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PET Recommendation Report 17

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

PET Imaging in Anal Canal Cancer

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PET Imaging in Anal Canal Cancer

Section 1: Recommendations and Key Evidence

OBJECTIVES

To provide a synthesis and summary of evidence surrounding the clinical utility of positron emission tomography (PET) imaging in patients with anal canal cancer.

TARGET POPULATION

Adult patients diagnosed with anal canal cancer.

INTENDED USERS

This recommendation report is intended to guide the Ontario PET Steering Committee in their decision making with respect to the development of indications. This recommendation report may also be useful to inform clinicians who are involved in the management of patients with anal canal cancer.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1

PET or positron emission tomography/computed tomography (PET/CT) may provide added benefit to the initial staging of patients with T2-4 squamous 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.

Qualifying Statements for Recommendation 1

- PET or PET/CT is sensitive in identifying but not characterizing already known primary tumours. It is not clear whether PET or PET/CT should be used to increase or decrease the gross tumour or clinical target volumes of the primary tumour compared with those defined by standard magnetic resonance imaging (MRI) of the pelvis.
- PET or PET/CT is able to identify nodes not seen on conventional imaging; however, specificity is modest and there would be the risk of overtreatment if the radiation field is expanded to include non-enlarged but PET-positive nodes.

Key Evidence for Recommendation 1

- Eight studies assessed the sensitivity of PET or PET/CT for the detection of primary tumour in situ [1-8]. The pooled sensitivity on a per-patient based analysis was 99% (95% confidence interval [CI], 97% to 100%). In comparison, the pooled sensitivity of CT from three studies [1,2,6] was 67% (95% CI, 50% to 82%).
- For the detection of inguinal lymph nodes, PET/CT had an overall sensitivity of 93% (95% CI, 76% to 99%) and specificity of 76% (95% CI, 61% to 87%) [6,7].
- Across four studies, PET/CT identified distant metastatic sites not seen on conventional imaging in 2.4% to 4.7% of cases [1,4,7,9].
- Eleven studies evaluated the impact of PET or PET/CT on patient management. Information from PET or PET/CT upstaged 5.1% to 37.5% of patients [1-4,6-12] and downstaged 8.2% to 26.7% of patients [1,3,6,8,9,11]. Patients staged T2-4 were more likely to have a change in the overall staging [3,8]. Treatment plans were modified in 12.5% to 59.3% of patients [2-4,6-8,11,12], which consisted mainly of radiotherapy dose or field changes. In one particular study [12], PET/CT led to changes in gross tumour volume (GTV) and clinical target volume (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 purposes were significantly greater than those drawn on CT (p=0.00006). Likewise, Mai et al [11] reported that 15.4% (6/39) of patients with CT-enlarged inguinal lymph nodes had a reduction in irradiation dose due to PET-negative findings; none of these patients developed recurrence or distant metastases.

Interpretation of Evidence for Recommendation 1

Despite the lack of comparison with pelvic MRI, which is considered the current standard in the diagnostic work-up of anal canal cancer, PET or PET/CT showed high sensitivity in visualizing the primary tumour and identifying involved lymph nodes as compared with CT. While there were uncertainties surrounding the interpretation of the index tests (PET or PET/CT, conventional imaging) and reference standard (post-surgical or post-biopsy histology, clinical or radiologic follow-up) across the studies, the Working Group believe that obtaining biopsy from all patients may not be feasible or practical and thus this was considered an acceptable study limitation.

Recommendation 2

There is insufficient evidence to recommend the use of PET or PET/CT in the assessment of treatment response.

Qualifying Statements for Recommendation 2

- Given that anal cancers tend to respond slowly after completion of chemoradiotherapy treatment, PET or PET/CT shortly after therapy should be avoided to minimize the number of false-positive findings.
- An appropriate timing of assessment remains controversial, and the optimal time point at which residual uptake of fluorodeoxyglucose (FDG) in a primary tumour should trigger salvage surgery is unknown.
- Complete response on PET or PET/CT is a good prognostic factor for overall and progression-free survival (PFS).

Key Evidence for Recommendation 2

- Mistrangelo et al [6] reported that at one month after the end of treatment, PET/CT detected persistent disease with a sensitivity of 66.6% (2/3), a specificity of 92.5% (37/40), a positive predictive value (PPV) of 40% (2/5), and a negative predictive value (NPV) of 97.4% (37/38). At three 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.
- Consistent across all studies, a partial response (PR) or no response (NR) on PET or PET/CT was predictive of significantly worse two-year PFS (complete response [CR]: 68% to 95% versus PR: 22% to 40%; p<0.0001 or NR: 0%, p<0.0001) [2,13,15], two-year disease-free survival (CR: 77.5% versus PR: 14%; p<0.0001) [16], two-year cause-specific survival (CR: 94% versus PR: 39%; p=0.0008) [13], and overall survival at two (CR: 95.7% versus PR: 49.9%; p<0.0001) [16] and five years (CR: 88% versus PR: 69%; p=0.03 or NR: 0%; p<0.0001) [15].

Interpretation of Evidence for Recommendation 2

Owing to the small number of studies evaluating the role of PET or PET/CT in the assessment of response after chemoradiotherapy and the inconsistent timing of assessment, the evidence is currently insufficient to support the use of PET or PET/CT in this setting.

Recommendation 3

There is insufficient evidence to recommend the use of PET or PET/CT for evaluation of

suspected or proven recurrence.
Qualifying Statements for Recommendation 3
• PET or PET/CT can be useful in the follow-up when persistence or recurrence of disease is suspected; however, it is unknown whether PET or PET/CT has a positive impact on overall survival.
Key Evidence for Recommendation 3
• Vercellino et al [5] reported that the sensitivity, specificity, PPV, NPV, and accuracy of PET/CT on a per-site basis 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 analyzed 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). • 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 [5,8].
Interpretation of Evidence for Recommendation 3
Owing to small sample size as well as the lack of data on the frequency and timing of routine follow-up, the evidence is currently insufficient to support the use of PET or PET/CT in this setting.

IMPLEMENTATION CONSIDERATIONS

The incorporation of PET or PET/CT into the current initial staging assessment would be feasible provided that there is capacity to support the new indication.

FUTURE RESEARCH

Future directions may include investigation into the role of PET/CT in assessing response to treatment at an appropriate time interval and its usefulness in routine follow-up. This may also help in exploring an option of more aggressive treatment approaches for partial responders.

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Section 2: Recommendation Report Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 3.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR RECOMMENDATION REPORT

A request was made by the Gastrointestinal Cancer Disease Site Group regarding the approval of PET imaging for patients with anal canal cancer in Ontario.

RECOMMENDATION REPORT DEVELOPERS

This recommendation report was developed by a Working Group consisting of a radiation oncologist, a medical oncologist, and a health research methodologist at the request of the Ontario PET Steering Committee.

The Working Group was responsible for reviewing the evidence base, drafting the recommendations and responding to comments received during the document review process. Conflict of interest declarations for all authors are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

RECOMMENDATION REPORT DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [17,18]. For Recommendation Reports, this process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by methodology experts, and final approval by the Sponsoring Committee.

The PEBC uses the AGREE II framework [19] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through the PET monitoring reports and, where appropriate, the addition of newer literature to the original evidence base. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing

guidelines for adaptation, using the ADAPTE framework [20], or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. The following sources were searched up to April 8, 2016 for existing guidelines that were based on a systematic review with well-described methods and addressed the research questions:

- Practice guideline databases: Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument [19].

RECOMMENDATION REPORT REVIEW AND APPROVAL

Internal Review

The recommendation report was reviewed by the Director of the PEBC. The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval.

Report Approval by the Ontario PET Steering Committee

After internal review, the report was presented to the Ontario PET Steering Committee. The committee reviewed the document and formally approved the document.

ACKNOWLEDGEMENTS

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- Max Chen for conducting a data audit.
- Sara Miller for copy editing.

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Section 3: Systematic Review

INTRODUCTION

Anal canal cancer is an uncommon disease, with an incidence of 1.7 per 100,000 person-years in Canada [21,22]. In 2010, there were 580 diagnosed cases, of which 385 (66.4%) occurred in women [21]. 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 [23-25]. As only a small proportion of patients will have distant metastatic disease, anal canal cancer is usually amenable to curative locoregional treatment. 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 [15]. Therefore, to achieve optimal management, accurate staging of primary tumour and regional lymph nodes is crucial for selecting treatment, especially for planning of 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, but are not routinely used in practice in Ontario. 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 six months post chemoradiotherapy, or earlier in the setting of tumour growth.

Presently, fluorine-18 (^{18}F) FDG-PET 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 [26]. The 2015 Version 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 [27]. Additionally, the European Society for Medical Oncology (ESMO)-European Society of Surgical Oncology (ESSO)-European Society of Radiotherapy and Oncology (ESTRO) clinical practice guidelines for anal cancer included PET/CT as an often recommended modality of the diagnostic work-up [28].

The purpose of this report is to develop an evidentiary base to inform recommendations with respect to the role of PET or PET/CT in the staging, response evaluation, and follow-up of anal canal cancer.

OBJECTIVES AND RESEARCH QUESTIONS

This Working Group developed the following objective(s) for this guideline in consultation with the Ontario PET Steering Committee.

- To provide a synthesis and summary of evidence surrounding the clinical utility of PET imaging in patients with anal canal cancer.

From these objectives, the following research questions were derived to direct the search for available evidence to inform recommendations to meet the objectives.

- What benefit to clinical management does PET or PET/CT contribute to the initial staging of anal canal cancer?
- What benefit to clinical management does PET or PET/CT contribute to the assessment of treatment response of anal canal cancer?
- What benefit to clinical management does PET or PET/CT contribute when the recurrence of anal canal cancer is suspected or proven?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews published as a component of practice guidelines were also considered eligible for inclusion. The search was aimed at finding a review that covered the research questions and could be used, at least in part, as the evidentiary basis for this recommendation report. The electronic databases MEDLINE (1946 to April Week 1 2016), Embase (1974 to 2016 Week 14), and Cochrane Database of Systematic Reviews (2005 to April 07, 2016) were searched through OVID. See Appendix 2 for the search strategy.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) [29] tool to determine whether existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

If no eligible systematic reviews were identified, a primary search of the literature was conducted and described below.

Literature Search Strategy

The primary literature was searched using MEDLINE (1946 to April Week 1 2016) and Embase (1974 to 2016 Week 14) databases through OVID. Details of the literature search can be found in Appendix 2. In addition, reference lists from relevant systematic reviews and primary literature were scanned for potentially useful studies.

Study Selection Criteria and Process

Inclusion Criteria

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. Post-surgical or post-biopsy histology, clinical follow-up, or radiologic follow-up were used as the reference standard.
4. Reported on at least one of the following outcomes:
    - Numeric data on diagnostic performance (e.g., sensitivity, specificity, PPV, NPV, accuracy).
    - Metrics representing change or impact on clinical management decisions.
    - Data on survival.

5. Included ≥12 patients for prospective studies/randomized controlled trials or ≥30 for retrospective studies.

Exclusion Criteria

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.

A review of the titles and abstracts that resulted from the search was conducted independently by one reviewer, as were the items that warranted full-text review.

Data Extraction and Assessment of Study Quality and Potential for Bias

One reviewer extracted data from the included studies. For each article, the principal author, country of origin, publication year, study design, number of patients, age and sex, the type of PET and conventional imaging performed as well as the outcomes of interest were recorded. All extracted data and information were audited by an independent auditor. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [30] tool was used to evaluate the risk of bias for studies that contributed data on diagnostic performance.

Synthesizing the Evidence

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, 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 version 11.2 using the metaprop command with the Freeman-Tukey double arcsine transformation and Meta-DiSc version 1.4, which implements meta-regression using a generalization of the Littenberg and Moses Linear model [31,32].

RESULTS

Search for Existing Clinical Practice Guidelines and Systematic Reviews

A search for existing guidelines did not yield an appropriate source document on which to build an evidence base. The search for existing systematic reviews identified two publications [33,34] that were considered relevant after full-text review. However, neither systematic review fully addressed the research questions or 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 recommendation report and therefore were not discussed further. As such, the AGREE II instrument and the AMSTAR tool were not used.

Search for Primary Literature

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. Twenty citations were considered as candidates, but upon full-text review, three did not meet the inclusion criteria. Finally, the remaining 17 studies were included in this systematic review. Data were not extracted from one study [35] owing to overlapping

patient population with a more recent article with the larger sample analyzed. See Appendix 3 for the PRISMA flow diagram.

Study Design and Quality

Among the 16 studies, seven studies enrolled patients prospectively [3-6,10,12,16] while nine studies were retrospective outcomes review [1,2,7-9,11,13-15]. PET scans were obtained in two studies [10,11], PET/CT scans in 11 studies [1,4-9,12-14,16], and PET or PET/CT scans in three studies [2,3,15]. Details of the study characteristics can be found in Table 3-1. The nine studies [1-9] that contributed data to the performance metrics outcome were assessed according to the four QUADAS-2 domains (Appendix 4). All studies were judged to have low concerns regarding applicability. For the domains relating to bias, one study [7] 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. Furthermore, readings for the index tests (e.g., PET or PET/CT, conventional imaging) were either not blinded to the results of the reference standard [5] or unclear as to whether they were interpreted without knowledge of the reference standard [1,2,6-9]. 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 [1-9]. No studies were assessed as being at risk due to patient selection. Owing to incomplete and inconsistent reporting across the studies, there are uncertainties surrounding the interpretation of the index tests and reference standard and as such the overall quality of the evidence was judged to be fair.

Table 3-1: Studies selected for inclusion.

Study, year	Country	Type of study	No. of patients	Median age	Gender (M/F)	PET imaging	CIM
Cotter et al, 2006 [1]	USA	Retrospective	41	52 (mean)	18/23	PET/CT	CT
Nguyen et al, 2008 [2]	Australia	Retrospective	50	58	19/31	PET or PET/CT	CT
de Winton et al, 2009 [3]	Australia	Prospective	61	57	34/27	PET or PET/CT	CT, MRI or both
Engledow et al, 2011 [4]	UK	Prospective	40	57	14/26	PET/CT	CT + MRI
Vercellino et al, 2011 [5]	France	Prospective	44	62 (mean)	13/31	PET/CT	NA
Mistrangelo et al, 2012 [6]*; Mistrangelo et al, 2010 [35]*	Italy	Prospective	53	57	19/34	PET/CT	CT
Sveistrup et al, 2012 [7]	Denmark	Retrospective	95	58	30/65	PET/CT	TAUS + US
Wells and Fox, 2012 [8]	UK	Retrospective	44	NA	NA	PET/CT	CT + MRI
Bhuva et al, 2012 [9]	UK	Retrospective	43	NA	NA	PET/CT	CT + MRI
Trautmann and Zuger, 2005 [10]	USA	Prospective	21	52	6/15	PET	CT
Mai et al, 2009 [11]	Germany	Retrospective	39	56	17/22	PET	CT
Krengli et al, 2010 [12]	Italy	Prospective	27	66	9/18	PET/CT	CT
Schwarz et al, 2008 [13]	USA	Retrospective	53	52 (mean)	20/33	PET/CT	CT
Kidd et al, 2010 [14]	USA	Retrospective	77	53 (mean)	33/44	PET/CT	NA
Day et al, 2011 [15]	Australia	Retrospective	48	56	22/26	PET or PET/CT	NA
Deantonio et al, 2016 [16]	Italy	Prospective	55	67	18/37	PET/CT	NA

Abbreviations: CIM, conventional imaging; CT, computed tomography; M/F, male/female; MRI, magnetic resonance imaging; NA, not available; PET, positron emission tomography; TAUS, transanal endoscopic ultrasound; US, ultrasound

*Overlapping patient population in these studies; data not presented for the Mistrangelo et al, 2010 report [33].

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 [1-8]. 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 (I^2=17.1%, p=0.29). Forest plot of the eight studies is presented in Figure 3-1. In comparison to conventional imaging, the sensitivity of CT ranged from 57.9% to 82.9% in three studies [1,2,6], with a pooled estimate of 67% (95% CI, 50% to 82%) (Figure 3-2) while one study reported a sensitivity of 100% for ultrasound (US) [7]. 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.

Figure 3-1: Forest plot of the sensitivity of PET or PET/CT in the detection of primary tumour in situ.

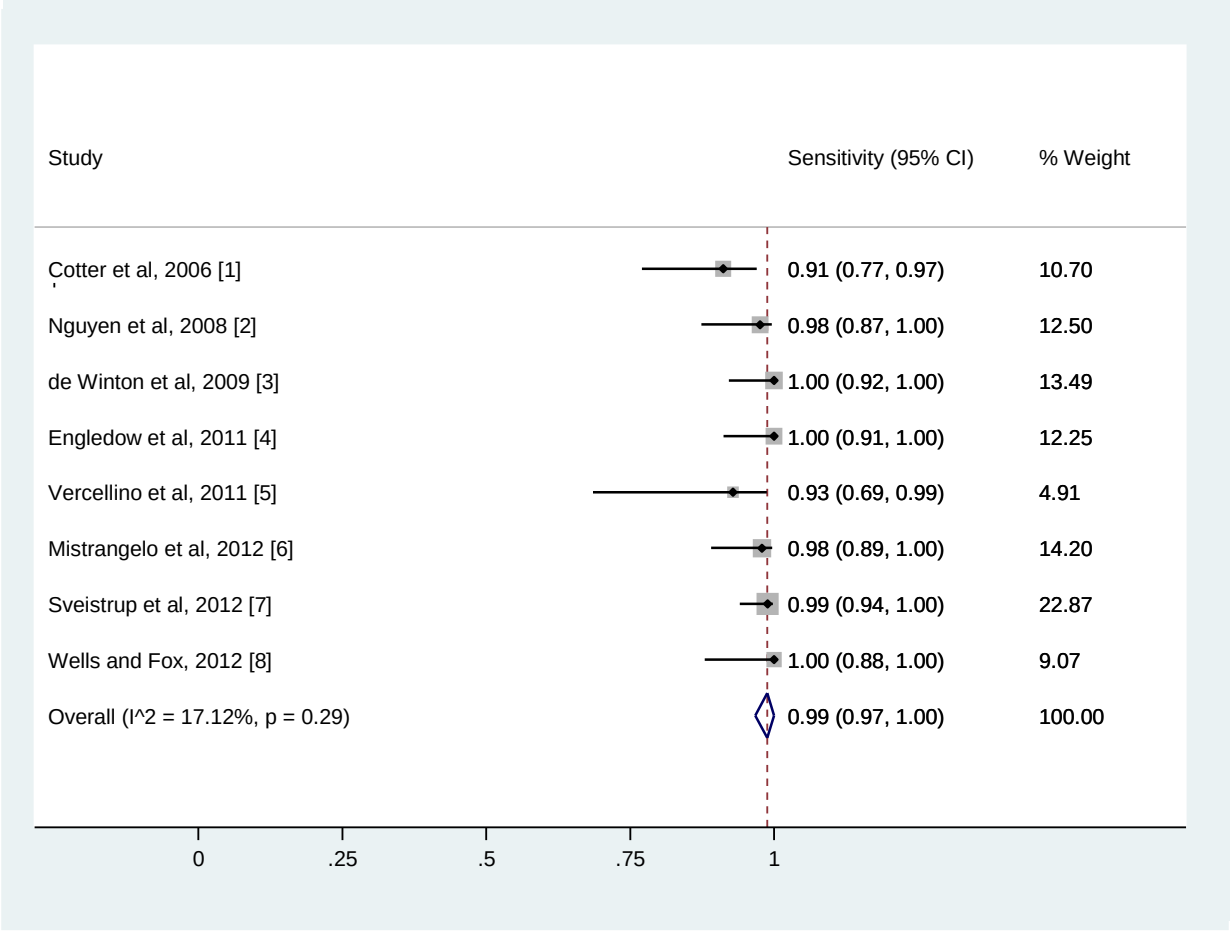
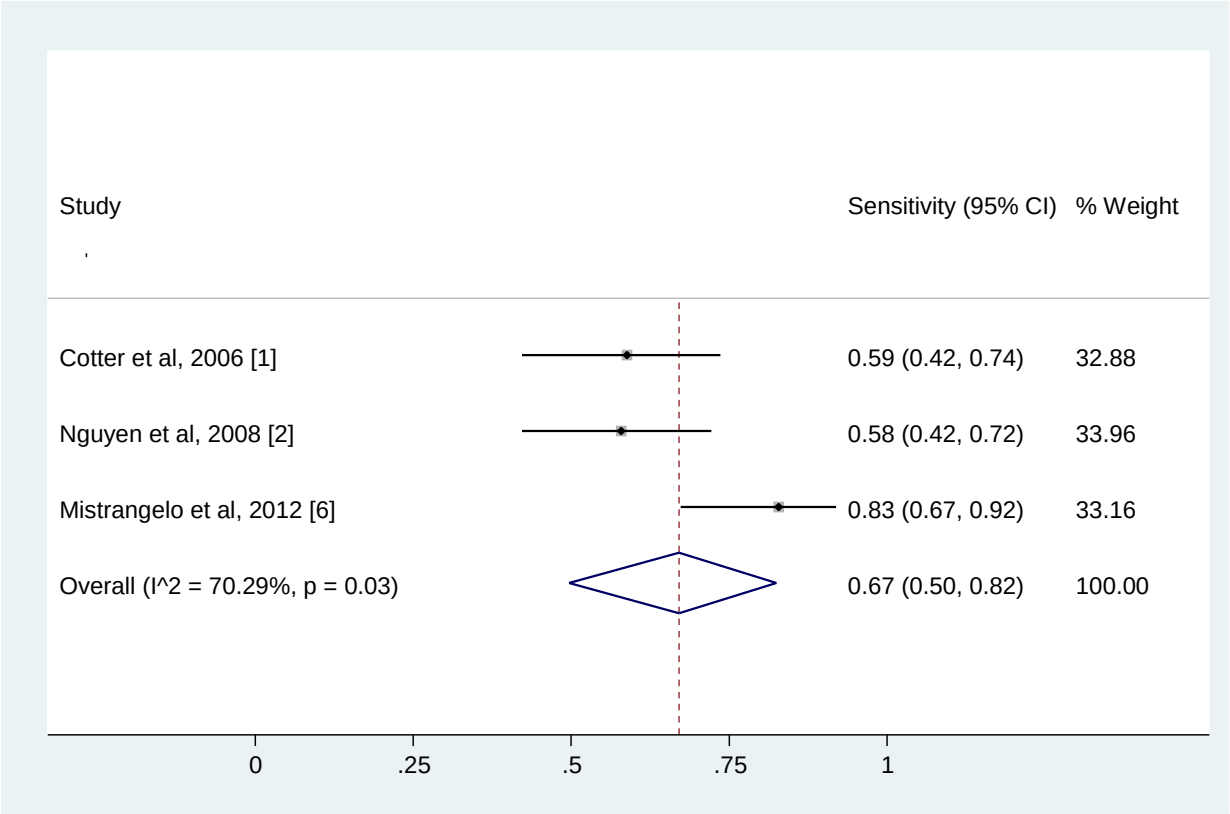


Figure 3-2: Forest plot of the sensitivity of CT in the detection of primary tumour in situ.



Lymph Nodes

For the detection of inguinal lymph nodes, two studies provided sufficient data to allow the aggregation of diagnostic information for PET/CT [6,7]. 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 3-3 and 3-4). With respect to conventional imaging, one study reported a sensitivity of 50.0% (4/8) and a specificity of 84% (22/26) for CT [6], and one study reported a sensitivity of 94.1% (16/17) and a specificity of 20.0% (3/15) for US [7]. An additional study compared PET or PET/CT with conventional imaging consisting of CT, MRI or both and found that the overall sensitivity for detecting regional nodal metastases (i.e., perirectal, inguinal, iliac, and intra-abdominal nodes) was 89% versus 62% [3] (Table 3-2).

Figure 3-3: Sensitivity of PET/CT in detecting inguinal lymph nodes.

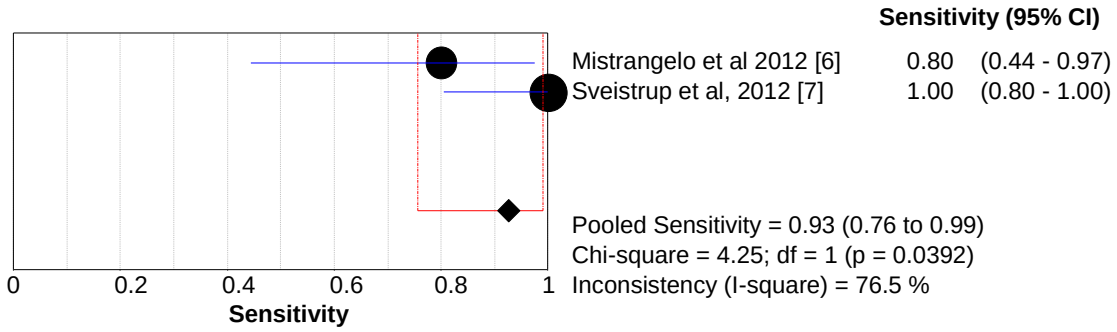


Figure 3-4: Specificity of PET/CT in detecting inguinal lymph nodes.

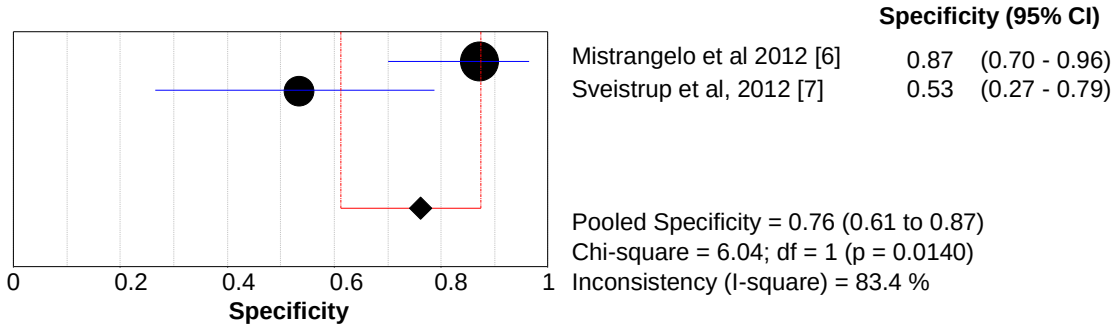


Table 3-2: Sensitivity of PET or PET/CT versus conventional imaging in detecting perirectal, inguinal, iliac, and intra-abdominal nodes.

Study, year	Regional nodal site	Sensitivity	
		PET or PET/CT	CIM
de Winton et al, 2009 [3]	Inguinal	100%	85%
	Perirectal	67%	50%
	Iliac	100%	50%
	Intra-abdominal	100%	0%
	Overall	89%	62%

Abbreviations: CIM, conventional imaging; CT, computed tomography; PET, positron emission tomography

Distant Metastases

In four studies, PET/CT identified distant metastatic sites not seen on conventional imaging in 2.4% to 4.7% of cases [1,4,7,9]; however, biopsy was not always performed to verify metastatic disease. Location of the distant metastatic sites can be found in Table 3-3.

Table 3-3: PET/CT in the identification of previously undetected distant metastatic disease.

Study, year	Detection rate	Location of distant metastatic disease
Cotter et al, 2006 [1]	2.4% (1/41)	1: pulmonary nodule
Engledow et al, 2011 [4]	2.5% (1/40)	1: lung
Sveistrup et al, 2012 [7]	4.2% (4/95)	1: superior pubic ramus and tuber ischiadicum 2: liver 1: right adrenal gland
Bhuva et al, 2012 [9]	4.7% (2/43)	1: distant pelvic lymph nodes 1: right supraclavicular lymph nodes

Abbreviations: CT, computed tomography; PET, positron emission tomography

Impact on Patient Management and Survival

Eleven studies evaluated the impact of PET or PET/CT on patient management (Table 3-4). 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 [1-4,6-12] and downstaged 8.2% to 26.7% of patients [1,3,6,8,9,11]. 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 [3,8]. 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 due to PET or PET/CT findings. Treatment plans were modified in 12.5% to 59.3% of patients [2-4,6-8,11,12], which consisted mainly of radiotherapy dose or field changes. In one particular study [12], 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 purposes were significantly greater than those drawn on CT (p=0.00006). Likewise, Mai et al [11] reported that 15.4% (6/39) of patients with CT-detected enlarged inguinal lymph nodes had a reduction in irradiation dose due 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. One study reported that changes in subsequent management were not implemented because PET/CT findings were not acknowledged during staging and before treatment [9].

Several studies provided data on the utility of PET or PET/CT in predicting patient outcome. One prospective study [3] reported a three-year PFS of 80% (95% CI, 57.2% to 92.3%) and a five-year PFS of 70% (95% CI, 42.8% to 87.9%) for N2-3 patients staged by PET or PET/CT. The corresponding three- and five-year PFS as staged by conventional imaging were 73.7% (95% CI, 50.2% to 88.6%) and 55.3% (95% CI, 23.3% to 83.4%), respectively. The three-year PFS for N0-1 patients staged by PET or PET/CT and conventional imaging were 87.1% (95% CI, 72.3% to 94.5%) and 89.8% (95% CI, 75.7% to 96.1%), respectively. 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. Although nodal status has been shown to be an important prognostic factor for a number of survival endpoints, Cotter et al [1] found no significant difference in overall survival or PFS between patients with PET-positive and PET-negative nodes. In contrast, Mai et al [11] demonstrated a significant difference in freedom from metastasis between patients with PET-positive and PET-negative nodes (61.4% versus 95.6%, respectively; p=0.045).

Table 3-4: 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
Cotter et al, 2006 [1]	Upstaged: 31.7% (13/41) Downstaged: 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 -negative inguinal or pelvic lymph nodes.
Nguyen et al, 2008 [2]	Upstaged: 16.7% (8/48)	18.8% (9/48)	9: radiotherapy dose was increased	NA
de Winton et al, 2009 [3]	Upstaged: 14.8% (9/61)[§] Downstaged: 8.2% (5/61)[§]	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, 2011 [4]	Upstaged: 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, 2012 [6]	Upstaged: 37.5% (15/40) Downstaged: 25.0% (10/40)	12.5% (5/40)	5: change in radiations fields	NA
Sveistrup et al,	Upstaged: 13.7% (13/95)	23.2% (22/95)	6: change in IMRT plan w/ or	NA

2012 [7]			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	
Wells and Fox, 2012 [8]	Upstaged: 20.0% (6/30)[L] Downstaged: 26.7% (8/30)[L]	36.7% (11/30)	NA	NA
Bhuva et al, 2012 [9]	Upstaged: 27.9% (12/43) Downstaged: 11.6% (5/43) T downstaged, N upstaged: 2.3% (1/43)	No change*	No change*	NA
Trautmann and Zuger, 2005 [10]	Upstaged: 9.5% (2/21)	NA	NA	NA
Mai et al, 2009 [11]	Upstaged: 5.1% (2/39) Downstaged: 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 –negative lymph nodes (61.4% vs. 95.6%, respectively; p=0.045)
Krengli et al, 2010 [12]	Upstaged: 18.5% (5/27)	59.3% (16/27)	1: curative to palliative 15: change in target volume	At a median follow-up of 18 months, locoregional control

			delineation**	was obtained in 66.7% (18/27) of patients. DFS and OS were 66.7% and 77.8%, respectively.

Abbreviations: 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/, with; w/o, without

[§]A 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.

[L]Overall 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.

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

**GTV 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.

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 [6]. Patients were treated with chemoradiotherapy, radiotherapy alone, chemoradiotherapy plus surgery, or surgery alone. At one month after the end of treatment, PET/CT detected persistent disease with a sensitivity of 66.6% (2/3), a specificity of 92.5% (37/40), a PPV of 40% (2/5), and an NPV of 97.4% (37/38). At three 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 [2,10,13-16]. Time of assessment following end of treatment varied considerably across the studies (Table 3-5). 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 [10,14], 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 [10], post-treatment PET was performed one 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 3-5). Consistent across all studies, a PR or NR on PET or PET/CT was predictive of significantly worse two-year PFS (CR: 68% to 95% versus PR: 22% to 40%; $p<0.0001$ or NR: 0%, $p<0.0001$) [2,13,15]; two-year disease-free survival (CR: 77.5% versus PR: 14%; $p<0.0001$) [16]; two-year cause-specific survival (CR: 94% versus PR: 39%; $p=0.0008$) [13]; and overall survival at two (CR: 95.7% versus PR: 49.9%; $p<0.0001$) [16] and five years (CR: 88% versus PR: 69%; $p=0.03$ or NR: 0%; $p<0.0001$) [15].

Table 3-5: 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, 2008 [2]	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, 2005 [10]	CRT	1 month	33.3% (6/18)	66.6% (12/18)		NA
Schwarz et al, 2008 [13]	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, 2010 [14]	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, 2011 [15]	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	CRT (IMRT/3D	4-6 months	61.8% (34/55)	38.2%	0	2-year DFS

al, 2016 [16]	CRT/5-FU + mito-C/5-FU + CDDP)			(21/55)		CR: 77.5% vs. PR: 14%; p<0.0001 2-year OS CR: 95.7% vs. PR: 49.9%; p<0.0001

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

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 [5]. The mean follow-up duration was 13 months (range: 4 to 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 analyzed 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 due to PET/CT [5,8]. 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. The modification details are given in Table 3-6. No survival data were found that correlated with follow-up PET/CT findings.

Table 3-6: Impact of follow-up PET/CT on patient management.

Study, year	Follow-up duration	Modification of treatment plan	Modification details
Vercellino et al, 2011 [5]	4-44 months *13 months (mean)*	25.0% (9/36)	2: avoided unnecessary biopsies 2: chemotherapy indicated 2: surgical intervention indicated 2: surgery to chemotherapy 1: prompted unnecessary cytology
Wells and Fox, 2012 [8]	6 weeks-2 years	16.7% (3/18)	NA

Abbreviations: CT, computed tomography; NA, not available; PET, positron emission tomography

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 study where most patients had T3-4 disease, PET/CT led to changes in GTV and CTV contours in 55.6% and 37.0% of cases, respectively. PET/CT-delineated GTV and CTV used for radiation therapy planning were significantly greater than those drawn based on CT alone (p=0.00006) [12]. 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. A lack of data in comparing PET or PET/CT with MRI is a 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 due 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% versus 62% [3]. 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 al [3] 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 [1,4,7,9]; however, biopsy was not always performed. Metastatic sites included lung, liver, distant nodes, bone, and adrenal. In practice, the recommendation would be to carry out a biopsy 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 one to six 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 due 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 evidence upon which the recommendations were based 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 physiologic uptake site such as heart, bladder, kidney, or liver. Therefore, 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

We conclude that PET/CT is recommended for 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.

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Appendix 1: Members of the Working Group and their COI Declaration

Name	Affiliation	Declarations of interest
Aamer Mahmud, MD, FRCPC Radiation Oncologist	Department of Oncology, School of Medicine, Queen's University	No conflict declared
Raymond Poon, MPH Health Research Methodologist	Department of Oncology, McMaster University, Juravinski Hospital Site	No conflict declared
Derek Jonker, MD, FRCPC Medical Oncologist	Department of Medicine, University of Ottawa	No conflict declared

Appendix 2: Literature Search Strategy

The search was conducted in MEDLINE (1946 to April Week 1 2016), Embase (1974 to 2016 Week 14), and Cochrane Database of Systematic Reviews (2005 to April 07, 2016) on April 07, 2016.

Medline

Section A: Disease and/or population	1	exp Anus Neoplasms/
	2	((anal or anus) adj3 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
	3	1 or 2
Section B: Intervention or diagnostic test	4	exp Deoxyglucose/ or deoxyglucose.mp. or deoxy-glucose.mp. or fluorodeoxyglucose.mp. or 18fluorodeoxyglucose.mp. or fludeoxyglucose.mp. or fdg$.mp. or 18fdg.mp. or f-18-dg.mp. or fluoro-2-deoxy-d-glucose.mp. or 2fluoro-2deoxyglucose.mp. or fluoro-d-glucose.mp. or 18 fdg.mp.
	5	(positron emission tomography computed tomography or pet ct or pet?ct).mp.
	6	exp Tomography, Emission-computed/
	7	(positron adj emission adj tomograph$).mp.
	8	(pet$ or pet scan$).mp.
	9	or/6-8
	10	4 and (5 or 9)
Section C: Exclusion strategy	11	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
	12	animal/ not (exp human/ or humans/)
	13	11 or 12
Combining Sections A, B, and C	14	(3 and 10) not 13
	15	limit 14 to English language

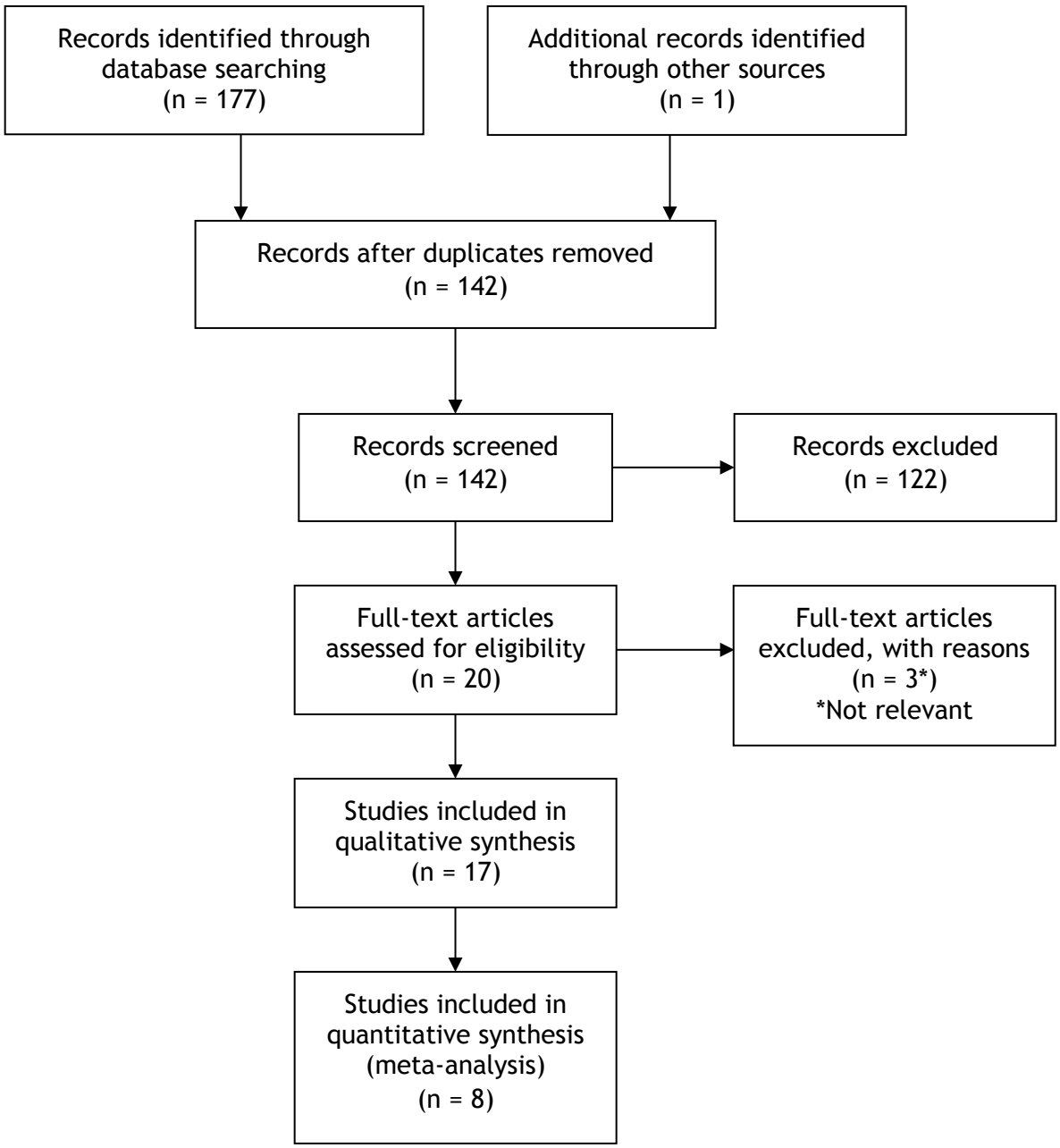
Embase

Section A: Disease and/or population	1	exp Anus Neoplasms/
	2	((anal or anus) adj3 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
	3	1 or 2
Section B: Intervention or diagnostic test	4	exp Deoxyglucose/ or deoxyglucose.mp. or deoxy-glucose.mp. or fluorodeoxyglucose.mp. or 18fluorodeoxyglucose.mp. or fludeoxyglucose.mp. or fdg$.mp. or 18fdg.mp. or f-18-dg.mp. or fluoro-2-deoxy-d-glucose.mp. or 2fluoro-2deoxyglucose.mp. or fluoro-d-glucose.mp. or 18 fdg.mp.
	5	(positron emission tomography computed tomography or pet ct or pet*ct).mp.
	6	exp Tomography, Emission-computed/
	7	exp positron emission tomography/
	8	(positron adj emission adj tomograph$).mp.
	9	(pet$ or pet scan$).mp.
	10	or/6-9
	11	4 and (5 or 10)
Section C: Exclusion strategy	12	(editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
	13	animal/ not (exp human/ or humans/)
	14	12 or 13
Combining Sections A, B, and C	15	(3 and 11) not 14
	16	limit 15 to English language

Cochrane Database of Systematic Reviews

Section A: Disease and/or population	1	((anal or anus) adj3 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$)).mp.
Section B: Intervention or diagnostic test	2	(deoxyglucose or deoxy-glucose or fluorodeoxyglucose or 18fluorodeoxyglucose or fludeoxyglucose or fdg$ or 18fdg or f-18-dg or fluoro-2-deoxy-d-glucose or 2fluoro-2deoxyglucose or fluoro-d-glucose).mp. or 18 fdg.mp.
	3	(positron emission tomography computed tomography or pet ct or pet?ct).mp.
	4	(positron adj emission adj tomograph$).mp.
	5	(pet$ or pet scan$).mp.
	6	4 or 5
	7	2 and (3 or 6)
Combining Sections A and B	8	1 and 7

Appendix 3: PRISMA Flow Diagram



Appendix 4: 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
Cotter et al, 2006 [1]	L	U	U	L	L	L	L
Nguyen et al, 2008 [2]	L	U	U	L	L	L	L
de Winton et al, 2009 [3]	L	L	U	L	L	L	L
Engledow et al, 2011 [4]	L	L	U	L	L	L	L
Vercellino et al, 2011 [5]	L	H	U	L	L	L	L
Mistrangelo et al, 2012 [6]	L	U	U	L	L	L	L
Sveistrup et al, 2012 [7]	L	U	U	H	L	L	L
Wells & Fox, 2012 [8]	L	U	U	L	L	L	L
Bhuva et al, 2012 [9]	L	U	U	U	L	L	L

L=Low Risk H=High Risk U=Unclear Risk