Received:
17 May 2017

Revised:
11 September 2017

Accepted:
19 September 2017

<https://doi.org/10.1259/bjr.20170370>

Cite this article as:

Mahmud A, Poon R, Jonker D. PET imaging in anal canal cancer: a systematic review and meta-analysis. *Br J Radiol* 2017; **90**: 20170370.

SYSTEMATIC REVIEW

PET imaging in anal canal cancer: a systematic review and meta-analysis

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Objective: The aim of this study was to systematically review the literature to synthesize and summarize the evidence surrounding the clinical utility of positron emission tomography (PET) imaging in patients with anal canal cancer.

Methods: The literature was searched using MEDLINE, EMBASE and Cochrane Database of Systematic Reviews databases. Studies comparing PET or PET/CT with conventional imaging in the staging, response evaluation and follow-up of anal canal cancer were deemed eligible for inclusion.

Results: 17 studies met the inclusion criteria. For the detection of primary tumour *in situ*, the pooled sensitivity was 99% for PET or PET/CT and 67% for CT. For the detection of inguinal lymph nodes, PET/CT had an overall sensitivity of 93% and specificity of 76%. PET

or PET/CT upstaged 5.1 to 37.5% of patients and downstaged 8.2 to 26.7% of patients. Treatment plans were modified in 12.5 to 59.3% of patients, which consisted mainly of radiotherapy dose or field changes. Complete response on PET or PET/CT is a good prognostic factor for overall and progression-free survival.

Conclusions: PET/CT seems to add value to conventional imaging in the initial staging of patients with T2-4 disease but further high-quality research is required to validate this. There is insufficient evidence at this time to recommend a routine use of PET/CT in the assessment of treatment response or follow-up.

Advances in knowledge: PET/CT appears to alter the disease stage and management in a meaningful number of patients to justify its use as part of staging investigations in locally advanced cases.

INTRODUCTION

Anal canal cancer is an uncommon disease, with an incidence of 1.7 per 100,000 person-years in Canada.^{1,2} In 2010, there were 580 diagnosed cases, of which 385 (66.4%) occurred in females.¹ On the contrary, there is no good data on worldwide incidence, nonetheless, anal canal cancer accounts for up to 4% of all anorectal malignancies and 1.5% of all gastrointestinal malignancies.^{3,4} Reports from the USA and France showed that the incidence of anal canal cancer increases considerably among people with HIV infection with rates ranging from 49 to 144 per 100,000 person-years.⁵⁻⁸ As only about 5% of patients will present with distant metastatic disease, anal canal cancer is usually amenable to curative locoregional treatment.^{9,10} Currently, the standard first-line treatment consists of combined chemoradiation using 5-fluorouracil and mitomycin C rather than surgical resection. This combined treatment approach allows preservation of the anal sphincter and avoidance of a colostomy.¹¹ Multiple Phase III clinical trials have demonstrated complete response rate of 90–95%

with a 5-year colostomy-free survival of 70%.¹²⁻¹⁵ Therefore, to achieve optimal management, accurate staging of primary tumour and regional lymph nodes is crucial for selecting treatment, especially for planning radiation therapy. Conventional staging of anal canal cancer varies among providers and centres but typically includes clinical examination, CT scans of the chest, abdomen and pelvis, and MRI of the pelvis. Transanal endoscopic ultrasound or other imaging techniques may provide additional information. While most patients can achieve cure with locoregional control after initial chemoradiation, some patients may have persistent disease or develop a recurrence. Treatment response is generally assessed by physical examination, an endoscopic review, pelvic MRI and/or CT several weeks after completion of treatment. Surgery (abdominoperineal resection) remains the mainstay of salvage therapy among patients with histologically confirmed residual or recurrent malignancy, and is generally considered if residual disease persists at 6 months post chemoradiotherapy, or earlier in the setting of tumour growth.

Presently, fluorine-18 (^{18}F) FDG-PET (fludeoxyglucose-positron emission tomography) or PET/CT is widely used in assessing the extent of disease as part of management for a number of malignancies. The role of PET or PET/CT in anal canal cancer is becoming of increasing interest as most anal cancers are FDG-avid. This imaging modality has the potential to demonstrate the extent of the primary tumour, detect lymph node involvement and identify sites of distant metastases, in a single whole-body imaging procedure.¹⁶ The 2015 v. 2 of the National Comprehensive Cancer Network Treatment Guidelines in anal carcinoma recommended that PET/CT be considered for patients with advanced primary tumour or node-positive disease to verify staging before treatment as well as for treatment planning.¹⁷ Additionally, the European Society for Medical Oncology -European Society of Surgical Oncology -European Society of Radiotherapy and Oncology clinical practice guidelines for anal cancer included PET/CT as an often recommended modality of the diagnostic work-up.¹⁸

The purpose of this report is to provide a summary of evidence and compare the role of PET or PET/CT with conventional imaging in the staging, response evaluation and follow up of patients with anal canal cancer.

METHODS AND MATERIALS

Search strategy

The literature was searched up to 8 April 2016 using MEDLINE, EMBASE and Cochrane Database of Systematic Reviews databases through OVID. Details of the literature search strategy can be found in Supplementary Table 1 (Supplementary material available online). In addition, reference lists from relevant systematic reviews and primary literature were scanned for potentially useful studies.

Study selection criteria and process

After duplicates of the retrieved articles were removed, the following criteria were used to screen for eligibility: (1) published as a full article in a peer-reviewed journal; (2) evaluated the use of PET or PET/CT with ^{18}F -FDG; (3) used post-surgical or post-biopsy histology, clinical follow-up or radiologic follow-up as reference standard; (4) reported on at least one of the following outcomes, (a) numeric data on diagnostic performance (*e.g.* sensitivity, specificity, positive-predictive value, negative-predictive value, accuracy) (b) metrics representing change or impact on clinical management decisions, (c) data on survival; (5) included ≥ 12 patients for prospective studies or ≥ 30 patients for retrospective studies. The exclusion criteria included: (1) conference abstracts, literature or narrative reviews, letters, editorials, historical articles or commentaries; (2) single case reports or case series; (3) reports published in a language other than English because translation was not available. A review of the titles and abstracts that resulted from the search was done independently by one reviewer as were the items that warranted full-text review.

Synthesizing the evidence

This systematic review and meta-analysis was performed following a predefined protocol (available from authors upon request) and reported in accordance with the preferred reporting items for

systematic reviews and meta-analyses (PRISMA) checklist (<http://www.prisma-statement.org/>). One reviewer extracted data from the included studies. For each study, the principal author, country of origin, publication year, study design, number of patients, age and sex, type of PET and conventional imaging as well as the outcomes of interest were recorded. All extracted data and information were audited by an independent auditor. Data were summarized in evidence tables and described in the text. When clinically homogenous results from two or more studies and sufficient data were available to reassess sensitivity and specificity of PET or PET/CT and conventional imaging and given that between-study heterogeneity is widespread for measure of diagnostic accuracy,¹⁹ a random effect model was used to produce summary estimates with 95% confidence intervals. The I^2 percentage was calculated as a measure of heterogeneity. Statistical analysis was undertaken using the statistical software STATA v. 11.2 (StataCorp. 2009. Stata Statistical Software:Release 11. College Station, TX: StataCorp LP) using the metaprop command with the Freeman-Tukey double arcsine transformation and Meta-DiSc v. 1.4, which implements meta-regression using a generalization of the Littenberg and Moses Linear model.^{20,21} The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)²² tool was used to evaluate the risk of bias and applicability concerns for each eligible study.

RESULTS

Literature search results

A search for primary literature was conducted and a total of 142 unique citations were identified from the electronic searches, of which 122 were excluded after a review of titles and abstracts. 20 citations were considered as candidates, but upon full-text review, 3 did not meet the inclusion criteria. Finally, the remaining 17 studies were included in this systematic review. Data were not extracted from one study²³ owing to overlapping patient population with a more recent article with the larger sample analysed. The search for existing systematic reviews identified two publications^{24,25} that were considered relevant after full-text review. However, neither systematic review used the same study selection criteria (*i.e.* the reference standard defined in those studies was suboptimal, included studies with small sample size) as this review and, therefore, were not discussed further. See Figure 1 for the PRISMA flow diagram.

Study design and quality

Among the 16 studies, 7 studies enrolled patients prospectively^{26–32} while 9 studies were retrospective outcomes review.^{11,33–40} PET scans were obtained in 2 studies,^{30,38} PET/CT scans in 11 studies^{27–29,31–33,35–37,39,40} and PET or PET/CT scans in 3 studies.^{11,26,34} Details of the study characteristics can be found in Table 1. All 16 studies were assessed according to the four QUADAS-2 domains (Table 2). All studies were judged to have low concerns regarding applicability. For the domains relating to bias, one study³⁵ was judged to have high risk of bias in patient flow and timing where histological confirmation of nodal disease was not consistently undertaken; hence, not all patients were included in the analysis. Although having all suspicious lesions biopsied is ideal, this is generally not practical or feasible. Another study excluded patients with adenocarcinoma or other histologies other than squamous cell carcinoma.³⁰ Furthermore, readings for the

Figure 1. Flow diagram of study selection; *n* denotes the number of citations.

index tests (e.g. PET or PET/CT, conventional imaging) were either not blinded to the results of the reference standard²⁸ or unclear as to whether they were interpreted without knowledge of the reference standard.^{29,31,33–40} Similarly, all studies lacked information about whether the reference standard results (post-surgical or post-biopsy histology, clinical or radiologic follow-up) were interpreted without the knowledge of the index test results. No studies were assessed as being at risk owing to patient selection.

Staging

Diagnostic accuracy

Primary tumour: In the initial staging of anal canal cancer, eight studies assessed the sensitivity of PET or PET/CT for the detection of primary tumour *in situ*.^{26–29,33–36} The sensitivity on a per-patient-based analysis ranged from 92.9 to 100%, with a pooled estimate of 99% (95% CI, 97 to 100%). The I^2 statistic did not reveal the presence of significant heterogeneity across studies

Table 1. Studies selected for inclusion

Study, year	Country	Type of study	No. of patients	Median age	Gender (M/F)	PET imaging	CIM
Day et al ¹¹	Australia	R	48	56	22/26	PET or PET/CT	NA
de Winton et al ²⁶	Australia	P	61	57	34/27	PET or PET/CT	CT, MRI or both
Engledow et al ²⁷	UK	P	40	57	14/26	PET/CT	CT + MRI
Vercellino et al ²⁸	France	P	44	62 (mean)	13/31	PET/CT	NA
Mistrangelo et al 2012 ^{29a} ; Mistrangelo et al ^{23a}	Italy	P	53	57	19/34	PET/CT	CT
Trautmann and Zuger ³⁰	USA	P	21	52	6/15	PET	CT
Krengli et al ³¹	Italy	P	27	66	9/18	PET/CT	CT
Deantonio et al ³²	Italy	P	55	67	18/37	PET/CT	NA
Cotter et al ³³	USA	R	41	52 (mean)	18/23	PET/CT	CT
Nguyen et al ³⁴	Australia	R	50	58	19/31	PET or PET/CT	CT
Sveistrup et al ³⁵	Denmark	R	95	58	30/65	PET/CT	TAUS + ultrasound
Wells and Fox ³⁶	UK	R	44	NA	NA	PET/CT	CT + MRI
Bhuva et al ³⁷	UK	R	43	NA	NA	PET/CT	CT + MRI
Mai et al ³⁸	Germany	R	39	56	17/22	PET	CT
Schwarz et al ^{37,39}	USA	R	53	52 (mean)	20/33	PET/CT	CT
Kidd et al ⁴⁰	USA	R	77	53 (mean)	33/44	PET/CT	NA

CIM, conventional imaging; M/F, male/female; NA, not available; P, prospective; PET, positron emission tomography; R, retrospective; TAUS, transanal endoscopic ultrasound; CT, computed tomography; MRI, magnetic resonance imaging.

^aOverlapping patient population in these studies; data not presented for the Mistrangelo et al²³ 2010 report.

Table 2. QUADAS-2 assessment of study quality

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Day et al ¹¹	L	L	U	L	L	L	L
de Winton et al ²⁶	L	L	U	L	L	L	L
Engledow et al ²⁷	L	L	U	L	L	L	L
Vercellino et al ²⁸	L	H	U	L	L	L	L
Mistrangelo et al ²⁹	L	U	U	L	L	L	L
Trautmann and Zuger ³⁰	H	L	U	L	L	L	L
Krengli et al ³¹	L	U	U	L	L	L	L
Deantonio et al ³²	L	L	U	L	L	L	L
Cotter et al ³³	L	U	U	L	L	L	L
Nguyen et al ³⁴	L	U	U	L	L	L	L
Sveistrup et al ³⁵	L	U	U	H	L	L	L
Wells and Fox ³⁶	L	U	U	L	L	L	L
Bhuva et al ³⁷	L	U	U	U	L	L	L
Mai et al ³⁸	L	U	U	L	L	L	L
Schwarz et al ³⁹	L	L	U	L	L	L	L
Kidd et al ⁴⁰	L	U	U	L	L	L	L

H, high risk; L, low risk; U, unclear risk.

Figure 2. Forest plot of the sensitivity of PET or PET/CT in the detection of primary tumour *in situ*.

($I^2 = 17.1\%$, $p = 0.29$). Forest plot of the eight studies is presented in Figure 2. In comparison to conventional imaging, the sensitivity of CT ranged from 57.9 to 82.9% in three studies,^{29,33,34} with a pooled estimate of 67% (95% CI, 50 to 82%) (Figure 3), while one study reported a sensitivity of 100% for ultrasound.³⁵ The I^2 statistic was significant for CT ($I^2 = 70.3\%$, $p = 0.03$), indicating a high percentage of variation among the studies. Nevertheless, the pooled sensitivity of PET or PET/CT was demonstrated to be higher (confidence intervals did not overlap) than that of CT in visualizing the primary tumour.

Lymph nodes: For the detection of inguinal lymph nodes, two studies provided sufficient data to allow the aggregation of diagnostic information for PET/CT.^{29,35} Biopsy confirmation was performed in all patients. There was significant heterogeneity in sensitivity ($I^2 = 76.5\%$) and specificity ($I^2 = 83.4\%$) between the two studies. Thus, a random effects model was used to calculate an overall sensitivity of 93% (95% CI, 76 to 99%) and specificity of 76% (95% CI, 61 to 87%) (Figures 4 and 5). With respect to conventional imaging, one study reported a sensitivity of 50.0% (4/8) and a specificity of 84% (22/26) for CT,²⁹ and one study reported a sensitivity

Figure 3. Forest plot of the sensitivity of CT in the detection of primary tumour *in situ*.

Figure 4. Sensitivity of PET/CT in detecting inguinal lymph nodes.

of 94.1% (16/17) and a specificity of 20.0% (3/15) for ultrasound.³⁵ An additional study compared PET or PET/CT with CT, MRI or both found that the overall sensitivity for detecting regional nodal metastases (*i.e.* perirectal, inguinal, iliac and intra-abdominal nodes) was 89 vs 62%.²⁶

Distant metastases: In four studies, PET/CT identified distant metastatic sites not seen on conventional imaging in 2.4 to 4.7% of cases^{27,33,35,37}; however, biopsy was not always performed to verify metastatic disease. Location of the distant metastatic sites included lung, bone, liver, distant lymph nodes and adrenal gland.

Impact on patient management and survival

11 studies evaluated the impact of PET or PET/CT on patient management (Table 3). All studies reported a change in the initial staging of patients following conventional imaging. Information from PET or PET/CT upstaged 5.1 to 37.5% of patients^{26,27,29-31,33-38} and downstaged 8.2 to 26.7% of patients.^{26,29,33-38} A large proportion of the staging changes were in patients being upstaged as a result of identifying occult nodal or metastatic disease. Patients staged T2-4 were also more likely to have a change in the overall staging.^{24,34} However, histological confirmation was not routinely available and this may lead to false upstaging or downstaging. Despite this limitation, eight of the studies reported changes to the therapeutic management of patients owing to PET or PET/CT findings. Treatment plans were modified in 12.5 to 59.3% of patients^{26,27,29,31,34-36,38} which consisted mainly of radiotherapy dose or field changes. For example, Mai *et al*³⁸ reported that 15.4% (6/39) of patients

with CT-detected enlarged inguinal lymph nodes had a reduction in irradiation dose owing to PET-negative findings; none of these patients developed recurrence or distant metastases. Other modifications to therapy included a change in treatment intent from curative to palliative, change in radiotherapy technique, planned surgery and the initiation of chemotherapy.

Several studies provided data on the utility of PET or PET/CT in predicting patient outcome. It is of interest to note that while nodal stage as assessed by conventional imaging was significantly associated with PFS, there was no significant difference in PFS between N0-1 and N2-3 patients as staged by PET or PET/CT.²⁶ The non-significant finding might be related to small sample size. Although nodal status has been shown to be an important prognostic factor for a number of survival endpoints, Cotter *et al*³³ found no significant difference in overall survival or PFS between patients with PET-positive and PET-negative nodes. In contrast, Mai *et al*³⁸ demonstrated a significant difference in freedom from metastasis between patients with PET-positive and PET-negative nodes (61.4 vs 95.6%, respectively; $p = 0.045$).

Assessment of treatment response

Diagnostic accuracy

The evidence demonstrating the diagnostic accuracy of PET/CT in post-treatment assessment is limited and came from one prospective study.²⁷ Patients were treated with chemoradiotherapy, radiotherapy alone, chemoradiotherapy plus surgery or surgery alone. At 1 month after the end of treatment, PET/CT detected persistent disease with a sensitivity of 66.6% (2/3), a

Figure 5. Specificity of PET/CT in detecting inguinal lymph nodes.

Table 3. Impact of PET or PET/CT on initial staging, treatment plan and survival

Study, year	Change in initial staging following CIM	Modification of treatment plan	Modification details	Survival outcomes
de Winton et al ²⁶	U: 14.8% (9/61) ^a D: 8.2% (5/61) ^a	16.4% (10/61)	8: change in radiotherapy fields or technique 2: change in treatment intent	3-year PFS N0-1 PET or PET/CT: 87.1% (95% CI, 72.3–94.5) vs CIM: 89.8% (95% CI, 75.7–96.1) N2-3 PET or PET/CT: 80.0% (95% CI, 57.2–92.3) vs CIM: 73.7% (95% CI, 50.2–88.6) 5-year PFS N2-3 PET or PET/CT: 70% (95% CI, 42.8–87.9%) vs CIM: 55.3% (95% CI, 23.3–83.4)
Engledow et al ²⁷	U: 12.5% (5/40)	12.5% (5/40)	3: received a boost of radiotherapy 1: change in radiotherapy fields 1: lung metastasis resection	NA
Mistrangelo et al ²⁹	U: 37.5% (15/40) D: 25.0% (10/40)	12.5% (5/40)	5: change in radiations fields	NA
Trautmann and Zuger ³⁰	U: 9.5% (2/21)	NA	NA	NA
Krengli et al ³¹	U: 18.5% (5/27)	59.3% (16/27)	1: curative to palliative 15: change in target volume delineation ^d	At a median follow up of 18 months, locoregional control was obtained in 66.7% (18/27) of patients, DFS and OS were 66.7 and 77.8%, respectively.
Cotter et al ³³	U: 31.7% (13/41) D: 17.1% (7/41)	NA	NA	The 2-year PFS and OS estimates were 75 and 76%, respectively. There was no significant difference in OS or PFS between patients with PET-positive and PET-negative inguinal or pelvic lymph nodes.
Nguyen et al ³⁴	U: 16.7% (8/48)	18.8% (9/48)	9: radiotherapy dose was increased	NA
Sveistrup et al ³⁵	U: 13.7% (13/95)	23.2% (22/95)	6: change in IMRT plan w/or w/o concomitant chemotherapy 6: received external boost w/or w/o concomitant chemotherapy 3: curative to palliative 2: change in radiation field + surgery 2: plan changed to IMRT 1: no concomitant chemotherapy 1: received surgery + chemoradiotherapy 1: brachy-boost to external boost	NA
Wells and Fox ³⁶	U: 20.0% (6/30) ^b D: 26.7% (8/30) ^b	36.7% (11/30)	NA	NA

(Continued)

Table 3. (Continued)

Study, year	Change in initial staging following CIM	Modification of treatment plan	Modification details	Survival outcomes
Bhuva <i>et al</i> ³⁷	U: 27.9% (12/43) D: 11.6% (5/43) T (D), N (U): 2.3% (1/43)	No change ^c	No change ^c	NA
Mai <i>et al</i> ³⁸	U: 5.1% (2/39) D: 20.5% (8/39)	15.4% (6/39)	6: radiotherapy dose was decreased	Local control rate and freedom from metastases at 3 years were 88 and 83%, respectively. There was a significant difference in freedom from metastasis between patients with PET-positive and PET-negative lymph nodes (61.4% vs 95.6%, respectively; $p = 0.045$)

CI, confidence interval; CIM, conventional imaging; CT, computed tomography; DFS, disease-free survival; IMRT, intensity-modulated radiation therapy; NA, not available; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; w/o, without; U, upstaged; D, downstaged.

^aA change in nodal or metastatic stage following PET or PET/CT occurred in 13.6% (3/22) of patients staged T1, in 41.7% (10/24) of patients staged T2 and in 40% (6/15) of patients staged T3-4.

^bOverall stage was changed in 20% (4/20) of patients staged T1, in 45.5% (5/11) of patients staged T2 and in 43.8% (7/16) of patients staged T3-4.

^cChanges in subsequent management were not implemented because PET/CT findings were not acknowledged during staging and before treatment.

^dGTV and CTV contours were changed in 55.6% (15/27) and 37.0% (10/27) of cases, respectively. Changes in GTV contours occurred in 80% (12/15) of cases staged T3-4 and in 25% (3/12) of cases staged T1-T2.

specificity of 92.5% (37/40), a PPV of 40% (2/5) and an NPV of 97.4% (37/38). At 3 months after the end of treatment, the sensitivity, specificity, PPV and NPV were 100% (2/2), 97.4% (37/38), 66.6% (2/3) and 100% (37/37), respectively.

Treatment response and survival

Six studies evaluated the response to chemoradiotherapy using PET or PET/CT.^{11,30,32,34,39,40} Time of assessment following end of treatment varied considerably across the studies (Table 4). The post-treatment PET or PET/CT showed a CR in 33.3 to 83.0% of patients and a PR or NR in 17.0 to 66.6% of patients. In two of the studies,^{30,40} it was not possible to distinguish between the proportion of patients with PR and NR, because this information is either not separated or considered the same. It is also noteworthy to mention that in the study by Trautmann and Zuger,³⁰ post-treatment PET was performed 1 month after completion of therapy for all patients, which is markedly earlier than the other studies. This study reported a CR rate of 33.3% and a PR or NR rate of 66.6%.

Among the six studies, four reported survival outcomes according to PET or PET/CT metabolic response (Table 4). Consistent across all studies, a PR or NR on PET or PET/CT was predictive of significantly worse 2-year PFS (CR: 68% to 95% vs PR: 22% to 40%; $p < 0.0001$ or NR: 0%; $p < 0.0001$),^{11,34,39} 2-year disease-free survival (CR: 77.5 vs PR: 14%; $p < 0.0001$)³²; 2-year cause-specific survival (CR: 94 vs PR: 39%; $p = 0.0008$)³⁹; and overall survival at 2 (CR: 95.7 vs PR: 49.9%; $p < 0.0001$)³² and 5 years (CR: 88 vs PR: 69%; $p = 0.03$ or NR: 0%; $p < 0.0001$).¹¹

Follow-up and recurrence

Diagnostic accuracy

Evidence on the diagnostic accuracy of PET/CT in suspected or proven recurrence after therapy is also limited to one prospective study.²⁸ The mean follow up duration was 13 months (range: 4–44 months). On a per-site basis, the sensitivity, specificity, PPV, NPV and accuracy of PET/CT in detecting persistent or recurrent disease were 86.4% (19/22), 96.8% (149/154), 79.2% (19/24), 98.0% (149/152) and 95.5% (168/176), respectively. When analysed by examination, the sensitivity was 93.3% (14/15), specificity was 81.0% (17/21), PPV was 77.8% (14/18), NPV was 94.4% (17/18) and accuracy was 86.1% (31/36).

Impact on patient management and survival

There were two studies that provided evidence of a change in patient management owing to PET/CT.^{28,36} Overall, management was altered in 16.7 to 25.0% of cases, which includes one case where PET/CT prompted unnecessary cytology as this patient was found to be disease free 11 months later. No survival data were found that correlated with follow-up PET/CT findings.

DISCUSSION

There is increasing evidence to better define the use of PET or PET/CT in the management of squamous cell cancer of the anal canal. PET, typically carried out as PET/CT, is sensitive in identifying the primary tumour but may not fully characterize it. In one particular study,³¹ PET/CT led to changes in GTV and CTV contours in 55.6% and 37.0% of cases, respectively, with the majority of cases (80%) in patients staged T3-4. Moreover, PET/CT-delineated GTV and CTV that were used for treatment

Table 4. Posttreatment PET or PET/CT metabolic response and survival

Study, year	Treatment	Time of assessment following treatment	CR	PR	NR	Survival outcomes
Nguyen et al ³⁴	CRT (EBRT/BT/5-FU + mito C/5-FU/5-FU based CT) or palliative RT	9–28 weeks 17 weeks (median)	80.0% (20/25)	20.0% (5/25)	0	2-year PFS CR: 68% vs PR: 40%
Trautmann and Zuger ³⁰	CRT	1 month	33.3% (6/18)	66.6% (12/18)		NA
Schwarz et al ³⁹	CRT (EBRT/5-FU + mito C/5-FU)	0.9–5.4 months 2.1 months (mean) 2.0 months (median)	83.0% (44/53)	17.0% (9/53)	0	2-year PFS CR: 95% vs PR: 22%; $p < 0.0001$ 2-year CSS CR: 94% vs PR: 39%; $p = 0.0008$
Kidd et al ⁴⁰	CRT (5-FU + mito C/5-FU/5-FU + CDDP/CAPE/CDDP + ETO)	0.9–24.8 months 2.0 months (median)	76.3% (45/59)	23.7% (14/59)		NA
Day et al ¹¹	CRT (EBRT/5-FU + mito C)	20–255 days 69 days (median)	79.2% (38/48)	14.6% (7/48)	6.3% (3/48)	2-year PFS CR: 95% (95% CI: 88–100) vs PR: 71% (95% CI: 45–100); $p = 0.19$ and NR: 0% (95% CI: 0–71); $p < 0.0001$ 5-year OS CR: 88% (95% CI: 78–100) vs PR: 69% (95% CI: 0–71); $p = 0.03$ and NR: 0% (95% CI: 0–71); $p < 0.0001$
Deantonio et al ³²	CRT (IMRT/3D CRT/5-FU + mito C/5-FU + CDDP)	4–6 months	61.8% (34/55)	38.2% (21/55)	0	2-year DFS CR: 77.5% vs PR: 14%; $p < 0.0001$ 2-year OS CR: 95.7% vs PR: 49.9%; $p < 0.0001$

3D CRT, three-dimensional conformal RT; 5-FU, 5-fluorouracil; BT, brachytherapy; CAPE, capecitabine; CDDP, cisplatin; CR, complete response; CSS, cause-specific survival; CT, chemotherapy; DFS, disease-free survival; EBRT, external beam RT; ETO, etoposide; IMRT, intensity-modulated RT; mito-C, mitomycin-C; NR, no response; PR, partial response; RT, radiation therapy.

purposes were significantly greater than those drawn on CT ($p = 0.00006$). Baseline PET/CT of primary disease may have a significant impact on radiotherapy treatment planning. Most studies use CT as a conventional imaging of choice when comparing with PET; however, MRI may offer a better definition of the soft tissue extension specifically in locally advanced cases.^{41,42} There is very little evidence comparing PET or PET/CT with MRI for the assessment of primary tumour and the findings are often difficult to interpret given MRI is considered the gold standard.^{37,42} Nevertheless, MRI has been demonstrated to be more sensitive than CT and could provide more consistent T stage assessment than clinical evaluation.⁴³ Thus, a lack of data in comparing PET or PET/CT with MRI is a major limitation of this review.

Nodal staging has a significant impact on radiotherapy treatment planning. Nodal involvement may also change the stage of disease that influences the prognosis. PET/CT is more sensitive than CT alone in identifying nodes. However, modest specificity is a limitation where a false-positive finding could be owing to an inflammatory condition. One study compared PET or PET/CT with CT, MRI or both and found that the overall sensitivity for detecting regional nodal metastases (*i.e.* perirectal, inguinal, iliac and intra-abdominal) was 89 vs 62%.²⁶ Kochhar et al⁴² suggested that PET/CT has a lower sensitivity than MRI in detecting perirectal nodes; however, this potential limitation would not affect

management because perirectal nodes are routinely included in the irradiated volume. The phenomenon of "upstaging" and/or "downstaging" based on PET may alter the definition of target volumes and doses used in radiation therapy planning of the nodal regions. The likelihood of disease control is dependent on delivery of an adequate radiation dose in prophylaxis (lower dose) or therapeutic (higher dose) when there is known malignancy. The initial assessment of likely nodal disease and appropriate radiation treatment planning reduces the risk of a disease relapse and morbidity of salvage therapies. De Winton et al²⁶ reported no significant difference in PFS between N0-1 and N2-3 patients as staged by PET or PET/CT. This may reflect a better staging and more accurate treatment of nodal sites; however, numbers were small and follow up time was short.

PET/CT can detect distant metastatic disease missed by conventional imaging, which has a significant prognostic value. In four studies, PET/CT identified distant metastatic sites not seen on conventional imaging in 2.4 to 4.7% of cases^{27,33,35,37}; however, biopsy was not always performed. We recommend considering biopsy whenever it is feasible prior to changing the intent of treatment.

PET or PET/CT is not routinely used to assess the response to chemoradiation therapy. Six reports were identified where timing

of PET assessment post-chemoradiotherapy varied from 1 to 6 months. It was noted that the complete responders had a better survival than non-responders. However, some of the reported partial responders could simply be owing to a slow response and not allowing enough time. The practice of premature scanning may lead to unnecessary invasive assessments and/or salvage surgeries. Currently, biopsy remains standard when there is a suspicion of persistent or recurrent disease once an adequate time is allowed after completion of treatment. Similarly, there is limited evidence in defining the role of PET/CT in follow up of patients managed for squamous cancer of anus. There is lack of survival outcome data in this regard.

In this review, the overall evidence was derived mostly from retrospective studies and smaller prospective studies. Heterogeneity between studies may also represent a potential source of bias. This is expected as anal squamous cell cancer is a relatively uncommon disease and the use of PET or PET/CT in this therapeutic area is not consistent in practice. Additionally, there are limitations of PET as FDG is not a cancer-specific agent. There could be false-positive findings with infection, inflammatory conditions, post-operative scenario, in tumours with low glycolytic activity (*i.e.* small tumour) or the location of disease near the physiological uptake site such as heart, bladder, kidney or liver.

Since there is no ideal cut-off value measured as the maximum standardized uptake value for determining malignancy, the interpretation of the PET image is often based on pattern recognition and may vary depending on the expertise of the reader. Additionally, technical differences in PET scans between the studies may impact the generalizability of the findings; however, only a minority of the studies employed a stand-alone PET scanner. It is unclear whether this would significantly impact the diagnostic yield of the test in anal canal cancer. In spite of that, FDG-PET is often complemented with other imaging modalities to confirm results and to minimize false-negative findings, since all enlarged or suspicious nodes should be included in the radiation treatment planning portals as it is not possible to perform multiple biopsies.

CONCLUSIONS

PET/CT is useful for the initial staging of patients with T2-4 disease. There is insufficient evidence at this time to recommend a routine use of PET/CT in the assessment of treatment response or follow-up. Future work will need to look into the appropriate timing of response assessment as this may help in exploring an option of more aggressive treatment approaches for partial responders.

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