

evidence | *note*

In response to an enquiry from the PET-CT Working Group

Number 67 April 2017

What is the most clinically effective and cost effective non-FDG tracer for use in PET-CT for staging and assessment of patients with suspected recurrent prostate cancer?

What is an evidence note?

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6 month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

Key points

- Several non-FDG tracers are available for use with PET-CT in the context of restaging suspected recurrence in patients previously treated for prostate cancer, including ^{11}C -choline, ^{18}F -fluoroethylcholine, ^{18}F -fluoromethylcholine, anti- ^{18}F -FACBC, and ^{68}Ga -PSMA.
- There is evidence for high sensitivity and specificity of choline-based tracers in detecting prostate cancer recurrence.
- ^{18}F -choline appears to be more effective than ^{11}C -choline in restaging prostate cancer.
- Based on a small number of studies, the novel tracer ^{68}Ga -PSMA had a high detection rate for recurrent prostate cancer and was more effective than choline tracers, particularly at low PSA levels.
- A single primary study comparing the novel tracer anti- ^{18}F -FACBC with choline reported higher detection rates with anti- ^{18}F -FACBC in patients with suspected prostate cancer recurrence.
- A systematic review demonstrated superior detection rates for ^{68}Ga -PSMA compared with choline and anti- ^{18}F -

FACBC tracers in patients with suspected prostate cancer recurrence.

- There is limited evidence to recommend replacing choline tracers with ^{68}Ga -PSMA or anti- ^{18}F -FACBC for detection of recurrent prostate cancer. Studies suggest that ^{68}Ga -PSMA is more accurate in detecting recurrent disease compared with radioactive labelled choline.

Definitions

Prostate cancer recurrence: initially demonstrated by a rise in total serum prostate specific antigen, often despite normal findings with conventional imaging. Known as a biochemical relapse or recurrence¹.

Tracer: a radioactive labeled (radiolabelled) molecule that, when used with imaging, produces images to provide information about tissue metabolism, distribution of the molecule within tissues, or passage of the molecule through the body².

Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test³, that is the number of true positive results divided by the total number with the disease.

Specificity: the probability that a person not having a disease will be correctly identified by a clinical test³, that is the number of true negative results divided by the total number of those without the disease.

Detection rate: this is variously defined at the level of individual patient or by type or location of lesion. It can denote the proportion of patients where a recurrence is detected, or the proportion of lesions detected in study participants compared with the number detected by another technology or test^{4, 5}.

Literature search

A systematic search of the secondary literature was carried out between 27 July and 3 August 2016 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Medline in process, Embase, Cinahl, and Web of Science databases were also searched for systematic reviews and meta-analyses.

The primary literature was systematically searched between 27 July and 3 August 2016 using the following databases: Medline, Medline in process, Embase, Cinahl and Web of Science. Results were limited to English language studies from 2011 onwards.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

Concepts used in all searches included: prostate cancer/neoplasm, relapse(d)/recurrence, non-fluorodeoxyglucose (FDG) or non-fluorodeoxyglucose tracers, ^{11}C -choline, ^{18}F -fluorocholine (FCH), ^{18}F -ethylcholine (FEC). A full list of resources searched and terms used are available on request.

Introduction

Functional imaging with positron emission tomography (PET)/computed tomography (CT) (PET-CT) is widely used in the diagnosis and staging of a variety of cancer types. Imaging with PET-CT has primarily utilised ^{18}F -2-fluoro-2-deoxy-D-glucose (FDG) as a radiolabelled tracer for oncological indications, however FDG PET-CT has a number of limitations in prostate cancer, notably due to low glucose metabolism in this cancer type but also rapid dephosphorylation and excretion^{6, 7}. Several non-FDG tracers have been developed for use with PET-CT in cancers, such as prostate cancer, where glucose metabolism is low. Non-FDG tracers include ^{11}C -acetate, ^{11}C -

choline, ^{18}F -fluoroethylcholine (^{18}F -FEC), ^{18}F -fluoromethylcholine (^{18}F -FCH), anti-1-amino-3- ^{18}F fluorocyclobutane-1-carboxylic acid (anti- ^{18}F -FACBC, also known as ^{18}F -fluciclovine) and ^{68}Ga prostate-specific membrane antigen (^{68}Ga -PSMA) (Annex 1). Currently choline-based PET-CT scanning is available at four centres across Scotland: Glasgow, Edinburgh, Dundee and Aberdeen (Dr S Han, Consultant in Nuclear Medicine, Glasgow Royal Infirmary. Personal communication, 27 Oct 2016). No Scottish facility currently uses anti- ^{18}F -FACBC or ^{68}Ga -PSMA but there is growing interest in using these tracers (G Gillen and J Owens, NHS Greater Glasgow and Clyde. Personal communication, 6 Sept 2016). Evidence on ^{11}C -acetate was excluded from this evidence note on the advice of Scottish PET-CT experts.

Staging of prostate cancer typically involves the use of routine imaging techniques such as magnetic resonance imaging (MRI) and CT for localised disease and lymph node involvement, and isotope bone scan for the assessment of bone metastases. Non-FDG PET-CT is also used in staging of prostate cancer and is reported to have greater diagnostic value in staging of suspected relapsed prostate cancer (restaging) compared with staging in primary disease⁶.

This evidence note compares the clinical effectiveness and cost effectiveness of choline tracers and novel non-FDG tracers, specifically anti- ^{18}F -FACBC and ^{68}Ga -PSMA, in restaging patients with suspected recurrent prostate cancer who have received treatment with curative intent.

Health technology description

PET-CT is a non-invasive imaging technique that combines information from two different imaging modalities: PET provides information about functional and metabolic cellular activity, while a CT scanner gives precise anatomical localisation⁸. The procedure usually involves injecting a radiolabelled tracer

into the body, but the tracer can be ingested or inhaled. The radiolabelled tracer can be a sugar (glucose), an amino acid, or a vitamin which is taken up and accumulates in metabolically active cells (such as malignant cells), and emits gamma rays detected by the PET and CT scanner to produce colour-coded images of the body demonstrating the cellular activity of both normal and malignant tissue. Images acquired from both PET and CT devices can be combined into a single superimposed image (PET-CT) and provide important diagnostic information as well as assessing the effectiveness of treatment in cancer. The radiolabelled tracers are then passed out of the body in the urine or bowel movement.

^{11}C - and ^{18}F -labelled choline tracers have been routinely used in PET-CT for staging and restaging of prostate cancer^{9,7}. Anti- ^{18}F -FACBC and ^{68}Ga -PSMA are promising novel tracers in PET-CT whose use in practice is currently limited (not presently used in Scotland). Annex 1 outlines the characteristics of non-FDG tracers as well as their advantages and limitations.

Epidemiology

Prostate cancer is the most common cancer among males in the UK, accounting for 26% of all male cancer diagnoses¹⁰. In 2014, there were 3,202 new cases of prostate cancer in Scotland¹⁰. Age is a risk factor for prostate cancer¹¹. Between 2011 and 2013 over half (54%) of prostate cancer cases in the UK were diagnosed in males aged 70 years and over¹⁰.

Most prostate tumours are initially located in the peripheral areas of the prostate, furthest from the urethra^{12, 13}. Prostate cancer can spread beyond the prostatic capsule via the bloodstream, and less commonly the lymphatic system, to surrounding tissues (known as locally-advanced disease) and then to regional lymph nodes and bone (advanced metastatic disease)¹⁴.

The diagnosis of localised prostate cancer involves the detection of abnormal prostate specific antigen (PSA) level and/or digital rectal examination, and confirmation by prostate biopsy. Staging of prostate cancer guides appropriate treatment and is driven by the results of imaging including PET-CT.

Following a diagnosis of prostate cancer, treatment can be deferred and disease monitored by watchful waiting or active surveillance. Active treatment can comprise radical prostatectomy, radiotherapy (which can be delivered externally (for example external beam radiotherapy) or internally (for example brachytherapy), or pelvic lymph node dissection plus radiotherapy. Prostate cancer can recur in up to one in three men who have undergone treatment with curative intent for localised disease^{1, 15}. Recurrence is initially demonstrated by a rise in total serum PSA often despite normal findings with conventional imaging; this is known as a biochemical relapse or recurrence. Although a precise PSA threshold for recurrence has not been defined¹, European Association of Urology guidelines define biochemical failure as:

- “two consecutive PSA values of >0.2 ng/mL and rising” after radical prostatectomy, and
- “any PSA increase >2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir” after primary radiotherapy, with or without short-term hormonal manipulation¹⁶.

Early detection and precise localisation of the site of recurrence is critical and provides a basis for further therapeutic decisions.

Clinical effectiveness

The literature search specifically sought evidence on PET-CT, although many of the reviews incorporated studies on both PET and PET-CT and these were included. Publications that searched for PET-CT, but only identified evidence for PET, were still eligible for inclusion. Where studies evaluated staging of both primary and recurrent prostate cancer patient populations, these were included but only data related to restaging of recurrent prostate cancer were extracted. No evidence was identified on the impact of diagnostic imaging with non-FDG PET-CT on patient outcomes; all studies focused on diagnostic accuracy outcomes.

Guideline recommendations

Guideline recommendations vary on the use of non-FDG PET-CT in restaging of suspected recurrent prostate cancer. Cancer Care Ontario does not routinely recommend choline PET-CT in this patient population and its use is considered investigational¹⁷. Choline PET-CT is also not recommended by one European guideline¹⁶ in patients with low PSA levels. Joint UK guidance from the Royal Colleges of Physicians, the Royal College of Radiologists and the British Nuclear Medicine Society¹⁸ supports the use of choline tracers and ⁶⁸Ga-PSMA in patients with suspected recurrent prostate cancer¹⁸. However, this guidance does not provide a description of the methodology used to develop the recommendations or link recommendations to published evidence. The recommendations from the Cancer Care Ontario, European and joint UK guidance are summarised in Table 1. These guidelines were all based on observational evidence and recommendations include various criteria used to select patients, for example PSA threshold or a negative or equivocal result on conventional imaging.

Table 1: Guideline recommendations on the use of non-FDG PET-CT in patients with biochemical recurrent prostate cancer

Guideline	Tracers	Recommendations
European Association of Urology (2015) ¹⁶	Choline (type not specified)	Choline PET-CT scan is not recommended in patients with biochemical recurrence and a PSA-level <1 ng/ml.
Cancer Care Ontario (2015) ¹⁷	Choline (¹⁸ F and ¹¹ C choline)	Use of choline PET is not usually appropriate, and should be considered experimental when <ul style="list-style-type: none"> salvage radiotherapy is planned after radical prostatectomy local salvage therapy is planned after radiotherapy.
UK guidance from the Royal Colleges of Physicians, the Royal College of Radiologists and the British Nuclear Medicine Society (2016) ¹⁸	¹¹ C-choline, ¹⁸ F-fluorocholine (both F-FEC and F-FCH) or ⁶⁸ Ga-PSMA	PET-CT is recommended in suspected recurrence in patients with a rapidly rising PSA and negative or equivocal conventional imaging where the results would directly influence patient management.

Comparison of choline tracers

Diagnostic accuracy of choline tracers in restaging patients with suspected prostate cancer recurrence was compared in two systematic reviews with meta-analyses^{4, 19} and one meta-analysis²⁰. The results of these analyses are presented in Table 2. Two studies by Von Eyben *et al.* reported detection rates^{4, 20}, while one systematic review with meta-analysis pooled sensitivity and specificity estimates¹⁹.

Table 2: Evidence comparing choline tracers in PET/PET-CT

Author (year)/ Study type	Population/ Site of disease	Index test	Results (diagnostic accuracy or detection rates)
		Reference test	
Von Eyben (2014) ²⁰ Meta-analysis	n=26 studies (19 studies for ¹¹ C-choline and 7 studies for ¹⁸ F-choline) 2,348 patients with biochemical recurrence after radical prostatectomy	¹⁸ F-choline PET-CT (FEH or FCH not stated) vs ¹¹ C-choline PET-CT	Detection rates ¹⁸ F-choline: 334/550 (60%) ¹¹ C-choline: 828/1798 (46%) (p<0.0005, Fisher's exact test)
		Histological evidence	
Von Eyben (2016) ⁴ Systematic review with meta-analysis	n=18 studies (12 studies for ¹⁸ F-FCH PET-CT, 6 studies for ¹¹ C-choline PET-CT) 2,219 patients in an early phase of biochemical recurrence (median/mean restaging PSA level <10 ng/ml)	¹⁸ F-FCH PET-CT vs ¹¹ C-choline PET-CT	Detection rates (mean ± standard deviation) ¹¹ C-choline: 30% ± 5% ¹⁸ F-FCH: 39% ± 5% (p=0.26, t-test)
		Positive biopsy or if treatment of site reduced PSA level by at least 50% for at least a month	

Evangelista (2013) ¹⁹ Systematic review with meta-analysis	n=19 studies (1,555 patients) All site recurrence (prostatic fossae, lymph node, bone) (n=12); Local recurrence (n=4); Lymph node metastases (n=4)	¹⁸ F-choline PET-CT (FEH or FCH not stated) vs ¹¹ C-choline PET or PET- CT	Pooled sensitivity (¹⁸ F-choline vs ¹¹ C-choline): 91.8% (95% CI 88.0 to 94.7) vs 81.8% (95% CI 77.9 to 85.2) Pooled specificity (¹⁸ F-choline vs ¹¹ C-choline): 95.6% (95% CI 91.2 to 98.2) vs 91.4% (95% CI 88.3 to 93.9)
---	---	---	--

Two publications by Von Eyben *et al* reported detection rates in patients with biochemical recurrence who had undergone radical prostatectomy (von Eyben *et al* 2014)²⁰ and either radical prostatectomy or radiotherapy (von Eyben *et al* 2016)⁴. Biochemical recurrence was well defined and had the same definition in both studies. The 2014 meta-analysis²⁰ was of poor methodological quality as it did not report patient characteristics or assess the quality of included studies. The 2016 meta-analysis⁴ was well conducted and reported all of the criteria missing from the 2014 meta-analysis. Although the reference standard was reported for the 2016 study, the authors reported that not verifying metastatic disease histologically was a limitation of the study. Detection rates were calculated differently, with the 2014 meta-analysis pooling patient numbers with positive findings and the 2016 report calculating the mean detection rate. In both publications, the detection rates were higher with ¹⁸F-choline than ¹¹C-choline. The difference between the rates of detection was not statistically significant for the 2016 meta-analysis but was statistically significantly in the 2014 meta-analysis (Table 2).

A good quality systematic review with meta-analysis of 19 studies by Evangelista *et al* (2013)¹⁹ compared pooled estimates of sensitivity and specificity for radiolabelled choline isotopes in patients with suspected prostate cancer recurrence. Included studies were judged by the reviewers to be of good or high quality. However, inconsistencies in some of the reported pooled analyses increase the risk of bias in the analysis comparing choline tracers. In this analysis, ¹⁸F-choline had

superior sensitivity compared with ¹¹C-choline in detecting all site recurrence but similar specificity (Table 2).

Overall, the findings from one systematic review with meta-analysis suggest that ¹⁸F-choline outperforms ¹¹C-choline in detecting recurrent disease based on its sensitivity¹⁹. Although detection rates were higher with ¹⁸F-choline than ¹¹C-choline tracers in other meta-analyses of PET-CT, there was inconsistency in the statistical significance of the difference between the tracers in these publications^{4, 20}.

Comparison of ⁶⁸Ga-PSMA with choline tracers

The diagnostic accuracy of ⁶⁸Ga-PSMA in PET-CT restaging of prostate cancer has been compared with choline tracers in one high quality systematic review²¹ and two good quality primary studies (Table 3)^{5, 22}. All three studies reported detection rates.

Table 3: Evidence comparing ⁶⁸Ga-PSMA with choline tracers in PET/PET-CT

Author (year)/ Study type	Population/ Site of disease	Index test	Outcome/Results
		Reference test	
Secondary evidence			
Evangelista (2016) ²¹ Systematic review	n=6 studies 1,837 patients ¹¹ C-choline/ ¹⁸ F-choline (2 studies for each tracer), ⁶⁸ Ga-PSMA PET-CT (2 studies) All site recurrence	Choline tracers (¹⁸ F- choline PET-CT (FEH or FCH not stated) and ¹¹ C- choline PET-CT) vs ⁶⁸ Ga- PSMA PET-CT	Detection rate by level of PSA Median (range) Choline PSA <1ng/ml: 20% (7-31) PSA 1-2 ng/ml: 46% (43-56) PSA >2ng/ml: 80% (72-81) ⁶⁸Ga-PSMA PSA <0.5 ng/ml: 49% (48-50) PSA 0.5-2 ng/ml: 68% (67-69) PSA >2 ng/ml: 90% (88-92)
		Histology/imaging	
Primary evidence			
Afshar-Oromieh (2014) ²² Retrospective study (Germany)	37 patients with biochemically confirmed recurrent prostate cancer following conventional treatment (radiotherapy, radical prostatectomy, hormone therapy and/or surgery)	⁶⁸ Ga-PSMA PET-CT	Detection rate ⁶⁸ Ga-PSMA PET-CT: 78 lesions detected in 32 patients ¹⁸ F-FCH PET-CT: 56 lesions detected in 26 patients. McNemar test, p=0.04 No lesion was found in 5 patients with both methods. PSA ≤ 0.82 ng/ml ⁶⁸ Ga-PSMA PET-CT: 68.8% with at least 1 lesion. ¹⁸ F-FCH PET-CT: 43.8% with at least 1 lesion.
		¹⁸ F-FCH PET-CT	
Schwenck (2017) ⁵ Retrospective study (Germany)	103 patients with biochemical recurrence after prostatectomy and/or radiotherapy	¹¹ C-choline PET-CT	Detection rate for specific lesions Lymph nodes ⁶⁸ Ga-PSMA: 94% ¹¹ C-choline: 71% (p<0.001) Bone lesions ⁶⁸ Ga-PSMA: 98% ¹¹ C-choline: 64% (p<0.001) Local recurrence ⁶⁸ Ga-PSMA: 26/27 ¹¹ C-choline: 24/27
		⁶⁸ Ga-PSMA PET-CT	

A comparison of ^{68}Ga -PSMA PET-CT with choline PET-CT in restaging of all sites of recurrent disease was conducted in a high quality systematic review of a small sample of primary studies²¹. Across all PSA categories, median detection rates were greater for ^{68}Ga -PSMA PET-CT than for choline PET-CT. Of note, ^{68}Ga -PSMA PET-CT was more accurate in detecting the presence of significant uptake for low levels of PSA compared with choline PET-CT, although different PSA cut-off levels make direct comparisons more complex (Table 3). The authors suggest the potential use of ^{68}Ga -PSMA PET-CT for detection of recurrent disease at low PSA levels and determining salvage treatment (such as lymph node dissection and salvage radiotherapy).

A small, high quality primary study comparing ^{68}Ga -PSMA PET-CT with ^{18}F -FCH PET-CT for prostate cancer restaging found that ^{68}Ga -PSMA PET-CT detected significantly more lesions characteristic for prostate cancer compared with ^{18}F -FCH PET-CT²². A second primary study compared ^{68}Ga -PSMA PET-CT with ^{11}C -choline PET-CT in patients with suspected prostate cancer recurrence⁵. This study did not blind assessors to the results of prior imaging tests, including the comparison tracer PET-CT. The detection rates for local recurrence, lymph node lesions and bone lesions, were significantly higher for ^{68}Ga -PSMA compared with ^{11}C -choline. In both primary studies, ^{68}Ga -PSMA detected significantly more lesions than choline tracers at low levels of PSA.

Comparison of anti- ^{18}F -FACBC vs ^{11}C -choline tracers

Only one primary study comparing the novel tracer anti- ^{18}F -FACBC PET-CT with standard choline-based PET-CT in the detection of prostate cancer recurrence was identified²³. This prospective Italian study enrolled 50 consecutive patients who had received radiotherapy or radical prostatectomy for prostate cancer and presented with rising PSA levels. Participants underwent both anti- ^{18}F -

FACBC PET-CT and ^{11}C -choline PET-CT within one week. This study had a low risk of bias across all domains, except the reference standard of conventional imaging which was not well reported. Detection rates were reported on a patient and lesion basis and analysed by site of relapse (local, lymph nodes and bone) and level of PSA.

In the patient-based analysis, 11 patients were positive for relapse with both tracers, in the same sites; an additional six patients were positive with anti- ^{18}F -FACBC but negative with ^{11}C -choline, and there was a statistically significant difference in terms of number of positive scans between ^{11}C -choline and anti- ^{18}F -FACBC ($p < 0.000001$, Fisher's exact test). In a lesion-based analysis, 41 patients had an identical lesion burden in both ^{11}C -choline and anti- ^{18}F -FACBC PET-CT; however in eight patients, additional lesions were detected by anti- ^{18}F -FACBC PET-CT compared with ^{11}C -choline PET-CT, this difference was statistically significant ($p < 0.0001$, chi square test). Across low, intermediate, and high PSA levels and all sites of recurrent disease, anti- ^{18}F -FACBC PET-CT had a superior detection rate compared with ^{11}C -choline ($p < 0.0001$, chi square test). These findings are consistent with earlier results from two preliminary studies of smaller patient populations by the same authors^{24, 25}.

Comparison of choline, ^{68}Ga -PSMA and anti- ^{18}F -FACBC tracers

A low quality systematic review, which did not assess the quality of studies included in the analysis, examined the performance of all three tracers in patients with biochemical recurrence of prostate cancer²⁶. The systematic review included 19 studies using choline tracers (^{11}C or ^{18}F), four studies using anti- ^{18}F -FACBC and two studies using ^{68}Ga -PSMA. They addressed heterogeneity in reference standards and patient cohorts, and disparity in the verification of recurrent disease, by using pre-defined criteria to categorise their data, for example by prior treatment (radiotherapy or radical

prostatectomy) or disease site. Mean proportions of patients with suspected disease were calculated for each tracer and patient cohort and analysed using a random effects model.

The proportion of patients with suspected recurrent disease after radiotherapy or radical prostatectomy is presented in Table 4. These results show that the detection rate of ^{68}Ga -PSMA was superior to other tracers but there did not seem to be any difference in detection rates between anti- ^{18}F -FACBC and choline (^{11}C or ^{18}F), which may be attributed to differences in study designs. Across sites of disease, anti- ^{18}F -FACBC had greater likelihood of detecting local recurrence, when compared with choline tracers, although this difference was not statistically significant.

Table 4: Average proportion of patients detected with disease

	Detection rates (average proportion of patients detected with disease)		
	^{68}Ga -PSMA	anti- ^{18}F -FACBC	Choline (^{11}C or ^{18}F)
After radiotherapy	96% (95% CI 79% to 99%)	80% (95% CI 67% to 91%)	81% (95% CI 74% to 88%)
After radical prostatectomy	82% (95% CI 69% to 92%)	40% (95% CI 27% to 54%)	48% (95% CI 37% to 60%)

Comparison among the tracers and patient treatment histories was done through a mixed effects logistic regression model. The odds ratios (ORs) and 95% CIs for all tracers and patient cohorts by site of recurrence were compared with choline tracers (established imaging technique) and radical prostatectomy. The odds ratios for detecting any recurrent disease for anti- ^{18}F -FACBC and ^{68}Ga -PSMA were 1.8 (95% CI 0.79 to 3.9) and 3.6 (95% CI 1.3 to 10.2) respectively. These results showed that compared with all other tracers, ^{68}Ga -PSMA exhibited greater odds of detecting any suspected disease and this difference was

statistically significant ($p=0.014$). Across sites of recurrence, ^{68}Ga -PSMA had a greater likelihood of detecting extra-prostatic disease and this difference was also statistically significant ($p=0.007$). This was based on two small studies.

Ongoing studies

A UK multicentre trial assessing the clinical utility of anti- ^{18}F -FACBC PET-CT in biochemically recurrent prostate cancer is due to complete in early 2017 (NCT02578940; FALCON trial). A comparison with choline tracers will be performed in a subset of patients in the study.

Safety

Evidence on the safety of non-FDG tracers in PET-CT in staging of recurrent prostate cancer was limited. In the secondary evidence identified, the safety of non-FDG tracers was not reported. In the primary evidence, Afshar-Oromieh *et al* (2014)²² and Nanni *et al* (2015)²³ reported that there were no adverse effects with ^{68}Ga -PSMA or ^{18}F -choline PET-CT, and anti- ^{18}F -FACBC or ^{11}C -choline PET-CT respectively.

Cost effectiveness

No primary or secondary evidence was identified which assessed the cost effectiveness of non-FDG tracers in PET-CT in recurrent prostate cancer.

Context/Organisational issues

Non-FDG tracers for use in PET-CT restaging of recurrent prostate cancer are produced by either cyclotrons (cholines and anti- ^{18}F -FACBC) or generators (^{68}Ga -PSMA). While cyclotrons are currently available within NHSScotland PET-CT centres, generators capable of producing ^{68}Ga -PSMA are not (Dr J Straiton, Consultant Radiologist, NHS Grampian. Personal communication, 24 Nov 2016).

Producing ^{68}Ga -PSMA, therefore, currently involves collaboration with universities with the necessary facilities for producing this tracer. Several of the PET-CT centres in Scotland are in the process of developing business cases for obtaining the equipment needed to set up ^{68}Ga -PSMA PET-CT services (Dr D Patel, Consultant Radiologist, NHS Lothian. Personal communication, 26 Jan 2017).

All non-FDG tracers have a specific half-life which limits how far they can be transported or how long they can be stored before being used in a PET-CT scan (Annex 1). In particular, the 20 minute half-life of ^{11}C -choline restricts its use to facilities with an on-site cyclotron located a short distance from the PET-CT scanner^{27, 28}. Other non-FDG tracers can be transported between facilities within the range of their half-life (Annex 1).

Producing ^{68}Ga -PSMA is further complicated by the need for staff qualified to use the equipment and UK regulations on manufacturing practices^{7, 29}. A proposal to introduce a ^{68}Ga -PSMA PET-CT scanning for recurrent prostate cancer in NHS Lothian estimated that a senior radiologist would require up-skilling and a new quality control pharmacist would need to be recruited to enable successful implementation of this service (Dr D Patel, Consultant Radiologist, NHS Lothian. Personal communication, 26 Jan 2017). Implementing ^{68}Ga -PSMA PET-CT scanning services in Scotland may, therefore, have staffing implications for local NHS boards.

The volume of patients requiring PET-CT scanning for restaging of prostate cancer recurrence nationally is unknown, but likely to vary between PET-CT centres. NHS Lothian has estimated it scans approximately 70 patients with suspected prostate cancer recurrence per year (Dr D Patel, Consultant Radiologist, NHS Lothian. Personal communication, 26 Jan 2017). The volume of patients requiring

annual ^{68}Ga -PSMA PET-CT for prostate cancer restaging is likely to be comparable to current number of choline-based PET-CT scans in this population.

Generally, one cyclotron cycle will produce sufficient ^{11}C -choline for a single dose for use in a PET-CT scan of one patient at a cost of approximately £3,000 per dose (Dr J Straiton, Consultant Radiologist, NHS Grampian. Personal communication, 24 Nov 2016). A single cyclotron run can also produce four doses of ^{18}F -choline at a cost of £500 per dose (Dr D Patel, Consultant Radiologist, NHS Lothian. Personal communication, 9 Feb 2017). In comparison, a ^{68}Ga -PSMA generator could produce enough tracer for two to four patients per cycle at a cost of approximately £500 to £1,000 per dose.

Anti- ^{18}F -FACBC has been marketed as Axumin™ in the USA by Blue Earth Diagnostics Inc at a cost of \$3,675 per unit dose (approximately £3,000)³⁰. Anti- ^{18}F -FACBC can also be produced using existing cyclotron and fastlab equipment within NHSScotland (Dr G Gillen, PET Physicist, NHS Greater Glasgow and Clyde. Personal communication, Aug 2016).

Initial capital costs for equipment for ^{68}Ga -PSMA production in NHS Lothian have been estimated at £117,000 (Dr D Patel, Consultant Radiologist, NHS Lothian. Personal communication, 26 Jan 2017). An estimated £175,000 per annum in revenue costs would then be required to provide a ^{68}Ga -PSMA PET-CT scanning service in NHS Lothian, including staff and lease costs. This annual cost could be reduced to £117,000 per annum by deducting savings from replacing scanning using In^{111} -pentetretotide and ^{18}F -choline with ^{68}Ga -PSMA scanning.

Conclusion

A recurrence of prostate cancer as indicated by rising PSA levels affects up to a third of men who have received treatment with curative

intent. Use of non-FDG PET-CT in these patients can help timely detection of prostate cancer recurrence and localisation of sites of recurrence.

A larger body of evidence was identified for ^{11}C - and ^{18}F -radiolabelled choline tracers in PET-CT in recurrent prostate cancer compared with the novel tracers anti- ^{18}F -FACBC and ^{68}Ga -PSMA. This reflects their use in clinical practice. All the evidence identified on non-FDG PET-CT restaging in prostate cancer patients with suspected recurrence addressed diagnostic accuracy outcomes, therefore no conclusions can be drawn about the effect on treatment decisions or patient outcomes in this population.

Findings from one systematic review with meta-analysis based on comparisons of choline tracers suggested that ^{18}F -choline outperforms ^{11}C -choline in detecting recurrent prostate cancer based on sensitivity¹⁹. Detection rates were higher with ^{18}F -choline than ^{11}C -choline tracers in PET/PET-CT restaging of prostate cancer in two meta-analyses^{4, 20}, but there was inconsistency in the significance of the difference. Choline has known limitations related to physiological biodistribution, therefore new alternative tracers have been considered for the assessment of recurrent prostate cancer.

A small number of studies suggest that ^{68}Ga -PSMA is more accurate in detecting recurrent disease compared with radiolabelled choline. This is particularly so at low levels of PSA. A recent systematic review²¹ and two primary studies^{5, 22} reported superior detection rates of recurrent prostate cancer for ^{68}Ga -PSMA compared with choline tracers, particularly at low PSA levels and shorter PSA doubling times. A second systematic review concluded that ^{68}Ga -PSMA also performed better than anti- ^{18}F -FACBC in detecting any suspected prostate cancer recurrence²⁶.

A single primary study was identified that compared anti- ^{18}F -FACBC to choline tracers in restaging prostate cancer and reported that anti- ^{18}F -FACBC had a higher detection rate than choline tracers²³.

From the limited evidence identified on safety, non-FDG tracers in PET-CT in recurrent prostate cancer appear to be safe.

No published economic analyses were identified so no cost-effectiveness conclusions can be drawn.

Implementing non-FDG PET-CT in Scotland for restaging patients with suspected prostate cancer recurrence has potential cost and infrastructure implications.

Identified research gaps

Large, prospective, multicentre studies are necessary to evaluate the cost effectiveness, diagnostic performance, impact on patient management and place in the patient care pathway of new non-FDG tracers (^{18}F -FACBC or ^{68}Ga -PSMA) in restaging of patients with suspected prostate cancer recurrence.

Prospective RCTs examining patient outcomes related to the use of radiolabelled choline and newer tracers in the management of patients with biochemically recurrent prostate cancer are required.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

This evidence note will be considered for review 2 years post-publication, and at 2-yearly intervals thereafter. For more information about the evidence note process see

www.healthcareimprovementscotland.org/our_work/clinical_cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

Acknowledgements

Healthcare Improvement Scotland and SHTG invited the following individuals and organisations to peer review the draft evidence note:

- Dr Jack Straiton, Consultant Radiologist, NHS Grampian
- Dr Gerry Gillen, Physicist, Nuclear Medicine and PET-CT, NHS Greater Glasgow and Clyde
- Dr John Shand, Consultant Radiologist, Clinical Lead for Nuclear Medicine and PET-CT, NHS Greater Glasgow and Clyde
- Jonny Savage, Senior Policy Officer, Prostate Cancer UK
- Rob Lester, Edinburgh & Lothian Prostate Cancer Support Group
- Dr Nicholas MacLeod, Clinical Oncologist, NHS Greater Glasgow and Clyde
- Lawrence Foulsham, Siemens Healthcare Limited
- Dr Sai Han, Clinical Lead for Nuclear Medicine and Pet-CT, NHS Greater Glasgow and Clyde
- Dr George Petrides, Radiologist for Nuclear Medicine and PET-CT, Royal Victoria Infirmary, Newcastle

Declarations of interest were sought from all peer reviewers. All contributions from peer reviewers were considered by the group. However, the peer reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

Healthcare Improvement Scotland development team

- Emma Riches and Jenny Harbour, Health Services Researchers
- Iain Stewart and Paul Herbert, Health Information Scientists
- Karen McGeary, Communications and Publications Co-ordinator
- Shonagh Ramsey, Project Officer
- Members of the SHTG evidence review committee

References

1. Ren J, Yuan L, Wen G, Yang J. The value of anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid PET/CT in the diagnosis of recurrent prostate carcinoma: a meta-analysis. *Acta Radiologica*. 2016;57(4):487-93.
2. WA Newland Dorland. *Dorland's illustrated medical dictionary*. Philadelphia (USA): WB Saunders Company; 2000.
3. Last J. *A dictionary of epidemiology*. 4th ed. New York: Oxford University Press; 2001.
4. von Eyben FE, Kairemo K. Acquisition with (11)C-choline and (18)F-fluorocholine PET/CT for patients with biochemical recurrence of prostate cancer: a systematic review and meta-analysis. *Ann Nuclear Med*. 2016;30(6):385-92.
5. Schwenck J RH, Reischl G, Kruck S, Stenzl A, Nikolaou K, Pfannenbergl C, la Fougere C. Comparison of 68Ga-labelled PSMA-11 and 11C-choline in the detection of prostate cancer metastases by PET/CT. *Eur J Nucl Med Mol Imaging*. 2017;44:92-101.
6. Shen G, Deng H, Hu S, Jia Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. *Skeletal Radiol*. 2014;43(11):1503-13. Epub 2014/05/21.
7. Scarsbrook AF, Barrington SF. PET-CT in the UK: current status and future directions. *Clin Radiology*.
8. Shen G, Deng H, Hu S, Jia Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. 2014 [cited 2017 Apr 18]; Available from: <http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12014034103/frame.html>.
9. Evangelista L, Cervino AR, Guttilla A, Zattoni F, Cuccurullo V, Mansi L. 18F-fluoromethylcholine or 18F-fluoroethylcholine pet for prostate cancer imaging: which is better? A literature revision. *Nuclear Med Biology*. 2015;42(4):340-8.
10. Cancer Research UK. Prostate cancer incidence by UK region. 2016 [cited 2016 Apr 26]; Available from: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence#heading-Zero>.
11. ISD Scotland. Cancer Statistics: male genital organ cancer. c2015 [cited 2016 Jun 24]; Available from: <http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Male-Genital-Organs/#prostate>.
12. Cancer Research UK. Prostate cancer symptoms. 2014 [cited 2016 Jun 16]; Available from: <http://www.cancerresearchuk.org/about-cancer/type/prostate-cancer/about/prostate-cancer-symptoms>.
13. National Collaborating Centre for Cancer. Prostate Cancer: diagnosis and treatment. 2014 [cited 2016 Jun 16]; Available from: <https://www.nice.org.uk/guidance/cg175/evidence/full-guideline-191710765>.
14. Macmillan Cancer Support. Prostate cancer. c2017 [cited 2016 Jun 24]; Available from: <http://www.macmillan.org.uk/information-and-support/prostate-cancer>.

15. Cancer Research UK. If prostate cancer comes back. 2014 [cited 2016 Jun 16]; Available from: <http://www.cancerresearchuk.org/about-cancer/type/prostate-cancer/treatment/if-prostate-cancer-comes-back>.
16. European Association of Urology. Guidelines on Prostate Cancer. 2015 [cited 2016 Jul 27]; Available from: <http://uroweb.org/wp-content/uploads/EAU-Guidelines-Prostate-Cancer-2015-v2.pdf>.
17. Matthew A, Souter LH, Breau RH, Canil C, Haider M, Jamnicky R, *et al*. Follow-up care and psychosocial needs of survivors of prostate cancer. 2015 [cited 2016 Jul 27]; Available from: <https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=342321>.
18. The Royal College of Radiologists, Royal College of Physicians of London, Royal College of Physicians and Surgeons of Glasgow, Royal College of Physicians of Edinburgh, British Nuclear Medicine Society, Administration of Radioactive Substances Advisory Committee. Evidence-based indications for the use of PET-CT in the United Kingdom 2016. 2016 [cited 2016 Jul 28]; Available from: https://www.rcr.ac.uk/sites/default/files/publication/bfcr163_pet-ct.pdf.
19. Evangelista L, Guttilla A, Saladini G, Zattoni F, Colletti PM, Rubello D. Choline PET or PET/CT and biochemical relapse of prostate cancer: a systematic review and meta-analysis. *Clin Nuclear Med*. 2013;38(5):305-14.
20. von Eyben FE, Kairemo K. Meta-analysis of (11)C-choline and (18)F-choline PET/CT for management of patients with prostate cancer. *Nuclear Med Communications*. 2014;35(3):221-30.
21. Evangelista L, Briganti A, Fanti S, Joniau S, Reske S, Schiavina R, *et al*. New clinical indications for (18)F/(11)C-choline, new tracers for positron emission tomography and a promising hybrid device for prostate cancer staging: a systematic review of the literature. *Eur Urol*. 2016;70(1):161-75.
22. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, *et al*. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*. 2014;41(1):11-20.
23. Nanni C, Schiavina R, Brunocilla E, Boschi S, Borghesi M, Zanoni L, *et al*. 18F-fluciclovine PET/CT for the detection of prostate cancer relapse: a comparison to 11C-choline PET/CT. *Clin Nuclear Med*. 2015;40(8):e386-91.
24. Nanni C, Schiavina R, Boschi S, Ambrosini V, Pettinato C, Brunocilla E, *et al*. Comparison of 18F-FACBC and 11C-choline PET/CT in patients with radically treated prostate cancer and biochemical relapse: preliminary results. *Eur J Nucl Med Mol Imaging*. 2013;40 Suppl 1:S11-7.
25. Nanni C, Schiavina R, Brunocilla E, Borghesi M, Ambrosini V, Zanoni L, *et al*. 18F-FACBC compared with 11C-choline PET/CT in patients with biochemical relapse after radical prostatectomy: a prospective study in 28 patients. *Clin Genitourin Cancer*. 2014;12(2):106-10.
26. Yu CY, Desai B, Ji L, Groshen S, Jadvar H. Comparative performance of PET tracers in biochemical recurrence of prostate cancer: a critical analysis of literature. *Am J Nucl Med Mol Imaging*. 2014;4(6):580-601. Epub 2014/09/25.
27. Umbehr MH, Muntener M, Hany T, Sulser T, Bachmann LM. The role of 11C-choline and 18F-fluorocholine positron emission tomography (PET) and PET/CT in prostate cancer: a systematic review and meta-analysis. *Eur Urol*. 2013;64(1):106-17.

28. Bauman G, Belhocine T, Kovacs M, Ward A, Beheshti M, Rachinsky I. 18F-fluorocholine for prostate cancer imaging: a systematic review of the literature. *Prostate Cancer Prostatic Diseases*. 2012;15(1):45-55.
29. UK Radiopharmacy Group. Guidance for introduction of a 68Ge/68Ga generator and labelling service into routine clinical practice. 2014 [cited 27 Feb 2017]; Available from: http://www.bnms.org.uk/images/stories/UKRG/2014/GMP_and_Practical_Requirements_for_68_Ga_Gallium_Radiolabelling_2014.pdf.
30. Blue Earth Diagnostics Inc. Axumin (TM) reimbursement Q&A. c2016 [cited 27 Jan 2017]; Available from: <http://www.axumin.com/pdf/Reimbursement-QA.pdf>.

Annex 1: Characteristics of non-FDG radiolabelled tracers

	¹¹ C- choline	¹⁸ F-choline (¹⁸ F-FEC or ¹⁸ F-FCH)	¹⁸ F-FACBC	⁶⁸ Ga-PSMA
Target	Choline is an essential component of phospholipids which comprise part of the cell membrane ²⁷	Choline is an essential component of phospholipids which comprise part of the cell membrane ²⁷	A synthetic amino acid analogue ¹	PSMA is a type II transmembrane protein with an extracellular portion expressed in the apical epithelium surrounding the prostatic ducts ³¹
Uptake	Alterations in choline metabolism during malignancy, including increased uptake via choline transporters in the cell membrane and increased activity of choline kinase ²⁸	Alterations in choline metabolism during malignancy, including increased uptake via choline transporters in the cell membrane and increased activity of choline kinase ²⁸	Uptake is via two amino acid transporters: alanine serine transporter 2 and L-type amino acid transporter 1 which are up-regulated during progression to metastatic disease ¹	Increased PSMA expression on luminal surface of prostatic ducts, with expression influenced by stage and grade of the tumour. Uptake via small molecule PSMA ligands/inhibitors labeled with ⁶⁸ Ga binding to the PSMA receptor. The inhibitor Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (⁶⁸ Ga-PSMA-HBED-CC) is the most commonly used agent ³¹
Uptake time (minutes)	4-6 ²¹	29 +/- 24 (¹⁸ F-FCH) ⁴	Mean 3.6 (range 1.8-8.5) ³²	Range 41-90 for restaging ³³
Half-life (minutes)	20 ²⁸	110 ²⁸	109 ¹	68 ³⁴
Production	Restricted to centres with onsite generation facilities ²⁷	Not restricted to centres with onsite generation facilities ²⁷	Not restricted to centres with onsite generation facilities ^{1, 23} .	Not restricted to centres with onsite generation facilities ³⁵
Advantages	Low urinary excretion Preferable biodistribution ²⁸	Short positron range leading to higher quality image and spatial resolution ²⁸	Slow renal excretion Favorable distribution with reduced distribution in urinary tract improving the detection of small sites of disease in the prostatic fossae ¹	Biological characteristics make it an ideal target for molecular imaging Expressed in nearly all prostate cancers Cleared quickly from the bloodstream ³¹

Limitations	Limited availability (restricted to centres with onsite generation facilities)	Renal excretion (which makes assessment of primary prostate cancer and local nodes difficult)	Uptake is not specific to malignant tumours ¹ Efflux of tracer from the tumour after approximately 30min ¹	Financial considerations Regulatory issues related to manufacturing Lack of qualified personnel to facilitate preparation at local level ⁷ Down-regulation of PSMA expression by androgen therapy ²¹
-------------	--	---	---	---