HTW GUIDANCE

Technoleg Iechyd Cymru
Health Technology Wales

The clinical and cost effectiveness of fluorine- or gallium- prostate-specific membrane antigen (PSMA) positron emission tomography (PET) radiotracers in the investigation of recurrent prostate cancer

Guidance Number:	FIELD: Cancer
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HEALTH TECHNOLOGY WALES (HTW) GUIDANCE 006 (December 2018)

The clinical and cost effectiveness of gallium- or fluorine-prostate-specific membrane antigen (PSMA) positron emission tomography (PET) radiotracers in the investigation of recurrent prostate cancer

The adoption of ^{68}Ga PSMA PET for the diagnosis of recurrent prostate cancer is partially supported by the evidence. The use of ^{68}Ga PSMA PET provides a high degree of diagnostic accuracy on which to base management decisions as compared with conventional tracers. However, evidence comparing ^{68}Ga PSMA PET to other tracers is limited, and estimating the cost of using ^{68}Ga PSMA PET for the investigation of possible recurrent prostate cancer is complex and uncertain. Therefore, ^{68}Ga PSMA PET is recommended if the service can be delivered at no greater cost than current standard care.

The adoption of ^{18}F PSMA PET for the diagnosis of recurrent prostate cancer is not supported by the evidence.

Why did HTW appraise this topic?

- Many men who have been treated for prostate cancer may develop a recurrence of the cancer at a variable time after their initial treatment. This may be detected as a result of new symptoms or after biochemical surveillance. When this happens, early detection and precise localisation of the site of recurrence is critical so that appropriate further treatment decisions can be made. PSMA PET tracers have been developed to improve the accuracy of the diagnosis of recurrent prostate cancer.

The status of HTW guidance is that NHS Wales should adopt this guidance or justify why it has not been followed. HTW will evaluate the impact of its guidance.

Appraisal Panel considerations

- The appraisal panel concluded from the evidence that ^{68}Ga PSMA PET provides a higher degree of diagnostic accuracy in patients being investigated for possible recurrent prostate cancer as compared with choline-based PET. The Panel agreed that it is plausible that an improvement in diagnosis is likely to lead to better management and decision-making and on this basis would support the adoption of ^{68}Ga PSMA PET. It noted, however, that there are currently no studies available that have defined clinical outcomes following management decisions made on the basis of the use of ^{68}Ga PSMA PET but it would welcome these in the future.
- There is very limited evidence available on the diagnostic accuracy and effectiveness of ^{18}F-PSMA PET in patients being investigated for recurrent prostatic cancer. The Panel were advised by an expert that there are relatively minor differences between the gallium- and fluorine-based tracers and the way in which they are handled by the body, but the Panel concluded that it would not be legitimate to extrapolate the clinical evidence from one to the other. The Panel considered that the current evidence for ^{18}F-PSMA PET is insufficient to be able to support its adoption.
- The Panel were advised by an expert that the production of PSMA PET tracers was feasible in Cardiff and that delivering a service to NHS Wales on this basis was a realistic objective. It recognized that geographical constraints do exist, for example in delivering a service to patients in North Wales, but the Panel concluded that these were surmountable.
- No published primary or secondary research on the cost effectiveness of PSMA-based PET for the investigation of recurrent prostate cancer was identified. Estimating the total cost of PSMA and the cost of producing the radioisotope is complex since it is based on a wide variety of factors. The Panel learnt that the current choline-based PET service for investigating recurrent prostate cancer is commissioned at an agreed cost and concluded that provided a ^{68}Ga PSMA based service could be delivered at no greater costs, adoption should be supported.

SUMMARY OF EVIDENCE APPRAISAL REPORT[1]

Context

In 2015, there were 2,552 new cases of prostate cancer in Wales. Between 27-53% of all men with prostate cancer develop recurrent disease despite radical prostatectomy or radiotherapy. Recurrence is initially demonstrated by a rise in total serum prostate specific antigen; this is known as a biochemical relapse or recurrence. Positron emission tomography (PET) is a non-invasive imaging technique used to detect metabolic activity or cell surface molecules that are usually associated with cancer. The test involves introducing a radiolabelled tracer into the body, which accumulates in metabolically active cells (such as malignant cells) and emits gamma rays which are detected by a PET scanner.

Several non-FDG tracers have been developed and used with PET in cancers where glucose metabolism is low, such as in prostate cancer. Prostate specific membrane antigen (PSMA) is a membrane protein that is highly expressed by prostate cancer cells. Small-molecule PSMA inhibitors labelled with radionuclides have been developed with the aim of producing tracers that localise to prostate cancer sites. The focus of this appraisal is on PET using tracers labelled with ^{68}Gallium or ^{18}Fluorine, commonly known as ^{68}Ga-PSMA PET and ^{18}F-PSMA PET.

Evidence on clinical effectiveness, safety, economic analysis and patient issues

There is evidence from two systematic reviews which show that ^{68}Ga PSMA PET has a higher sensitivity and specificity than other imaging modalities. However, these studies may be at risk of bias, primarily due to the small population sizes studied. The lack of studies directly comparing the diagnostic accuracy of tracers makes comparisons of their effectiveness difficult. Formal statistical comparison of diagnostic accuracy is therefore not possible. One prospective study published subsequent to the systematic reviews reports very high sensitivity (98.8%, 95% confidence interval 95.7 to 99.8%) and specificity (100.0%, 95% confidence interval 83.4 to 100.0%) for ^{68}Ga-PSMA PET in identifying prostate cancer recurrence.

Although no studies exist of head-to-head comparisons of the diagnostic accuracy of ^{68}Ga-PSMA PET to other imaging techniques, several studies consistently showed higher detection rates with ^{68}Ga-PSMA PET than with any of the comparators investigated (choline-based PET/CT, or conventional imaging such as CT and MRI). Clinical utility outcomes for PSMA-based PET were reported by one systematic review (ten relevant studies included) and nine studies (919 patients in total) that were published subsequent to the systematic review, all using ^{68}Ga-PSMA. All these studies demonstrated that the findings of ^{68}Ga-PSMA PET can influence subsequent treatment planning, although the percentage of patients affected varied widely between studies.

Data on the effectiveness of ^{18}F-PSMA PET/CT is only available from three retrospective case series. These only reported detection rates for positive lesions, and did not include any data on verification of test results. Reported detection rates ranged from 75 to 95%.

No published primary or secondary research on the cost effectiveness of PSMA-based PET for the investigation of recurrent prostate cancer were identified.

[1]Summary of Evidence Appraisal Report intended for use by decision-makers in NHS Wales.

Organisational issues

There are currently two PET centres in Wales: 1 fixed site in Cardiff and 1 mobile site in Wrexham. PETIC have facilities to produce both ^{68}gallium and ^{18}fluorine, although the shorter half life of ^{68}gallium makes transport of this to other centres more difficult. Introduction of ^{68}Ga-based tracers could result in differences in production capacity and availability of the technology across Wales.

Further research

Large, prospective, comparative multicentre studies are recommended to evaluate the impact on patient management and outcomes of PSMA-based PET tracers compared to currently-used imaging modalities. Such studies should also define the cost effectiveness of this investigation and help clarify the indications and point in the care pathway when ^{68}Ga PSMA PET should be considered. Further research on the diagnostic accuracy and clinical performance of ^{18}F-PSMA PET should also be undertaken.

Responsibilities for consideration of this Guidance

Health Technology Wales (HTW) was established by Ministerial recommendation[1,2] to support a strategic, national approach to the identification, appraisal and adoption of non-medicine health technologies into health and care settings. The HTW Appraisal Panel comprises senior representation from all Welsh boards with delegated authority to produce guidance 'from NHS Wales, for NHS Wales'. The status of HTW guidance is 'adopt or justify'. There is an expectation from Welsh Government that HTW guidance is implemented with adoption regularly audited by HTW.[3]

The guidance in this document is intended to assist Welsh care system decision makers to make evidence-informed decisions when determining the place of health technologies and thereby improve the quality of care services.

The content of this HTW guidance was based upon the evidence and factors available at the time of publication. An international evidence base was reviewed and external topic experts and HTW committee members consulted to contextualise available evidence to Wales. Readers are asked to consider the generalisability of the evidence reviewed to NHS Wales and that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. It is acknowledged that evidence constitutes only one of the sources needed for decision making and planning.

This guidance does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

No part of this guidance may be used without the whole of the guidance being quoted in full. This guidance represents the view of HTW at the date noted. HTW guidance is not routinely updated. It may, however, be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the guidance given.

Standard operating procedures outlining HTWs evidence review methods and framework for producing its guidance are available from the HTW website.

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Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by HTWs Assessment Group. However, reviewers had no role in authorship or editorial control and the views expressed are those of Health Technology Wales.

Chair, Health Technology Wales Appraisal Panel

1. National Assembly for Wales, Health and Social Care Committee. Access to medical technologies in Wales. December 2014.
2. Response to Recommendations from the Health & Social Care Committee: Inquiry into Access to Medical Technologies in Wales. February 2015.
3. Gething, V. Letter to all Health Board Chairs re Funding for Sacral Nerve Stimulation in Wales. VG_01655_17. September 2017.