Healthcare Improvement Scotland | SHTG Advice on health technologies

Evidence Note
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In response to an enquiry from SCIN PET-CT Working Group

What is the clinical and cost effectiveness of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography – computed tomography (PET-CT) in routine staging and monitoring of treatment response in patients with anal cancer?

What is an evidence note?

Evidence notes are rapid reviews of the evidence surrounding health technologies that are 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 evidence notes 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 Notes.

Key points

- The evidence on ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT), hereafter referred to as PET-CT, in patients with anal cancer consisted of four systematic reviews with meta-analysis of mainly retrospective non-randomised diagnostic studies. There was a high degree of overlap of studies included in the reviews.
- Two meta-analyses reported PET-CT had a sensitivity of 99% (95% confidence intervals (CI) 96% to 100% and 97% to 100%) for detection of the primary tumour in patients with anal cancer. Specificity was not reported in either analysis.
- One meta-analysis (2 studies, 148 patients) reported a per-patient sensitivity of 93% (95% CI 76% to 99%) and a specificity of 76% (95% CI 61% to 87%) for PET-CT detection of inguinal lymph node involvement. In a second meta-analysis (6 studies) PET-CT had a per-lesion sensitivity of 56% (95% CI 45% to 67%) and a specificity of 90% (95% CI 86% to 93%) for detection of locoregional lymph node involvement.

- Studies included in the systematic reviews reported upstaging and downstaging of anal cancer for 5.1% to 37.5% and 8.2% to 26.7% of patients, respectively. In a meta-analysis PET-CT identified distant metastases of anal cancer which had been missed on conventional imaging in an estimated 3% (95% CI 1% to 5%) of patients.
- Radiotherapy target volume definition was altered following PET-CT imaging in an estimated 23% (95% CI 18% to 29%) of patients compared with CT alone.
- Based on PET-CT imaging, patient treatment plans were modified for 12.5% to 59.3% of patients; lymph node treatment increased in 15% of patients and decreased in 9% of patients; and treatment intent changed from curative to palliative in 3% (95% CI 2% to 6%) of patients.
- There was insufficient evidence (one study, n=40) to draw conclusions about the effectiveness of PET-CT for assessing treatment response in patients with anal cancer.
- No cost-effectiveness evidence was identified relating to the use of PET-CT in patients with anal cancer.

Definitions

A list of abbreviations used in this evidence note are provided in appendix 1.

Adenocarcinoma: a rare anal cancer that develops from glandular cells that produce mucus for the anal canal[1].

Squamous cell anal carcinoma: a type of anal cancer that starts in the squamous cells lining the anal canal[1].

TNM staging: a numbering system used to define the tumour, lymph node and metastases stage of a cancer[1].

Definitions of terms relating to diagnostic test accuracy are provided in Appendix 2.

Literature search

A systematic search of the secondary literature was carried out between 17 and 18 October 2018 to identify systematic reviews and meta-analyses. The Medline, Medline in process, Embase, and Web of Science databases were searched.

The primary literature was systematically searched between 17 and 18 October 2018 using the following databases: Medline, Medline in process, Embase and Web of Science. Results were limited to diagnostic studies in English.

Key websites, including the Guidelines International Network, Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Health and Care Excellence (NICE) websites, were searched for guidelines. The Cochrane Database of Systematic Reviews was also searched.

Concepts used in all searches included: anal carcinoma, anal cancer/neoplasm, squamous cell carcinoma of the anus, positron emission tomography and PET. A full list of resources searched and terms used are available on request.

Introduction

Anal cancer is a relatively rare cancer that develops in the anal canal, the anal margin, or glandular cells where the anal canal joins the rectum[1]. The anal canal, anal margin and anus form a 3-4cm long section at the end of the large bowel. The most common type of anal cancer is squamous cell carcinoma which forms in the lining of the anal canal and accounts for 75% to 80% of cases. Anal cancers that arise in the glandular cells are referred to as adenocarcinoma and comprise approximately 15% of anal cancer patients. There are other forms of anal cancer that are far less common including two types of skin cancer (basal cell carcinoma and malignant melanoma) that affect the skin tissue around the anus.

The symptoms of anal cancer are similar to non-cancerous bowel conditions such as haemorrhoids or anal fissures[1]. The most common symptom is bleeding from the back passage or blood in the stool. Other symptoms include pain in the anal area, sensation of a lump around the anus, severe itching, mucus discharge from the back passage, severe constipation and difficulty passing stools or faecal incontinence.

Since approximately 95% of patients with anal cancer have no distant metastatic disease at diagnosis, anal cancer is usually amenable to curative locoregional treatment with chemoradiation rather than surgery, thus avoiding the need for a colostomy[2, 3]. Surgical intervention is generally reserved for patients with residual or recurrent disease following treatment and patients with very early-stage localised tumours. Accurate staging of the primary tumour and regional lymph nodes is important for selecting the most appropriate treatment for anal cancer and subsequent radiation therapy planning. In particular, volumetric arc therapy (VMAT) can be used to differentially allocate radiation doses to specific targets during radiotherapy based on accurate staging using imaging techniques.

Routine staging of anal cancer currently involves a detailed clinical assessment, magnetic resonance imaging (MRI) of the pelvis and computed tomography (CT) of the chest, abdomen and pelvis. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) could potentially be used as an addition to the current diagnostic process for routine staging of anal cancer, staging of lymph nodes, radiotherapy planning, or assessment of treatment response[3].

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[4]. The procedure, for patients with anal cancer, involves injecting a radiolabelled tracer into the body. The radiolabelled tracer accumulates in metabolically active cells (such as malignant cells) and emits gamma rays detected by the PET technology to produce colour-coded images demonstrating the cellular activity of both healthy 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 and planning information, as well as assessing the effectiveness of cancer treatments. The radiolabelled tracers are then passed out of the body in the urine or bowel movement. ^{18}F-fluorodeoxyglucose (FDG) is the most common radiolabelled tracer used with PET-CT imaging, and all the evidence reviewed for this Evidence Note related to FDG PET-CT. Hereafter, FDG PET-CT has been abbreviated to PET-CT.

PET-CT is already used in some cancer centres in Scotland as part of initial diagnostic staging in patients with anal cancer (Dr L Samuel, Macmillan Consultant Oncologist, Aberdeen Royal Infirmary. Personal communication, 23 Jan 2019). Some centres also use PET-CT for re-staging patients with recurrent or persistent anal cancer who are being considered for surgery. Some centres fuse PET-CT images with radiotherapy planning CT scans to assist in delineating the anal tumours.

Epidemiology

Anal cancer is relatively rare, accounting for less than 1% of all new cancer diagnoses in the UK[1]. However, anal cancer incidence rates have increased by an estimated 34% over the last decade. There were 143 new cases of anal cancer diagnosed in Scotland in 2014-15 (table 1). Mortality rates for patients with anal cancer have also increased by 22% to 25% in the last decade. In Scotland 44 people died from anal cancer in 2015-16.

Anal cancer affects approximately twice as many women compared with men. Anal cancer incidence also increases with age; approximately 50% of new diagnoses are in people aged 65 or older.

Table 1: incidence and mortality data on anal cancer in Scotland[1]

	Cases	European age-standardised incidence per 100,000 population (95% confidence interval (CI))	Deaths	European age-standardised mortality per 100,000 population (95% CI)
Female	94	3.4 (2.7 to 4.0)	29	1.0 (0.6 to 1.4)
Male	49	2.0 (1.4 to 2.5)	15	0.6 (0.3 to 0.9)
All persons	143	2.7 (2.3 to 3.2)	44	0.8 (0.6 to 1.1)

Data taken from Cancer Research UK who collated Scottish data from ISD. Incidence data are from 2015, mortality data are from 2016.

The main risk factor for anal cancer is human papilloma virus (HPV) infection, which is linked to approximately 90% of cases of anal cancer in the UK. People with a history of genital warts, who have anal intercourse, or who have a greater number of sexual partners, are at increased risk of anal cancer. Some studies have suggested the risk of anal cancer is also increased in women with a history of abnormal cells or cancer of the cervix, vulva or vagina. Finally, people with a compromised immune system, particularly people with human immunodeficiency virus (HIV), have an increased risk of developing anal cancer.

Guidelines

Four national guidelines were identified that include recommendations on use of PET-CT in patients with squamous cell anal carcinoma (table 2)[3, 5-7]. All four guidelines recommend PET-CT as an optional adjunct to routine staging of anal cancer. Although the guidelines refer to PET-CT potentially being used to evaluate patients' response to therapy, they did not find sufficient evidence on which to base a recommendation.

Table 2: recommendations from national guidelines on the use of PET-CT in patients with squamous cell anal carcinoma

Guideline	Recommendations
National Comprehensive Cancer Network (NCCN), 2018[5]	Consider PET-CT for verifying staging of anal carcinoma prior to treatment in addition to CT/MRI pelvis, CT chest and abdomen.
American Society of Colon and Rectal Surgeons, 2018[7]	PET-CT may be considered as an adjunct radiologic study in the staging of anal squamous cell carcinoma, although it does not replace CT for clinical staging.
Association of Coloproctology of Great Britain and Ireland (ACPGBI), 2017[3]	PET-CT (if available) should be considered in addition to routine staging using clinical assessment, MRI and CT imaging, for patients with T2-4 tumours who are suitable for radical chemoradiotherapy.
Cancer Care Ontario, 2017[6] *[This guideline appears to be based on the systematic review by Mahmud et al (2017) which is described in the Clinical Effectiveness section]*	PET-CT may provide added benefit in the initial staging of patients with T2-4 squamous cell carcinoma of the anal canal with or without evidence of nodal involvement on anatomical imaging. However, no strong evidence is currently available to justify its use as part of routine investigation, and access should be restricted to the registry-type setting. There is insufficient evidence to recommend the use of PET-CT in the assessment of treatment response.

Clinical effectiveness

Four systematic reviews with meta-analyses were identified that evaluated the use of PET-CT in patients with anal cancer[2, 8-10]. There was a high degree of overlap in studies included in the four reviews, although the systematic review authors assessed different aspects of PET-CT use: staging primary tumours, staging lymph nodes, evaluating treatment response and planning radiotherapy (table 3).

Table 3: characteristics of included systematic reviews on PET-CT in patients with anal cancer

Mahmud (2017)[2]	Jones (2015)[10]	Caldarella (2014)[9]	Albertsson (2018)[8]
Population			
Anal canal cancer	Histologically confirmed anal squamous cell carcinoma	Biopsy proven anal canal cancer	Newly diagnosed anal carcinoma intended for curative radiotherapy
Intervention and comparator			
PET or PET-CT vs. conventional imaging	PET or PET-CT vs. conventional imaging (CT or MRI)	PET or PET-CT (no comparator specified)	Radiotherapy dose-planning PET-CT vs. dose-planning CT
Reference standard			
Histology, clinical or radiologic follow-up	Conventional imaging	Histology	–
Outcomes			
Diagnostic performance; change in clinical management; survival	Primary tumour detection; lymph node staging; distant metastases detection	Diagnostic performance (locoregional lymph nodes)	Survival; quality of life; change in treatment intent; target volume definition
Inclusion and exclusion criteria			
Inclusion: ≥12 patients in prospective studies; ≥30 patients in retrospective studies ***Exclusion:*** case reports or case series; non-English language	***Exclusion:*** anal adenocarcinoma, perianal cancer, rectal cancer	***Inclusion:*** ≥10 patients; data on sensitivity and specificity; no data overlap ***Exclusion:*** case reports or small case series	***Inclusion:*** RCTs, non-randomised trials, systematic reviews or case series; published 2000-2016; English or Scandinavian language

Included studies			
Total = 16 9 retrospective; 7 prospective	Total = 12 8 retrospective; 4 prospective	Total = 13 8 retrospective; 4 prospective; 1 NR	Total = 10 7 retrospective; 3 prospective

NR = not reported

The systematic review with meta-analysis by Mahmud *et al* (2017) compared PET or PET-CT with conventional imaging (CT or MRI) for initial staging and assessment of treatment response in patients with anal canal cancer (table 3)[2]. Sixteen studies (n=791) were included in the review; 11 assessed PET-CT, three incorporated PET or PET-CT and two assessed PET alone. Results were not presented separately for PET and PET-CT in the meta-analysis. Overall, the included studies were rated as 'low concern' for applicability issues such as patient selection and relevance of the index and reference standard used. Studies were also judged to have low or unclear risk of bias by the systematic review authors using the QUADAS-2 appraisal tool. However, one study had a high risk of bias for the index test due to unblinded interpretation of images, one study had high risk of bias associated with patient selection, and one study had a high risk of bias relating to study flow and timing. All studies were unclear about whether the reference standard was interpreted without knowledge of the index test results. Median age of participants in studies included in the review ranged from 52 to 67 years, and 44% to 71% of study participants were female.

Key findings from the meta-analysis by Mahmud *et al* (2017)[2] are presented in table 4. No studies included in the meta-analysis compared PET-CT with MRI. Only sensitivity was reported for PET-CT staging of primary tumours in patients with anal canal cancer. Sensitivity of PET-CT for detecting the primary tumour *in situ* was higher than the pooled sensitivity estimate for CT alone (67%, 95% CI 50% to 82%, 3 studies, 144 patients, I^2=70.3%). Between-study heterogeneity was high for both sensitivity (I^2=76.5%) and specificity (I^2=83.4%) in a meta-analysis of two studies (n=148) on PET-CT staging of inguinal lymph nodes. Pooled specificity for staging inguinal lymph nodes was relatively low at 76% (95% CI 61% to 87%) which may result in patients with anal canal cancer receiving unnecessary treatment due to false positive findings on PET-CT. In four studies, PET-CT identified distant metastases which had been missed on conventional imaging in 2.4% to 4.7% of patients; these metastases were not verified by biopsy in all patients.

Upstaging and downstaging of patients (table 4) was mainly attributed to detection of occult nodal or distant metastatic disease on PET-CT imaging, and patients staged T2-4 were more likely to have a change in overall staging following PET-CT. However, not all upstaging and downstaging was verified by biopsy, so these estimates may be exaggerated. Modifications to patient treatment plans following PET-CT included changing the radiotherapy dose or field, changing the treatment intent from curative to palliative, altering the radiotherapy technique, planning surgery, and initiating chemotherapy.

A single prospective study (n=40) in the systematic review by Mahmud *et al* (2017) reported diagnostic accuracy of PET-CT for assessment of treatment response at one and three months after completion of treatment for anal canal cancer (table 4). As anal cancers typically respond slowly to

therapy, taking up to six months to completely respond[3], this study may have attempted to measure treatment response too soon to reliably assess the effectiveness of PET-CT for this purpose. In studies that reported survival outcomes, partial or no response to treatment as shown on PET-CT, was predictive of significantly worse 2-year progression-free, disease-free, and overall survival (table 4).

Table 4: results from a meta-analysis by Mahmud *et al* (2017) on PET or PET-CT for staging, clinical decision-making and assessment of therapy response in patients with anal canal cancer[2]

Outcome	N studies	N patients	Findings
Diagnostic accuracy			
Detection of primary tumour *in situ*	8	428	Sensitivity 99% (95% CI 97% to 100%)
Detection of inguinal lymph nodes	2	148	Sensitivity 93% (95% CI 76% to 99%) Specificity 76% (95% CI 61% to 87%)
Diagnostic accuracy: treatment response 1 month post-therapy	1	40	Sensitivity 66.6% Specificity 92.5% Positive predictive value (PPV) 40.0% Negative predictive value (NPV) 97.4%
Diagnostic accuracy: treatment response 3 months post-therapy	1	40	Sensitivity 100% Specificity 97.4% PPV 66.6% NPV 100%
Impact on patient management			
Change in initial staging	11	Median n=46 (IQR 40 to 54)	Upstaging 5.1% to 37.5% of patients Downstaging 8.2% to 26.7% of patients
Treatment plan modified	8	423	12.5% to 59.3% of patients
Association of PET-CT assessed treatment response with survival			
PET-CT reported treatment response (complete vs. partial/no response) and survival	3	151	**2-year progression-free survival** Complete response 68% to 95% vs. partial response 22% to 40% vs. no response 0%, p<0.0001 *[Values from 2 or 3 studies, not a range]*
	1	55	**2-year disease-free survival** Complete response 77.5% vs. partial response 14%, p<0.0001 **2-year overall survival**

			Complete response 95.7% vs. partial response 49.9%, p<0.0001
	1	48	**5-year overall survival** Complete response 88% vs. partial response 69%, p=0.03 Complete response 88% vs. no response 0%, p<0.0001

The authors of a second systematic review with meta-analysis (Jones *et al*, 2015) also compared PET or PET-CT with conventional imaging (CT or MRI) for initial tumour staging and assessment of treatment response in patients with squamous cell anal carcinoma (table 3)[10]. Two of the 12 studies in this systematic review were not included in the analysis by Mahmud *et al* (2017). Although there was overlap of included studies, Jones *et al* (2015) considered several studies in their review to have high risk of bias based on QUADAS-2 appraisal; five studies had high risk of selection bias and seven studies were at high risk of bias due to unblinded interpretation of the index test. Three studies in the Jones *et al* (2015) systematic review reported on PET only, three on PET or PET-CT, and six focused on PET-CT. Median age of study participants ranged from 44 to 61 years and 25% to 71% of patients were female (overall 56% of patients were female).

In this meta-analysis PET-CT had a sensitivity of 99% (95% CI 96% to 100%) compared with 60% (95% CI 46% to 75%) sensitivity for CT alone for detection of primary tumours[10]. These estimates are very similar to those reported by Mahmud *et al* (2017). Specificity of PET-CT for detecting primary disease was not reported. PET-CT findings resulted in a nodal upstaging rate of 21% (95% CI 13% to 30%) and downstaging rate of 17% (95% CI 11% to 23%). These rates are within the range provided by Mahmud *et al* (2017) who did not perform a meta-analysis for this outcome. Not all studies confirmed upstaging or downstaging using biopsy and therefore estimates may be exaggerated. Nodal upstaging and downstaging rates were provided separately for when MRI was a component of imaging and for CT alone (table 5). Distant metastases not detected on conventional imaging were identified by PET or PET-CT in 3% (95% CI 1% to 5%) of patients with anal carcinoma. This is within the range provided in the systematic review by Mahmud *et al* (2017) which did not perform a meta-analysis for this outcome. As a consequence of PET-CT imaging, 41% of patients with anal carcinoma had a change in TNM stage (upstaged, downstaged, metastases detected) which would affect treatment and management of patients, particularly radiotherapy planning.

Although Jones *et al* (2015) intended to evaluate PET-CT for assessing treatment response, this was not reported in the published paper[10]. The systematic review only reported the proportion of patients with complete response to treatment, detected using PET-CT, at several time intervals after treatment. This does not allow for an assessment of the effectiveness of PET-CT for detecting treatment response, rather it describes the proportion of patients with anal carcinoma who respond to treatment.

Table 5: comparison of nodal upstaging and downstaging rates using PET-CT, MRI and CT alone, in patients with anal cancer[10]

Imaging modality	Nodal upstaging rate (95% CI)	Nodal downstaging rate (95% CI)
PET-CT	21% (13% to 30%)	17% (11% to 23%)
MRI	15% (9% to 20%)	14% (8% to 20%)
CT	16% (8% to 24%)	17% (9% to 25%)

The systematic review with meta-analysis by Caldarella *et al* (2014) assessed the diagnostic performance of PET or PET-CT for detection of locoregional lymph node involvement in patients with biopsy confirmed anal canal cancer (table 3)[9]. Locoregional lymph nodes for anal cancer include peri-rectal, inguinal, pelvic or iliac and intra-abdominal lymph nodes. This is a wider range of lymph nodes than Mahmud *et al* (2017) considered, and it is not clear which lymph nodes were considered by Jones *et al* (2015). The meta-analysis by Caldarella *et al* (2014) was performed using a sub-set of six studies that reported sufficient data to calculate sensitivity and specificity. One study in the meta-analysis assessed PET alone and five assessed PET-CT. Three of the studies were included in the systematic review by Mahmud *et al* (2017) but were not used in the meta-analysis on diagnostic performance of PET-CT for detecting lymph nodes – which may be due to the wider range of lymph nodes considered by Caldarella *et al* (2014). Using the Oxford Centre for Evidence Based Medicine tool for appraising diagnostic studies, Caldarella *et al* (2014) concluded the studies in their meta-analysis were of moderate methodological quality. The main limitation reported for included studies was use of a poor or non-independent reference standard. The proportion of females in the included studies ranged from 25% to 70% and mean age of participants ranged from 44 to 62 years.

Caldarella *et al* (2014) report their meta-analysis as a per-lesion analysis, although the results are referred to as per-patient in the discussion section of the review. Pooled sensitivity for PET-CT detection of locoregional lymph node involvement was 56% (95% CI 45% to 67%) and pooled specificity was 90% (95% CI 86% to 93%). There was high between-study heterogeneity for estimates of both sensitivity (I^2=84.6%) and specificity (I^2=90.5%). Unlike the two more recent meta-analyses (Mahmud *et al*, 2017; Jones *et al*, 2015) sensitivity of PET-CT was lower than specificity in the meta-analysis by Caldarella *et al* (2014). This may be the result of including a wider range of lymph nodes, and therefore additional studies, in the meta-analysis. Alternatively, it may reflect the reporting of a per-lesion analysis in this review compared with a per-patient analysis in the more recent reviews.

The final systematic review with meta-analysis (Albertsson *et al*, 2018) explored the use of PET-CT for radiotherapy planning in patients with newly diagnosed anal carcinoma[8]. This meta-analysis included many of the same studies as the systematic reviews described previously, however the authors focused on comparing radiotherapy dose-planning using PET-CT with dose-planning using CT alone (table 3). Two studies were unique to this analysis. Of ten studies, four focused on PET-CT, two reported on PET alone, two included both PET and PET-CT and two were unclear in this regard. Studies included in the review were appraised using what the authors described as a “slightly

modified checklist for case series". Based on this checklist, Albertsson *et al* (2018) concluded that approximately half the included studies were at risk of bias due to lack of blinding of interpretation of PET-CT images, and none of the studies reported the cut-off level they used to indicate a significant change in target volume definition. The proportion of female participants in studies ranged from 29% to 70% and mean age of patients ranged from 56 to 66 years.

Albertsson *et al* (2018) did not identify any studies reporting survival or health-related quality of life for anal cancer patients undergoing PET-CT for radiotherapy planning. The proportion of patients with a change in target volume definition following PET-CT ranged from 12.5% to 43%, with a summary estimate of 23% (95% CI 18% to 29%, 9 studies, n=275). The review authors rated the certainty of the evidence for this outcome as moderate using GRADE criteria. There was moderate between-study heterogeneity for this outcome (I^2=52.8%). Albertsson *et al* (2018) also noted that the extent to which changes in target volume definition following PET-CT impact on patient outcomes in anal cancer treatment remains unclear. Lymph node treatment increased in 15% of patients and decreased in 9% of patients following PET-CT. Across all 10 studies treatment intent changed from curative to palliative for 0% to 5% of patients following PET-CT findings; summary estimate 3% (95% CI 2% to 6%, 10 studies, n=312). The certainty of evidence for this outcome was rated low based on GRADE criteria.

Safety

No adverse events relating to PET-CT in patients with anal cancer were reported in the systematic reviews. However, undergoing a PET-CT scan represents an additional radiation burden for patients compared to CT alone. A PET-CT scan exposes patients to a radiation dose equivalent to eight years of natural radiation exposure, for example from the sun, while a basic CT scan exposes patients to the equivalent of three years natural radiation[11, 12]. Radiation experts believe the increased risk of cancer from this additional radiation exposure is likely to be very small[11].

Cost effectiveness

No cost-effectiveness evidence was identified relating to PET-CT in patients with anal cancer.

Conclusion

The evidence for PET-CT in patients with anal cancer consisted of four meta-analyses based on an overlapping set of diagnostic studies with some risk of bias relating to unblinded interpretation of images. Two of these meta-analyses reported higher sensitivity (lower false negative rates) for PET-CT compared with CT alone for detecting the primary tumour suggesting PET-CT is a useful adjunct to the current staging process. The specificity of PET-CT for initial tumour staging remains unknown as it was not reported in any of the reviews. Performance of PET-CT compared with MRI was not reported in the literature identified.

The ability of PET-CT to detect lymph node involvement was inconsistently reported across two meta-analyses, possibly due to different included studies or reporting of per-patient versus per-lesion analyses in these reviews.

Using PET-CT for staging and radiotherapy planning in patients with anal cancer resulted in changes to treatment for many patients. Estimates of the proportion of patients where anal cancer was upstaged ranged from 5% to 37%, cancer was downstaged for 8% to 27% of patients, and distant metastases were detected in 2% to 5% of patients. Combined with a change in radiotherapy target volume definition for approximately 1 in 4 patients, these changes in staging suggest PET-CT can have a substantial impact on management of patients with anal cancer. However, some caution is warranted as not all changes in tumour staging were verified using histology.

There is currently insufficient evidence to support use of PET-CT for assessing treatment response in patients with anal cancer.

No evidence was identified on the cost-effectiveness of PET-CT in patients with anal cancer.

Identified research gaps

Current evidence on PET-CT in patients with anal 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 are needed to evaluate the effectiveness of PET-CT for assessing treatment response in patients with anal cancer.
- Economic analyses are required to evaluate the use of PET-CT in patients with anal cancer.

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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Evidence Notes are produced to inform a decision at a particular point in time and are therefore not routinely updated. They will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further 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.

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

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Appendix 1: Abbreviations

18F-FDG	18F-fluorodeoxyglucose
ACPGBI	Association of Coloproctology of Great Britain and Ireland
AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR	assessing the methodological quality of systematic reviews
CT	computed-tomography
GRADE	Grading of Recommendations Assessment Development and Evaluation
HIV	human immunodeficiency virus
HPV	human papilloma virus
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
NR	not reported
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PPV	positive predictive value
QUADAS	quality assessment tool for diagnostic accuracy studies
RCT	randomised controlled trial
SIGN	Scottish Intercollegiate Guidelines Network

Appendix 2: Definitions of diagnostic accuracy terms

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[13].

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[13].

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[13].

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[13].

Receiver operating characteristic (ROC) curve: a graph used to assess the ability of a diagnostic test to discriminate between people with or without the target condition. For most diagnostic test data the ROC curve plots sensitivity against 1-specificity for different cut-off values[13]. Area under the ROC curve (AUROC) can be used to compare the diagnostic accuracy of tests when multiple ROC curves are plotted on the same graph.

Positive predictive value (PPV): the probability that someone with a positive test result truly has the disease of interest[13].

Negative predictive value (NPV): the probability that some receiving a negative test result truly does not have the disease[13].