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Nuclear-based science benefiting all Australians

1. About ANSTO

As the home of Australia's nuclear expertise, the Australian Nuclear Science and Technology Organisation (ANSTO) is one of Australia's largest research organisations.

Nuclear science and technology is a dynamic area of research that focuses on the building blocks of matter. Many of the most important questions society faces in areas such as health, the environment and industry are being investigated by ANSTO researchers.

At the heart of ANSTO is the OPAL reactor, which is one of the world's newest and best multi-purpose research reactors. OPAL is used for scientific research using neutrons, the production of medical radioisotopes, and the irradiation of silicon used for electronics.

ANSTO operates the Centre for Accelerator Science, which is used to analyse materials to determine their elemental composition and age. It also manages the Melbourne-based Australian Synchrotron, a world class light source that uses electrons to enable researchers to examine sub-microscopic structures in new ways. The imaging and medical therapy beamline of the Synchrotron offers high-resolution, phase-contrast x-ray imaging of biomedical samples and enables research into new cancer treatments.

As a Commonwealth Government agency, ANSTO provides policy advice to Government on all matters relating to nuclear science, technology and engineering, supporting its implementation of Australia's international roles and obligations. ANSTO is connected with all Australian and New Zealand universities through the Australian Institute of Nuclear Science and Engineering (AINSE), providing researchers access to Australia's nuclear science, technology and engineering expertise.

2. About ANSTO Health and ANSTO LifeSciences

ANSTO Health is the business arm of ANSTO that produces 10,000 patient doses of nuclear medicine for Australians each week, and is set to expand to become a major supplier to the

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rest of the world. One in two Australians can expect to use an ANSTO-produced radioisotope in their lifetime.

ANSTO LifeSciences is the research division of ANSTO that uses the unique capabilities of nuclear technologies to probe the fundamental properties of living matter. Its researchers address interdisciplinary research questions in health, medicine, biology, agriculture, food and nutrition. ANSTO LifeSciences is involved in multiple collaborations and partnerships with leading researchers from Australia and overseas.

3. The role nuclear medicines currently play in skin cancer diagnosis

The accurate diagnosis of the metastasis of skin cancer to other parts of the body is crucial for good patient outcomes.

Nuclear medicine plays a very important role in diagnosing the metastases of skin cancer, so that the most effective treatment options can then be applied, and doctors are able to offer their patients the best chance of survival.

Diagnostic nuclear imaging procedures are currently used to detect the spread of melanoma and non-melanoma skin cancers to the lymph nodes, and for evaluation of distant metastases.

In early stage melanoma, lymphatic mapping agents labelled with the radioisotope Technetium 99-m (Tc-99m) are used to locate sentinel nodes for sentinel lymph node biopsy which aims to detect microscopic cellular metastases. In advanced stage melanoma and non-melanoma skin cancer, FDG-PET/CT is used to evaluate disease in the lymph nodes and other distant metastases. Further information about each of these important diagnostic tools is provided below.

a) Tc-99m Based Lymphatic Mapping for Early Stage Malignant Melanoma

Lymphatic mapping via lymphoscintigraphy is used in disease staging for patients with high risk early stage (stage I or II) melanoma.[1] Gamma signals emitted from Tc-99m[2] based radiotracers are detected with either a hand-held gamma counter or with a Single Photon Emission Computed Tomography (SPECT) camera. Lymphoscintigraphy determines which lymph node fields contain the node or nodes which receive direct drainage from the tumour site, known as the sentinel node(s).

Lymphoscintigraphy identifies 94.5% of sentinel nodes. Subsequent to lymphoscintigraphy, sentinel node biopsy is performed.[3] Sentinel nodes are removed via wide surgical excision and examined for metastatic spread. Sentinel node biopsy provides important information on disease prognosis and can result in complete regional lymph node dissection if sentinel nodes are found to contain metastatic melanoma cells. Alternatively, sentinel node biopsy avoids complete regional lymph node dissection, which can result in significant morbidity in patients with no evidence of metastatic disease.[4]

In Australia, Lymphoscintigraphy is reimbursed on the Medicare Benefits Schedule (MBS). Colloidal Antinomy Sulphide cold kits for combination with Tc-99m are registered on the Australian Register of Therapeutic Goods (ARTG) for lymphatic mapping. Other radiolabelled colloid based tracers can also be used for lymphatic mapping, although they are not currently registered on the ARTG.

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[1] Emmett & Ho, 2012, Imaging for Melanoma and Non-Melanoma Skin Cancers, *CancerForum*, 36(3)

[2] Tc-99m is derived from Molybdenum-99, which is manufactured at ANSTO from targets irradiated in the OPAL reactor.

[3] Melanoma Institute Australia, Sentinel Node Biopsy Procedure, Patient Information, http://www.melanoma.org.au/files/15842_SENTINEL_NODE_BIOPSY_w.pdf

[4] Chen, S., Iddings, D., Scheri, R., Bilchik, A. 2006, Lymphatic Mapping and Sentinel Node Analysis: Current Concepts and Applications, *CA: A Cancer Journal for Clinicians*, 56(5): 292-309

b) FDG-PET/CT for Metastatic Malignant Melanoma

Positron Emission Tomography–Computed Tomography (better known as PET/CT) is a three-dimensional medical imaging technology that uses the agent **FDG**, (fluoro deoxy glucose). FDG is an intravenously administered radiopharmaceutical used to help diagnose certain medical conditions[5].

FDG-PET/CT has an important role in identifying lymph node disease in patients with stage III and IV melanoma. FDG-PET has been demonstrated to have a high diagnostic accuracy in stage III and IV disease and has been shown to change patient management. FDG-PET can be used in stage III and IV melanoma as a surgical planning tool, to guide resection of metastases, in assessment of disease recurrence, for planning treatment fields for radiation therapy, and for assessing treatment response.[6] FDG-PET can also serve as a prognostic indicator, with localisation of visceral metastases being a poor prognostic indicator relative to localisation of metastases to the skin. In Australia FDG-PET is reimbursed via the MBS for evaluation of suspected metastatic or recurrent malignant melanoma in patients considered suitable for active therapy, following initial therapy.

c) FDG-PET/CT for Merkel Cell Carcinoma

The use of FDG-PET in Merkel Cell Carcinoma (MCC) has not been fully established, with a lack of larger prospective studies, but results obtained to date are promising.[7] An Australian study of 102 patients who underwent FDG-PET scans for staging purposes at the Peter MacCallum Cancer Centre in Melbourne found that FDG-PET changed the management of 37% of MCC patients and altered stage of 22%.

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[5] Flourine-18, the active ingredient of FDG, is produced in cyclotrons. There are a number of cyclotrons in Australia used for the production of F-18, including two operated by the ANSTO subsidiary PETNET Solutions Australia.

[6] Bourgeois, A., Chang, T., Fish, L., Yong, B. 2013, Positron Emission Tomography/Computed Tomography in Melanoma, *Radiologic Clinics of North America,* 51(5): 865-879

[7] Siva, S., Byrne, K., Seel, M., Bressel, M., Jacobs, D., Callahan, J., Laing, J., MacManus, M., Hicks, R. 2013, 18F-FDG PET Provides High-Impact and Powerful Prognostic Stratification in the Staging of Merkel Cell Carcinoma: A 15-Year Institutional Experience, *Journal of Nuclear Medicine*, 54(8)1223-1229

d) FDG-PET/CT in Basal and Squamous Cell Carcinoma

Most basal and squamous cell carcinomas do not require diagnostic evaluation, but in high-risk patients with aggressive disease FDG-PET/CT is the modality of choice for evaluating nodal involvement and distant metastatic spread. FDG-PET is reimbursed on the MBS for the evaluation of metastatic squamous cell carcinoma of unknown primary site involving cervical lymph nodes. The sensitivity and specificity of PET/CT in staging and follow up for aggressive non-melanoma skin cancers has not yet been fully elucidated.

4. The future of nuclear medicine in skin cancer diagnosis and treatment

Nuclear medicine will continue to play a key role in the diagnosis of skin cancer, and the ability of some radiopharmaceuticals to target cancers in the body offers the exciting possibility of the development of therapeutic applications.

Current research on improving nuclear imaging techniques is focused on improving detection and localisation of lymph nodes, because their condition can provide much information about the prognosis of a patient. For example, a recent study demonstrated that combining SPECT with Computerised Tomography (CT) in a hybrid system to provide anatomical information changed management in 57% of patients with head and neck melanoma[8]. The optimisation of imaging protocols and quantification with FDG PET/CT will further improve early detection of metastasis, thereby improving long-term prognosis.

The greatest value brought by PET will be in improving radio-ligands (or imaging agents') ability to target the metastasis for better therapy management.

There are also exciting new developments in the possible use of radioisotopes in the treatment of skin cancers. For example, new nanoparticles have been functionalised with

[8] Zender C, Guo T, Weng C, Faulhaber P, Rezaee R, Utility of SPECT/CT for periparotid sentinel lymph node mapping in the surgical management of head and neck melanoma, Am J Otolaryngol. 2014 Jan-Feb;35(1):12-8. doi: 10.1016/j.amjoto.2013.08.004. Epub 2013 Oct 18

tumour-targeting molecules and metal chelates which can host Gallium-68. The first validation has been performed in rodents, targeting micro-vasculature receptors (over-expressed mostly in melanoma and breast cancers)[9]

[9] Gallo J, Alam IS, Jin J, Gu YJ, Aboagye EO, Wong WT and Long NJ, PET imaging with multimodal upconversion nanoparticles, Dalton Trans. 2014 Feb 18