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Guest Editorial

Nuclear medicine in oncology

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Abstract

Oncological applications of nuclear medicine have entered a new era as a result of a greater understanding of the biological characteristics of tumours and the increasing availability of Positron Emission Tomography (PET). Fluorine-18 labelled flurodeoxyglucose has been shown to be effective in differentiating malignant from benign tumours and in determining the extent of disease. New opportunities exist for predicting and evaluating response to therapy. This paper sets out to explain and comment on some of the key developments in this field. It is not intended to be a comprehensive review but as a useful reference for those working on oncology.

Keywords

Nuclear medicine; detection of skeletal metastases; bone scanning; PET

INTRODUCTION

There has always been a strong association of nuclear medicine with oncology. Ever since the very early days of iodine-131 in thyroid disease and from the beginning of the technetium-99m era, nuclear medicine techniques have contributed to the diagnosis and treatment of malignant disease. Bone scanning with technetium-99m labelled phosphates, for example, quickly became established as the method of choice for the detection of skeletal metastases and is probably the most frequently requested investigation in the majority of nuclear medicine departments.

However, in the last few years there has been a particular surge of interest in oncological applications reflected in a recent paper prepared by the Task Group of Oncology organised by the World Federation of Nuclear Medicine and Biology[1] in which 103 applications are listed covering 47 tumour groups. Sixty of these applications are categorised as being indicated in solving a diagnostic problem; 38 are integrative i.e. complementary to other information and 5 alternative to other procedures. This list does not include research applications but only procedures for which there is good published evidence of their efficacy. For example a bone scan is *indicated* in staging cancer of the prostate whilst a thyroid scan is classified as *integrative* as it should be used in association with ultrasonography.

Nuclear medicine contributes in a variety of different ways to the management of the oncological patient including:

- Diagnosis of disease.
- Staging of disease and determination of extent.
- Providing information on tumour characteristics and assessment of prognostic factors
- Evaluation of response to treatment
- Search for relapses at follow up of treated patients.
- Functional evaluations of organs and systems before and after treatment.

This recent interest is associated with two separate, but in part linked, developments – the growth of Positron Emission Tomography (PET) and a greater understanding of the biological characteristics of tumours.

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POSITRON EMISSION TOMOGRAPHY (PET)

Twenty six percent of the applications listed in the Task Group report concerned PET imaging of which 12 were classified as "indicated" and 15 as "integrated" procedures. This is surprising in light of the fact that, to many, PET is still an expensive research tool only available in specialist centres. Clearly this is not the case. PET is making an increasing contribution to the routine management of patients in oncology. This is also reflected in the increasing literature and reports from departments of nuclear medicine and oncology throughout the world. There are two key factors which have contributed to PET developing from a research tool into a routine investigative modality – the availability of less expensive imaging systems and the role of F-18 Fluorodeoxyglucose (FDG) in tumour imaging. In addition a major factor in the USA was the recognition of the clinical effectiveness of PET by the Health Care Financing Administration (HCFA) resulting in the reimbursement of the costs of certain procedures.

PET scanners and gamma cameras

PET is based on the coincidence imaging of the 511keV annihilation radiation from positron emitting radionuclides. The technique is not new, in fact its feasibility was first reported as far back as 1953[2] and the first tomographic PET scanner was described by Ter-Pogassian et al. in 1975.[3] Images obtained using positron emitters are normally much better than those obtained using single photon emitting radionuclides, such as technetium-99m in conventional nuclear medicine imaging, because there is no need to use a collimator and it is easy to correct for attenuation within the patient.

Until a few years ago all PET imaging was carried out on dedicated PET scanners based on multiple small detectors in hexagonal or circular arrays. The systems with the highest performance (and most expensive) used multiple bismuth gennanate (BGO) detectors and although less expensive scanners became available, installations were restricted to a limited number of specialist centres. It was not until the development of dual-headed gamma cameras capable of coincidence imaging that PET imaging became affordable by the majority of nuclear medicine departments.

Until recently the gamma camera approach could not be pursued due to the limitations in counting rates and computer processing rates. However, these have been overcome and although PET cameras still have a much lower sensitivity compared to PET scanners there is growing evidence of their clinical effectiveness. Various studies have showed them to deliver approximately 80–90% of the performance of a scanner but they are particularly limited in the detection of tumours less than 1 cm in size.[4]

One added advantage of PET cameras is the flexibility in use. PET scanners can only image positron emitters and there has to be sufficient number of referrals for PET investigations to make them cost effective. PET cameras on the other hand can be used for the full range of nuclear medicine procedures without compromising performance. This flexibility makes them extremely attractive to both the Diagnostic Imaging and Oncology departments.

F-18 fluorodeoxyglucose

The commonly used positron emitting radionuclides have low atomic numbers and short half-lives such as oxygen-15 (123s), nitrogen-13 (9.8 min), carbon-11 (20 min) and fluorine-18 (110 min). All are produced in cyclotrons which, when using such short-lived radionuclides, have to be on site alongside the imaging systems. Only fluorine-18 can be used at centres remote from the production facility, as its half-life is long enough to allow transport of material to centres within a 150-mile radius.

The current clinical interest in tumour imaging relates to fluorine-18 labelled fluorodeoxyglucose (FDG).[5] FDG is a chemical analogue of glucose in which one of the hydroxyl groups in the glucose molecule is substituted by fluorine. Most cells under anaerobic conditions derive their energy from glycolysis, the process in which glucose is broken down eventually into lactic acid. In the early stages of this process, glucose is taken into cells through the presence of glucose transporter proteins on the cell surface (GLUT 1–5; SGLT I) and becomes phosphorylated by the enzyme hexokinase. Warburg, many years ago, observed that malignant cells have a higher glucose utilisation rate than do normal cells.[6] This is thought to be due to higher levels of glucose transporters[7] and hexokinase.[8]

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FDG has the same biochemical properties as glucose competing with plasma glucose for the glucose transporters in the cell membrane and is phosphorylated by hexokinase to FDG 6-phosphate. However, unlike glucose 6-phosphate it is not a substrate for further metabolism in the tricarboxylic acid cycle and as it cannot diffuse back across the membrane it becomes trapped in the cell. Although most organs do not differentiate between FDG and glucose this is not the case in the kidneys. FDG is filtered by the kidneys and is hence cleared from the circulation. The optimum imaging time is related to the maximum uptake of FDG in the cell, the background circulating activity and the activity of the fluorine-18. Most protocols start scanning at approximately 1 hour post injection but there is some evidence that the target to background ratio continues to increase for several hours longer.

CLINICAL APPLICATIONS OF PET

At the 1999 American Society of Clinical Oncology meeting it was reported that, following a survey of referring physicians, whole body PET changes the clinical staging and major management decisions in 40% and results in major surgery being avoided in 25% of cancer patients.[9] This gives an indicator of the clinical impact of PET, which is reinforced in a recent editorial in the *European Journal of Nuclear Medicine*[10] predicting that most nuclear medicine departments in Europe will gain access to PET technology in the next decade and that PET whole body imaging could become the benchmark investigation for staging and restaging in a wide range of malignancies. In fact it suggested that failure to obtain such a study in the future might be regarded as malpractice.

PET imaging has gained rapid acceptance to date particularly in the differentiation of malignant from benign tumours, the determination of the extent of disease and the identification of residual tumour following therapy or surgery.

In a comprehensive review of PET imaging in cancer staging and therapy assessment at the 1999 ASTRO meeting,[11] the following applications were described:

- Brain Tumours: high FDG uptake in a brain tumour is associated with poor prognosis. After "definitive treatment" FDG uptake in a lesion suggests viable tumour whereas the absence of uptake suggests necrosis.
- Lung Nodules and Lung Carcinoma: PET has 90% to 100% sensitivity and 80% to 90% specificity in evaluating solitary lung nodules for the presence or absence of neoplasm and is far superior to CT for staging mediastinal lymph nodes. PET is also accurate in determining systemic metastases with approximately 10% to 15% of patients with lung cancer thought to be operable on conventional assessment shown to have stage 4 disease.
- Colorectal Carcinoma: PET is more sensitive than CT for the detection of primary and secondary disease as well as assessing treatment response. The results change patient management in 15 to 30% of cases.
- Melanoma: PET identifies 93% of metastases seen by conventional imaging methods at intervals up to 6 months earlier
- Head and Neck Carcinomas: PET is superior to CT and MRI in detecting recurrent tumour after surgery or radiation-chemotherapy or both.
- Lymphomas: PET is useful in assessing response to therapy and determining whether a residual mass represents viable tumour or not.
- Breast Carcinoma: PET is effective in identifying primary lesions and has been shown to accurate in assessing axillary nodal status.
- Other Cancers: Although promising in Oesophageal carcinoma, pancreatic adenocarcinoma, ovarian cancer and thyroid, PET does not yield good results in prostate cancer, low grade hepatomas and in tumours of the GU tract.

PREDICTING AND EVALUATING RESPONSE TO THERAPY

The literature on the clinical applications of PET is growing rapidly but it is important that the technique is not seen as simply another imaging technique for tumours. Nuclear medicine differs from other imaging modalities because it demonstrates function rather than anatomy. As a result it provides opportunities to gain information on tumour function and the response of tumours to treatment, both of which are critical for effective patient management.

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Currently the criterion for measuring the response of a tumour to therapy is to measure its reduction in volume usually by CT, MR or ultrasound. However, there are serious limitations to this approach. Although there may be significant reduction in size of a tumour following therapy this clearly cannot guarantee the total elimination of tumour cells. Alternatively, tumour cell death may not result in a significant change in size as tumours contain non-tumour cells such as fibrosis and inflammatory cells. Furthermore the approach does not lend itself to predicting a response to therapy as it is not until the course of treatment has been completed that an assessment be made of its effectiveness. As a consequence many patients are treated with inappropriate regimens. This is neither clinically effective nor cost effective management.

As PET-FDG distinguishes between malignant and non-malignant cells it is able to separate recurrent tumour from radiation necrosis, chemonecrosis or post surgical changes in patients with previously treated tumours. This has been shown to be particularly effective in brain tumours, head and neck tumours and lymphomas.

Resistance to chemotherapeutic drugs continues to be one of the major unsolved problems in the treatment of cancer. Multidrug resistance is defined as the ability of cells exposed to a single drug to develop resistance to a broad range of structurally and functionally unrelated drugs. This is due to the drugs being actively transported out of the cells mediated by P-glycoprotein, which is encoded by multidrug resistance genes. In some tumours there is over expression of P-glycoprotein leading to rapid efflux of the drug out of the cells and as a consequence low therapeutic response. This property has been investigated using nuclear medicine techniques.

Tc-99m-methoxyisobutyl isonitrile (MIBI) is a single photon radiopharmaceutical that is widely used in nuclear medicine for myocardial perfusion studies, scintimammography and parathyroid imaging. High uptake of MIBI occurs in various tumours associated in part with increased blood flow, altered cell membrane potentials and/or altered metabolism. Recent evidence has shown that MIBI is a suitable transport substrate for P-glycoprotein and that the uptake and efflux rate of MIBI provides an in-vivo test for P-glycoprotein expression with the potential for predicting early response to chemotherapeutic agents.

In patients with small cell lung cancer it has been shown[12] that there is significantly higher tumour uptake of MIBI prior to starting therapy in those patients who had complete or partial remission following chemotherapy than in those who did not respond. Similarly in hepatocellular cancer uptake of MIBI is dependent on whether the tumours expressed P-glycoprotein.[13] In 30 out of 35 patients in whom P-glycoprotein expression had been measured there was no uptake of MIBI in the tumours but in the remaining 5 patients with no evidence of no Pgp expression uptake of MIBI was observed.

In breast cancer it has been shown that there is a significant correlation between early uptake in the tumour and subsequent washout of MIBI with angiogenesis and P-glycoprotein expression.[14] In patients with locally advanced breast tumours there is a large change in uptake of MIBI (-35%) after two months of chemotherapy in clinical responders compared to +17% for nonresponders.[15]

PET is also being explored as a method of predicting therapeutic response. FDG uptake is known to relate to both viable cell number and proliferative status of cells, both of which can be affected by therapy. There have been a number of reports that have measured the uptake of FDG before and after therapy. Head and neck cancers, malignant lymphoma, breast and bronchogenic tumours, which are responding to either chemotherapy or radiotherapy, show decreased FDG uptake. It might be possible to predict the outcome of the full course of treatment of breast tumours from the changes in FDG uptake before and after one course of chemotherapy.

DEVELOPMENTS

As with any new technology there is continuous development and often rapid change with increasing acceptance and demand from the medical community. Already there have been appreciable developments in PET cameras from the initial systems and this trend is set to continue. The use of thicker sodium iodide crystals to improve detection of 511 keV photons, new algorithms using

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iterative reconstruction rather than filtered back projection for image reconstruction and attenuation correction techniques, which proved to be essential in dedicated PET scanners have already been introduced. New detector systems, improved count rate processing and attenuation correction methodologies and new methods of image reconstruction are all potential developments with the aim to improve the detection of small tumours.

As more centres invest in PET technology the demand for F-18 FDG will increase and outstrip the current supplies. New cyclotrons and radiopharmaceutical production facilities will have to be installed, strategically located to meet the clinical need.

It is also likely that new F-18 labelled compounds, which target specific properties of cells, will appear. There is promising research in the possible use of fluoroethyl tyrosine[16] linked to amino acid metabolism, fluoromethyl thymidine[17] to demonstrate DNA turnover and fluorine labelled oestradiol derivatives[18] to investigate receptor status.

Whilst F-18 fluorouracil[19] has the potential to provide information on uptake mechanisms and pharmokinetics of the chemotherapeutic agent.

CONCLUSION

Nuclear medicine applications in oncology have entered a new era. The next decade will see increasing use of PET brought about by improvements in instrumentation and a greater variety of specific radiopharmaceuticals for characterising tumours. Many of the current developments will be consolidated into clinical practice with significant consequences on the management of patients in oncology.

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