


Cervical cancer - staging and restaging with ^{18}F -FDG PET/CT


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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.

The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Cervical cancer is the third most frequent tumor and the fourth in mortality among Brazilian woman. In 2018, it is estimated there were over 16,000 new cases of the disease¹. Its etiologic agent is the Human Papillomavirus (HPV), which is transmitted through sex and also causes other neoplasms, such as of the head and neck, penis, and oropharynx².

Positron emission tomography (PET) is an exam with ample indication for staging and restaging of solid tumors with precise and well-established indication for other gynecological tumors, such as breast cancer. When it is associated with a computed tomography (CT) study, it is called PET/CT. The tracer most commonly used in PET or PET/CT is the fludeoxyglucose marked with fluorine-18 (^{18}F -FDG).

International guidelines already recommend considering a ^{18}F -FDG PET/CT in cases of cervical cancer from staging IB1³. However, cervical cancer is still not established as an indication of PET/CT in our country in the Single Health System or the National Supplementary Health Agency.

In this scenario, it is necessary to determine the role of ^{18}F -FDG PET/CT in the staging and restaging of cervical cancer patients. (ANNEX I)

RESULTS

The characteristics of the bias evaluation of the studies using QUADAS-2 are described in Table 1 (APPENDIX). The evaluation includes the criteria used for selecting patients, the type of test used, the gold standard, and the interval between the test and the gold standard. Of the 17 studies included, there was a high risk of bias in patient selection in 1 study (6%), high risk of bias in interpretation of PET/CT in 10 studies (59%), and high risk of bias in the conduct or interpretation of the gold standard in 13 studies (76%). The reasons for exclusion were: data that included other types of cancer associated with cervical cancer, such as ovary or endometrium, papers with PET/MRI or that used PET radiotracers other than FDG, stud-

ies that evaluated only the prognostic role of PET or the therapeutic response.

After the systematic review, it was possible to meta-analyze and evaluate the outcomes of detection in the following situations: detection of lymph node metastases to the staging, detection of local recurrence, and evaluation of distant metastases.

FDG-PET in comparison with CT/MRI for detecting lymph nodes in staging

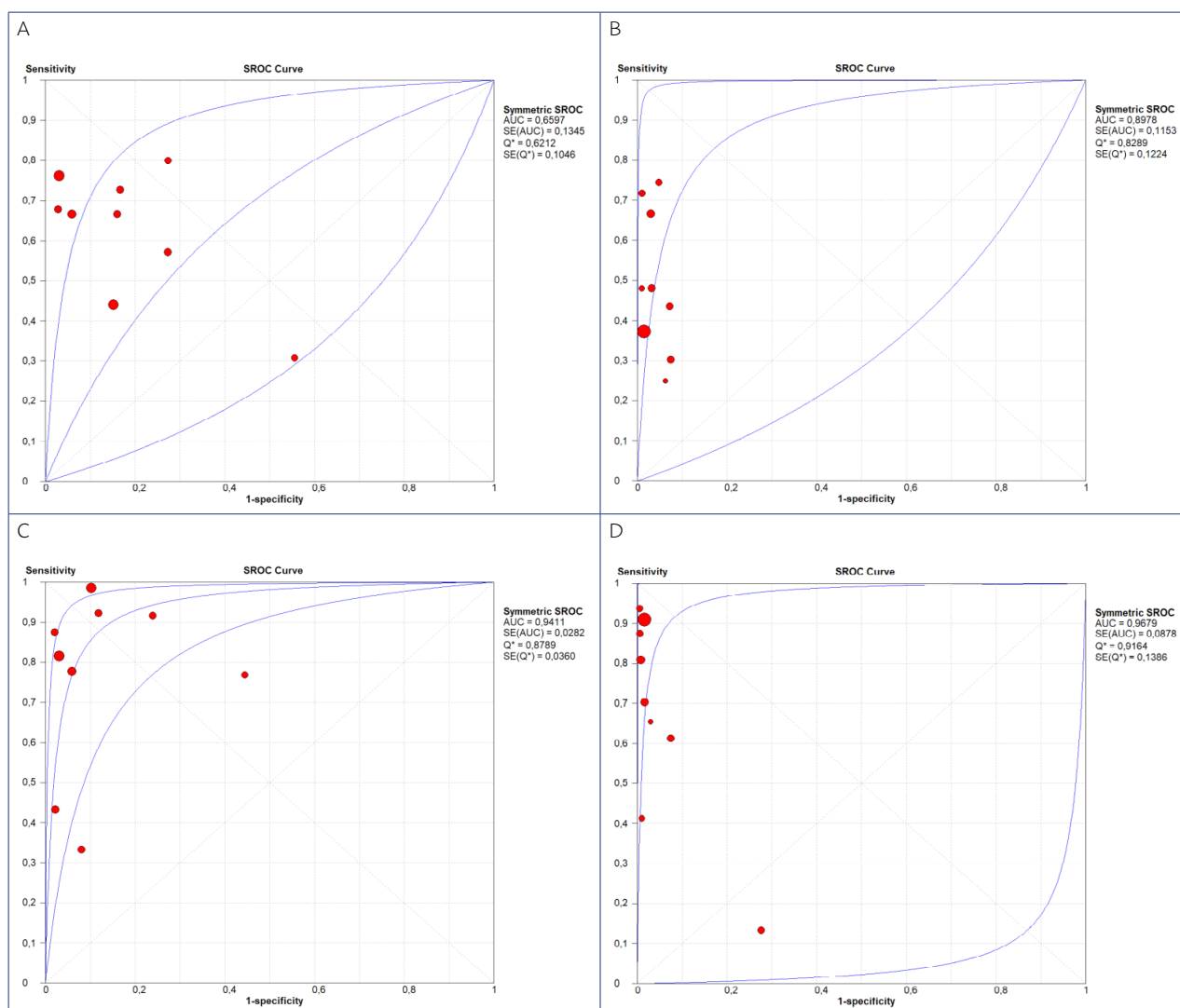
To analyze the detection of lymph nodes, we included studies that evaluated the sensitivity and specificity of FDG-PET in comparison with CT or MRI for detecting pelvic and para-aortic lymph node involvement in cervical cancer patients using as gold

standard surgical staging. In total, 11 studies were included totaling 552 patients presented in Table 2 (Annex II). Eight studies⁶⁻¹³(B) analyzed the detection per number of patients and seven studies^{6,10,12-16} (B) per total number of lymph nodes identified, so the results were separated into two groups.

The FDG-PET showed significantly higher performance with a wider area under the curve for the detection of pelvic and para-aortic lymph nodes in relation to the control group (CT/MRI) in the analysis per patients (AUC control = 0.6597; AUC FDG-PET = 0.9411; $p < 0.000001$) and in the analysis per number of lymph nodes (AUC control = 0.8978; AUC FDG-PET = 0.9679; $p = 0.0001$) (Figure 2).

These results were expected since the anatomi-

FIGURE 2: ROC CURVE OF THE CONTROL (CT/MRI) IN DETECTING PELVIC AND AORTIC LYMPH NODES PER PATIENTS (A) AND NUMBER OF LYMPH NODES (B). ROC CURVE OF FDG-PET PER PATIENT (C) AND NUMBER OF LYMPH NODES (D).



cal methods are capable of detecting late neoplastic changes after the metabolic alterations, which may be present in lymph nodes that still have a preserved anatomy. It is already recommended by international guidelines that PET/CT can be used instead of CT/MRI for detecting lymph node involvement from the staging IB2³ (D).

FDG-PET in comparison with CT/MRI for detecting local recurrence

Six studies¹⁷⁻²² (B), totaling 233 patients evaluated the detection of FDG-PET in relation to CT and/or MRI for detecting local recurrence of cervical cancer (Table 3 - Annex II).

The FDG-PET showed significantly higher performance with a larger area under the curve for detecting recurrence in relation to the control (AUC control = 0.606; AUC FDG-PET = 0.982; $p < 0.000001$) (Figure 3).

The treatment for cervical cancer depends on the staging of the disease. In initial stagings, the curative treatment is surgical. In advanced cases, it can also include chemotherapy and radiotherapy. These treatments, especially surgery and local radiotherapy can bring huge challenges for the analysis of the anatomical images. FDG-PET, because it is a functional image, offers superior performance in this indication.

The use of diuretics and late images, 40 minutes after the first FDG-PET image, can facilitate the locoregional evaluation of the pelvis by reducing the ra-

dioactive urine in the bladder and ureters. Different protocols were used in the studies included in this analysis. A study¹⁷ (B) used a diuretic at the time of injection of the tracer and made no reference to late images. Other studies¹⁹⁻²² (B) used a diuretic and a vesical catheter, and also made no reference to late images. One study used late images and a diuretic²¹. Two studies¹⁸⁻²⁰ did not use any protocol, which may have reduced their sensitivity.

FDG-PET in comparison with CT/MRI for detecting distant metastasis

To our surprise, we found no studies comparing the PET/CT with other diagnostic tools for assessing distant metastasis. We found very few studies comparing PET with CT and/or MRI.

Four studies^{15,19,21,23} (B), totaling 162 patients evaluated the detection of metastatic lesions with FDG-PET in relation to CT and/or MRI (Table 4 - Annex II) in patients of staging and/or suspected recurrence. These four studies were performed by the same group of researchers, with a small number of patients. The authors did not mention whether there is an overlap of patients. FDG-PET showed superior performance with a larger area under the curve in relation to the control group (Figure 4).

Due to all the factors mentioned, this analysis has huge limitations. Nevertheless, it seems logical that PET has a higher accuracy for assessing distant metastasis since this is the greatest indication for PET

FIGURE 3: ROC CURVES FOR DETECTING LOCAL RECURRENCE WITH CONTROL (A) AND WITH THE FDG-PET (B), WHICH SHOWED SIGNIFICANTLY HIGHER PERFORMANCE WITH A LARGER AREA UNDER THE CURVE.

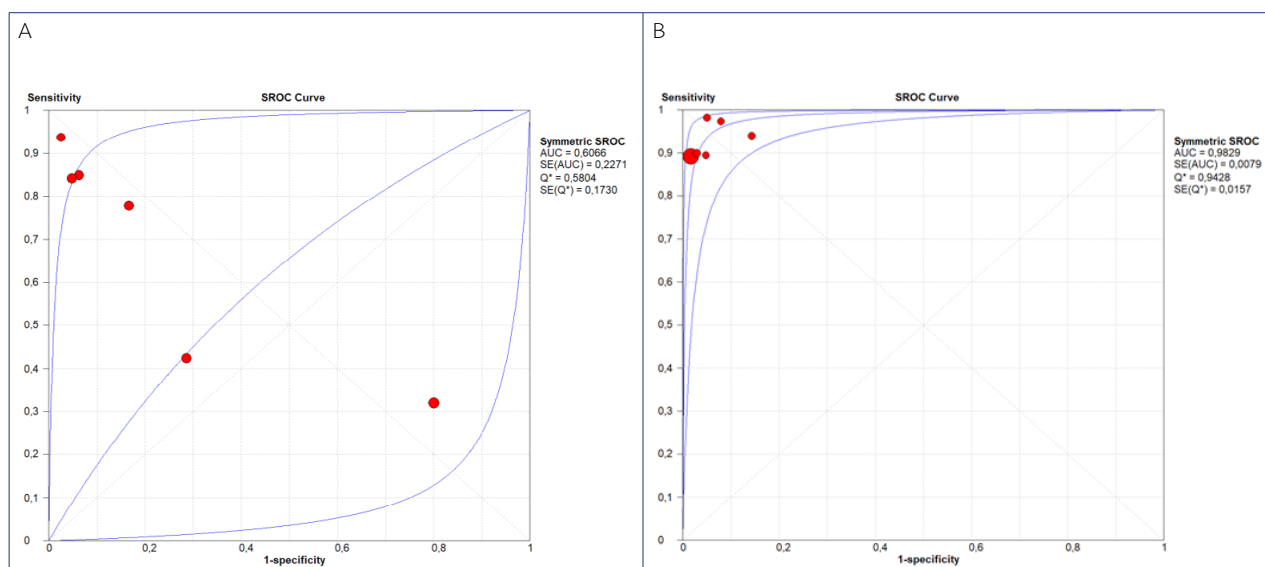
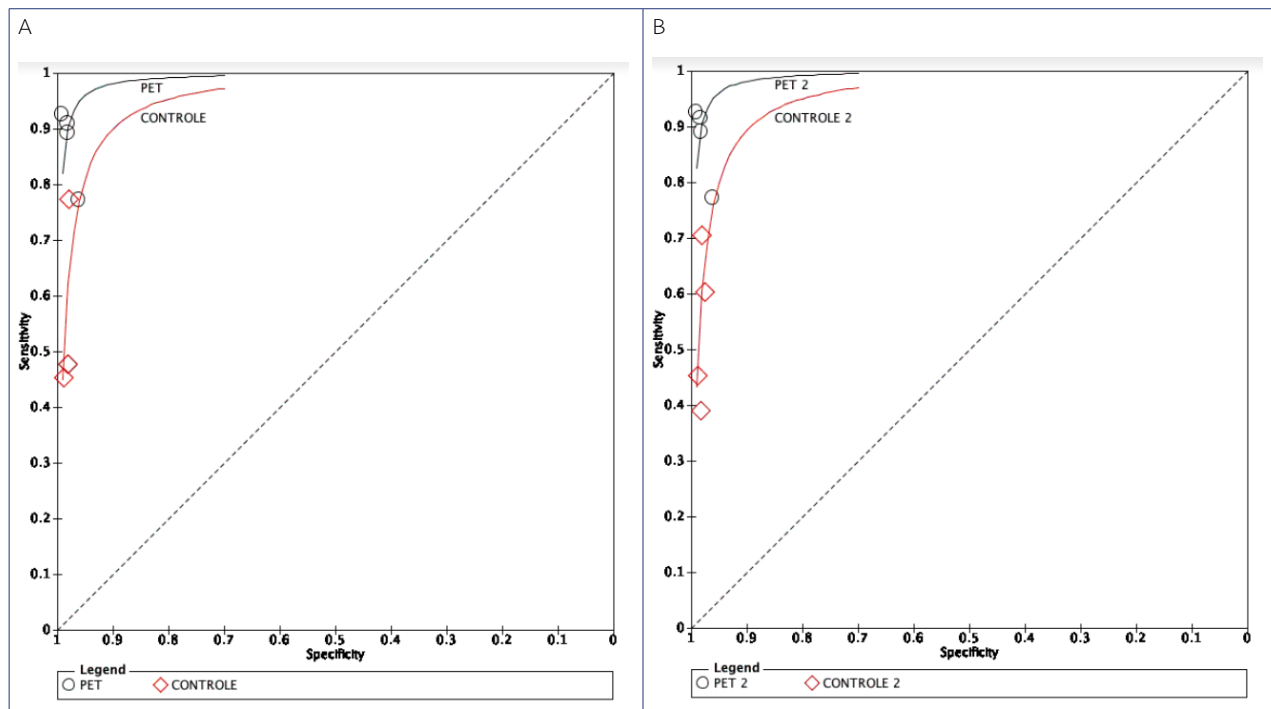


FIGURE 4: FDG-PET SHOWED SUPERIOR PERFORMANCE WITH A LARGER AREA UNDER THE CURVE FOR DETECTING METASTATIC LESIONS IN RELATION TO THE CONTROL GROUP.



in several types of solid tumors. In addition, international guidelines recommend the preferential use of PET/CT in relation to CT from stage II for searching for distant lesions ³(D).

RECOMMENDATION

FDG-PET is indicated in the staging and restaging of cervical cancer since it is superior to conventional

methods of imaging (CT and MRI) for detecting neoplastic lymph nodes in staging, local recurrence, and search for metastatic lesions (staging and relapse).

In our country, virtually all PET equipment is PET/CT, i.e., superior to PET equipment.

Considering these data, it is imperative to include the ¹⁸F-FDG PET/CT as a diagnostic tool for the Brazilian population with cervical cancer in the indications described above.

ANNEX I**Clinical Question**

Is ¹⁸F-FDG PET/CT indicated in the staging and restaging of cervical cancer?

Structured question

P	patient with cervical cancer
I	PET/CT-FDG or FDG-PET
C	conventional diagnostic methods (CT, MRI)
O	staging/restaging/recurrence

[P (Patient); I (Intervention or Exposure); C (Comparison); O (Outcome)]

Eligibility criteria

Our initial proposal was to assess only studies on ¹⁸F-FDG PET/CT since it is already well documented in the literature that PET/CT presents enormous superiority in establishing the anatomical location of lesions and consequently better diagnostic accuracy compared to PET⁴. However, to our surprise, no studies were found on PET/CT that fit our inclusion criteria for searching for distant metastases. Thus, studies on ¹⁸F-FDG PET (FDG-PET) were also included in the analysis.

The reasons for exclusion were: data that included other types of cancer associated with cervical cancer, such as ovary or endometrium, papers with PET/MRI or that used PET radiotracers other than FDG, studies that evaluated only the prognostic role of PET or the therapeutic response.

We included studies of staging, restaging, or detection of recurrence in patients with cervical cancer.

We included prospective and retrospective diagnostic studies.

The exclusion criteria were case reports and studies on animals.

No restriction of language or time was applied. In addition, other primary articles were included after reading other reviews and meta-analyses.

Search for papers

Databases

The scientific database consulted was Medline (via PubMed) and manual search.

Research strategy

- (Neoplasms Uterus OR Neoplasm Uterus OR Neoplasms Uterine OR Neoplasm Uterine OR Cancer Uterus OR Uterus Cancers OR Uterine Cancer OR Cancers Uterine OR uterine

neoplasms OR uterine neoplasm OR Cervical Neoplasms OR Cervical Neoplasm OR Cervix Neoplasms OR Cervical Cancer OR Cervical Cancers OR Cervix Neoplasm OR Cervix Cancer OR cervix cancers) AND (Positron Emission Tomography OR PET) AND (FDG OR fluorodeoxyglucose OR fludeoxyglucose).

- Manual search - Reference of references, reviews, and guidelines.

Critical evaluation

Relevance - clinical importance

This guideline was prepared by means of a clinically relevant question in order to gather information in medicine to standardize approaches and assist in decision-making.

Reliability - Internal validity

The search for scientific evidence followed these steps: determining the clinical questions, structuring the questions, searching for evidence, critical evaluation and selection of evidence, presenting the results and recommendations.

The selection of the studies and the evaluation of the titles and abstracts obtained from the search strategy in the databases consulted were independently and blindly conducted, in total accordance with the inclusion and exclusion criteria. Finally, studies with potential relevance were separated. When the title and the summary were not enlightening, we sought for the full article. Only studies with texts available in its entirety were considered for critical evaluation.

The research was carried out by two nuclear medicine physicians, and in the event of a discrepancy, a third nuclear physician was consulted.

Method of extraction and analysis of results**Data Analysis**

A meta-analysis of the outcomes related to the use of FDG-PET in the staging and restaging of cervical cancer patients was performed. When the same paper had more than one outcome, it was included in both.

The studies included were classified using QUADAS-2⁵ for determining the risk of bias.

Metadisc and RevMan 5.3 were used to analyze the data. The ROC curves were calculated and compared with the control to determine the best diagnosis method.

Results

In the search conducted in MEDLINE (Pubmed) in April 2018, we recovered 1,335 articles, which were selected based on the title (100), summary (81), and full text (47) by two nuclear medicine physicians. In addition, 4 articles were added after reading systematic reviews on the subject. Thus, 51 articles were included in this selection. Then, a few studies were excluded because they did not have the necessary values for a meta-analysis of the results. In the end, 17 studies were meta-analyzed (Figure 1).

The characteristics of the bias evaluation of the studies using QUADAS-2 are described in Table 1 (Annex II). The evaluation includes the criteria used for selecting patients, the type of test used, the gold standard, and the interval between the test and the gold standard. Of the 17 studies included, there was a high risk of bias in patient selection in 1 study (6%), high risk of bias in interpretation of PET/CT in 10 studies (59%), and high risk of bias in the conduct or interpretation of the gold standard in 13 studies (76%). The reasons for exclusion were: data that included other types of cancer associated with cervical cancer, such as ovary or endometrium, papers with PET/MRI or that used other PET radiotracers other than FDG, studies that evaluated only the prognostic role of PET or the therapeutic response.

After the systematic review, it was possible to me-

ta-analyze and evaluate the outcomes of detection in the following situations: detection of lymph node metastases to the staging, detection of local recurrence, and evaluation of distant metastases.

Application of evidence - Recommendation

The recommendations were designed by the review authors with the initial characteristic of the synthesis of evidence and were submitted to validation by all authors who participated in the creation of the guidelines.

The global synthesis was elaborated considering the evidence described.

Conflict of interest

There is no conflict of interest related to this review that can be declared by any of the authors.

Final declaration

The Guidelines Project, an initiative of the Brazilian Medical Association in partnership with the Specialty Societies, aims to reconcile medical information in order to standardize approaches that can aid the physician's reasoning and decision-making process. The information contained in this project must be submitted to the evaluation and criticism of the physician, responsible for the conduct to be followed, given the reality and clinical condition of each patient.

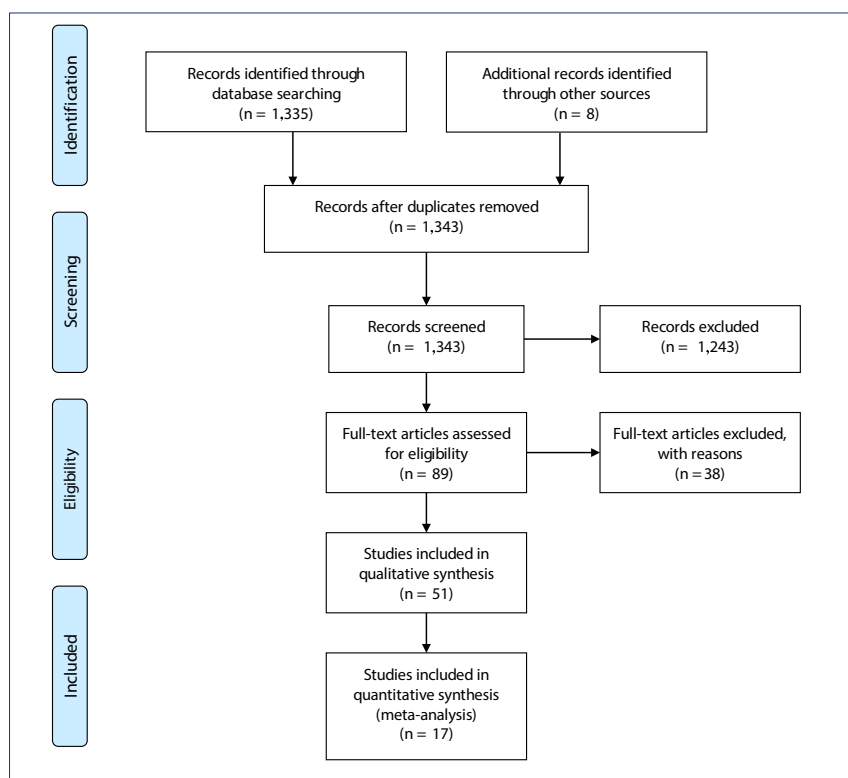


FIGURE 1: PRISMA FLOWCHART OF THE STUDIES EVALUATED

ANNEX II

TABLE 1: TABLE OF BIASES OF THE STUDIES INCLUDED.

Author/Year	Patient selection			Test (PET or PET/CT)			Gold Standard			
	Questions			Risk of bias	Questions		Risk of bias	Questions		Risk of bias
	Were the patients consecutive or random?	Was case-control avoided?	Were unnecessary exclusions avoided?	Did the selection of patients introduce a bias?	Was the PET interpreted without the knowledge of the outcome of the gold standard?	If a threshold was used, was it predetermined?	Is it possible that the interpretation of the PET introduced a bias?	Did the gold standard supposedly correctly classify the presence/absence of the disease?	Was the gold standard conducted/interpreted without knowledge of the PET results?	Is it possible that the conduct or interpretation of the gold standard introduced a bias?
Lv 2014 ⁶	Y	Y	Y	N	Y	Y	N	Y	NA	N
Kitajima2014 ⁷	Y	Y	Y	N	NA	Y	N	Y	NA	N
Perezmedina2013 ⁸	Y	Y	Y	N	Y	N	Y	Y	Y	N
Monteil2011 ⁹	Y	Y	Y	N	NA	N	N	Y	N	Y
Park2005 ¹⁰	Y	Y	Y	N	NA	Y	Y	Y	NA	Y
Ma2003 ¹¹	Y	Y	Y	N	Y	Y	Y	Y	NA	Y
Reinhardt2001 ¹²	Y	Y	Y	N	Y	Y	Y	Y	NA	Y
Choi2006 ¹³	Y	Y	Y	N	NA	N	N	Y	NA	Y
Chou2010 ¹⁴	Y	Y	Y	N	Y	Y	N	Y	NA	Y
Yen2003 ¹⁵	Y	Y	Y	N	Y	Y	Y	Y	NA	Y
Belhocine 2002 ¹⁶	N	Y	Y	Y	Y	N	Y	N	Y	Y
Bjurberg2013 ¹⁷	Y	Y	Y	N	Y	N	N	N	N	Y
Pallardy2010 ¹⁸	Y	Y	Y	N	Y	N	Y	Y	N	Y
Lin2006 ¹⁹	Y	Y	Y	N	Y	Y	N	Y	NA	N
Yen2004 ²³	Y	Y	Y	N	NA	Y	Y	Y	NA	Y
Lai2004 ²¹	Y	Y	Y	N	Y	Y	Y	Y	NA	Y
Park2000 ²²	Y	Y	Y	N	Y	Y	Y	Y	NA	Y

Legend: Y: yes; N: No; NA: not available.

TABLE 2: GENERAL CHARACTERISTICS OF THE STUDIES INCLUDED FOR FDG-PET IN COMPARISON WITH CT/MRI FOR DETECTING LYMPH NODES.

Author/Year	Disease	Population (N)	Test (T)	Gold Standard (P)	Comparison	Time interval (T→P)
Lv 2014 ⁶	Stage	87	PET/CT	Anatomopathological	MRI	2 weeks
Kitajima2014 ⁷	Stage	30	PET/CT	Clinical and anatomopathological follow-up	MRI	20 days
Perezmedina2013 ⁸	Staging	52	PET/CT	Anatomopathological	MRI	NA
Monteil2011 ⁹	Staging	40	PET/CT	Anatomopathological	MRI	NA
Park2005 ¹⁰	Staging	36	PET	Anatomopathological	MRI	7 days
Ma2003 ¹¹	Staging	104	PET	Clinical and anatomopathological follow-up	CT or MRI	1 week
Reinhardt2001 ¹²	Staging	35	PET	Anatomopathological	MRI	1 week
Choi2006 ¹³	Staging	22	PET/CT	Anatomopathological	MRI	7 days
Chou2010 ¹⁴	Staging	83	PET/CT	Anatomopathological	MRI	1 week
Yen2003 ¹⁵	Staging	41	PET	Clinical and anatomopathological follow-up	MRI	1 week
Belhocine2002 ¹⁶	Staging	22	PET	Anatomopathological	Conventional Imaging (CT and MRI)	-

TABLE 3: GENERAL CHARACTERISTICS OF THE STUDIES INCLUDED FOR PET IN COMPARISON WITH CT/MRI FOR DETECTING LOCAL RECURRENCE.

Author/Year	Disease	Population (N)	Test (T)	Gold Standard (P)	Comparison	Time interval (T→P)
Bjurberg2013 ¹⁷	Suspected recurrence	36	PET/CT	Clinical and anatomopathological follow-up	Conventional Imaging (CT and MRI)	-
Pallardy2010 ¹⁸	Suspected recurrence	40	PET/CT	Clinical and anatomopathological follow-up	Conventional Imaging (CT and MRI)	-
Lin2006 ¹⁹	Suspected recurrence	26	PET	Anatomopathological and follow-up	CT and MRI	2 weeks
Yen2004 ²³	Suspected recurrence	55	PET	Follow-up	CT or MRI	2 weeks
Lai2004 ²¹	Suspected recurrence	40	PET	Anatomopathological	CT or MRI	2 weeks
Park2000 ²²	Suspected recurrence	36	PET	Clinical and anatomopathological follow-up	CT	-

TABLE 4: GENERAL CHARACTERISTICS OF THE STUDIES INCLUDED FOR PET IN COMPARISON WITH CT/MRI FOR METASTATIC LESIONS.

Author/Year	Disease	Population (N)	Test (T)	Gold Standard (P)	Comparison	Time interval (T→P)
Lin2006 ¹⁹	Suspected recurrence	26	PET	Anatomopathological and follow-up	CT and MRI	2 weeks
Yen2004 ²³	Suspected recurrence	55	PET	Follow-up	CT or MRI	2 weeks
Lai2004 ²¹	Suspected recurrence	40	PET	Anatomopathological	CT or MRI	2 weeks
Yen2003 ¹⁵	Staging	41	PET	Clinical and anatomopathological follow-up	MRI	1 week

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Erratum

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