Overview

- Introduction
- Overview of molecular imaging in prostate cancer
- Limitations and future prospects
- Current UK perspective
Introduction

- Clinical staging and treatment paradigms in prostate cancer based on conventional imaging (CT and bone scintigraphy) with well-established predictive and prognostic value.
- Multi-parametric MRI is a relatively recent addition following rigorous evaluation in clinical trials.
- Molecular imaging (MI) has rapidly entered clinical practice in many parts of the world but without thorough evaluation in well designed clinical trials.
- As yet there is no consensus agreement on whether MI should supplement or supersede conventional imaging.
Introduction

- Economic forces vary markedly between countries and create a challenge to unification of imaging technology application
- Regulatory oversight of PET radiotracers differs across the globe, posing barriers to harmonized adoption of novel tracers and clinical trials
- In some countries e.g. Australia radiotracers produced on site in hospital radiopharmacies are exempt from regulatory brakes which enables early adoption but can create a disincentive to prospective evaluation in well-designed trials
Applying information from new imaging techniques without having first learned their value from systemic analyses of data collected in a standardized approach risks putting the cart before the horse.
PET tracers in Prostate Cancer

- Choline
- Fluoride
- Fluciclovine (FACBC)
- Prostate Specific Membrane Antigen (PSMA)
Choline PET-CT
Background

- Choline is a precursor for biosynthesis of cellular membrane phospholipids and a marker of membrane metabolism and turnover which are increased in prostate cancer\(^1\)

- European Association of Urology recommendation\(^2\) to use Choline PET-CT in assessment of patients with biochemical relapse of prostate cancer after prior local treatment with curative intent if:
  - PSA is > 1 ng/mL
  - Results would influence patient management

- Can also be used to stage patients pre-op with high-risk features e.g. possible nodal disease on CT or MRI

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\(^1\)Podo F. NMR Biomed 1999; 12: 413
\(^2\)Heidenreich et al. Eur Urol 2014; 65: 467
Detection in biochemical recurrence

- Diagnostic yield of conventional imaging is poor – CT 11-14% positivity rate; bone scan < 5% when PSA < 7
- Choline PET-CT sensitivity 86-89%
- Choline PET-CT specificity 89-93%
- Low detection rate when PSA < 1 (5-24%)
- Optimal cut-off for Choline PET-CT use is PSA between 1 and 2 ng/ml
Optimal use of Choline PET-CT

- Specific patient characteristics which increase the likelihood of a positive Choline PET-CT
  - High Gleason score\(^1\)
  - Rapid PSA doubling time (\(<\ 6\ months\))\(^2\)
  - Increasing PSA level despite androgen deprivation therapy\(^3\)

\(^1\)Cimitan et al. J Nucl Med 2015; 56: 209
Prostatectomy bed recurrence
Bone metastasis
Nodal and bone recurrence
Fluoride PET-CT
Why Fluoride PET-CT?

- Fluoride PET-CT has higher sensitivity and specificity than bone scintigraphy for evaluation of bone metastases but a relative lack of specificity and limited ability to assess soft tissue metastases\(^1\)

- Uptake time and imaging is shorter but the radiation exposure is approximately double compared to bone scintigraphy

- Allows more accurate assessment of the extent of bony metastatic disease particularly in breast and prostate cancer and treatment response assessment\(^2\)

- Data from the USA has shown significant clinical impact on patient management in use of Fluoride PET-CT in cancer patients\(^3\)

\(^1\) Even-Sapir et al. J Nucl Med 2006; 47: 287


\(^3\) Hillner B et al. J Nucl Med 2015; 56: 222
18Fluoride PET for bone metastases

Conventional Bone Scan  SPECT Scan  F-18 PET
Gleason 4+4=8 cancer

Bone scan & CT normal
Confident localisation of osseous metastases with Fluoride PET-CT, not seen on conventional imaging
Fluoride PET-CT Summary

- More accurate than bone scintigraphy
- Faster and more convenient for patients
- Radiation exposure higher than bone scintigraphy
- Specificity and ability to assess non-osseous disease limited
- Cost effectiveness uncertain
- Reduced availability of PET-CT scanners compared to gamma cameras limits use
Fluciclovine (FACBC) PET-CT
**18F-Fluciclovine**

- *Anti*-1-amino-2-[18F]fluorocyclobutane-1-carboxylic acid (FACBC)
- Synthetic amino acid taken up by amino acid transporters\(^1\) that are upregulated in many cancers, including prostate cancer
- Approved in US and Europe for PET imaging in biochemically recurrent (BCR) prostate cancer as Axumin\(^{TM}\)

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\(^{1}\) Fuchs and Bode. Semin Cancer Biol. 2005
**18F-Fluciclovine**

- Prospective multi-centre study (LOCATE) of 213 patients assessing impact of Fluciclovine PET-CT on management decisions in patients with biochemical recurrence of prostate cancer following previous curative-intent treatment and negative or equivocal conventional imaging reported a major treatment change directly influenced by PET-CT in 70% of patients\(^1\)

- Results concordant with a similar multi-centre study (FALCON) in the UK which showed a 60% major management change\(^2\)

- National Comprehensive Cancer Network prostate cancer guidelines published in 2018 state Fluciclovine PET-CT use should be considered in recurrence or disease progression\(^3\)

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\(^1\) Andriole GL et al. J Urol 2019
\(^2\) Teoh EG et al. J Clin Oncol 2018
\(^3\) NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer 2018
Imaging detection rate

*Extraprostatic region includes lymph nodes, soft tissue and bone

Teoh EJ et al. J Clin Oncol 2018
PSMA PET-CT
Prostate specific membrane antigen (PSMA) PET-CT

- PSMA is a cell surface protein up-regulated in a range of malignancies (particularly prostate cancer) with low expression in normal tissues

- Provides a tumour-specific imaging target and various PSMA-based ligands for PET imaging in prostate cancer have been developed

- Gallium-68 PSMA has rapidly emerged into routine clinical practice in mainland Europe and Australia
PSMA: prostate specific membrane antigen

- Expressed in normal prostate tissue
- Highly over-expressed in prostate cancer
- Increased in castrate-resistance & metastatic disease

Immunohistochemistry demonstrating high FOLH1 expression in prostate cancer
From the The Human Protein Atlas
First in-human Ga-68 PSMA PET-CT

PET imaging with a $[^{68}\text{Ga}]$gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions
Library of PSMA PET radiotracers now available

- $^{68}$Ga-PSMA11 (HBED-CC)
- $^{68}$Ga-THP-PSMA (GalliProst™)
- $^{18}$F-DCFPyL (F-PSR)
- $^{18}$F-PSMA1007
PSMA PET: highly specific

Conventional staging: bone metastasis

68Ga-PSMA: benign bone island

- no uptake in sclerotic lesion
- intense uptake in prostate 1°

Gleason 5 + 4 = 9, staging

Patient proceeded to prostatectomy with undetectable PSA on follow-up
Better than Choline PET

- Rising PSA two years after radical prostatectomy
- Additional sub-cm per-sacral LN identified with PSMA PET

1 Afshar-Oromieh et al EJNMMI 2014 (SUV higher in 79% of lesions)
2 Morigi et al JNM 2015 (detection rate 66% vs 32%)
PSMA PET: identifies micrometastatic disease

T3b Gleason 4+4
Prostatectomy -2 yrs
Rising PSA 24
Normal CT
Normal Fluoride PET-CT

U/S guided core biopsy of 7mm node confirmed prostatic adenocarcinoma
Biochemical recurrence: high detection rate

Meta-analysis

48% at 0.2 ng/ml
56% at 0.5 ng/ml
70% at 1.0 ng/ml

Perera et al Eur Urology 2016
Accuracy for nodal staging
(compared to histopathology after pelvic node dissection)

N=130
PET-MR: 95 | PET-CT: 85
35 | 32% pN1
3% sensitivity
<5mm LN
almost no false positive results

- PSMA PET superior to CT or MRI for nodal staging
- Most false negative results in small volume LN, 3 ± 1mm²
- PSMA PET superior to bone scintigraphy, sensitivity approx. 99% vs 87%³

¹ Maurer T, J Urol 2016
² Van Leeuwen, BJUI 2016
³ Pyka T et al EJNMMI 2016
Visualising systemic metastatic disease

all findings confirmed by histopathology
Also excellent for imaging the prostate

N=53: intermediate-to-high risk primary PCa

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<th>Spec (%)</th>
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- PSMA PET appears superior to standalone MRI for identification of 1° prostate cancer
- PET-MRI may increase accuracy beyond either modality alone

1 Eiber et al, Eur Urol 2016
2 Fendler et al, JNM 2016
Not all prostate carcinomas are PSMA-avid

- Gleason 5+5=10 prostate carcinoma
- No uptake on $^{68}$Ga-THP-PSMA or $^{68}$Ga-HBED-PSMA PET-CT

PSMA PET -ve  MRI PIRADS 5

immunohistochemistry

PSMA 1+ 10% (low staining)

IHC courtesy of Dr Catherine Mitchell, PeterMac
PSMA PET-CT has rapidly emerged as a potential new gold standard

- May supersede other imaging as a ‘one stop shop’ single investigation
- Potential for wide clinical availability at relatively low cost
- Produces images with high tumour-to-background contrast
- Very little prospective data on accuracy or improvement of patient outcomes
Struggling with Accuracy
Struggling with Accuracy

Receiver operator curve (ROC)
Which is the most accurate?

- CT
- Whole body MRI
- Bone scintigraphy
- Choline PET-CT
- Fluoride PET-CT
- FACBC PET-CT
- PSMA PET-CT

The gold standard
What is the gold standard?

- Not all golds are equal – rose gold is currently tipping plain yellow or white gold as the metal du jour

- What is the gold standard in imaging?
Paradox of the Gold Standard

Sensitivity in Detecting Osseous Lesions Depends on Anatomic Localization: Planar Bone Scintigraphy Versus $^{18}$F PET

Holger Schirmeister, Albrecht Gubelmann, Klaus Elsner, Jörg Kotzerke, Gerhard Glatting, Marion Rentschler, Bernd Neumaier, Harald Trüger, Karin Nüttle and Sven N. Reske

Radionuclide bone scanning (RNB) is considered to be the most practical screening technique for assessing the entire skeleton for skeletal metastases. However, RNB has been shown to be of lower sensitivity than MRI and CT in detecting osteolytic metastases. A prospective study was designed to evaluate the accuracy of planar RNB versus tomographic bone imaging with $^{18}$F-labeled NaF and PET ($^{18}$F PET) in detecting osteolytic and osteoblastic metastases and its dependency on their anatomic localization.

Methods: Forty-four patients with known prostate, lung or thyroid carcinoma were examined with both planar RNB and $^{18}$F PET. A panel of reference methods including MRI of the spine, $^{99m}$Tc scintigraphy, conventional radiography and spiral CT was used as the gold standard. RNB and $^{18}$F PET were compared by a lesion-by-lesion analysis using a five-point score for receiver operating characteristic (ROC) curve analysis. Results: $^{18}$F PET showed 96 metastases (67 of prostate carcinoma and 29 of lung or thyroid cancer), whereas RNB revealed 46 metastases (39 of prostate carcinoma and 13 of lung or thyroid cancer). All lesions found with RNB were also detected with $^{18}$F PET. Compared with $^{18}$F PET and the reference methods, RNB had a sensitivity of 82.5% in detecting malignant and benign osseous lesions in the skull, thorax and extremities and a sensitivity of 40.4% in the spine and pelvis. The area under the ROC curve was 0.99 for $^{18}$F PET and 0.64 for RNB. Conclusion: $^{18}$F PET has overall better performance than RNB in detecting osseous lesions. With RNB, sensitivity in detecting osseous metastases is highly dependent on anatomic localization of these lesions, whereas detection rates of osteoblastic and osteolytic metastases are similar. Higher detection rates and more accurate differentiation between benign and malignant lesions with $^{18}$F PET suggest the use of $^{18}$F PET when possible.

Key Words: $^{18}$F PET; radionuclide bone scanning; bone metastases


$^{18}$F bone PET the perfect test!

- The area under the ROC curve was
  - 0.99 for $^{18}$F PET and
  - 0.64 for bone scintigraphy
Paradox of the **Gold Standard**

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the perfect test!
The area under the ROC curve was
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The ‘Gold Standard’ test is, by definition, the best performing test available, there is no criterion standard against which it can be compared.
MDP vs Fluoride vs PSMA PET-CT
MDP vs Fluoride vs PSMA PET-CT
pelvic lymph node dissection: no nodal involvement (pN0)

Is this a PSMA “False Positive” or Histopathology “False Negative”?
Struggling with Management
Rising PSA: normal CT & bone scan

- Observation
- Hormones

Management options based on negative CT
Rising PSA: normal CT & bone scan

Management options based on negative CT
Rising PSA: normal CT & bone scan

- Observation
- Hormones

Management options based on negative CT

-Surgery
-Radiotherapy
-Chemotherapy

Additional management options after PSMA PET-CT
Rising PSA: normal CT & bone scan

-Surgery
pelvic & retroperitoneal nodal dissection
4 months after extended nodal dissection...

biochemical response
... shortly after followed by progression
“Oligometastatic” disease

Rising PSA. PSMA PET-CT demonstrates 4mm external iliac oligometastasis
“Oligometastatic” disease

Rising PSA. PSMA PET-CT demonstrates 4mm external iliac oligometastasis

-Surgery
-Radiotherapy
-Chemotherapy

-Oligometastatic disease

-stereotactic radiotherapy (SABR)
“Oligometastatic” disease, 6 months later…

PSMA PET-CT 6 months later:

Failure at “upstream” LN
Good intentions → Unintended Consequences

- Identification of “new” disease ≠ progression
- Cannot define “oligometastatic” at T0
- PSMA PET-CT provides a powerful new means to monitor disease (??better than PSA)
Just Because you Can **See It**
Doesn’t Mean you Should **Treat It**

Rising PSA 8 years after prostatectomy

- Enables localisation of ↑PSA
- But no current evidence for benefit from early intervention
- Potential to cause more harm-than-good

Imaging micrometastatic disease with PSMA PET-CT
Platinum Opinion

“Gotta Catch ’em All”, or Do We? Pockemet Approach to Metastatic Prostate Cancer

Declan G. Murphy\textsuperscript{a,b,c,*}, Christopher J. Sweeney\textsuperscript{d}, Bertrand Tombal\textsuperscript{e}

- Salvage lymph node dissection or stereotactic radiotherapy: feasible but it is worthwhile?

“Do we really need to ablate all the lesions we see popping up, Pockemet if you like?”

- Long-term recurrence-free survival rare: should therefore be considered experimental
PSMA PET: the new “gold standard”

- Significantly superior to existing imaging techniques
- Must generate prospective high level evidence
- Some prostate cancers do not express PSMA
- Images micrometastatic disease
- Don’t play “Pokemet” and treat everything you see
- PSMA theranostics is also a game changer

The Leeds Teaching Hospitals NHS Trust
proPSMA Trial: 10 centres around Australia
A prospective randomised multi-centre study of the impact of Ga-68 PSMA PET-CT imaging for staging high risk prostate cancer prior to curative-intent surgery or radiotherapy

Patient Selection: untreated, biopsy-proven prostate cancer, being considered for curative intent treatment.
- PSA ≥ 20 ng/mL or Gleason Grade Group 3-5 or clinical stage ≥T3

Randomisation 1:1

PSMA PET-CT ↔ CT + bone scan

Crossover to other arm unless ≥3 distant metastases

Implementation of Final Management

6 months follow-up: repeat imaging

Up to 54 months follow-up if PSMA -ve patients
Trial Ongoing

A prospective randomized multicentre study of the impact of gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): clinical trial protocol

Michael S. Hofman*, Declan G. Murphy†Id, Scott G. Williams*, Tatenda Nzenza††Id, Alan Herschtal§, Richard De Abreu Lourenco†, Dale L. Bailey**, Ray Budd††, Rodney J. Hicks†, Roslyn J. Francis‡‡§§ and Nathan Lawrentschuk*††Id

*Genitourinary Oncology Tumour Multidisciplinary Team, Departments of Cancer Imaging, Cancer Surgery and Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, †Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, ‡Olivia Newton John Cancer Research Institute, Austin Health, §Centre for Biostatistics and Clinical Trials (BaCT), Peter MacCallum Cancer Centre, Melbourne, ‡‡Centre for Health Economics Research and Evaluation, University of Technology Sydney, Sydney, **Nuclear Medicine, Royal North Shore Hospital, St Leonards, NSW, ††Medical Physics, Peter MacCallum Cancer Centre, Melbourne, Vic., ‡‡Nuclear Medicine, Sir Charles Gairdner Hospital, Perth, and §§Scientific Committee Chair, Australasian Radiopharmaceutical Trials Network (ARTnet), Australia
Current clinical use data from Twitter!

The Advent of PET Imaging for Prostate Cancer

Axumin (fluciclovine F18) PET:
- Currently available at >800 imaging sites across the US
- FDA-approved for use in biochemical recurrence, reimbursed by Medicare and many private payers
- More than 28,000 patients have received Axumin PET imaging (P Gardiner, Blue Earth)

Presented at: 2019 Genitourinary Cancers Symposium | #GU19

Presented by: Felix Feng, MD

The Leeds Teaching Hospitals NHS Trust
Current situation in the UK

• Choline and Fluoride PET-CT funded and available

• FACBC and PSMA PET-CT not currently funded but available at a few centres for insured/self-funding patients

• PSMA PET-CT might replace other tracers in future clinical practice but needs high level evidence of patient benefit 1st

• Rapid roll-out to many centres may be limited by the complexities of Gallium-68 production and costs associated with infrastructure development

• Fluorine-18 labelled tracers easier to distribute as with FDG
Thank you

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- Professor Michael Hofman, Nuclear Medicine Physician, PeterMacCallum Cancer Centre, Melbourne kindly provided multiple slides/clinical cases covering PSMA PET-CT

Further reading


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