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Nuclear Medicine in the Era of Personalised Medicine

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Abstract

Personalised medicine is the new landscape in the practice of medicine around the world. Nuclear medicine techniques, through the use of advanced technology and diverse range of radiopharmaceuticals have allowed the non-invasive assessment of diseases, treatment response, and ability to recommend targeted therapies, through the concept of "theranostics".

The field of nuclear medicine has seen a polarising change in practice over the last two decades. Nuclear medicine has traditionally been characterised by the use of different radiopharmaceuticals to assess the physiologic nature of diseases afflicting various organs noninvasively applying quantitative analysis of tracer uptake and distribution. Through this approach, alterations in organ function, early detection and monitoring of disease (before the onset of anatomical abnormalities), and measurement of changes in body physiology have been possible.

The advent of three-dimensional (3D) imaging known as SPECT (Single Photon Emission Computed Tomography) and PET (Positron Emission Tomography), and the integration of this 3D imaging with anatomical imaging provided by computed tomography (CT) and magnetic resonance imaging (MRI), has revolutionised the acquisition and interpretation of functional nuclear medicine images. This includes imaging for myocardial ischaemia and viability, ventilation/perfusion lung scans for the diagnosis of pulmonary embolism and preoperative quantitation of regional lung function, cerebral perfusion studies for neurodegenerative disease, and imaging of endocrine diseases.

^{18}F-Fluorodeoxyglucose (^{18}F-FDG) PET/CT imaging has become integral in the staging, restaging and monitoring of therapy response in many solid and haematological malignancies, and several indications are now funded by Australian Medicare. Whilst the most commonly used radiotracer in PET in oncology is ^{18}F-FDG, many other radiotracers are available, which are able to assess the biochemical and metabolic hallmarks of cancer described by Hanahan[1]. In neurodegenerative disorders, there are new radiotracers which are able to assess amyloid and tau deposition in Alzheimer's disease, and differentiate this from other types of dementia[2,3]. Newer applications of radiotracers for SPECT and PET have also extended to more accurate diagnosis of inflammation and infection, neurologic conditions, and myocardial reserve.

Personalised medicine is now an essential part of the management of patients with lymphoma, with worldwide consensus on standards of PET acquisition and reporting, which has enabled PET to be the imaging biomarker for treatment response assessment in these patients[4-6]. However, there have been clinical trials which support PET-related personalised management of lymphoma, to de-escalate chemotherapy, or to perform more selective radiotherapy. There are clinical trials underway to assess the role of PET to eliminate consolidation radiotherapy in patients with diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma. In Hodgkin's lymphoma, there are several trials which have established the role of interim PET performed during the chemotherapy regimen which allows modification of chemotherapy requirements in patients, depending on their tumour metabolic response to treatment assessed by PET scans (response-adapted therapy)[7,8]. In follicular lymphoma, PET has been shown to be a reliable predictor of outcome in patients treated with rituximab and chemotherapy, and prospective trials to test PET-guided therapy in this disease are underway[9].

Over the last decade, there has been increasing use of the term "theranostics" in medicine, which is simply described as the concept of Therapy guided by Diagnostics. This concept has been used for over 70 years in the treatment of thyroid cancer with radioiodine, with the

therapeutic dose guided by pre-treatment diagnostic radioiodine scans. More recently, there has been remarkable progress in the application of theranostics to other tumour types, in particular, neuroendocrine tumours (NET) and prostate cancer.

Somatostatin receptor (SSTR) PET/CT using somatostatin analogues labelled with gallium-68 (^{68}Ga) is now accepted as the most accurate imaging test for the evaluation of patients with SSTR-expressing neuroendocrine neoplasms. This translates into additional therapy options with increasing evidence that peptide receptor radionuclide therapy (PRRT) may be the treatment of choice for advanced or progressive NET.

Prospective trials of PRRT in neuroendocrine tumour patients have shown improved progression-free and overall survival, as well as marked symptomatic improvement. The pivotal study to date has been a phase III study of 229 patients with progressive midgut NET treated with high dose, long-acting somatostatin analogue (Sandostatin-LAR), or a somatostatin analogue labelled with a radionuclide, lutetium-177 (^{177}Lu-DOTATATE). In this study, the median progression-free survival (PFS) in the patients treated with ^{177}Lu-DOTATATE and Sandostatin-LAR had not been reached, compared to 8.4 months in patients with high dose Sandostatin-LAR treatment alone[10]. This treatment option is now integrated into multidisciplinary guidelines for this tumour type (eg, National Comprehensive Cancer Network [NCCN], European Neuroendocrine Tumour Society [ENETS]), and is now licensed for use in Europe and the United States. Whilst this treatment is available in Australia, this is primarily in trial settings, it is currently not reimbursed through Medicare, although imaging of SSTR in NET with ^{68}Ga-DOTATATE PET is likely to receive Medicare funding in the near future.

Another area of increasing theranostic use is in the evaluation and treatment of patients with metastatic castrate-resistant prostate carcinoma using radiolabelled prostate-specific membrane antigen (PSMA)[11]. PSMA is a transmembrane protein which is markedly overexpressed in prostate carcinoma[12]. Numerous radiopharmaceuticals have emerged over the last few years to target PSMA for both diagnostic imaging and therapy[13]. There is a growing body of evidence for the use of PSMA imaging for both primary staging of intermediate to high risk prostate cancer, and to use this information to treat patients with radioligand therapy. A prospective multicenter trial in Australia showed that ^{68}Ga-PSMA PET/CT scans detected previously unsuspected disease in both primary staging and restaging of patients with biochemical recurrence in a high proportion of patients with prostate cancer, and there was a change in management in 51% of patients[14]. The impact was greater in the group of patients with biochemical failure after definitive surgery or radiation treatment, in whom management changed in 62% compared to 21% of patients undergoing primary staging[14]. By identifying sites of target overexpression, PSMA PET permits selection of patients eligible to receive personalized PSMA radioligand therapy, which has been found to be feasible, safe and effective in appropriately selected patients [15]. In the primary staging of prostate cancer, there is an increasing body of evidence that more accurate staging of patients at the time of initial diagnosis may also change the natural history of the disease and the rate of biochemical recurrence[11], but this remains to be proven, with a prospective multicenter trial in Australia underway at the moment to address these questions.

In the contemporary practice of nuclear medicine, access to new diagnostic radiotracers, and theranostics of molecular targets leading to new therapeutic approaches to disease, have transformed the specialty to integrate imaging techniques into personalised molecular medicine.

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