A Bright Future for PSMA PET Imaging in Prostate Cancer*

About 1 in 8 men will be diagnosed with prostate cancer during his lifetime[1]. In Europe, it is the most common cancer in men and the third leading cause of death in men[2,3]. Prostate cancer typically affects men over the age of 70.

In the UK, about 1 in 8 men will get prostate cancer at some point in their lives.

Figure 1: *Prostate cancer risk in the UK.*

Figure 2: *Estimated number of new cases (incidence), death (mortality) and total number of cases (prevalence) of prostate cancer in 2018 in Europe in males among all cancers[2,3].*

Today it can be very difficult to identify patients with oligometastases using conventional imaging techniques, such as CT and bone scan.

Prof. Joe M. O'Sullivan, MD
Professor of Radiation Oncology, Queen's University Belfast.

Recent improvements in prostate cancer treatment strategies

Since 1994, there has been a 40% reduction in the prostate cancer mortality rate, with the most dramatic reduction in men aged 70-79[4].

There are several factors leading to improved survival, according to Joe M. O'Sullivan, MD, Professor of Radiation Oncology, Queen's University Belfast and a Consultant Oncologist at Northern Ireland Cancer Centre, Belfast (Ireland).

First, oncologists are getting better in treating non-metastatic prostate cancer with a variety of therapies—surgery, robotic surgery, brachytherapy and external beam radiation. Several studies have demonstrated the addition of castration therapy to radiation therapy improves overall survival[5-7].

"*However, metastatic prostate cancer and particularly metastatic disease that no longer responds to the castration therapy, remains a lethal disease for the majority men,*" says Professor O'Sullivan. Responses to Androgen deprivation therapy (ADT), currently the best systemic therapy available, typically last 12 months. Men who no longer respond to hormone therapy and have progressive metastatic disease have a median survival of 22 months, he adds.

Results reported from randomized control trials over the past decade are changing clinical practice in Metastatic Castration Resistant Prostate Cancer (mCRPC). Specifically, the emergence of a number of new drugs which have all improved survival.

"*We have many more treatments today for castration-resistant disease and many of these treatments are moving upstream into the hormone sensitive metastatic patient, especially docetaxel and abiraterone, again with big survival benefits,*" Professor O'Sullivan explains.

Challenges in prostate cancer management

While there have been significant improvements in outcomes for patients due to survival-prolonging therapies, treating prostate cancer has become more complex. For example, biochemical recurrence (BCR) is still a frequent clinical problem with an estimated 20-30 percent recurrence rate in patients that have received localized therapy and is typically detected by a rise in PSA levels[8].

"*We are overtreating many stages of prostate cancer and this is resulting in an increase in costs, especially with these expensive new drugs that are now available,*" says Professor O'Sullivan. "*We have no ideal treatment sequence and this is where our colleagues in radiology and nuclear medicine can help.*"

Multi-parametric MRI (mpMRI) is a widely used imaging method to aid in the evaluation of prostate cancer. The mpMRI results can be combined with PET either through fusion of exams acquired separately, or imaged simultaneously using hybrid PET/MR systems.

PET imaging has a key role to play to optimize patient management, particularly with the emergence of Prostate-Specific Membrane Antigen (PSMA) PET imaging. Specifically, PSMA PET is helpful to study patients with BCR to early localize the site of disease recurrence, says Stefano Fanti, MD,

Professor of Diagnostic Imaging at University of Bologna.

"*PSMA PET may early identify patients with oligometastatic disease, meaning those with less than 5 localizations. These patients are likely to have a longer survival than those with advanced cancer,*" he explains. "*Today it can be very difficult to identify patients with oligometastases using conventional imaging techniques, such as CT and bone scan. If we can identify these patients with a very sensitive tracer such as PSMA, we may be able to offer more treatment options to them.*"

PSMA PET/CT imaging revolutionizes prostate cancer staging and relapse diagnosis

Professor O'Sullivan believes that PSMA PET imaging is likely to become a standard in PET imaging of prostate cancer and can help in several ways.

According to Professor Fanti, there is no question regarding the superiority of PSMA over other molecules such as Choline (either labelled with C-11 or F-18) based on the current literature. To date, there are about 1,000 papers from the nuclear medicine community regarding the use of PSMA PET in prostate cancer diagnosis and treatment.

The main indication for PSMA PET imaging is BCR; however PET can help better stage the disease at diagnosis, especially in patients at high risk, by showing metastases that are not seen with conventional imaging. In such setting, a recent review paper reported a 70 percent detection rate with PSMA PET, far higher than the 40 to 50 percent detection rate with C-11-Choline[9] (Figures 3, 4).

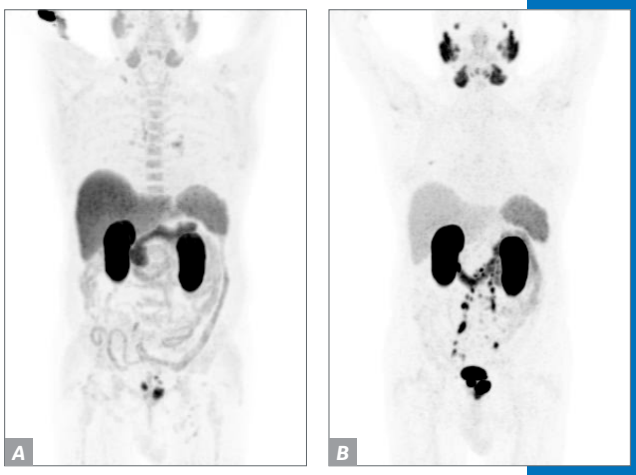

Figure 3: *PET/CT images from the same patient with (a) C^{11}-Choline and (b) Ga^{68}-PSMA. Images demonstrated superiority of Ga-PSMA in staging prostate cancer.*

Of course PSMA PET can be usefully applied to re-stage patients already operated on. The superior accuracy of PSMA over Choline may help make better decisions such as avoiding unnecessary treatments or escalating treatments depending on the spread of disease (Figure 4).

PSMA PET imaging is able to detect oligometastases, with high sensitivity and very high specificity[10]; and oligometastases in some cases could be treated with focally directed therapy. The outcome of those treatments could be the extension of the population of curable patients (Figure 5) or the improvement of patients' quality of life delaying time to commencement of Androgen deprivation therapy or other systemic therapies.

Now we are able to better meet the needs of prostate cancer patients with 68-Gallium from the PETtrace cyclotron.

Peter Scott, PhD,
Director, PET Chemistry and Research Associate Professor, Radiology, at the University of Michigan.

PSMA PET can surely help identify small areas of relapse earlier in BCR to optimize therapy. In 2019 the European Association of Urology updated its guidelines on prostate cancer to include PSMA PET/CT as the preferred imaging method at biochemical recurrence or persistent PSA.

Low availability of Gallium-68 PSMA agent has been a limiting factor to the development of PET PSMA imaging. It is now possible to produce Gallium-68 in cyclotrons helping increase access to the tracer and reduce cost per examination.

"*We have never sent this much PSMA to our clinic before,*" says Peter Scott, PhD, Director, PET Chemistry and Research Associate Professor, Radiology, at the University of Michigan. "*Now we are able to better meet the needs of prostate cancer patients with 68-Gallium from the PETtrace cyclotron.*"

PSMA PET imaging can be further improved using Q.Clear, a Bayesian penalized-likelihood reconstruction algorithm designed to improve image quality and quantification by controlling or penalizing noise during image reconstruction. A recent publication demonstrated[11] PSMA images reconstructed with Q.Clear improved target-to-background uptake ratio compared to OSEM. Q.Clear can also enable a shorter acquisition time.

Professor Fanti says images reconstructed with Q.Clear are sharper than conventional reconstruction techniques, especially for visualization of smaller lesions. And that makes him more confident in seeing and assessing lesions in his report.

"*The better we can see the lesions, the more confident we are with our reporting,*" explains Professor Fanti.

Last but not least, theranostics with PSMA targeted therapy may lead to a therapy revolution.

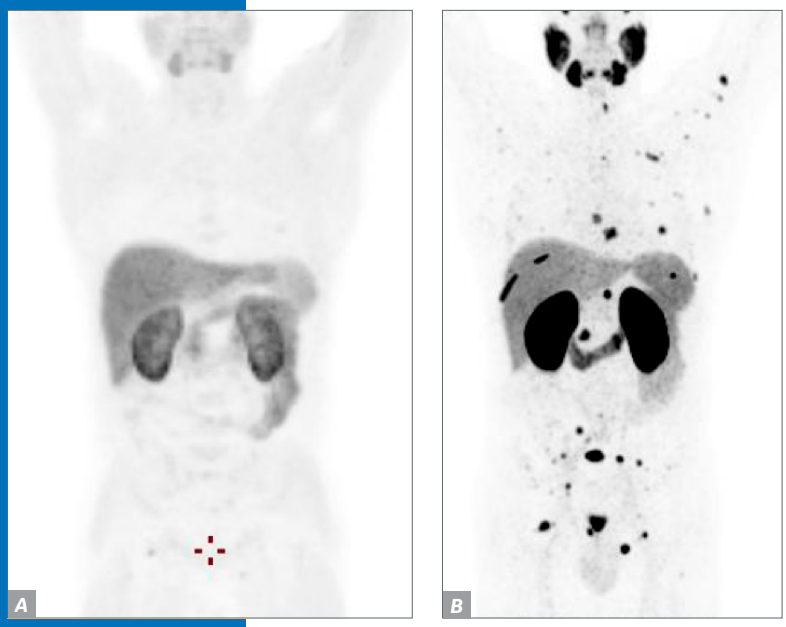

Figure 4: PET/CT images from the same patient who had previously undergone treatment for prostate cancer with (a) C^{11}-Choline and (b) Ga^{68}-PSMA. Images were acquired 10 days apart and showed superiority of Ga^{68}-PSMA in detecting prostate cancer metastases.

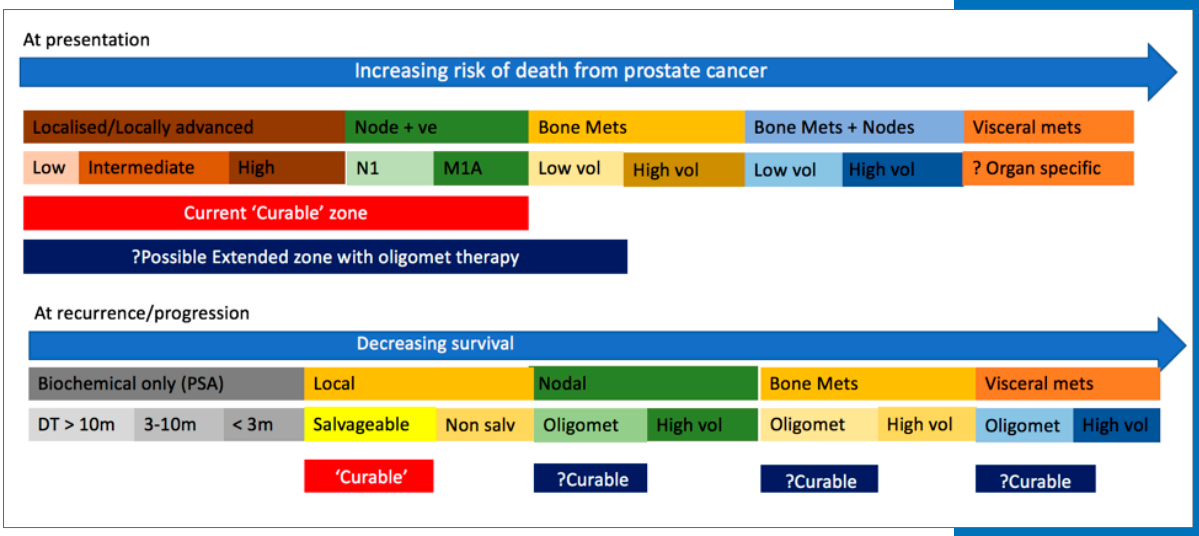

Figure 5: *Potential extension of the curable zone for patients suffering from prostate cancer.*

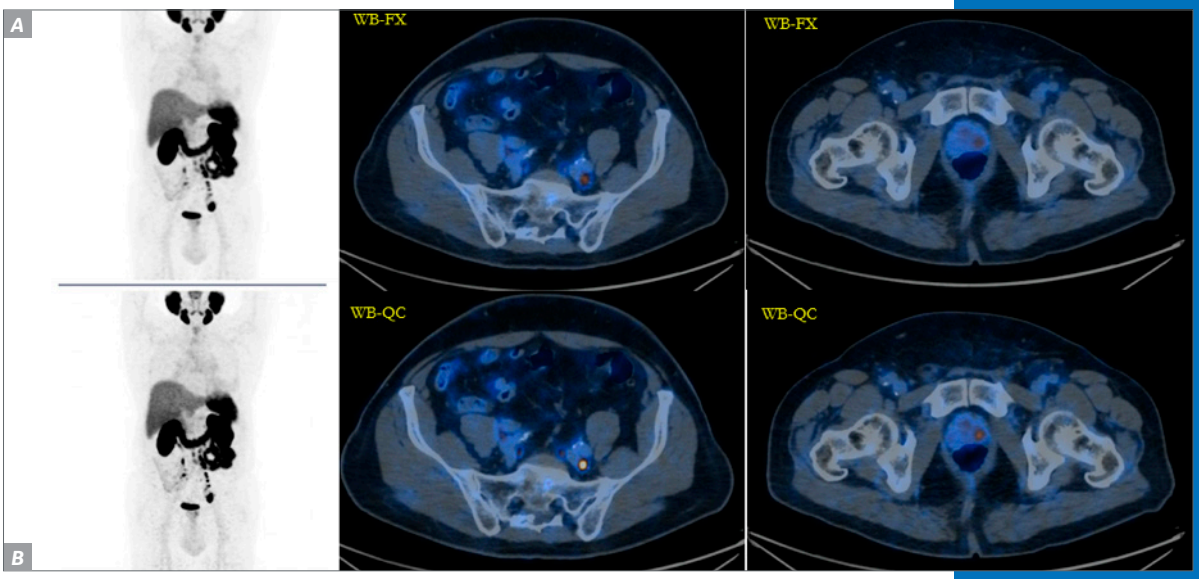

Figure 6: *68-Gallium PSMA images acquired on Discovery MI 3 rings system and reconstructed with PSF OSEM reconstruction (a) and Q.Clear reconstruction (b) demonstrating Q.Clear produces sharper images with better visualization of small lesions in this specific case.*

Emergence of PSMA Theranostics

Theranostics combines therapeutics and diagnostics by using one radioactive drug to detect disease and another to treat it. In prostate cancer, PSMA is usually labelled with a ß- (positron) emitter, such as Gallium 68, for PET diagnosis and can be labelled with a ß+ emitter, such as Lutetium 177, for therapy and SPECT imaging and dosimetry.

The concept of theranostics is very simple, as "*What we see is what we treat*" explains Professor Fanti. "*With PSMA PET, we have a great tracer that delivers an improvement in what we can visualize.*" And replacing the imaging isotope with a therapeutic isotope is feasible and allows to treat exactly the same lesions that you have demonstrated by imaging.

The first patient was treated with 177-Lutetium – PSMA-617 in 2014.

With PSMA PET, we have a great tracer that delivers an improvement in what we can visualize.

Prof. Stefano Fanti, MD,
Professor of Diagnostic Imaging at University of Bologna.

"The initial data are promising with the safety profile of PSMA being reasonably favorable and a good impact on overall survival," says Professor Fanti. In one of the first multi-center studies on PSMA therapy, researchers demonstrated a decline in PSA in 70 percent of the patients and a reduction of more than 50 percent PSA in approximately 40 percent of the subjects[12].

Another single center phase 2 study published in Lancet Oncology reported high response rates, low toxicity, and less pain in men with metastatic castration-resistant prostate cancer with disease that progressed after conventional treatments[13].

"The original results reported by the Peter MacCullum Cancer Center was greater than 50 percent reduction in PSA in more than half of the patient enrolled," Professor Fanti explains.

There are currently at least 10 clinical trials recruiting on 177-Lutetium PSMA making this a very active field.

Some other ongoing research are investigating treatment using PSMA labelled with an alpha emitter, such as Actinium-225, with impressive results[14]: however, there are a limited number of trials due to the lack of availability of Actinium.

Still, PSMA theranostics is only accessible to a minority of patients as it is currently only used as a last line opportunity in patient that have exhausted their options with other therapies. In many instances, PSMA theranostics is not a reimbursable procedure, rather patients are paying out-of-pocket for the therapy.

To change this, Professor Fanti explains, nuclear medicine must pursue well-designed trials that deliver the scientific evidence that oncologists need to include new therapies in their arsenal and that insurers demand to initiate reimbursement.

"It is easy to predict a bright future, either for PSMA imaging and therapy, as we have seen results that are absolutely incredible," says Professor Fanti.

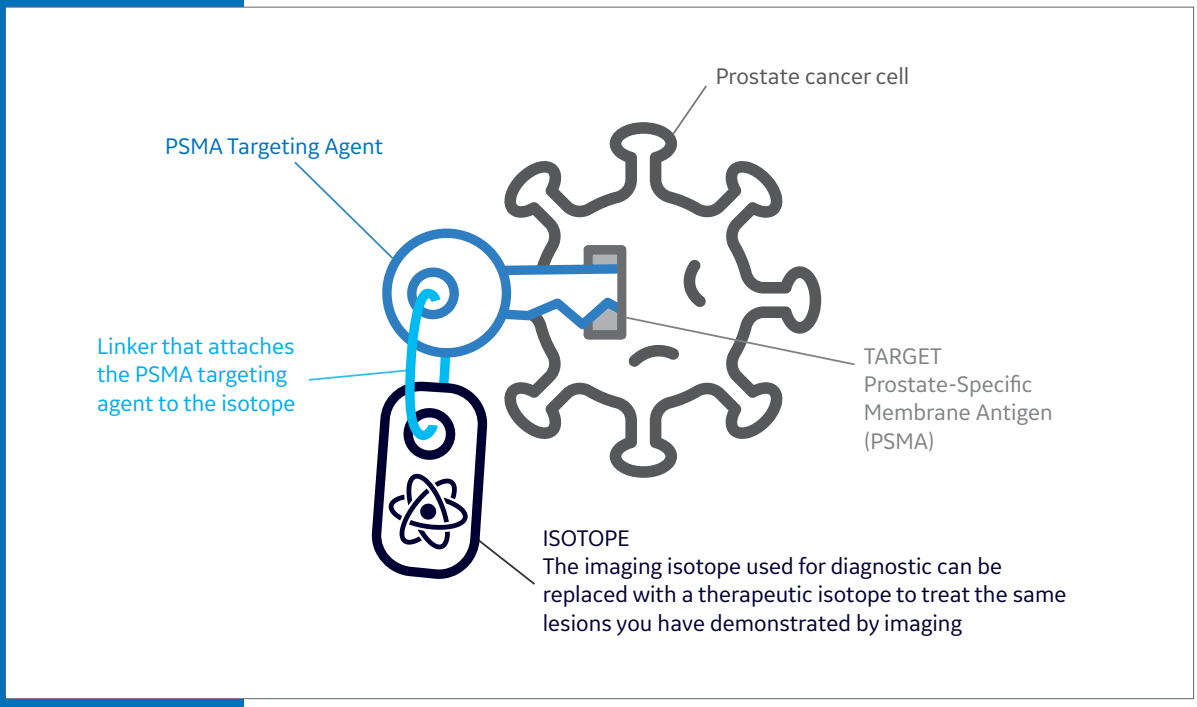

Figure 7: *Targeted imaging and treatment of prostate cancer using PSMA theranostics.*

References

1. *Prostate cancer UK. Available at: https://prostatecanceruk.org/prostate-information/are-you-at-risk/infographic-what-is-my-risk. Accessed June 2019.*

2. *Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.*

3. *Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe:Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018 Nov;103:356-387.*

4. *Prostate cancer mortality statistics. Cancer Research UK. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/mortality#heading-Three (accessed May 2019)*

5. *Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiation Oncology Biol Phys 2005;61:1285–1290.*

6. *Bolla M et al. Long term results of immediate adjuvant hormonal therapy with goserelin in patients with locally advanced prostate cancer treated with radiotherapy — A phase III EORTC study. Eur J Cancer 1999;35(Suppl_4);S82.*

7. *Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 2011;378:2104–2111.*

8. *Kolodziej M. Management of Biochemically Recurrent Prostate Cancer Following Local Therapy. Am J Manag Care. 2014;20:S273-S281.*

9. *Tan N, Bavadian N, Calais J, et al. Imaging of a Prostate Specific Membrane Antigen Targeted Radiotracers for the Detection of Prostate Cancer Biochemical Recurrence After Definitive Therapy: A Systematic Review and Meta-Analysis. J Urol. 2019 Feb 25:101097JU0000000000000198. doi: 10.1097/JU.0000000000000198. [Epub ahead of print]*

10. *Perera M, Papa N, Christidis D, et al. Sensitivity, Specificity, and Predictors of Positive 68Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. 2016 Dec;70(6):926-937.*

11. *Lindström E, Velikyan I, Regula N, et al. Regularized reconstruction of digital time-of-flight 68Ga-PSMA-11 PET/CT for the detection of recurrent disease in prostate cancer patients. Theranostics 2019; 9(12): 3476-3484.*

12. *Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. J Nucl Med. 2017 Jan;58(1):85-90. doi: 10.2967/jnumed.116.183194. Epub 2016 Oct 20.*

13. *Hofman MS, Violet J, Hicks RJ, et al. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018 Jun;19(6):825-833.*

14. *Sathekge M, Bruchertseifer F, Knoesen O, et al. 225Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study. Eur J Nucl Med Mol Imaging. 2019 Jan;46(1):129-138.*

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* PSMA radiopharmaceutical may not be approved by ministers of health in all regions.
This article is based on Prof. Stefano Fanti and Prof. Joe O'Sullivan presentations at Meet the experts' event in Bologna JB70503XX & JB70502XX.

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