libreria Scientifica Dott. Lucio di Biasio “AEIOU”, Via Coronelli 6, I-20146 Milan
Telephone: +39 02 48 95 45 52 or 48 95 45 62 • Fax: +39 02 48 95 45 48
Email: info@libreriaaeiou.eu • Website: www.libreriaaeiou.eu

JAPAN
Maruzen Company, Ltd., 13-6 Nihonbashi, 3 chome, Chuo-ku, Tokyo 103-0027
Telephone: +81 3 3275 8582 • Fax: +81 3 3275 9072
Email: journal@maruzen.co.jp • Web site: http://www.maruzen.co.jp

REPUBLIC OF KOREA
KINS Inc., Information Business Dept. Samho Bldg. 2nd Floor, 275-1 Yang Jae-dong SeoCho-G, Seoul 137-130
Telephone: +02 589 1740 • Fax: +02 589 1746 • Web site: http://www.kins.re.kr

NETHERLANDS
De Lindeboom Internationale Publicaties B.V., M.A. de Ruyterstraat 20A, NL-7482 BZ Haaksbergen
Telephone: +31 (0) 53 5740004 • Fax: +31 (0) 53 5729296
Email: books@delindeboom.com • Web site: http://www.delindeboom.com

Martinus Nijhoff International, Koraalrood 50, P.O. Box 1853, 2700 CZ Zoetermeer
Telephone: +31 793 684 400 • Fax: +31 793 615 698
Email: info@nijhoff.nl • Web site: http://www.nijhoff.nl

Swets and Zeitlinger b.v., P.O. Box 830, 2160 SZ Lisse
Telephone: +31 252 435 111 • Fax: +31 252 415 888
Email: infoho@swets.nl • Web site: http://www.swets.nl

NEW ZEALAND
DA Information Services, 648 Whitehorse Road, MITCHAM 3132, Australia
Telephone: +61 3 9210 7777 • Fax: +61 3 9210 7788
Email: service@dadirect.com.au • Web site: http://www.dadirect.com.au

SLOVENIA
Cankarjeva Zalozba d.d., Kopitarjeva 2, SI-1512 Ljubljana
Telephone: +386 1 432 31 44 • Fax: +386 1 230 14 35
Email: import.books@cankarjeva-z.si • Web site: http://www.cankarjeva-z.si/uvoz

SPAIN
Díaz de Santos, S.A., c/ Juan Bravo, 3A, E-28006 Madrid
Telephone: +34 91 781 94 80 • Fax: +34 91 575 55 63
Email: compras@diazdesantos.es, carmela@diazdesantos.es, barcelona@diazdesantos.es, julio@diazdesantos.es
Web site: http://www.diazdesantos.es

UNITED KINGDOM
The Stationery Office Ltd, International Sales Agency, PO Box 29, Norwich, NR3 1 GN
Telephone (orders): +44 870 600 5552 • (enquiries): +44 207 873 8372 • Fax: +44 207 873 8203
Email (orders): book.orders@tso.co.uk • (enquiries): book.enquiries@tso.co.uk • Web site: http://www.tso.co.uk

On-line orders
DELTA Int. Book Wholesalers Ltd., 39 Alexandra Road, Addlestone, Surrey, KT15 2PQ
Email: info@profbooks.com • Web site: http://www.profbooks.com

Books on the Environment
Earthprint Ltd., P.O. Box 119, Stevenage SG1 4TP
Telephone: +44 1438748111 • Fax: +44 1438748844
Email: orders@earthprint.com • Web site: http://www.earthprint.com

UNITED NATIONS
Dept. I004, Room DC2-0853, First Avenue at 46th Street, New York, N.Y. 10017, USA
(UN) Telephone: +800 253-9646 or +212 963-8302 • Fax: +212 963-3489
Email: publications@un.org • Web site: http://www.un.org

UNITED STATES OF AMERICA
Bernan Associates, 4501 Forbes Blvd., Suite 200, Lanham, MD 20706-4346
Telephone: 1-800-865-3457 • Fax: 1-800-865-3450
Email: customercare@bernan.com · Web site: http://www.bernan.com

Renouf Publishing Company Ltd., 812 Proctor Ave., Ogdensburg, NY, 13669
Telephone: +888 551 7470 (toll-free) • Fax: +888 568 8546 (toll-free)
Email: order.dept@renoufbooks.com • Web site: http://www.renoufbooks.com

Orders and requests for information may also be addressed directly to:

Marketing and Sales Unit, International Atomic Energy Agency
Vienna International Centre, PO Box 100, 1400 Vienna, Austria
Telephone: +43 1 2600 22529 (or 22530) • Fax: +43 1 2600 29302
Email: sales.publications@iaea.org • Web site: http://www.iaea.org/books

10-15181

A GUIDE TO CLINICAL PET IN ONCOLOGY: IMPROVING CLINICAL MANAGEMENT OF CANCER PATIENTS
IAEA TECDOC Series No. 1605
IAEA-TECDOC-1605 (58 pp; 2008)
ISBN 978–92–0–110608–7 Price: €15.00

THE ROLE OF PET/CT IN RADIATION TREATMENT PLANNING FOR CANCER PATIENT TREATMENT
IAEA TECDOC Series No. 1603
IAEA-TECDOC-1603 (40 pp.; 2008)
ISBN 978–92–0–110408–3 Price: €15.00

QUALITY MANAGEMENT AUDITS IN NUCLEAR MEDICINE PRACTICES
STI/PUB/1371 (57 pp.; 2008)
ISBN 978–92–0–112108–0 Price: €25.00

STRATEGIES FOR CLINICAL IMPLEMENTATION AND QUALITY MANAGEMENT OF PET TRACERS
STI/PUB/1344 (197 pp.; 2009)
ISBN 978–92–0–107008–1 Price: €44.00

OPERATIONAL GUIDANCE ON HOSPITAL RADIOPHARMACY: A SAFE AND EFFECTIVE APPROACH
STI/PUB/1342 (75 pp.; 2008)
ISBN 978–92–0–106708–1 Price: €32.00

QUALITY ASSURANCE FOR PET AND PET/CT SYSTEMS
IAEA Human Health Series No. 1
STI/PUB/1393 (145 pp.; 2009)
ISBN 978–92–0–103609–4 Price: €32.00

RADIATION PROTECTION IN NEWER MEDICAL IMAGING TECHNIQUES: PET/CT
Safety Reports Series No. 58
STI/PUB/1343 (54 pp.; 2008)
ISBN 978–92–0–106808–8 Price: €28.00

CYCLOTRON PRODUCED RADIONUCLIDES: GUIDELINES FOR SETTING UP A FACILITY
Technical Reports Series No. 471
STI/DOC/010/471 (213 pp.; 2009)
ISBN 978–92–0–103109–9 Price: €45.00

APPROPRIATE USE OF FDG-PET FOR THE MANAGEMENT OF CANCER PATIENTS
IAEA Human Health Series No. 9
STI/PUB/1438 (80 pp; 2010)
ISBN 978–92–0–101610–2 Price: €39.00

This publication presents a comprehensive overview of the steps involved in the establishment of a clinical PET facility, from strategy formulation to cyclotron implementation, radiopharmaceutical production and clinical applications. Also covered are staff requirements and radiation protection issues. It is intended for health care administrators, project and site planners, as well as professionals involved in providing PET services.

IAEA HUMAN HEALTH SERIES

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA
ISBN 978–92–0–104610–9
ISSN 2075–3772