Review

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# Technological Advancements in Nuclear Medicine and Molecular Imaging

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## Abstract

As in most other specialties, technological advancements had their share in nuclear medicine. New synthesis equipment lets departments locally synthesize new radiopharmaceuticals (rfs), to diagnose new pathologies, and treat new conditions. More specific, more sensitive and newer rfs pave the way to diagnosing newer pathologies. On the other hand, new hardware and software increased the image acquisition time and the resolution of images. Once only a scientific interest for few centers, artificial intelligence is now more widespread, more commercialized, from working on improving image quality to diagnosing diseases as well as-and even better than-expert physicians.

**Keywords:** Technological advancements, nuclear medicine, pet, gamma camera

## INTRODUCTION

Developments in technology have let the Nuclear Medicine Departments synthesize new radiopharmaceuticals (rts); image and treat new pathologies; acquire new Positron emission tomography (PET) and gamma cameras with smaller, faster, and more efficient detectors with sharper resolutions, and in more convenient positions for the patient. New software has also increased the speed of acquisition and image sharpness and detail, and it helped to reduce the patient exposure to radiation, sometimes even complementing physicians in diagnosing of diseases.

### New Radiopharmaceuticals

As of 2018, there are approximately 50 rts approved by the Food and Drug Administration, and of these, 17 are Technetium 99m labeled. Yttrium 90 and Lutetium 177 are used for treatment; Xenon is used for lung studies; N13-Ammonia , Rubidium 82, and Thallium 201 are used for cardiac imaging; Samarium 153 and Strontium 89 are used for bone pain palliation; Iodine-labeled rfs are commonly used for thyroid and for renal imaging; Gallium 68 is used for neuroendocrine imaging and other applications that are obsolete now; and all-favorite oncology probe fluorodeoxyglucose is also used for dementia imaging and cardiac imaging. Most of these rts have a well-established clinical application and a relatively long history and clinical experience. Inside and outside this list, there are some less used but important agents that shed some light on the future of nuclear medicine.

### Prostate Cancer

C11 Choline reflects the speed of cell wall synthesis, and for some time, it played a role in suspected prostate cancer recurrence detection (Figure 1), but it was soon replaced by Ga68-labeled prostate specific membrane antigen (PSMA) antibodies. PSMA, not exactly specific, although first documented in a prostate cell culture approximately 30 years ago, have been efficiently targeted recently. Still not 100% sensitive nor 100% specific, it is currently by far the best agent to detect the lymph node involvement or finding sites of recurrence, and it is possibly as effective as multiparametric prostate magnetic resonance imaging (MRI) to detect clinically significant prostate cancer. Fluorine 18-labeled synthetic amino acid derivative fluciclovine (Axumin, Blue Earth Diagnostics) competes with PSMA for the same setting, but preliminary studies favor the PSMA targeting (1).

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While fluciclovine has been introduced into the NCCN guidelines, there has been no even application from any producer to have PSMA agents approved, possibly due to regulatory and commercial issues. The latest European urology guidelines discuss the PSMA imaging in staging and post-surgical and post-radiotherapy recurrence of prostate cancer (2, 3).

**Dementia**

One group of tracers that major pharmaceutical companies have invested in are the amyloid-seeking agents, florbetaben (Piramal, Neuraceq), florbetapir (Elly Lilly, Amyvid), and flutemetamol (GE Healthcare, Vizamyl, Figure 2). Imaging for the amyloid has shown that some patients without Alzheimer's had an amyloid build up, even in some apparently normal aging subjects, hence lowering the positive predictive value. On the other hand, a negative amyloid scan (i.e., no significant amyloid deposition) effectively rules out Alzheimer's disease (4).

Although these tracers have not gained firm integration into guidelines for the diagnosis of Alzheimer's disease, there are three clinical situations where amyloid imaging is appropriate; the atypical age of onset, atypical presentations of Alzheimer's, and unexplained minimal cognitive impairment (5).

**Brain Tumors**

Several rts have emerged to image brain gliomas, and researchers have accumulated clinical evidence on the benefits and limitations of each. There are two properties of rfs that create the image of a brain tumor: transport through the blood-brain barrier and metabolism in tumor cells (Figure 3).

While malignant brain tumors accumulate FDG F18 as elsewhere in the body, a strong and variable uptake by the brain gray matter limits the use of this tracer. Also, F18-labeled compounds have the advantage of production outside the facility and easier transport, in contrast to carbon-11-labeled compounds that need to be produced on site.

The group of tracers composed of large neutral amino acids (i.e., C11 MET-methionine-, F18 FET-fluoroethyltyrosine-, C11 AMT-alphamethyltryptophan, F18 FDOPA) provide better differentiation of benign versus malignant lesions, even between low-grade versus high-grade gliomas. The extent of the uptake of these tracers reflects tumoral extension and provides complementary information to the MRI-enhanced region (6). In addition, time-variant uptake of FET may provide prognostication further than the 1p19q deletion or the IDH mutation status of tumor (7) (Figure 4).

Proliferation markers such as F18 FLT-fluorothymidine and C11 Choline have also been used, where their sensitivity is slightly lower than amino acid tracers to detect malignant gliomas, and they do not have a significant uptake in low-grade gliomas. Still, they provide similar prognostication and post-RT/post-surgical follow-up of gliomas as the amino acid tracers.

Targeting biopsy of brain tumors have been consistently shown to be more accurate using information provided by amino acid tracers. They show the most malignant part, which in turn determines the prognosis. GTVs from amino acid PET scans can be used for radiotherapy planning, in conjunction with MRI GTV, expecting better clinical outcomes. Another agent, F18 Fluoromisonidazole shows tissue hypoxia, and these regions of tumor are more radioresistant. Targeting these regions with higher radiotherapy doses is tempting. For therapy monitoring, especially amino acid tracers seem more immune to the effects of pseudoprogression and pseudoresponse, which is a significant problem in MRI imaging.

**New Radionuclide Therapies**

Therapy of thyroid cancer, Graves' disease, and hyperactive nodules with radioactive iodine (I131) has been in the field of interest of nuclear medicine for decades. In recent years, there have been advances in palliation of bone metastases with alpha-emitting radionuclides, local therapies of hepatic tumors, and systemic therapies of prostate cancer and neuroendocrine tumors.

The key point of alpha-emitting radionuclides is that the tissue penetration of these particles is very short, preserving healthy tissues and irradiating tumor cells with a high energy transfer. Ra223 is an important alpha-emitting radionuclide, which is primarily used for the treatment of prostate cancer bone metastases.

Injecting beta-emitting particles through the hepatic artery is an important treatment choice for unresectable primary hepatic tumors and liver metastases. Labeling glass microspheres or resin microspheres with Y90 is a good alternative especially for liver-limited unresectable disease. The terms selective internal radiation therapy and transarterial radioembolization are commonly used to define this therapy. Ho166 is also a promising radionuclide in this field.

The concept of *theranostics* became popular with the advance of the Ga68 PET/CT imaging. Personalized therapy and the use of appropriate agent, as well as the appropriate dose, are the key facts of this term. A combination of therapy and diagnostics form this concept. Ga68 PSMA avid prostate cancer metastases and Ga68 DOTATATE avid neuroendocrine tumor lesions can be treated with Lu-177-labeled PSMA and Lu177-labeled DOTATATE, respectively. The Ga68 imaging guides the therapy dose and potential utility of Lu177 therapies. Developing new radionuclides such as Ac225 also seem promising in therapy.

**New Hardware**

After reports showing a significant contribution of myocardial perfusion SPECT studies to medical radiation and increased awareness of radiation in medical and nonmedical community, the medical device/software manufacturers raced to bring new technology to address the issue.

In gamma cameras, the solid-state cadmium zinc telluride detectors (CZT) instead of traditional NaI crystals brought an improved sensitivity to detect photons. This let physicians use less of the rts (less radiation) and less imaging time. Radiation exposure was reduced 2-4 times in addition to quicker and more comfortable procedures (Figures 5 and 6).

New reconstruction algorithms from manufacturers promise resolution recovery, decreased image noise, scatter and attenuation corrections, altogether to decrease necessary radioactivity and study times (*8*).

These improvements also came with innovations in detection physics, sometimes in the form of moving collimators to focus on the organ to be imaged, collecting only the information from the

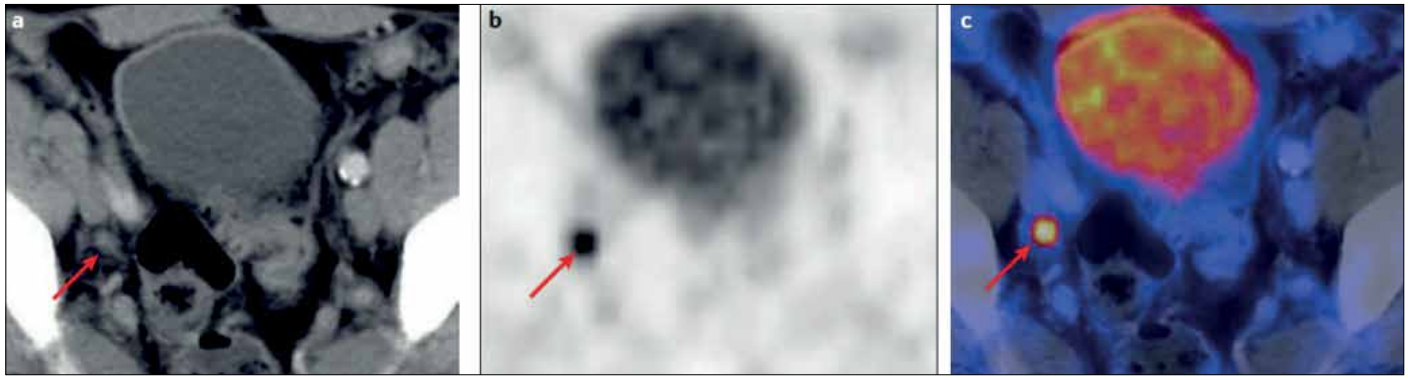


Figure 1. Choline PET. Pelvic lymph node metastasis of prostate cancer

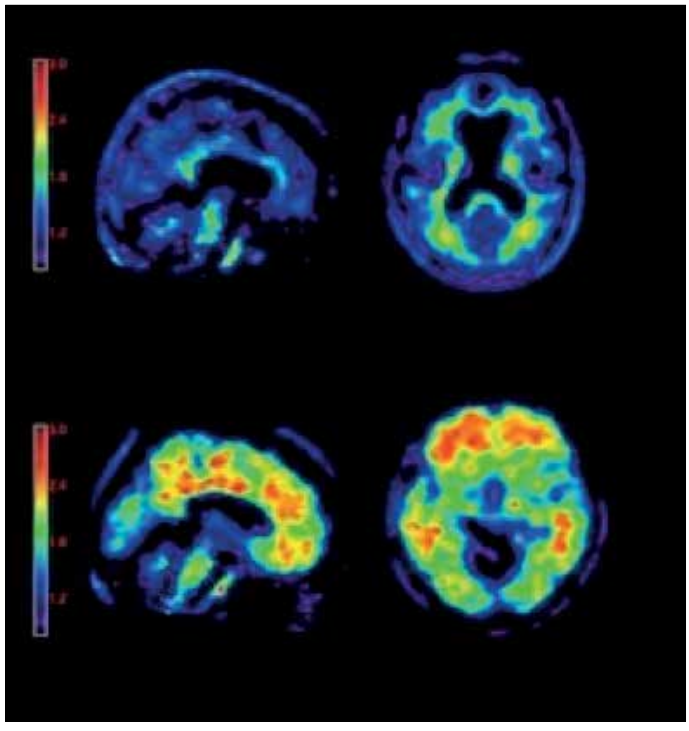

Figure 2. Negative and positive amyloid PET scans with flutemetamol

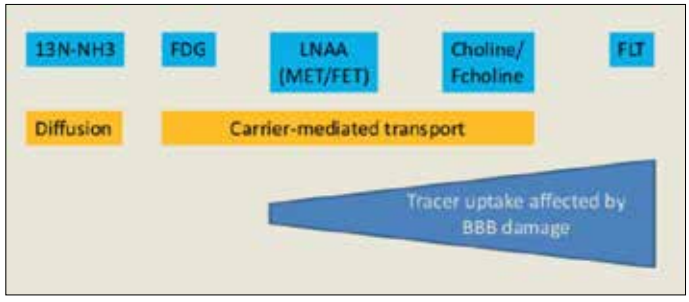


Figure 3. Mechanisms of uptake for radiopharmaceuticals for brain tumor imaging

target volume of interest.

Positron emission tomography always enjoyed the inherent creation of 3D images with a 360-degrees gantry and detectors completely surrounding the patient, while gamma camera de-

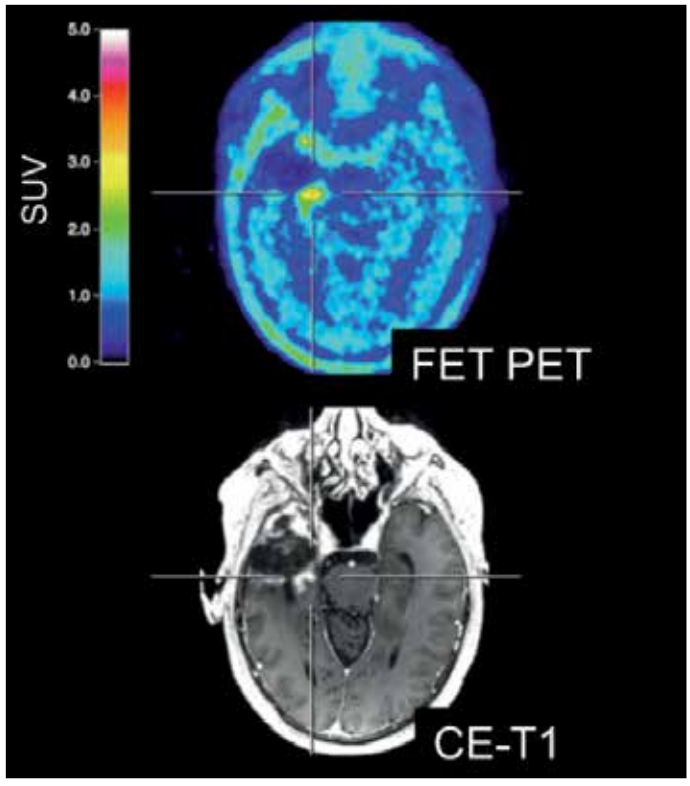


Figure 4. FET and MRI images of glioma

tectors (1 to 3 in number) needed to turn to create tomography images. Recent introduction of a gamma camera with 12 detectors will be able to create PET-like 3D images of a whole-body gamma camera scan (Figure 7).

A conventional PET scanner images 10-30cm at each bed position. After acquiring required counts from each position, the bed advances, and this continues until required parts of the body, typically head to thighs, are imaged, taking approximately 10-15 minutes. A recent development was introduction of a whole-body PET scanner that can image a whole body in under a minute. It is still under construction, but it may greatly decrease the radiation exposure and increase lesion to background ratios (9) (Figure 8).

**New Software and Artificial Intelligence**

Even before its recent popularity, the artificial intelligence (AI) was present in molecular imaging, evaluating bone and renal scans.

However, it was mostly single-center produced and not commercialized. Thanks to the already massive technical knowledge built up in myocardial perfusion imaging, reconstructing, detecting borders of myocardium, aligning images, quantifying its perfusion, and millions of SPECT scans performed in the world, this subfield was ready for deeper learning. Previous studies mentioned AI algorithms matching physicians in disease detection. This year, researchers using a multi-institution database comprising about 20,000 patient data, reported that AI predictions were better than those of expert physicians (10). Another study reports development of software that predicts survival from an index of metastasis burden of prostate cancer patients from their bone scans (11).

Artificial intelligence may also help reduce the radiation exposure of patients. A group of researchers trained AI starting from


Figure 5. Spectrum Dynamics D-SPECT gamma camera with CZT detectors

Figure 6. GE Discovery NM 530C with CZT detectors and focused collimators

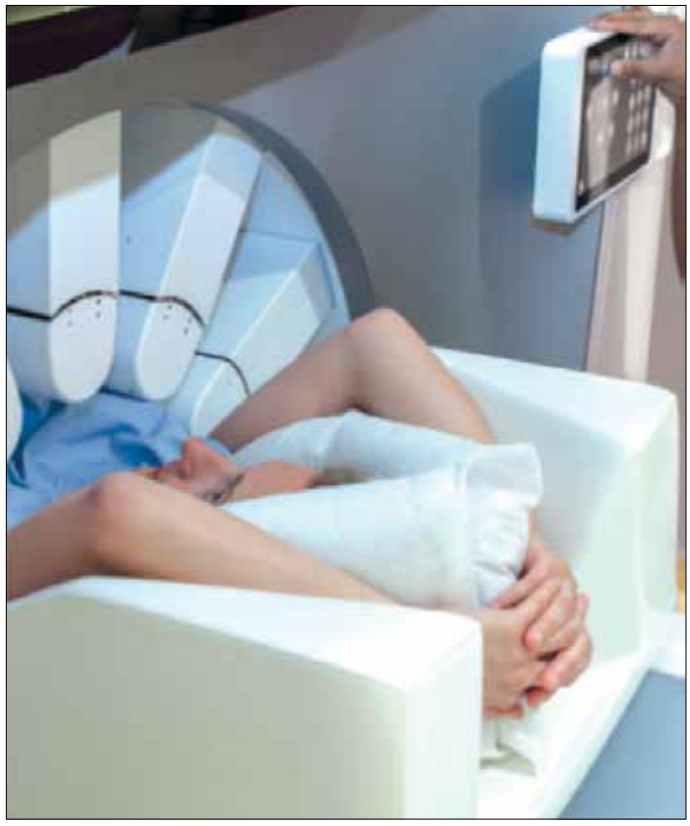

Figure 7. GSpectrum dynamics, veriton gamma camera

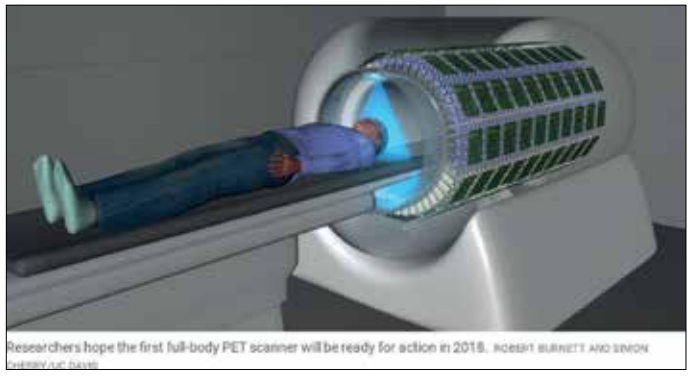


Figure 8. Whole-body PET scanner under development

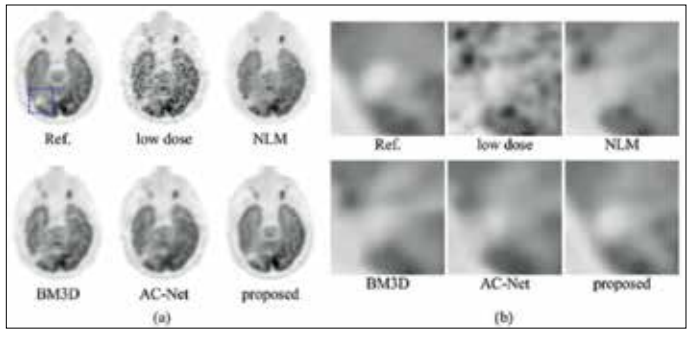


Figure 9. The low dose image in top row, center, left corner original image, NLM, BM3D and AC-Net are alternative methods compared with the proposed AI trained recreated image. Zoomed patches on the right half

an ultralow dose PET image-1/100 to 1/200$^{th}$ of normal dose-to create a high quality image that could then be evaluated visually or quantitatively by physicians (12) (Figure 9).

Another AI was trained and diagnosed dementia from the FDG PET and amyloid scans, 2 years before the onset of symptoms for amyloid scans (13).

## CONCLUSION

The future looks bright and exciting for nuclear medicine/molecular imaging. The new pharmaceuticals open up new horizons, and we may be able to treat, even cure, new diseases. With new cameras and better, quicker detectors, images are sharper, acquisitions are faster, and radiation burden on patients is reduced. AI may prove to be an important aid to physicians.

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