Is positron emission tomography/computed tomography (PET-CT) clinically and cost effective for staging and/or restaging in patients with suspected renal or bladder cancer following an abnormal result on contrast-enhanced computed tomography or magnetic resonance imaging?

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

Renal cancer
- In a meta-analysis of seven studies (n=535), 18F-fluorodeoxyglucose (FDG) PET-CT had a pooled sensitivity of 0.88 (95% confidence interval (CI) 0.84 to 0.91) and pooled specificity of 0.88 (95% CI 0.82 to 0.92) for restaging of renal cell carcinoma.
- One retrospective study reported that, following FDG PET-CT, patient management was altered for 43% (n=45) of patients with suspected renal cell carcinoma recurrence or metastases. In the same study, a positive FDG PET-CT finding was associated with statistically significantly lower 3-year progression-free survival (20% versus 67%, p<0.05) and 5-year overall survival (19% versus 69%, p=0.05) compared with a negative FDG PET-CT finding.

Bladder cancer
- A meta-analysis of seven studies (n=253) reported diagnostic accuracy for FDG PET-CT separately for primary staging and restaging/metastases detection in patients with suspected bladder cancer:
- primary staging (two studies) - pooled sensitivity was 0.9 (95% CI 0.70 to 0.99) and pooled specificity was 1.00 (95% CI 0.74 to 1.00) and
- restaging/metastases (five studies) - pooled sensitivity was 0.82 (95% CI 0.72 to 0.89) and pooled specificity was 0.89 (95% CI 0.84 to 0.95).

- Four observational studies (n=293) reported a change in patient management in 20-47% of patients with bladder cancer based on FDG PET-CT findings.
- In one of these studies (retrospective, n=41), a positive FDG PET-CT result was associated with lower 2-year survival (47% versus 88%, p<0.05) 3-year survival (25% versus 87%, p<0.05), and 2-year progression-free survival (24% versus 85%, p<0.05) compared with a negative FDG PET-CT finding in patients with suspected recurrence or metastases of bladder cancer.
- No evidence was identified which assessed the cost effectiveness of FDG PET-CT in patients with urological cancers. Therefore, no conclusions can be drawn about the cost effectiveness of FDG PET-CT in this patient group.

**Definitions**

**Sensitivity:** the probability that a person having a disease will be correctly identified by a clinical test, 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 test, that is the number of true negative results divided by the total number of those without the disease.

**Positive likelihood ratio:** the probability that a positive test result will occur in a person with the target condition divided by the probability of a positive test result occurring in a person without the disease, that is the sensitivity divided by one minus specificity.

**Negative likelihood ratio:** the probability that a negative test result will occur in a person with the target condition divided by the probability of a negative test result occurring in a person without the disease, that is the 1-sensitivity divided by specificity.

**Diagnostic odds ratio:** the ratio of the odds of testing positive when having the target condition to the odds of testing positive without having the target condition.

**Cystectomy:** surgical removal of the urinary bladder.

**Literature search**

A systematic search of the secondary literature was carried out between 8 and 16 May 2017 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Medline in process, Medline ePUB ahead of print, Embase, Cinahl and Web of Science databases were searched for systematic reviews and meta-analyses.

The primary literature was systematically searched between 19 and 21 July 2017 using the following databases: Medline, Medline in process, and Medline ePUB ahead of print. Results were limited to primary studies on renal or bladder cancer that were published in English in the last 5 years, and reported patient management outcomes.
Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

Concepts used in all searches included urological cancer/neoplasm, renal/kidney, renal pelvis, bladder and positron emission tomography/computed tomography (PET/CT). A full list of resources searched and terms used are available on request.

Introduction

The most common cancers of the kidney are renal cell carcinomas, which affect the outer tissues of the kidneys and account for approximately 85% of renal cancers\(^4\). Renal cell carcinomas can be divided into three subtypes: clear cell, papillary and chromophobe. The majority of renal cell carcinomas (80%) arise from clear cells. Average 5-year survival for people with renal cell carcinoma is estimated at 64%, making this one of the most lethal urological malignancies\(^4, 5\). The 5-year survival rate for metastatic disease, which occurs in 20-40% of people with renal cancer, is less than 10%\(^4, 6\).

More than 90% of cancers of the urinary bladder are urothelial carcinomas\(^7\). Approximately three quarters of these cancers are superficial tumours; the remaining 25% involve tumour invasion of the bladder muscle wall, which may require major surgery to remove the urinary bladder\(^8\). Even with radical surgical intervention, mortality in patients with high risk muscle invasive bladder cancer is roughly 50%. In the case of bladder cancers, appropriate treatment is strongly linked to the extent of the disease and treatment is associated with significant morbidity, therefore accurate tumour staging in people with suspected bladder cancer is important for clinical decision-making\(^9\).

Conventional radiological imaging for suspected urological cancers includes ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy\(^5, 10, 11\). \(^{18}\)F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (FDG PET-CT) is an alternative imaging modality that could potentially be used for staging, restaging or metastases detection in patients with suspected renal or bladder cancer following indeterminate findings on conventional imaging\(^6\).

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 CT images give precise anatomical localisation\(^{12}\). The procedure usually involves injecting a radiolabelled tracer into the body, but the tracer can be ingested or inhaled. The radio-labelled tracer is taken up and accumulates in metabolically active cells (such as malignant cells) and emits gamma rays detected by the PET and CT technology 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 cancer treatments. The radio-labelled tracers are then passed out of the body in the urine or bowel movement. \(^{18}\)F-fluorodeoxyglucose (FDG) is the most common radio-labelled tracer used with PET-CT imaging.

As the kidneys and bladder form part of the urinary excretion pathway, background activity from radiotracers in the urine can interfere with FDG PET-CT imaging in people with renal or bladder cancer\(^10\). In Scotland, FDG PET-CT is, therefore, mainly used for detecting cancer recurrence (restaging), identifying and locating metastases, or characterising tumours in patients with suspected kidney or bladder cancer who have equivocal findings on conventional imaging (J Brush, Consultant Radiologist & Lead Clinician for Radiology, NHS Lothian. Personal communication, 8 May 2017). Most kidney or bladder cancer patients
undergoing FDG PET-CT in Scotland will have previously received treatment for one of these conditions. The FDG PET-CT results are used to determine the most appropriate future treatment for each of these patients (P Mariappan, Consultant Urological Surgeon, NHS Lothian. Personal communication, 25 September 2017).

**Epidemiology**

Renal cell carcinomas account for 2-3% of all new cancers globally, making this one of the 10 most common cancers in the world. In Scotland, kidney cancers account for 3.2% of all cancers. Table 1 summarises incidence and mortality data for kidney cancers in Scotland.

Renal cell carcinomas are twice as common in men, who tend to have a poorer prognosis because they often present with more advanced disease at diagnosis. In the last 10 years there has been a 25% increase in kidney cancer incidence in Scotland. It is unclear why kidney cancer incidence is rising, but it may be due to increased prevalence of risk factors, such as obesity and smoking, or improved medical imaging leading to more incidental findings.

**Table 1: incidence and mortality statistics for kidney cancers in Scotland in 2015**

<table>
<thead>
<tr>
<th>Registrations</th>
<th>European age standardised incidence per 100,000 person-years at risk</th>
<th>Deaths</th>
<th>European age standardised mortality per 100,000 person-years at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>634</td>
<td>26.8 (95% CI 24.7 to 28.9)</td>
<td>214</td>
</tr>
<tr>
<td>Female</td>
<td>379</td>
<td>13.5 (95% CI 12.1 to 14.8)</td>
<td>147</td>
</tr>
<tr>
<td>All persons</td>
<td>1,013</td>
<td>20.1 (95% CI 18.9 to 21.4)</td>
<td>361</td>
</tr>
</tbody>
</table>

Table 2 presents incidence and mortality data for bladder cancer in Scotland. Bladder cancer is the seventh most common type of cancer in the UK, accounting for 2.6% of all cancers in Scotland. Although bladder cancer is 3-4 times more common in men, the prognosis is generally poorer for women. It is unclear why this is the case.

In the last 10 years, incidence of bladder cancer has decreased in both males (6%) and females (2%) in Scotland, although these decreases were not statistically significant. The main risk factors for bladder cancer are increasing age, male gender and smoking.

**Table 2: incidence and mortality statistics for bladder cancer in Scotland in 2015**

<table>
<thead>
<tr>
<th>Registrations</th>
<th>European age standardised incidence per 100,000 person-years at risk</th>
<th>Deaths</th>
<th>European age standardised mortality per 100,000 person-years at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>551</td>
<td>26.1 (95% CI 23.9 to 28.4)</td>
<td>329</td>
</tr>
<tr>
<td>Female</td>
<td>277</td>
<td>9.7 (95% CI 8.6 to 10.8)</td>
<td>193</td>
</tr>
<tr>
<td>All persons</td>
<td>828</td>
<td>17.9 (95% CI 16.6 to 19.1)</td>
<td>522</td>
</tr>
</tbody>
</table>
Clinical effectiveness

Guidelines

Three clinical practice guidelines were identified that make recommendations on FDG PET-CT in patients with renal cancer (Table 3)\textsuperscript{16-18}. The UK guidance limited its recommendations on FDG PET-CT for renal carcinoma to selected cases where there were inconclusive results from conventional imaging\textsuperscript{18}. It is unclear what evidence this recommendation is based on.

Four clinical guidelines, including two from the UK, make recommendations on FDG PET-CT in patients with bladder cancer (Table 3)\textsuperscript{18,19-20}. Guidelines from the Royal College of Radiologists recommend the use of FDG PET-CT in patients with advanced muscle invasive bladder cancer that may be radically treated\textsuperscript{18}. The NICE guideline on bladder cancer recommends consideration of FDG PET-CT in patients with high risk bladder cancer who have indeterminate findings from CT or MRI\textsuperscript{18}.

Table 3: guideline recommendations on FDG PET-CT for renal and bladder cancer

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Evidence base</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indications for use of FDG PET-CT in the UK\textsuperscript{18}</td>
<td>Unclear: the guideline cites a single study on FDG PET-CT in urological cancers</td>
<td>FDG PET-CT can be used for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>renal carcinoma staging in selected cases with equivocal findings on other imaging modalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>assessment of metastatic renal carcinoma in complex cases or when conventional imaging is inconclusive</td>
</tr>
<tr>
<td>American College of Radiology appropriateness criteria for staging renal cell carcinoma\textsuperscript{16}</td>
<td>Two meta-analyses and two primary studies</td>
<td>FDG PET-CT from skull base to mid-thigh is usually not appropriate for renal cell carcinoma staging</td>
</tr>
<tr>
<td>Renal cancer in adults (Belgium)\textsuperscript{17}</td>
<td>The guideline developer conducted a meta-analysis using two studies from a previous meta-analysis plus three more recent primary studies</td>
<td>FDG PET-CT is not routinely recommended for diagnosis, staging or follow-up in patients with renal cell carcinoma</td>
</tr>
</tbody>
</table>

| Bladder cancer |  |  |
| Indications for use of FDG PET-CT in the UK\textsuperscript{18} | Unclear: the guideline cites three primary studies on FDG PET-CT in bladder cancer | FDG PET-CT can be used for assessment of advanced muscle invasive bladder cancer that is potentially radically treatable |
| NICE bladder cancer guideline\textsuperscript{8} | Two primary studies | Consider FDG PET-CT for patients with muscle invasive bladder cancer or high risk non-muscle invasive bladder cancer before radical treatment if there are indeterminate findings on conventional imaging |
| American College of Radiology appropriateness criteria for pre-treatment staging of bladder cancer\textsuperscript{19} | Nine primary studies and one overview | Whole body FDG PET-CT may be appropriate for pre-treatment staging of muscle invasive bladder cancer |
Diagnostic accuracy to patients definition, the results of the meta analysis with a positive likelihood ratio greater than 5.0 and a negative likelihood ratio less than 0.2. In the meta analysis, separate pooled diagnostic accuracy results are provided for FDG PET-CT. Eight FDG PET-CT studies with a total of 850 participants were included in the systematic review. Seven of these studies were retrospective, which may have introduced interpretation bias if the outcome of the reference standard was known prior to analysing FDG PET-CT results. Studies in the systematic review enrolled participants with a variety of renal cell carcinoma sub-types, including clear cell, papillary, chromophobe and sarcomatoid carcinomas. Studies used histopathology, clinical follow-up and/or imaging follow-up as reference standards. This lack of consistency in the reference standard used by primary studies was identified by the meta-analysis authors as a limitation of their analysis. It is unclear whether study participants had undergone conventional imaging prior to an FDG PET-CT scan.

Quality of studies in the meta-analysis was assessed using the validated Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool and presented as the proportion of included studies that were rated high, unclear or low risk of bias for each QUADAS domain. Two studies on FDG PET-CT were rated high or unclear risk for selection bias because patients were not consecutively or randomly enrolled in the study. One FDG PET-CT study was excluded from the meta-analysis in an effort to reduce heterogeneity. It is not clear how the authors selected this study for exclusion. The excluded study was the largest in the systematic review (n=315), with at least three times as many participants as other studies, and substantial heterogeneity remained after this study was excluded (I²>50%). This heterogeneity, measured using the I²-square value, is difficult to interpret as sensitivity and specificity are expected to vary between studies due to the situation the test is being used in and threshold effects.

In the meta-analysis, pooled sensitivity and specificity of FDG PET-CT for restaging of renal cell carcinoma were 0.88 (95% confidence interval (CI) 0.84 to 0.91) and 0.88 (95% CI 0.82 to 0.92), respectively. The positive likelihood ratio for FDG PET-CT was 6.82 (95% CI 4.05 to 11.48) and the negative likelihood ratio was 0.13 (95% CI 0.08 to 0.22). A clinically useful test was defined by the meta-analysis authors as a test with a positive likelihood ratio greater than 5.0 and a negative likelihood ratio less than 0.2. Based on this definition, the results of the meta-analysis indicate that FDG PET-CT may be a clinically relevant test in patients with suspected recurrence of renal cell carcinoma. A diagnostic odds ratio of 67.04 (95% CI 24.84 to 180.87) is given in the meta-analysis, however it is unclear if this is an appropriate measure of diagnostic accuracy and there is a very wide confidence interval. Pooled effect estimates for FDG PET-CT

<table>
<thead>
<tr>
<th>American College of Radiology appropriateness criteria for post-treatment surveillance of bladder cancer</th>
<th>Eight primary studies</th>
<th>Whole body FDG PET-CT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- is usually not appropriate for post-treatment surveillance in patients with superficial urothelial carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- may be appropriate for patients with muscle invasive urothelial carcinoma with or without cystectomy</td>
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</table>

Renal cancer

One systematic review with meta-analysis provided evidence on the diagnostic accuracy of FDG PET-CT in patients with suspected recurrence of renal cell carcinoma. A retrospective observational study evaluated the effect of FDG PET-CT findings on treatment decisions in patients with suspected renal cancer. In a prospective observational study, the authors assessed the ability of FDG PET-CT to differentiate between malignant and benign renal lesions.

A systematic review with meta-analysis evaluated the diagnostic accuracy of FDG PET or FDG PET-CT in patients with suspected recurrence of renal cell carcinoma. Although the main meta-analysis combined FDG PET and FDG PET-CT studies, separate pooled diagnostic accuracy results are provided for FDG PET-CT. Eight FDG PET-CT studies with a total of 850 participants were included in the systematic review. Seven of these studies were retrospective, which may have introduced interpretation bias if the outcome of the reference standard was known prior to analysing FDG PET-CT results. Studies in the systematic review enrolled participants with a variety of renal cell carcinoma sub-types, including clear cell, papillary, chromophobe and sarcomatoid carcinomas. Studies used histopathology, clinical follow-up and/or imaging follow-up as reference standards. This lack of consistency in the reference standard used by primary studies was identified by the meta-analysis authors as a limitation of their analysis. It is unclear whether study participants had undergone conventional imaging prior to an FDG PET-CT scan.

Quality of studies in the meta-analysis was assessed using the validated Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool and presented as the proportion of included studies that were rated high, unclear or low risk of bias for each QUADAS domain. Two studies on FDG PET-CT were rated high or unclear risk for selection bias because patients were not consecutively or randomly enrolled in the study. One FDG PET-CT study was excluded from the meta-analysis in an effort to reduce heterogeneity. It is not clear how the authors selected this study for exclusion. The excluded study was the largest in the systematic review (n=315), with at least three times as many participants as other studies, and substantial heterogeneity remained after this study was excluded (I²>50%). This heterogeneity, measured using the I²-square value, is difficult to interpret as sensitivity and specificity are expected to vary between studies due to the situation the test is being used in and threshold effects.

In the meta-analysis, pooled sensitivity and specificity of FDG PET-CT for restaging of renal cell carcinoma were 0.88 (95% confidence interval (CI) 0.84 to 0.91) and 0.88 (95% CI 0.82 to 0.92), respectively. The positive likelihood ratio for FDG PET-CT was 6.82 (95% CI 4.05 to 11.48) and the negative likelihood ratio was 0.13 (95% CI 0.08 to 0.22). A clinically useful test was defined by the meta-analysis authors as a test with a positive likelihood ratio greater than 5.0 and a negative likelihood ratio less than 0.2. Based on this definition, the results of the meta-analysis indicate that FDG PET-CT may be a clinically relevant test in patients with suspected recurrence of renal cell carcinoma. A diagnostic odds ratio of 67.04 (95% CI 24.84 to 180.87) is given in the meta-analysis, however it is unclear if this is an appropriate measure of diagnostic accuracy and there is a very wide confidence interval. Pooled effect estimates for FDG PET-CT
studies were similar to pooled results from FDG PET and FDG PET-CT studies combined, and not statistically significantly different from analyses of FDG PET only studies.

One study incorporated in the meta-analysis discussed above reported the impact of FDG PET-CT findings on treatment decisions, and the use of FDG PET-CT for predicting survival or risk of disease progression in patients with recurrent or metastatic renal cell carcinoma. This retrospective study selected 104 post-surgery renal cell carcinoma patients, most with suspected recurrence of renal clear cell carcinoma (n=94), from a hospital database. Results from FDG PET-CT scans were verified using histology and/or other forms of imaging, such as CT, MRI or bone scans. As the study was retrospective, clinicians interpreting FDG PET-CT images had knowledge of previous imaging results and clinical data for each patient, which may have introduced interpretation bias to the study. Study participants had previously been treated by nephrectomy (n=81) or partial nephrectomy (n=8) for renal cell carcinoma, while previous treatment data was missing for 15 participants.

Following FDG PET-CT, treatment decisions were changed in 43% (n=45) of patients with suspected renal cell carcinoma recurrence/metastases. Sixteen patients were transferred from palliative care to curative interventions: 12 moved to repeat surgery and four underwent radiotherapy. Twenty-four patients moved from curative treatment to palliative chemotherapy, and five patients were assigned to a ‘wait and watch’ category for continued surveillance. These changes in treatment represent both a change in treatment method and a change in treatment intent. In this study, a positive FDG PET-CT finding was associated with lower 3-year progression-free survival (20% versus 67%, p<0.05) and 5-year overall survival (19% versus 69%, p=0.05), compared with a negative FDG PET-CT result. In multivariate Cox regression analysis, a positive FDG PET-CT finding was associated with a significantly increased risk of disease recurrence compared with a negative FDG PET-CT finding (hazard ratio (HR) 4.01, 95% CI 1.6 to 6.3, p<0.05).

An additional primary study investigated the ability of FDG PET-CT to differentiate between malignant and benign lesions in patients with indeterminate primary renal masses detected on CT, MRI or ultrasound (n=18). This small, prospective diagnostic study conducted a FDG PET-CT scan within 4 weeks of a patient receiving an inconclusive result from conventional imaging. All diagnoses were confirmed using histopathology as the reference standard. Clinicians were not blinded to previous test results or clinical data which may have introduced interpretation bias. Fifteen patients had clear cell or papillary renal carcinoma, two had benign cortical cysts, and one patient had a benign oncocytoma. Imaging with FDG PET-CT correctly detected seven malignant lesions, and returned a false-negative result in eight patients with malignant lesions. The two cortical cysts were correctly identified as benign lesions, but the patient with an oncocytoma received a false positive FDG PET-CT result. Overall sensitivity, specificity and accuracy of FDG PET-CT for renal malignancies were 46.6%, 66.6%, and 50% respectively. FDG PET-CT correctly detected vascular, pulmonary and bone metastases of renal cell carcinoma in three patients with metastases. No lymph node metastases were present on FDG PET-CT or histology. The authors concluded that FDG PET-CT should have a limited role in characterising primary renal tumours due to low sensitivity, but was effective for detecting distant metastases in patients with equivocal results from conventional imaging. This conclusion appears to be based on very limited evidence, as only three patients had metastases and no participants had lymph node metastases.

Bladder cancer

Three meta-analyses were identified that evaluated the diagnostic accuracy of FDG PET-CT in patients with suspected bladder cancer. Two prospective primary studies and two retrospective primary studies evaluated the effect of FDG PET-CT findings on treatment decisions in patients with suspected bladder cancer.
A meta-analysis incorporating 10 studies (n=433) assessed the diagnostic accuracy of FDG PET or FDG PET-CT in patients with bladder cancer. Nine studies in the meta-analysis were retrospective. Studies in this meta-analysis evaluated FDG PET-CT for primary staging (one study), detection/location of metastases (five studies), or restaging (three studies) of bladder cancer. Results from the meta-analysis were not presented separately for each of these purposes, which complicates interpretation of results from the analysis. All the included studies evaluated FDG PET-CT, either exclusively or in addition to FDG PET alone. Histopathology or clinical follow-up were used as the reference standard. The review authors noted potential publication bias in their analysis, however it is unclear if this bias was significant due to the small number of included studies.

The quality of included studies was assessed using both the validated QUADAS appraisal tool and the Standards for Reporting Diagnostic Accuracy Studies (STARD) criteria. It is unclear why the review authors chose to evaluate study quality using both these tools, particularly as the STARD criteria are aimed at improving quality of reporting rather than appraising methodological quality of studies. The results of the quality assessment are reported as scores for each study but it is unclear what these mean in terms of study biases. In addition, the authors stated they performed a sensitivity analysis using meta-regression to explore the effect of study quality on results of the meta-analysis. This sensitivity analysis is not reported with the published meta-analysis, and “high quality” studies seem to have been identified based on the less appropriate STARD criteria, rather than QUADAS.

Pooled sensitivity and specificity for FDG PET or FDG PET-CT in patients with bladder cancer were 0.82 (95% CI 0.75 to 0.88) and 0.92 (95% CI 0.87 to 0.95), respectively. There was statistically significant heterogeneity in the sensitivity meta-analysis (sensitivity range 50% to 100%, I²=55.7%, p=0.0162), which is difficult to interpret as sensitivity and specificity are expected to vary between studies due to the situation the test is being used in and the threshold effect. The authors do not appear to address this heterogeneity in their analysis. The pooled positive likelihood ratio was 6.80 (95% CI 4.31 to 10.74) and the negative likelihood ratio was 0.27 (95% CI 0.19 to 0.36). A diagnostic odds ratio of 25.18 (95% CI 17.58 to 70.4) was reported, but the debatable validity of this measure and the wide confidence interval limit the usefulness of this result. The area under the curve in this meta-analysis was 0.93 (95% CI 0.86 to 0.99), which suggests that FDG PET-CT has high overall accuracy in patients with bladder cancer. The meta-analysis authors concluded that FDG PET-CT was a useful tool for detecting and staging bladder cancer. Due to the inclusion of studies on primary staging, metastatic and restaging patient populations in the meta-analysis, it is unclear which group(s) of patients with bladder cancer this conclusion relates to, or if it relates to all three groups equally.

Two older meta-analyses also evaluated the diagnostic accuracy of FDG PET-CT in patients with bladder cancer. Both of these meta-analyses included FDG PET and FDG PET-CT studies and selected studies based on similar criteria to the meta-analysis described above. There was overlap of included studies between the three meta-analyses, with all the studies in Lu et al (2012) appearing in the most recent meta-analysis. Unlike the other two meta-analyses, Lu et al (2012) analysed FDG PET-CT for primary staging separately from restaging or metastases detection. The diagnostic accuracy results from the three meta-analyses can be compared in Table 4.
Table 4: diagnostic accuracy of FDG PET-CT in bladder cancer, as reported in published meta-analyses

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>433</td>
<td>143</td>
<td>46</td>
<td>207</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.82 (95% CI 0.75 to 0.88)</td>
<td>0.80 (95% CI 0.71 to 0.87)</td>
<td>0.9 (95% CI 0.70 to 0.99)</td>
<td>0.82 (95% CI 0.72 to 0.89)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.92 (95% CI 0.87 to 0.95)</td>
<td>0.84 (95% CI 0.69 to 0.93)</td>
<td>1.00 (95% CI 0.74 to 1.00)</td>
<td>0.89 (95% CI 0.81 to 0.95)</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>6.80 (95% CI 4.31 to 10.74)</td>
<td>3.47 (95% CI 1.03 to 11.65)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.27 (95% CI 0.19 to 0.36)</td>
<td>0.31 (95% CI 0.13 to 0.70)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Diagnostic odds ratio</td>
<td>25.18 (95% CI 17.58 to 70.4)</td>
<td>13.86 (95% CI 2.84 to 67.74)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Area under the curve</td>
<td>0.93 (95% CI 0.86 to 0.99)</td>
<td>0.86 ± 0.07 (SE)</td>
<td>Not reported</td>
<td>0.97 ± 0.03 (SE)</td>
</tr>
</tbody>
</table>

SE = standard error.

In addition to meta-analyses on the diagnostic accuracy of FDG PET-CT in patients with bladder cancer, four primary studies assessed the impact of FDG PET-CT on patient management9,23-25. Although these studies assess the impact of FDG PET-CT on treatment decisions, they do not report long term oncological outcomes for patients undergoing a consequent change in treatment.

A small (n=41) retrospective study evaluated the use of FDG PET-CT as a second-stage examination for detecting lesions or metastases in patients with suspected recurrence of bladder cancer based on conventional imaging or clinical data25. All participants received conventional imaging with contrast enhanced CT or MRI. Participants had transitional cell, papillary transitional cell or squamous cell bladder carcinomas, and had previously been treated with radical cystectomy (56%), transurethral resection or intravesical immunotherapy. A change in treatment following FDG PET-CT was observed in 39% (n=16) of patients: six patients with negative findings were placed in a wait and watch category, three patients moved from palliative therapy to curative surgery, five patients started new chemotherapy or immunotherapy, and two patients received targeted radiotherapy. In this study, a positive FDG PET-CT finding was associated with lower 2-year survival (47% versus 88%, p<0.05), 3-year survival (25% versus 87%, p<0.05), and 2-year progression-free survival (24% versus 85%, p<0.05) compared with a negative FDG PET-CT result. In multivariate Cox regression analysis, a positive FDG PET-CT result was associated with an increased risk of disease progression (HR 16.3, p=0.001). It is not clear why no confidence interval was reported for the hazard ratio in this analysis. None of the study participants had metastatic disease and, therefore, they had a better prognosis than patients with metastases; overall and progression-free survival estimates may, therefore, be exaggerated in this study.

A prospective study assessed the use of FDG PET-CT in patients with high risk muscle invasive bladder cancer scheduled for radical cystectomy (n=103)24. Participants in this study appear to have primary bladder cancer. All participants received conventional CT, either before FDG PET-CT or on the same
occasion as FDG PET-CT. Provisional treatment decisions were reviewed following FDG PET-CT imaging and altered if appropriate. The authors defined a treatment change as any major alteration to a patient’s treatment plan based on FDG PET-CT findings. Treatment was changed for 27% (n=28) of patients following FDG PET-CT: for 16 patients curative cystectomy was cancelled as the cancer was too advanced (although two patients later had cystectomy for symptom control), and 12 patients had additional chemotherapy prior to cystectomy. A weakness of the study was the lack of histopathology confirmation of metastases in 21 of the 28 patients who had their treatment changed. The results of this study suggest that FDG PET-CT could reduce futile interventions in patients with advanced bladder cancer who would not benefit from curative attempts.

A second study also evaluated the use of FDG PET-CT in patients with carcinoma invading the bladder muscle³. In this retrospective study, 96 patients received both FDG PET-CT and contrast enhanced CT. The study authors defined impact on patient management following FDG PET-CT as a change of treatment between three pre-defined categories: local curative treatment (cystectomy or brachytherapy), neoadjuvant/induction chemotherapy, and palliative treatment. Treatment recommendations were changed in 13.5% (n=13) of patients: six patients moved from cystectomy to neoadjuvant/induction chemotherapy and seven patients moved from curative to palliative treatment. These treatment alterations reflect a change in both intervention method and overall intent. In four additional patients, metastases were detected on FDG PET-CT which led to a change from curative to palliative treatment, and two patients required additional surgery. In total, treatment changes were recommended for almost 20% of patients following FDG PET-CT. Due to patient preferences and characteristics, such as age and comorbidities, five patients did not receive the recommended treatment following FDG PET-CT. This likely reflects clinical reality for patients with bladder cancer.

A final prospective study conducted a survey of clinicians (n=53) to collect data on patient treatment plans before and after FDG PET-CT²⁹. All patients had indeterminate findings on CT or MRI prior to being referred for FDG PET-CT. Reviewers of the FDG PET-CT scans were not blinded to previous test and imaging results, which may have introduced interpretation bias. In 70% (n=37) of cases, patients had previously been treated for bladder cancer. Participants had superficial (12%), muscle invasive (44%) or metastatic (44%) bladder cancer. Clinicians reported that FDG PET-CT led to avoidance of additional tests in 70% (n=37) of patients and a change in treatment plan for 68% (n=36) of participants. Tests avoided included biopsy (21%) and additional imaging (21%). Treatment alterations included changing organ confined treatment to systemic chemotherapy for metastases treatment (19%), swapping from surveillance to intervention (6%), and changing local radiotherapy to chemotherapy (2%). Based on a review of medical records, the change in patient management was deemed appropriate in 34 of 36 patients. The authors noted that the impact of FDG PET-CT may have been overestimated as the patient treatment plan prior to FDG PET-CT in some cases was to request further imaging. In an analysis where this was adjusted for, the proportion of patients where treatment was changed decreased from 68% to 47% (n=25).

Safety

In the studies considered, no adverse events were identified relating to the use of FDG PET-CT in patients with suspected renal or bladder cancer.

Cost effectiveness

No cost-effectiveness evidence was identified relating to the use of FDG PET-CT in people with suspected renal or bladder cancer.
Conclusion

There was evidence from a meta-analysis of seven small studies that FDG PET-CT was effective for detecting recurrence or metastases of renal cell carcinoma. One small primary study suggested that FDG PET-CT may influence clinical decision-making in patients with recurrent renal cell carcinoma or renal cancer metastases.

There was evidence from a meta-analysis of 10 studies that FDG PET-CT may be a clinically effective test in patients with bladder cancer. Inclusion of studies reporting primary staging, restaging (recurrence) and metastases detection in this meta-analysis makes it difficult to determine the effectiveness of FDG PET-CT in specific groups of patients with suspected bladder cancer. An older meta-analysis, which separated primary staging and restaging/metastases, suggested there is stronger evidence that FDG PET-CT is clinically effective for the detection of recurrent or metastatic bladder cancer. Four small observational studies suggested that FDG PET-CT influenced treatment decisions in up to half of patients with bladder cancer.

No studies, on either renal or bladder cancer, reported oncological outcomes following changes in patient management based on FDG PET-CT findings.

No evidence was identified which assessed the cost effectiveness of FDG PET-CT in patients with urological cancers. Therefore, no conclusions can be drawn about the cost effectiveness of FDG PET-CT in this patient group.

Identified research gaps

Current evidence on FDG PET-CT in patients with renal or bladder cancer appears to be at stage three or four of the IDEAL-D framework. Therefore, future studies should be controlled, blinded, diagnostic studies, or economic evaluations.

- Diagnostic studies should evaluate the impact of FDG PET-CT imaging on treatment decisions and subsequent oncological outcomes in patients with suspected renal or bladder cancer following equivocal results on initial imaging.
- Cost-effectiveness analyses are required to evaluate the use of FDG PET-CT in patients with suspected renal or bladder cancer based on indeterminate CT or MRI results. Studies should consider long term oncological outcomes.

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
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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.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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