PET Six-Month Monitoring Report 2024-2

Evidence from Primary Studies and Meta-analyses
July to December 2024

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QUESTION

What is the role of positron emission tomography (PET) in the clinical management of patients with cancer, non-cardiac sarcoidosis, epilepsy, or dementia, fever or inflammation of unknown origin (FUO), infection, cardiac ischemia, and metastases of unknown primary with respect to:

- Diagnosis and staging
- Assessment of treatment response
- Detection and restaging of recurrence
- Evaluation of metastasis

Outcomes of interest are:

- Change in clinical management or patient outcome (e.g., survival, quality of life, prognostic indicators, time until recurrence) or safety outcome (e.g., avoidance of unnecessary surgery).
- Diagnostic parameters (e.g., sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], accuracy)

INTRODUCTION

In 2010, the Ontario PET Steering Committee (the Committee) requested that the Program in Evidence-Based Care (PEBC) provide regular updates to the Committee of recently published literature reporting on the use of PET in patients with cancer, sarcoidosis, epilepsy, or dementia. The PEBC recommended implementing a regular monitoring program, with a systematic review of recent evidence conducted every six months. The Committee approved this proposal, and this is the 28th issue of the six-month monitoring reports. This report is intended to be a high-level summary of the identified evidence, and not a detailed evaluation of its quality and relevance.

METHODS

General methods involve a comprehensive literature search, screening and data extraction. Expert opinion on the new evidence with regards to current indications to PET guidance are also documented. The detailed protocol for PET Six-Month Monitoring Reports, Version 2 is available upon request. A short summary is detailed here.

Eligibility Criteria:

- Study **populations** of patients with any type of cancer (including cancer of unknown primary) or with non-cancers that included: dementia, non-cardiac ischemia, epilepsy, fever of unknown origin, infection, and sarcoidosis were eligible. Both adults (≥18 years) and paediatric populations (< 18 years) were eligible. Excluded populations were those that evaluated participants with health conditions other than those listed here.

- Studies **interventions** included those that evaluated the use of PET/CT or PET/MRI used with radiopharmaceuticals that are currently approved by Health Canada and the Food and Drug Administration (FDA) of the United States (see Appendix 1, Table 1); dual tracer PET/CT/MRI were also eligible. Studies of PET/CT/MRI-directed strategies (e.g., PET used to select patients' subgroups for whom therapy can be escalated or de-escalated) were included. Excluded studies were those with interventions that evaluated radiopharmaceuticals that are currently not approved for clinical use and considered experimental and those that evaluated radiomics (i.e., artificial intelligence computations).

- Studies **comparators** included were those with a suitable reference standard (i.e. histopathologic or clinical imaging follow-up (e.g., MRI or CT alone). In studies of Dementia, fluid biomarkers are an appropriate reference standard: the most used fluid biomarkers include: 1) Amyloid-beta (Aß) peptides (ratio of Aß42 to Aß40 reflects amyloid plaque pathology); 2) Total tau (t-tau) (indicates the extent of neuronal damage and degeneration); 3) Phosphorylated tau (p-tau) (p-tau181 and p-tau231 are markers of tau pathology associated with Alzheimer's Disease); 4) Neurofilament light (NFL) (a marker of neurodegeneration). Excluded studies were those without a comparator/ suitable reference standard or prognostic studies without a PET comparator.

- Studies that reported on **outcomes** listed above (i.e., diagnostic accuracy parameters or changes in patient management) or outcome (staging or survival) or harms (prevented unnecessary surgery) related to the use of the PET/CT/MRI scans.

- Study **designs** included prospective studies retrospective studies with two groups. Systematic reviews/meta-analyses, narrative reviews, scoping reviews, prognostic

studies, validation and proof of concept studies, case studies, editorials/commentaries, conference abstracts, practice guidelines, and economic studies were excluded.

- Studies with **sample sizes** less than 10 participants were excluded.

Search strategy:

Publications from July 1 to December 31, 2024 were screened for eligibility. Appendix 1, Table 2 shows the search strategy for OVID MEDLINE.

Screening and Data Extraction

Studies were screened in Endnote (Version 24. Clarivate 2024) at title and abstract and full text. Eliglible studies had information about the author, country, purpose of the study, population, sample size, type of PET/CT/MRI, radionuclide, reference standard, and outcomes of interest were extracted. A summary of the evidence is in Appendix 2, Table 1 where studies are organised by the type of health condition and in alphabetical order.

RESULTS

Literature Search Results

Primary Studies

Ninety-three studies published between June and December 2024 met the inclusion criteria. An evidence table that provides a summary of the evidence across the different health conditions from the 93 studies can be found in Appendix 2: Table 1: Summary of studies from June to December 2024.

Breast Cancer

Six studies met the inclusion criteria [1-6]. Two were prospective cohort studies [2,5], and the other four were retrospective trials. One prospective study [2] reported on change in management and diagnostic outcomes, and the others reported on diagnostic outcomes.

The study by Jannusch et al. [2] showed that PET/magnetic resonance imaging (MRI) had better diagnostic properties than conventional imaging; however, major changes in therapeutic management occurred only in 2% of the patients. Therefore, the authors concluded that PET/MRI may be more useful in selecting high-risk cases rather than as a routine procedure for all patients.

Ulaner et al. [5] found no statistically significant difference when comparing 16α-^{18}F-fluoro-17β-estradiol (FES) PET/computed tomography (^{18}F-FES PET/CT) with standard imaging (i.e., CT+ bone scan or ^{18}fluorine-fluorodeoxyglucose [^{18}F-FDG] PET/CT) in 124 women with estrogen receptor (ER)-positive locally advanced breast cancer.

Shin et al. [4] compared ^{18}F-FES PET/CT with standard imaging (i.e., mammography, breast ultrasound, chest/abdomen/pelvis CT, bone scintigraphy, regional MRI, or ^{18}F-FDG PET/CT in 162 patients with ER-positive breast cancer with recurrence or metastases. ^{18}F-FES PET/CT was highly accurate, and statistically significantly superior to the conventional imaging in the per region analysis.

Alshaibani et al. 2024 [1] compared the diagnostic accuracy of MRI and PET/CT in predicting treatment response to neoadjuvant chemotherapy in 138 patients with locally advanced or human epidermal growth factor receptor-2 (HER2) breast cancer. PET/CT had significantly higher sensitivity (93.8% vs. 26.2%, p=0.001) and lower specificity (68.5% vs. 90.4%, p=0.001) than MRI; the accuracy for predicting pathologic complete response (pCR) was 95.2% in the PET versus 71.4% in the MRI datasets. The authors concluded that PET/CT can be used early on to identify those patients that will have a complete pathological response.

Usmani et al. [6] evaluated the diagnostic accuracy of ^{18}F-FDG PET/CT in 135 patients with invasive lobular carcinoma of the breast. PET/CT showed a low sensitivity (33.33%) in detecting sclerotic bone metastases. The authors suggest alternative imaging modalities for this population.

Ozsoy et al. [3] tested the diagnostic performance of ^{18}F-FDG PET/CT in 44 women with invasive breast cancer to detect axillary lymph node metastases compared with sentinel lymph node biopsy (SLNB). SLNB had a better sensitivity (86.36% vs. 54.5%), NPV (87.5% vs. 68.5%) and overall accuracy (90.91% vs. 77.27%) than PET/CT. PET imaging had perfect specificity, but its sensitivity was significantly lower, indicating that it misses more true positive cases.

Cardiac Ischemia

No studies met the inclusion criteria

Cancer of Unknown Primary

Two, relatively large, studies met the inclusion criteria [7,8]. Both studies focused on patients with extra-cervical metastases. One was a cross-sectional study [7], and the other a retrospective cohort trial [8]. Droste et al. 2024 [8] evaluated the impact of integrating PET with CT for biopsies in patients with bone lesions of unknown origin. These authors found that the rate of conclusive biopsies significantly increased with the integration of PET (Appendix 2: Table 1). Sivakumaran et al 2024 [8] evaluated the diagnostic utility of adding PET for the detection of the primary site and the impact of the use of PET on treatment decisions, and they compared overall survival (OS) of patients with and without a detected primary site. Although the sensitivity of PET was 60%, when PET was used to identify the primary site median OS was statistically significant longer (i.e., 19.8 months) when the primary site was detected versus when it was not (i.e., 8.5 months, p=0.016).

Dementia

One large retrospective, longitudinal cohort study [9,10] investigated the diagnostic and prognostic value of brain ^{18}F-FDG PET for the risk of dementia conversion and the risk of occurrence of a neurodegenerative pathology in patients with cognitive complaints. The sensitivity of PET for detecting the risk of conversion to dementia and the diagnosis of a neurodegenerative pathology was high (Appendix 2: Table 1), and the authors concluded that PET can effectively predict conversion to dementia and neurodegenerative pathology if used early in the diagnostic work-up.

Epilepsy

No studies were found during this interval.

Esophageal Cancer

Two small retrospective studies met the inclusion criteria [11,12]. Ge et al. 2024 [11] analyzed four dynamic PET/CT parameters: metabolic rate of FDG (MRFDG), maximum volume of distribution (DVmax), lesion/background ratio of MRFDG (LBR-MRFDG), and lesion/background ratio of DVmax (LBR-DVmax). LBR-MRFDG had the highest diagnostic performance in both cancer types with the area under the curve (AUC) greater than 0.92 and sensitivities greater than 90%. All four parameters (only LBR-MRFDG is shown in Table 1) had statistically significant differences between recurrence and inflammation groups ($p<0.05$). These results support the use of dynamic PET/CT imaging, especially LBR-MRFDG, for differentiating recurrent tumours from inflammatory lesions after surgery. Sun et al. 2024 [12] compared the diagnostic performance of dual-energy CT with ^{18}F-FDG PET/CT individually and in combination for detecting lymph node metastases in patients with esophageal squamous cell

carcinoma. The authors concluded that the combined strategy had the best diagnostic performance and recommended it for preoperative staging and for guiding therapeutic strategies.

Fever of Unknown Origin (FUO)

Three studies [13-15] were identified for PET in FUO. A large retrospective cohort study [13] evaluated the diagnostic properties of ^{18}F-FDG PET/CT in patients with FUO. The underlying cause of FUO was identified by PET in 49% of cases. PET had a sensitivity of 72%, a low specificity of 29%, and a high rate of false positives. Nonetheless, the authors support the use of PET, particularly when conventional imaging is inconclusive.

A large ambispective study [14] (all the data about clinical details and history, physical examination, laboratory investigations and imaging modalities were collected retrospectively and prospectively) evaluated the potential role of ^{18}F-FDG PET/CT for early diagnosis of the etiology of FUO and for guiding investigations in the diagnostic process. A final diagnosis was reached in 219 of 573 patients (38%) and categorized into malignant, infectious, inflammatory non-infectious. The site of biopsy was guided by PET imaging for 104 patients to facilitate a quick diagnosis. PET/CT was able to guide physicians in directing the site of a biopsy in 36 of 104 patients (34.6%).

A small retrospective study [15] aimed to determine which group of patients with FOU would benefit most from the use of PET compared with standard imaging. FDG PET/CT was particularly helpful in older patients with markers of inflammation of unknown origin, and the authors recommended it early in the work-up of these patients. Results are reported in Table 1.

Gastrointestinal Cancer

Six studies met the inclusion criteria [16-21]; three retrospective studies included patients with colorectal cancer [16,19,21]; a retrospective study examined patients with anal squamous cell carcinoma [17]; a prospective study examined patients with liver cancer [18] and a retrospective study included patients with locally advanced rectal cancer [20].

Colorectal cancer

In a large retrospective cohort of patients with colorectal cancer, Engel et al. [16] compared the diagnostic properties of ^{18}F-FDG PET/CT with those of CT in staging lymph node involvement and distant metastases and evaluated the impact of PET on OS and cost. PET/CT provided added diagnostic value across colon and rectal cancer subgroups and showed a trend toward improved survival, though not statistically significant after adjusting for age. While PET/CT incurs higher upfront costs, its superior accuracy may reduce unnecessary treatments and improve staging precision, especially relevant in the context of evolving neoadjuvant therapies. These findings support considering PET/CT as a valuable adjunct in colorectal cancer staging.

Mihailovic et al. [19] evaluated the diagnostic properties of ^{18}F-FDG PET/CT in detecting recurrent colorectal cancer compared with standard imaging and reported the changes in management due to PET. ^{18}F-FDG FDG PET/CT demonstrated high diagnostic accuracy and sensitivity for detecting recurrent colorectal cancer, outperforming conventional imaging and tumour markers. It significantly influenced patient management and the authors suggested that it should be considered for routine surveillance in patients with elevated tumour markers.

Zhang et al. [21], in a small retrospective study, compared the diagnostic performance of ^{18}F-fibroblast-activation protein inhibitors (FAPI)-42 PET/CT and ^{18}F-FDG PET/CT in patients with colorectal cancer and synchronous or metachronous peritoneal metastases. ^{18}F-FAPI-42

PET/CT offered superior diagnostic accuracy for peritoneal metastases in colorectal cancer, especially in regions with high physiological FDG uptake.

Anal squamous cell carcinoma

A very small retrospective study by Horvat et al. [17] compared baseline staging of ^{18}F-FDG PET/CT and other imaging strategies and the resultant impact on radiation plans. Despite differences in T-category classification, treatment plans were largely consistent across modalities.

Liver cancer

In a small prospective study of patients with liver cancer, Liang et al. [18] compared the diagnostic performance of ^{18}F-FAPI-04 PET/CT and ^{18}F-FDG PET/CT in evaluating liver cancer lesions. ^{18}F-FAPI-04 showed higher sensitivity and greater impact on clinical management than ^{18}F-FDG PET/CT.

Rectal cancer

Zhang et al. [20] in a very small prospective study evaluated and compared the diagnostic properties and the effectiveness of three imaging modalities (i.e., ^{68}Ga Ga-FAPI-04 PET/MRI, ^{18}F-FDG PET/CT, contrast-enhanced MRI) in predicting pCR in treatment-naïve patients who had histologically confirmed T3–4N0M0 or T1–4N1M0 rectal adenocarcinoma after neoadjuvant short-course radiotherapy combined with immune-chemotherapy. The authors concluded that ^{68}Ga Ga-FAPI-04 PET/MRI demonstrated a strong potential for predicting pCR.

Genitourinary Cancer

Twenty-five studies met the inclusion criteria [22-46]. Twenty-four focused on prostate cancer and one on bladder cancer [34].

Bladder cancer

In the single bladder cancer study, patients (n=199) underwent radical cystectomy and pelvic node dissection [34]. However, the scan used was ^{18}F-FDG) PET/CT for lymph node assessment before radical cystectomy and pelvic node dissection. The outcomes of this study focused on comparing per-patient and per-region analyses of diagnostic accuracy and showed high specificity for both PET and standard CT scan with very similar estimates. Sensitivity was very low in both PET and CT scan for both per-patient and per-region estimates.

Prostate cancer

Five from 24 studies had a prospective, non-randomized design [30,31,38,39,45], and one was a post-hoc subgroup analysis of a Phase II randomized controlled trial [32]. The remaining studies were of a retrospective design. The prospective studies had sample sizes <100 patients, except for Wong et al. 2024 [45], which included 236 patients. The retrospective trials had sample sizes that varied from to 30 [28] to 1337 [26].

All but three studies (that evaluated suspected prostate cancer [44-46]) included patients with intermediate- to high-risk prostate cancer disease either before or after treatment evaluating for presence of metastases or recurrence. One study evaluated participants with very low prostate-specific antigen (PSA) (0.5 ng/mL after radical prostatectomy [30].

The type of PET/CT used most often in the prostate cancer studies included [^{68}Ga] prostate-specific membrane antigen (PSMA) PET/CT (n=16 studies) and the remaining studies used variants of ^{18}F PSMA PET/CT. In the bladder cancer study the ^{18}F-FDG PET/CT was used. [34]. From 24 studies, eight focused on outcomes of changes in: 1) survival [22,26,31-33,37,39];

2) staging [22,29,30]; 3) treatment management [22,27]; and 4) treatment response [39]. No study evaluated potential for changes in harms. All other studies focused on diagnostic accuracy outcomes.

Gynecologic Cancer

Four studies met the inclusion criteria [48-50]. Two studies were prospective in design [47,48] and another had a historical cohort compared to a prospective group [49]. Sample sizes were all less than 100 participants and varied from 62 to 95 patients. Two studies were conducted in China [47],[49], one in Serbia [50] and one in Australia [48].

Clinical populations evaluated with PET scan included three studies with ovarian cancer: 1) advanced ovarian cancer [47,48]; 2) ovarian cancer in populations after neoadjuvant chemotherapy to detect recurrence [49]; and 3) a single study evaluating newly diagnosed epithelial cervical cancer for preoperative staging [50].

All studies used ^{18}F-FDG PET/CT with one study reported using gated scanning for the ^{18}F FDG radionuclide [48], and the comparators included MRI or enhanced CT [47-49] and intraoperative examination [50].

All four studies included some diagnostic performance analyses but only one study evaluated changes in staging and management [48]. Virili et al., 2024 [48] evaluated advanced epithelial cancer and showed that PET scans results changed International Federation of Gynaecology and Obstetrics stages where 46% were upstaged (from stages III and IV) and 8% down staged; conventional CT provisionally staged patients as 33% stage IV at baseline. Specifically, there were improvements in detecting thoracic and extra-abdominal metastases. However, little difference occurred with respect to changes in treatment management.

With respect to diagnostic accuracy the relative improvement of PET/CT showed mixed results. In one study evaluating participants with advanced ovarian cancer, the combination of PET/CT, MRI and contrast-enhanced CT had the highest ability to detect recurrent metastatic lesions relative to each type of imaging modality in isolation (which had similar accuracy overall) [47]. Similarly, in a population of newly advanced ovarian cancer, PET/CT scan showed improved ability to detect major organs in the trunk resulting in 46% restaging but no important change in treatment [48]. In contrast, another study attempting to detect residual disease after neoadjuvant chemotherapy in patients with ovarian cancer showed that PET/CT had no additional benefit relative to contrast-enhanced CT [49].

Head and Neck Cancer and Cancer of Unknown Primary

Sixteen studies met the inclusion criteria for head and neck cancers studies using PET. Of these, six were prospective [51-56] and sample sizes varied from 33 [52] to 132 participants [53]. There were nine retrospective studies [57-66] and samples sizes varied from 20 [55] to 908 participants [62].

The populations were classified as head and neck cancers (type not specified) (n=5) [54,57,60,62,64]; brain tumours (n=4) [52,55,58,59]; nasopharyngeal carcinoma (n=2) [56,61]; oropharyngeal or hypopharyngeal squamous cell carcinoma (n=1) [65]; sinonasal squamous cell carcinoma (n=1) [63]; oral cavity squamous cell carcinoma (n=1) [51]; thyroid nodules [53]; and thyroid cancer [66].

The majority of studies (n=9) used ^{18}F-FDG-PET CT [51-53,57,60,62-65]. The remaining studies used ^{18}F F-DOPA PET/CT [59,66]; ^{18}F-F-DOPA PET/MRI [59]; ^{18}F fluoroethyl)-L-tyrosine (FET) PET/MRI [55]; ^{18}F-NaF PET/CT [56,61]; or an unspecified PET/CT [54]. The reference standard in these studies was always histopathology or clinical follow-up.

Six studies [51,55,59,62,64,65] evaluated changes in staging or treatment or survival and the remaining studies focused primarily on diagnostic accuracy.

Hematologic Cancer

Five studies met the inclusion criteria; one was prospective study [67] and one exceeded 100 participants. [68] Two studies evaluated diffuse large B-cell lymphoma [68,69]; another two evaluated general lymphoma during the process of early staging [67,70]; and one study evaluated Hodgkin lymphoma compared to non-Hodgkin lymphoma [71].

All five studies use the ^{18}F-FDG PET/CT and compared this to reference standards of bone marrow biopsy or other histopathology.

Two studies reported on change in staging [71] or change in survival [69]; the remaining three studies focused on diagnostic accuracy [67,68,70].

Infection and Inflammation

Five studies met the inclusion criteria [72-76] Of these, a single study used a prospective design [76] and the rest were retrospective. All studies had less than 100 participants. The populations within the study were varied and included: 1) diverse clinical population of inpatients with suspected infection not defined by stringent fever of unknown origin (FUO) criteria [72]; 2) immune checkpoint inhibitor-induced hypophysitis in patients with metastatic melanoma [73]; 3) monitor treatment responses in necrotizing otitis externa [74]; 4) infections related to cardiac implantable electronic devices [75]; and 5) diagnosis and pathological classification of hepatic echinococcosis, specifically distinguishing between hepatic cystic echinococcosis and hepatic alveolar echinococcosis [76].

All studies used ^{18}F-FDG PET/CT except one study [73] that used unspecified FDG PET/CT. The comparators were context specific to the infection or clinical condition (see Evidence Table 1 in Appendix 2).

Two studies [75,76] focused only on diagnostic performance and the remaining studies considered results focusing on changes in treatment [72], changes in classification [73], and changes in recovery [74].

Lung/Thoracic Cancer

Twelve studies met the inclusion criteria. [77-88] Of these, four studies [79,83,84,88] were prospective in design and the remaining eight studies were retrospective. For the prospective studies, sample sizes varied from 41 to 172 participants and the retrospective studies varied from 19 to 4264 participants.

Of six studies specifying the type of lung cancer, five evaluated non-small cell lung cancer (NSCLC) [77,79,84-86] and one evaluated small cell lung cancer.[80]

Four studies focused on lung cancer (all types), with one evaluating patients' before and after biopsy [81], after major surgery [88], in stage IV only [87] and in stage T1 only [78]. There were only two studies that did not focus exclusively on lung cancer and this included a study evaluating patients with cardiac tumours or suspected pericardiac masses study that included participants with NSCLC [82] and another study evaluating confirmed mesothelioma [83].

All but three studies (n=9) used only ^{18}F-FDG PET/CT; these three studies used ^{68}Ga-FAPI-46 PET/CT compared to ^{18}F-FDG PET/CT [83], only ^{18}F-FAPI-42 PET/CT [86], and only ^{68}Ga Ga-FAPI-46 PET/CT [88]. The reference standard was always histology in all but two studies that did not report a reference standard [80,84].

Seven studies reported on diagnostic accuracy outcomes [77] [81-83,85,87,88] Five studies [77-79,81,84] evaluated changes in survival; additionally, four studies evaluated changes in harm [80,81,84,87] and two studies evaluated changes in management. [79,87]

Melanoma

A single study was eligible for this update [89]. Gideonse et al., 2024 [89] evaluated patients with high-risk melanoma who had undergone radical resection (stage III and IV) and

were also treated with adjuvant immune checkpoint inhibitors. Participants were recruited from the Danish Metastatic Melanoma Database. The accuracy of ^{18}FDG-PET-CT to diagnose immune-related adverse events showed differences in metrics between the different body organs presenting both high sensitivity (except for skin and heart) and high specificity estimates.

Neuro-oncology cancer

There were no studies found for neuro-oncological cancers during this interval.

Pancreatic Cancer

One study met the inclusion criteria [90] and conducted a retrospective analysis of 43 participants to evaluate the value of ^{68}Ga-DOTATATE PET/CT in the diagnosis and localization of insulinomas, whether sporadic, malignant or MEN-1-associated insulinoma. The focus of the result was on reporting diagnostic accuracy overall, with benign sporadic insulinomas, malignant insulinomas, and MEN-1 syndrome-associated insulinomas. Sensitivities and specificities varied among these three different clinical groups. The authors suggested it may be best suited as an adjunct test when imaging studies fail to localize a tumour in patients with insulinoma.

Other Cancers

Two studies were placed into this category of "other cancers" [91,92]. One study [91] was a prospective study with 273 patients with bone metastases and the study sought to evaluate the accuracy of PET relative to CT for guiding bone biopsy. In addition, the study considered changes in accuracy with the combination of maximum standardized uptake value (SUVmax) with serum alkaline phosphatase levels. The second study [92] was a retrospective analysis of 192 patients (330 lesions) in the liver (both benign and malignant) and sought to explore how accuracy was affected by attributes of PET or patient characteristics with respect to liver metastases. The focus of both these studies was on diagnostic accuracy.

Pediatric Cancer

A single study [93] was found for pediatric cancers and PET use. This single-centre retrospective study evaluated whether ^{18}F-FDG-PET/CT assessment at interim and end-of-treatment timepoints reduced unnecessary exposure to radiotherapy compared to conventional CT in pediatric Hodgkin lymphoma. Change in treatment and survival were the outcomes of interest and showed some advantages in preventing unnecessary treatment.

Sarcoidosis

There were no studies evaluating sarcoidosis during this search interval.

Sarcoma

One study [94] met the inclusion criteria. This study was a sub-study from a larger prospective trial (COMBINAIR3 trial [NCT03011528]); however, there were only 42 participants in this sub-study. The population was histologically confirmed as very-high-risk (primary extra-pulmonary metastases) Ewing sarcoma and the age range was wide (from 6 to 47 years). The type of scan used was ^{18}F-FDG PET/CT and this was compared to bone marrow aspiration and biopsy. Assessment of diagnostic accuracy suggested improved detection of bone metastases and high specificity (100%). There were no changes to treatment or survival reported.

CLINICAL EXPERT REVIEW

Breast Cancer

Current Indications for Breast Cancer

Locally advanced invasive ductal breast cancer

- PET for the staging of patients with histologically confirmed clinical stage 2b or stage 3 breast cancer being considered for curative intent combined modality treatment; and/or repeat PET on completion of neoadjuvant therapy, prior to surgery (when there is clinical suspicion of progression)
- PET for re-staging of patients with locoregional recurrence, after primary treatment, being considered for ablative or salvage therapy.

Oligometastatic invasive ductal breast cancer

- PET for staging or re-staging of patients with oligometastatic disease (four or fewer metastases) on conventional imaging prior to radical intent or ablative therapy.

Reviewer's Comments – Dr. Muriel Brackstone

Current recommendations based on the PET-ABC Trial have been implemented, utilizing PET as a diagnostic staging modality in patients with stage IIB-III breast cancer prior to neoadjuvant therapy, if progression is suspected following neoadjuvant treatment prior to surgery, or upon locoregional recurrence. The publications identified over the past six-month period have not provided any relevant data to recommend a change to these current guidelines.

A prospective cohort study (Jannusch et al., 2024) [2] demonstrated that while PET/CT increased the diagnostic accuracy, it resulted very minimal clinical change in treatment plans. Another (Ozsoy et al, 2024) evaluated the role of PET/CT in predicting residual nodal disease after neoadjuvant systemic therapy and found that surgery (sentinel node biopsy) remains a more accurate axillary staging procedure, similar to the prior PET/PREDICT trial.

Retrospective data from one study [1] have been used in an attempt to evaluate whether PET/CT accurately predicts complete pathological response to neoadjuvant systemic therapy , finding that the sensitivity is higher with PET/CT than conventional imaging, but given that there is no clinical implication of this finding and that there was no significant difference in PPV along with the lower level of evidence of this retrospective study, there is insufficient evidence to recommend any change in guidelines.

Three other retrospective studies (Shin et al, 2024; Ulaner et al, 2024; Usmani et al, 2024) confirmed existing randomized data demonstrating that PET/CT had a higher sensitivity in detecting distant metastases than conventional imaging. Usmani et al. did highlight however that this may be more limited in specific circumstances, such as invasive lobular cancer metastases to bone. While it is helpful to understand that there may be specific circumstances within the current Stage IIB-III patients for whom PET/CT may be less sensitive at diagnostic staging, there are currently insufficient data to restrict its use in any patient subset.

In summary, there are insufficient new published data to recommend any change to current guidelines in regard to the use of PET/CT for diagnostic staging or repeat staging of patients with Stage IIB/III breast cancer, or in cases of locoregional recurrence.

Epilepsy

Current Indications for Epilepsy

- PET for patients with medically intractable epilepsy being assessed for epilepsy surgery.

Reviewer's Comments Dr. Jorge Burneo

No epilepsy studies were found for this interval.

Esophageal Cancer

Current Indications for Esophageal Cancer or Gastroesophageal Junction cancer

- PET for baseline staging assessment of those patients diagnosed with esophageal/ gastroesophageal junction cancer being considered for curative therapy and/or repeat PET/CT scan on completion of pre-operative/neoadjuvant therapy, prior to surgery **OR**
- For re-staging of patients with locoregional recurrence, after primary treatment, being considered for definitive salvage therapy.

Reviewer's Comments - Dr. Rebecca Wong

This evidence suggests that the specific type of PET/CT and quantitative metric (dynamic PET, and dual-energy CT with PET/CT) may be better in diagnosing anastomotic recurrence and nodal staging, respectively.

As such, I do not think it changes the recommendations. It maybe worthwhile asking the PET Steering Committee whether there is sufficient evidence form this type of literature to suggest that MRFDG) and LBR metrics should at some point be included in the routine reporting of esophageal cancer PETs.

Fever of Unknown Origin

Current indications for FUO

Currently, Ontario Health's PET Scans Ontario Indications List does not explicitly include FUO as a funded indication for PET scans. However, there are several related conditions under the Cardiology category that may overlap with clinical scenarios involving FUO, such as:

- Infective endocarditis/graft infection: PET is indicated when there is high clinical suspicion or laboratory evidence of infection, especially with suspected extra-cardiac complications such as septic emboli.
- Device infections: For suspected infections of cardiac devices (e.g., pacemakers, implantable cardioverter defibrillators).
- Myocarditis and pericarditis: When there are persistent or recurrent symptoms despite treatment.
- Vasculitis/aortitis: For suspected large-vessel vasculitis or polymyalgia rheumatica with elevated inflammatory markers.
- Other cardiovascular infection or inflammatory processes: Includes systemic inflammatory conditions with compelling evidence.

If a patient with FUO has clinical features suggestive of one of these conditions, a PET scan may be considered under the Cardiac Special Access Program, which allows for case-by-case evaluation when standard criteria are not met.

For patients who do not meet listed criteria but may benefit from PET, referring physicians can apply through the PET Access Program.

Reviewer's Comments – Dr. Amit Singnurkar

No action required at this point. We will bank this information as we plan to do a more formal and comprehensive evaluation with the PET Steering Committee in the near future.

Gastrointestinal Cancer

Current Indications for Colorectal Cancer (apparent limited metastatic):

- PET for the staging or re-staging of patients with apparent limited metastatic disease (for example, organ-restricted liver or lung metastases) or limited local recurrence, who are being considered for radical intent therapy.
- As chemotherapy may affect the sensitivity of the PET scan, it is strongly recommended to schedule PET at least six weeks after last chemotherapy, if possible.

Current Indications for Colorectal Cancer (Recurrent)

- PET where recurrent disease is suspected on the basis of an elevated and/or rising carcinoembryonic antigen level(s) during follow-up after surgical resection, but standard imaging tests are negative or equivocal.

Current Indication for Anal Canal Cancer (staging or re-staging):

- PET for the initial staging of patients with stages II to IV squamous cell carcinoma of the anal canal or when conventional imaging is equivocal for a specific stage: or for re-staging of patients with limited recurrence, after primary treatment, being considered for definitive salvage therapy.

Reviewer's Comments - Dr. Aamer Mahmud

This report is well-written, and I found a few interesting results. I do not see a good reason to suggest changing the current CCO guideline regarding indications at this time.

Genitourinary Cancer

Current Indication for Bladder Cancer (muscle invasive):

- PET for the staging of patients with newly diagnosed muscle-invasive urothelial carcinoma of the bladder being considered for curative intent treatment with either radical cystectomy or radiation-based bladder preservation therapy; TNM stage T2a-T4a, N0-3, M0.

Current Indications for Germ Cell Tumours (recurrent/ persistent disease)

- PET where recurrent disease is suspected on the basis of elevated tumour marker(s) - (beta human chorionic gonadotrophin and/or alpha fetoprotein) and standard imaging tests are negative, OR
- Where persistent disease is suspected on the basis of the presence of a residual mass after primary treatment for seminoma when curative surgical resection is being considered.

Current Indications for Prostate Cancer (PSMA PET)

- Prostate-specific membrane antigen (PSMA) PET for initial staging of patients with a new diagnosis of high-risk prostate cancer being considered for radical (curative) therapy **OR**
- Staging of patients with recurrent prostate cancer who fall into one of the following pre-defined cohorts:
    - Post-prostatectomy node-positive disease or persistently detectable PSA
    - Biochemical failure post-prostatectomy

- Biochemical failure following radical prostatectomy followed by adjuvant or salvage radiotherapy
- Rising PSA post-prostatectomy despite salvage hormone therapy
- Biochemical failure following treatment for oligometastatic disease
- Biochemical failure following primary radiotherapy
- Rising PSA and/or progression on conventional imaging despite prior second line hormone therapy or chemotherapy for castrate-resistant prostate cancer

Reviewer's Comments - Dr. Glenn Bauman

Based on this literature, the only change I might suggest is extending the indication for primary stage PSMA PET/CT to include high intermediate/unfavourable intermediate risk patients (see Ettema et al. 2024 [26] and Evangelista et al. 2024 [27] in particular). No other changes.

Gynecologic Cancer

Current Indications for Cervical Cancer (staging)

- PET for the staging of locally advanced cervical cancer when:
  - CT/MRI shows positive or indeterminate pelvic nodes (greater than 7 mm and/or suspicious morphology) **OR**
  - CT/MRI shows borderline or suspicious para-aortic **OR**
  - CT/MRI shows suspicious or indeterminate distant metastases (for example, chest nodules)

Current Indication for Gynecologic Malignancies (recurrent, prior to salvage therapy)

- PET for re-staging of patients with recurrent gynecologic malignancies under consideration for radical salvage surgery (for example, pelvic exenteration)

Reviewer's Comments - Dr. Ji-Hyung Jang

The most recent literature review suggests, given the higher sensitivity and specificity of PET over standard CT, that consideration can be had for PET playing a role in patients with advanced-stage ovarian cancer with ambiguous CT findings that may change management.

This may be somewhat vague, but in situations where CT is not clear and for example consideration is between upfront surgery versus neoadjuvant chemotherapy, PET might help delineate the better management option for the patient.

Head and Neck Cancer and Unknown Primary

Current indication for Head and Neck Cancer

- PET for the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiologic and clinical investigation.
  ***Note*:** A pan endoscopy is not required prior to the PET scan.

Nasopharyngeal (baseline staging)

- PET for the staging of nasopharyngeal cancer.
  Note: *for cervical esophageal cancer, see Gastrointestinal Cancers*

Head & Neck Node Positive (baseline staging)

- PET for the baseline staging of node positive (N1-N3) H&N cancer where PET will impact radiation therapy (e.g., radiation volume or dose).

Head & Neck (re-staging after chemoradiotherapy)

- PET to assess patients with N1-N3 metastatic squamous-cell carcinoma of the head and neck after chemoradiation (human papillomavirus [HPV] negative); or who have residual neck nodes ≥1.5 cm on re-staging CT performed 10-12 weeks post therapy (HPV positive).

Thyroid (recurrent)

- PET where recurrent or persistent disease is suspected on the basis of elevated and/or rising tumour markers (e.g., thyroglobulin) with negative or equivocal conventional imaging work-up.

Anaplastic Thyroid (staging)

- PET for the staging of histologically proven anaplastic thyroid cancer with negative or equivocal conventional imaging work-up.

Medullary Thyroid (staging & recurrent)

- PET for the baseline staging of histologically proven medullary thyroid cancer being considered for curative intent therapy or where recurrent disease is suspected on the basis of elevated and/or rising tumour markers (e.g., calcitonin) with negative or equivocal conventional imaging work-up.

Reviewer's Comments – Dr. Amit Singnurkar

No change in indications resulting from this review. We have a PEBC evidence summary on PET imaging in gliomas [95]. The evidence for this tracer is intensifying with better studies being published and a commercial tracer in the USA. Please continue to monitor for studies with this tracer and it may be time to revisit and update this PEBC-related publication.

Hematologic Cancer

Current Indications for Lymphoma

- Staging: PET for the baseline staging of patients with Hodgkin or non-Hodgkin lymphoma.
- Interim response assessment for Hodgkin lymphoma: PET for the assessment of response in Hodgkin lymphoma following two or three cycles of chemotherapy when curative therapy is being considered.
- Interim response assessment for non-Hodgkin lymphoma (pediatric patients only, younger than 18 years; or 18 to 20 years old and treated at a pediatric centre): PET for the assessment of response in non-Hodgkin lymphoma after a minimum of two cycles of chemotherapy when curative therapy is being considered.
- End of therapy response assessment:
    - PET for the evaluation of residual mass(es) or lesion(s) (for example, bone) following chemotherapy in a patient with Hodgkin or non-Hodgkin lymphoma when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered; **or**
    - PET to assess response to chimeric antigen receptor T-cell therapy, 90 days post transfusion.

Current Indications for Multiple Myeloma or Plasmacytoma

- To evaluate the impact of PET on the management of patients with plasmacytoma or myeloma for the following indications:

- Solitary plasmacytoma: For patients with presumed solitary plasmacytoma, who are candidates for curative intent radiotherapy (to determine whether solitary or multifocal/extensive disease).
- Smoldering myeloma: Work-up of patients with smoldering myeloma (to determine whether smoldering or active myeloma)
- Non-secretory myeloma, oligo-secretory myeloma, or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes): Baseline staging and response assessment
- Newly diagnosed secretory multiple myeloma: Work-up of patients with newly diagnosed secretory multiple myeloma.

Reviewer's Comments - Dr. Jill Dudebout

There are no recommended changes to our current indications for PET in lymphoma.

Melanoma

Current Indications for Melanoma

- PET for the staging of patients with localized "high-risk" melanoma or Merkel cell carcinoma, or for the evaluation of patients with isolated melanoma metastases when surgery or other ablative therapies are being considered.

Metastatic Melanoma (Immunotherapy)

- Baseline staging: PET for the staging of patients before starting immunotherapy; or for patients receiving immunotherapy and have not previously had a baseline PET
- Early response assessment: PET after two to four cycles of immunotherapy for early response assessment of patients with metastatic melanoma or Merkel cell carcinoma currently receiving immunotherapy
- Response assessment: PET for response assessment of patients with Merkel cell carcinoma (only) after a specified number of immunotherapy cycles
- End of therapy response assessment: PET for response assessment of patients with metastatic melanoma or Merkel cell carcinoma at end of immunotherapy

Reviewer's Comments - Dr. Nicole Look Hong

I reviewed the included study and while interesting, I do not think that this would change any of our current indications for PET/CT in melanoma.

Pancreatic Cancer

- No indication currently exists for the utilization of PET/CT in pancreatic cancer.

Reviewer's Comments – Dr. Derek Jonker

No expert reviewed the evidence at this time.

Pediatric Cancer

Current Indications for pediatric cancer (patients must be <18 years of age)

Pediatric Registry Indications (data collection/partnership with the Pediatric Oncology Group of Ontario):

- For the following cancer types (ICCC – International Classification of Childhood Cancer):
  - Bone/cartilage – osteosarcoma, Ewing sarcoma
  - Connective/other soft tissue – rhabdomyosarcoma, other
  - Kidney – renal tumour

    - Liver – hepatic tumour
    - Lymphoma/PTLD – **See Hematological Oncology Section**
    - Primary brain – astrocytoma, medulloblastoma, ependymoma, other
    - Reproductive – germ cell tumour
    - Sympathetic nervous system – neuroblastoma MIBG negative
    - Other – LCH, melanoma of the skin, thyroid
- For the following indications:
    - Initial staging
    - Monitoring response during treatment or determine response-based therapy
    - Rule out progression prior to further therapy
    - Suspected recurrence or relapse
    - Rule out persistent disease
    - Select optimal biopsy site

Reviewer's Comments - Dr. Amer Shammas

No need to change the current indication for pediatric PET at this point. Although the included study is interesting, interim and end-of-treatment PET has already been approved for pediatric Hodgkin lymphoma.

Sarcoma

Current Indications for Sarcoma:

- PET for the initial staging of patients with histologically confirmed high-grade (≥ Grade 2), or ungradable, soft tissue or bone sarcomas, when conventional work-up is negative or equivocal for metastatic disease, prior to curative intent therapy, **OR**
- For re-staging of patients with suspicion of, or histologically confirmed, recurrent sarcoma (local recurrence of limited metastatic disease) when radical salvage therapy is being considered.

Current Indication for Plexiform Neurofibromas:

- PET for patients with suspicion of malignant transformation of plexiform neurofibromas.

Reviewer's Comments - Dr. Gina Di Primio

I think it is a well written and well-performed study. Though the study number is small I think it supports the use of PET/CT for sarcoma staging in Ewing sarcoma. All studies will be small in this specific study group given that Ewing sarcomas are rare. I would support including this in the Evidence-Based Summary report for imaging.

Thoracic Cancer

Lung – Non-small Cell Lung Cancer (clinical stage I-III)

- PET for initial staging of patients with NSCLC (Clinical Stage I – III) being considered for potentially curative therapy; OR for re-staging of patients with locoregional recurrence, after primary treatment, being considered for definitive salvage therapy.

Note: Histological proof is not required prior to PET if there is high clinical suspicion for NSCLC (e.g., based on patient history and/or prior imaging)

Note: PET is appropriate for patients with either histological proof of locoregional recurrence or strong clinical and radiological suspicion of recurrence who are being considered for definitive salvage therapy

Lung – Small Cell Lung Cancer (clinical stage I-III)

- PET for initial staging of patients with limited-disease small cell lung cancer where combined modality therapy with chemotherapy and radiotherapy is being considered.

Lung – Solitary Pulmonary Nodule

- PET for a **semi-solid or solid** lung nodule for which a diagnosis could not be established by a needle biopsy due to unsuccessful attempted needle biopsy; the solitary pulmonary nodule is inaccessible to needle biopsy; or the existence of a contra-indication to the use of needle biopsy

Lung – Mesothelioma

- PET for the staging of patients with histologic confirmation of malignant mesothelioma.

Reviewer's Comments - Dr. Donna Maziak

Overall, none of the studies will change the current indications. PET scan before CT-guided biopsy is already being done as this greatly increases the yield to ensure that the biopsy is in a PET-avid area, especially in big tumours. The one thing that we do need to look on the horizon is with increasing use of neoadjuvant chemotherapy and immunotherapy that restaging following induction may prove to be better with PET scan rather than CT scan of the chest and upper abdomen. In Canada, this is limited because of issues with access in a timely fashion.

We will have to look for more studies using ^{68}GA–FAPI46 PET/CT scan versus the usual ^{18}F-FDG PET/CT scan in mesothelioma. This may be a potential change in the future.

Another potential change would be the use of ^{18}F–FAPI PET scan versus the usual ^{18}F-FDG PET/CT scan for detecting mediastinal lymph nodes and non-small cell lung cancer. However, based on all the studies the current indications for a PET/CT scan do not need to be altered.

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Appendix 1: Elements of the Protocol for Monitoring Report 2 2024

Table 1: Radiotracers and theranostics that are approved (Health Canada or FDA). As of November 25, 2024*

Approved Radiotracer Name	New Generation of Tracers - NOTES	Target Cancer Type
18F-FDOPA	Experimentation is ongoing: newer generations are: 18-fluoro-D-DOPA (not yet approved) 18F-4-FDF (not yet approved)	Neuroendocrine tumours tracer (neuro-oncology), neuropsychiatric diseases, certain cancers
18F-FET PET ([18F]fluoroethyl)-L-tyrosine)	Other amino acid based radiotracers (18F-FDOPA and 18F-FACBC (fluciclovine)	Brain Cancer
18F-florbetaben		Dementia ß-amyloid tracer
18F-florbetapir		Dementia ß-amyloid tracer
18F-flortaucipir		Dementia Tau Tracer
18F-FLT ([18F]3-deoxy-3F-fluorothymidine)		Various Types of Cancer (tumor cell proliferation tracer)
18F-sodium fluoride/18F-NaF	[18F]triflyl fluoride	Bone-seeking tracer
18F-flurpiridaz		Cardiac tracer (myocardial perfusion (MPI) imaging tracer)
18F-fluoroestradiol (18F-FES) CT/PET		Breast cancer - *Note: This is not experimental any longer although it does not appear in the Health Canada website. It has been FDA approved in 2020, not yet approved in Canada though. It needs to be monitored.*
223RaCl2	Approved in 2019 by Health Canada, and in 2013 by FDA	Treatment for castration-resistant prostate cancer (mCRPC)
177Lu-iPSMA	Approved by both Health Canada and FDA in 2022	
68Ga-PSMA /18F-DCFPyL / 18F-PSMA 1007	68Ga-NeoB (this is a theranostic)	Prostate Cancer - prostate-specific membrane antigen 18F-PSMA 1007 is not approved yet but it will receive Health Canada authorization in the near future
68Ga-SSA (68Ga-DOTA-SSA) PET/CT	68Ga-DOTANOC	Neuroendocrine tumours Not approved yet, needs to be monitored - has longer half-life
	68Ga-DOTATOC	
	68Ga-DOTATATE	
	64-Cu radiolabeled tracers (DOTATATE PET/CT)	
	18F-SiTATE (a SiFAlin tagged [Tyr3]-octreotate (TATE) PET tracer)	

Approved Radiotracer Name	New Generation of Tracers - NOTES	Target Cancer Type
68Ga-FAPI	68Ga-FAPI-04	Fibroblast activation protein (FAP)-expressing tumors
	68Ga-FAPI-46	
	18F-FAPI-42	Various cancers
	18F-FAPI-74	Various cancers
	18F-FAPI-74	Various cancers

*NOTE: Most of the radiopharmaceuticals listed as approved may NOT be approved for clinical use; however, they may have been approved for clinical trials. There are other radiopharmaceuticals that belong to this category, and they are not listed here because we never encountered them in this current search.

Appendix 1: Elements of the Protocol for Monitoring Report 2 2024

Table 2: Example Search Strategy from OVID MEDLINE (March 10 2025)

1.	exp Positron-Emission Tomography/ or (Positron Emission Tomography or PET or PET Scan or PET Scans or PET imaging or Positron Emission Tomography Scan).tw. or (PET adj2 FDG).tw. or (PET adj CT).tw. or PET$CT.tw.
2.	exp Neoplasms/ or exp neoplasms by site/ or Neoplasm Staging/ or Neoplasm Grading/ or Neoplasm Metastasis/ or Neoplasm Recurrence, Local/ or (cancer$ or tumor$ or tumour$ or carcinoma$ or neoplasm$ or staging or metastas$ or metastatic or neoplastic process$ or malignan$ or lesion$ or mass$ or lump$ or nodule$ or adenocarcinoma$).tw. or neoplasms, second primary/ or neoplastic processes/ or anaplasia/ or carcinogenesis/ or neoplasm invasiveness/ or exp neoplasm metastasis/ or extranodal extension/ or lymphatic metastasis/ or neoplasm micrometastasis/ or neoplasm seeding/ or neoplasms, unknown primary/ or neoplastic cells, circulating/ or neoplasm regression, spontaneous/ or neoplasm, residual/ or neoplastic syndromes, hereditary/ or exp neoplasms, multiple primary/ or Infections/ or infection$.tw. or Bacterial infections/ or virus diseases/ or waterborne diseases/ or wound infection/ or zoonoses/ or Mycoses/ or Parasitic Diseases/ or exp myocardial ischemia/ or coronary artery disease/ or coronary occlusion/ or coronary stenosis/ or coronary thrombosis/ or coronary vasospasm/ or exp myocardial infarction/ or acute coronary syndrome/ or angina pectoris/ or coronary disease/ or cardiac ischemia.tw. or heart ischemia.tw. or coronary ischemia.tw. or (ischemic adj2 heart).tw. or (myocardial adj2 ischemia).tw. or angina pectoris.tw.
3.	exp Sarcoma/ or myosarcoma/ or exp soft tissue neoplasms/ or rhabdomyosarcoma/ or angiosarcoma.tw. or hemangiosarcoma.tw. or haemangiosarcoma.tw. or lymphangiosarcoma/ or stewart-treves syndrome.tw. or hemangiopericytoma/ or hemangiopericytoma.tw. or cystosarcoma.tw. or malignant phylloides tumor.tw. or dermatofibrosarcoma/ or fibrosarcoma/ or gastrointestinal stromal tumor/ or GIST.tw. or leiomyosarcoma/ or liposarcoma/ or histiocytoma, malignant fibrous/ or MFH.tw. or malignant peripheral nerve sheath tumor.tw. or MPNST.tw. or myxosarcoma/ or neurofibrosarcoma/ or malignant synovioma.tw. or adamantinoma/ or neuroectodermal tumors, primitive/ or PNET.tw. or neurosarcoma.tw. or exp chondrosarcoma/ or Mesenchymoma/ or osteoclastoma.tw. or osteosarcoma/ or exp giant cell tumors/ or chordoma/ or dermatofibrosarcoma protuberans.tw. or DFSP.tw. or giant cell fibroblastoma.tw. or mixed tumor, mullerian/ or endometrial stromal tumors/ or carcinosarcoma/ or adenosarcoma/ or oligosarcoma.tw. or mixed tumor, mesodermal/ or MMMT.tw.
4.	exp Epilepsy/ or exp Seizures/ or (epileptic or seizure disorder or epilepsy$ or convulsions).tw.
5.	exp Dementia/ or (dementia$ or Alzheimer's or cognitive impairment or memory loss).tw.
6.	Fever of Unknown Origin/ or ((pyrexia or fever or inflammation) adj2 unknown origin).tw. or (FUO or PUO or unexplained fever).tw.
7.	((exp hematologic neoplasms/ or Leukemia/ or (Leuk*mia$ or blood cancer$ or hematologic malingnac$ or acute leuk*mia or chronic leuk*mia or AML or CLL or CML).tw. or Lymphoma/ or Lymphoma$.mp.) adj2 (Hodgkin or Non-Hodgkin or B-cell l or T-cell or Burkitt or Mantle cell or Follicular or Diffuse large B-cell or Anaplastic large cell or Cutaneous T-cell or Primary central nervous system).tw.) or Multiple myeloma/ or (Multiple Myeloma or Plasma Cell Myeloma or Myelomatosis or Kahler's Disease or Waldenstrom Macroglobulinemia or Waldenstrom's Disease or Lymphoplasmacytic Lymphoma).tw. or exp Myelodysplastic

	Syndromes/ or (Myelodysplastic Syndromes or Refractory Anemia or Refractory Cytopenia or Ring Sideroblasts or Excess Blasts or Chronic Myelomonocytic Leukemia).tw. or Splenic Neoplasms/
8.	exp breast neoplasms/ or "hereditary breast and ovarian cancer syndrome"/ or Breast carcinoma In Situ/ or Carcinoma, Ductal, Breast/ or Carcinoma, Lobular/ or Inflammatory Breast Neoplasms/ or Triple Negative Breast Neoplasms/ or (Breast Cancer$ or Breast Tum*r$ or Breast Carcinoma$ or (Mammary adj2 (Tum*r$ or Carcinoma$ or Cancer$)) or ((Ductal or Lobular) adj2 Carcinoma$) or (Triple Negative adj2 Breast Cancer$) or (Inflammatory adj2 Breast Cancer$)).tw.
9.	exp melanoma/ or Hutchinson's Melanotic Freckle/ or Melanoma, Amelanotic/ or Melanoma, Cutaneous Malignant/ or Carcinoma, Merkel Cell/ or (melanotic adj2 freckle$).tw. or melanoma$.tw. or (cutaneous adj2 melanoma$).tw. or (maligna$ adj2 lentigo).tw. or exp skin neoplasms/ or basal cell nevus syndrome/ or dysplastic nevus syndrome/
10.	(((Non-Small Cell Lung or Small Cell Lung or Recurrent Lung) adj2 Cancer) or (NSCLC or SCLC)).tw. or lung neoplasms/ or "adenocarcinoma of lung"/ or adenocarcinoma, bronchiolo-alveolar/ or bronchial neoplasms/ or carcinoma, bronchogenic/ or carcinoma, non-small-cell lung/ or small cell lung carcinoma/ or mesothelioma, malignant/ or multiple pulmonary nodules/ or pancoast syndrome/ or pulmonary blastoma/ or pulmonary sclerosing hemangioma/ or exp thoracic neoplasms/
11.	(Gastrointestinal tum*r$ or gastrointestinal neoplasm$ or GI tum*r$ or Esophageal squamous cell carcinoma or gastrointestinal stromal tum*r$ or GIST$ or ((Gastric or colon or Rectal or Esophageal or Stomach or pancreatic or colorectal or small intestine) adj2 (cancer$ or tum*r$ or carcinoma or adenocarcinoma or neoplasm$))).tw. or exp abdominal neoplasms/ or anal gland neoplasms/ or exp digestive system neoplasms/ or exp biliary tract neoplasms/ or gastrointestinal neoplasms/ or exp esophageal neoplasms/ or intestinal neoplasms/ or exp cecal neoplasms/ or exp colorectal neoplasms/ or duodenal neoplasms/ or ileal neoplasms/ or jejunal neoplasms/ or stomach neoplasms/ or exp liver neoplasms/ or exp pancreatic neoplasms/ or peritoneal neoplasms/ or exp adenomatous polyposis coli/ or peutz-jeghers syndrome/
12.	(exp urogenital neoplasms/ or Genital neoplasms, Male/ or (Prostat$ or bladder or urothelial or kidney or renal or penile or testicular).tw.) adj2 (cancer or tum*r$ or carcinoma or adenocarcinoma or neoplasm$).tw.
13.	pelvic neoplasms/ or Genital neoplasms, Female/ or ((ovarian or cervical or endometrial or uterine or vulvar or vaginal or fallopian tube$) adj2 (cancer or tum*r)).tw.
14.	exp eye neoplasms/ or exp "head and neck neoplasms"/ or ((squamous cell or nasopharyngeal) adj2 carcinoma).tw. or ((oral cavity or oropharyngeal or laryngeal or hypopharyngeal or salivary gland or thyroid or parathyroid or brain) adj2 (cancer or tum?r)).tw. or (Glioma$ or meningioma$ or brain metastas*s or primary central nervous system lymphoma).tw.
15.	exp Wilms tumour/ or Neuroblastoma/ or (Medulloblastoma$ or Langerhans Cell Histiocytosis or LCH or neuroblastoma).tw.
16.	exp bone neoplasms/ or exp nervous system neoplasms/ or hamartoma syndrome, multiple/ or exp multiple endocrine neoplasia/ or tuberous sclerosis/ or birt-hogg-dube syndrome/ or Colorectal Neoplasms, Hereditary Nonpolyposis/ or exostoses, multiple hereditary/ or li-fraumeni syndrome/ or exp neurofibromatoses/ or pregnancy complications, neoplastic/ or exp trophoblastic neoplasms/ or histiocytosis, langerhans-cell/ or eosinophilic granuloma/ or exp endocrine gland neoplasms/ or ((Cancer$ or metastas$) adj2 unknown primary).tw. or (CUP or MOUP).tw.

17.	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18.	1 and 17
19.	limit 18 to (address or autobiography or bibliography or biography or case reports or clinical conference or comment or congress or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or editorial or "expression of concern" or festschrift or guideline or historical article or interactive tutorial or interview or lecture or legal case or legislation or letter or meta-analysis or news or newspaper article or observational study, veterinary or overall or patient education handout or periodical index or personal narrative or portrait or practice guideline or randomized controlled trial, veterinary or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or "systematic review" or validation study or video-audio media or webcast)
20.	Radiomics/ or Case reports/ or "proof of concept Study"/
21.	19 or 20
22.	18 not 21
23.	exp animal/ not (exp human/ or humans/)
24.	22 not 23
25.	limit 24 to dt=20240701-20241231
26.	limit 24 to rd=20240701-20241231
27.	25 or 26

Appendix 2: Table 1 is a summary of eligible studies from June to December 2024.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
Breast cancer								
Alshaibani et al, 2024 [1] Bahrain	Single center Retrospective cohort study **Objectives:** to compare the diagnostic accuracy of MRI and PET/CT in predicting treatment response to neoadjuvant chemotherapy in breast cancer patients.	138 patients with locally advanced breast cancer or HER2-positive, hormone receptor-negative cancers who underwent breast-conserving surgeries between June 2018 and December 2022 No patient demographics reported	^{18}F-FDG PET/CT	MRI	Histopathology	Sens: 93.8%* Spec: 68.5%* PPV: 72.6%** NPV: 92.6%* *p=0.001 **p=0.875	Sens: 26.2%* Spec: 90.4%* PPV: 70.8%** NPV: 57.9%* *p=0.001 **p=0.875	Using the prediction model, a confusion matrix was generated for the training data. The model indicated that the accuracy for predicting the pathologic complete response was 95.2% in PET vs. 71.4% in MRI datasets. **In summary:** PET/CT shows higher sensitivity and can serve as an early marker for predicting complete pathological response in post-neoadjuvant breast cancer patients. However, the prediction of residual disease is optimized by combining both MRI and PET/CT as diagnostic modalities.
Jannusch et al, 2024 [2] Germany	Double centre Prospective study **Objective**: To assess whether ^{18}F-FDG PET/MRI, in addition to guideline-recommended conventional staging, changes therapeutic management and improves diagnostic accuracy in newly	208 women with newly diagnosed, therapy-naïve breast cancer at high risk for distant metastases (tumour stage T2 or higher, triple-negative tumours, or tumours with high-risk molecular features like Ki-67 >14%, grade 3, or HER2 over expression)	^{18}F-FDG PET/MRI	Conventional staging (ultrasound, X-ray mammography, CT, bone scintigraphy)	Histopathology and clinical follow-up	UICC correct determination: 170/208 patients (81.9%; 95% CI: 75.8%–86.7% False positives: 1.4% (3 patients) (95% CI, 0.3%–4.2%)	UICC correct determination: 130/208 patients (62.5%; 95% CI: 55.5%–69.1%)	Major change in therapeutic management occurred in 5/208 patients (2.4%; 95% CI: 0.78%–5.2%) **In summary:** Although ^{18}F-FDG PET/MRI demonstrated superior diagnostic accuracy compared to conventional staging in determining the correct UICC stage in newly diagnosed breast cancer patients, its impact on therapeutic decision-making was minimal.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	diagnosed breast cancer patients.							
Ozsoy et al, 2024 [3] Turkey	Single centre Retrospective study **Objective:** To evaluate the diagnostic accuracy of FDG-PET/CT as a non-invasive technique and intraoperative SLNB in detecting axillary lymph node metastasis.	44 female patients with biopsy-proven invasive breast cancer Mean age (SD): 56.61 ± 13.03 (range: 28-84) years	^{18}F FDG PET/CT	Histopathology	Histopathology	Sens: 54.5% Spec: 100% PPV: 100% NPV: 68.75% Accu: 77.27%	Sens: 86.36% Spec: 95.45% PPV: 95.00% NPV: 87.50% Accu: 90.91%	NA **In summary:** SLNB was superior to PET in detecting axillary involvement. PET imaging may help in selecting patients for SLNB. PET imaging detected multifocal and multicentric tumours and provided staging insights, potentially influencing treatment planning.
Shin et al, 2024 [4] Korea	Single centre Retrospective **Objectives**: To evaluate the diagnostic accuracy of ^{18}F-FES PET/CT for detecting recurrence or de novo metastasis in ER-positive breast cancer. To assess diagnostic accuracy by clinical setting (recurrence vs. de novo metastasis) To identify causes of false-positive and false-negative results To compare per-region detection rates with standard-of-care imaging.	162 patients, of which 104 with suspected recurrence, and 58 with suspected de novo metastases Mean Age (range): 55 (46-61)	^{18}F-FES PET/CT	Mammography Breast ultrasound Chest/abdominopelvic CT Bone scintigraphy Regional MRI ^{18}F-FDG PET/CT (if indicated)	Histopathology (biopsy) in 19% of cases. Composite imaging follow-up (≥6 months) using ≥2 standard modalities (81% of cases)	Overall (n=162): Sens: 95% Spec: 89% PPV: 96% NPV: 87% Accu: 93% Recurrence group (n=104) Sens: 95% Spec: 96% PPV: 99% NPV: 85% De Novo Metastasis Group (n=58) Sens: 94% Spec: 82% PPV: 89% NPV: 90% Per region detection rate (n=1458 regions) 92% (95% CI: 89-94%)* *p<0.001	Per region detection rate Standard of care imaging: 83% (95% CI: 79-87%)*	NR **In summary** ^{18}F-FES PET/CT is a highly accurate, non-invasive imaging tool for evaluating suspected recurrence or de novo metastasis in ER-positive breast cancer. It offers superior detection of regional and distant lymph node involvement compared to standard imaging and provides critical information on ER status, which can guide endocrine therapy decisions. However, its limited sensitivity for liver metastases and potential for false positives in ER-expressing non-breast tumours should be considered. Integration of ^{18}F-FES PET/CT into diagnostic workflows is supported, especially when biopsy is not feasible or when ER status reassessment is clinically relevant.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
Ulaner et al, 2024 [5] USA	Single centre Prospective phase 2 non-randomized trial (NCT04883814) **Objectives**: To compare the detection rate of 16α-^{18}F-FES PET/CT with standard-of-care imaging for: Distant metastases in ER-positive LABC Recurrences in ER-positive breast cancer with suspected recurrence.	124 women Cohort 1: 62 with ER-positive LABC (stage IIB–IIIC) (median [IQR] age, 52 [32-84] years Cohort 2: 62 with ER-positive BC and suspected recurrence (median [IQR] age, 66 [30-93] years).	^{18}F-FES PET/CT	Either CT + bone scan or FDG PET/CT	Histopathology	Cohort 1 (LABC): Sens: 78.5% (11/14) Spec: 100% (0 false positives) Cohort 2 (Suspected recurrence): Sens: 78.2% (18/23) Spec: 97.7% (1 false positive)	Cohort 1: Sens: 85.7% (12/14) Spec: 93.5% (4 false positives) Cohort 2: Sens: 69.6% (16/23) Spec: 96.8% (2 false positives)	NA **In summary:** FES PET/CT demonstrated comparable sensitivity and higher specificity, with fewer false positives than standard imaging. However, no statistically significant difference was found overall.
Usmani et al, 2024 [6] Oman	Retrospective cross-sectional study **Objectives**: To evaluate the diagnostic accuracy of ^{18}F-FDG PET/CT in detecting bone metastases in patients with ILC of the breast.	135 patients with ILC of the breast From this 52 had PET scan for (a) routine primary staging, or (b) when clinical suspicion of bone metastases prompted new imaging workup (e.g., bone pain, elevated tumour marker, suspicious lesions on conventional radiological modality). From this 21 met eligibility criteria as the remaining 21 had missing	^{18}F-FDG PET/CT	CT MRI Bone scans (in follow-up)	Clinical and radiological follow-up (≥6 months)	Sens: 33.33% (2/6 true positives) Spec: 93.33% (14/15 true negatives) PPV: 66.67% NPV): 77.78% Accu: 76.19%	NA	NA **In summary:** The results showed low sensitivity (33.3%) but high specificity (93.3%), highlighting the limitations of FDG PET/CT in detecting sclerotic bone metastases, which are more common in ILC. The study suggests that alternative imaging modalities, such as ^{18}F-FES or ^{68}Ga-FAPI PET/CT, may offer improved detection in this patient population. These findings underscore the need for tailored imaging strategies in ILC and support further research into more effective molecular imaging techniques.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
		demographic or scan specific data. Mean age (SD): 53.85 ± 10.6; (range 38–74) years						
Cardiac ischemia								
No studies met the inclusion criteria								
Cancer of unknown primary								
Droste et al, 2024 [7] Netherlands	Single centre Cross-sectional study **Objectives:** **a) Evaluate the diagnostic value** of integrating ^{18}F-FDG PET/CT with conventional CT-guided bone biopsies. **b) Compare biopsy success rates** and diagnostic yield between patients who underwent PET/CT prior to biopsy and those who had CT alone. **c) Assess the impact** of PET/CT on reducing inconclusive biopsy results and the need for repeat procedures.	106 patients undergoing pathohistological-confirmed CT-guided bone biopsy (vertebral or peripheral bone) for metastases of unknown primary. Median age: 63 (range: 37–75) years % male PET group: 56% % male CT group: 60%	^{18}F-FDG-PET/CT	Morphological CT scan	Histopathology	NA	NA	There was a significant difference between the PET and CT groups with respect to the conclusiveness of the biopsy (92% vs 76%, p<0.05). The inconclusive rate in PET-guided biopsies compared with CT guidance alone decreased significantly (8% vs 24%, p < 0.05). The number of malignant histopathological confirmations significantly increased in the PET group vs. the CT group (69% vs. 36%), p < 0.001). The number of benign confirmations increased in the CT group (8% vs. 26%, p=0.03). **In summary:** This study evaluated the impact of integrating ^{18}F-FDG PET/CT with conventional CT-guided bone biopsies in patients with bone lesions of

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								uncertain origin. The authors found that PET/CT guidance significantly improved diagnostic accuracy, increasing the rate of conclusive biopsies from 76% to 92% and reducing inconclusive results by threefold. PET/CT was particularly beneficial in identifying metabolically active regions within heterogeneous or morphologically subtle lesions, thereby enhancing first-attempt biopsy success and reducing the need for repeat procedures. These findings support the use of PET/CT to augment biopsy planning, especially in complex oncologic cases.
Sivakumaran et al, 2024 [8] Australia	Single centre Retrospective **Objectives**: To evaluate the diagnostic utility of ^{18}F-FDG PET/CT in detecting the primary site in patients with extra cervical CUP. To assess the impact of PET/CT on treatment decisions. To compare OS between patients with and without a detected primary site.	147 patients with biopsy-proven CUP Mean age (range): 61 (20 to 84) years % male: 56%	^{18}F-FDG PET/CT	Standard diagnostic work-up: CT chest/abdomen/pelvis, ultrasound, MRI, bone scan, mammography Genomic profiling: Gene expression profiling and next-generation sequencing in 65% of patients	Histopathology, clinical follow-up, genomic analysis	Sens: 60% Spec: 34% Accu: 52% Detection rate: 41%	NR	Site-specific therapy based on combined data (PET/CT + clinical + genomic): Median OS: 19.8 months (vs. 8.5 months without primary site detection, p=0.016) Management Changes Due to PET/CT: Occult disease detection: 37% Change in treatment plan: 23% Overall median OS: 16.8 months Favourable CUP Subtype: 104.7 months Unfavourable CUP Subtype: 12.1 months **In summary:** ^{18}F-FDG PET/CT identified a potential primary site in 41% of cases and led to a change

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								in management in 23%. While diagnostic accuracy was modest, PET/CT provided valuable staging information and helped guide treatment decisions. Patients with a detected primary site—based on PET/CT, clinical, and genomic data—had significantly improved overall survival. The findings support the complementary role of PET/CT in CUP work-up, especially when integrated with genomic and clinical data.
Dementia								
Heyer et al, 2024 [9,10] France	Retrospective longitudinal cohort using real-world data (NCT04804722) **Objectives:** to estimate the value of brain ^{18}F-FDG PET for predicting the risk of dementia conversion and the risk of occurrence of a neurodegenerative pathology.	403 patients with cognitive complaints but no diagnosis of dementia at the time of recruitment referred by a tertiary memory clinic for brain ^{18}F-FDG PET Median age total sample (SD): 69.9 (11.4) years % male: 56%	^{18}F-FDG PET	NR The study evaluates the prognostic and diagnostic value of ^{18}F-FDG PET against: Clinical outcomes CFS biomarkers National health and Alzheimer's databases	For Dementia Conversion: Designation of long-term condition for dementia in the French National Health Data System Dementia diagnosis in the NAB For neurodegenerative disease: CSF biomarker profiles (A/T/N classification)	Conversion to Dementia (National Health Data System data): Sens: 83% Spec: 35% Acc: 47% PPV: 31% NPV: 85% Conversion to Dementia (NAB data): Sens: 79% Spec: 46% Acc: 55% PPV: 37% NPV: 85% Diagnosis of Neurodegenerative Disease (NAB): Sens: 84% Spec: 58% Acc: 70% NPV: 81%	NA	Dementia-Free Survival: PET not supporting neurodegeneration: 83.6 months PET supporting neurodegeneration: 45.4 months (p<0.001) Overall Survival: PET not supporting neurodegeneration: 86.8 months PET supporting neurodegeneration: 63.4 months (p<0.001) **In summary:** A normal ^{18}F-FDG PET scan can effectively rule out conversion to dementia and neurodegenerative pathology, supporting its use in early diagnostic workup and patient management planning.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						For Alzheimer's disease: NPV = 91%, Accuracy = 87% Prediction of CSF Biomarkers (Nancy Hospital): NPV for N biomarker: 95% NPV for A/T combination: 79% In MCI subgroup: NPV for N biomarker = 100%		
Epilepsy								
No studies met the inclusion criteria								
Esophageal cancer								
Ge et al, 2024 [11] China	Single centre Retrospective **Objectives:** to investigate the clinical value of whole-body dynamic ^{18}F-FDG PET/CT imaging in differentiating recurrent anastomotic tumours and inflammation after gastric and esophageal cancer surgery.	53 patients with recurrent anastomotic tumour of the digestive tract after gastric (n=29) or esophageal cancer (n=24) surgery. These patients underwent whole-body dynamic ^{18}F-FDG PET/CT imaging and showed abnormal uptake of FDG at the anastomoses. Gastric cancer: mean age (SD) 60.03 ± 10.56 % male: 90% Esophageal cancer:	^{18}F-FDG PET/CT	NR	Pathology	LBR-MRFDG: Gastric cancer: Sens: 92.31% Spec: 81.25% Inflammation vs recurrence (Mean ± SD) 1.60 ± 0.42 vs 2.93 ± 1.05. Esophageal cancer: Sens: 90.91%, Spec: 76.92% Inflammation vs recurrence (Mean ± SD) 1.60 ± 0.45 vs 3.14 ± 1.14 p<0.05	NA	NA **In summary:** Whole-body dynamic ^{18}F-FDG PET/CT imaging can accurately differentiate postoperative anastomotic recurrence and inflammation and has the potential to be an effective monitoring method for patients with upper digestive tract tumours after surgical treatment.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
		mean age (SD): 62.04 ± 9.43 % male: 83%						
Sun X et al, 2024 [12] Japan	Single centre Retrospective **Objectives**: To evaluate the diagnostic performance of dual-energy CT and FDG PET/CT, individually and in combination, for detecting LN metastases in patients with esophageal squamous cell carcinoma.	27 patients with pathologically confirmed squamous cell carcinoma Mean Age, 73.7 [range: 56–84] years % male:	^{18}F-FDG PET and ^{18}F-FDG PET/CT	CT	Histopathology	SUVmax Cut-off: 1.94 Sens: 88.9% Spec: 70.3% AUC: 0.833 PET/CT IC+ SUVmax Cut-off: - Sens: 83.3% Spec: 86.5% AUC: 0.884	CT Iodine Concentration Cut-off: 1.8 mg/mL Sens: 66.7% Spec: 86.5% AUC: 0.809 Combined Modality Performance (CT + PET) Sens: 83.3% Spec: 86.5% AUC: 0.884	NA **In summary:** While PET/CT (SUVmax) showed high sensitivity and dual-energy CT (iodine concentration) showed high specificity, combining both modalities yielded the best diagnostic performance (AUC 0.884, sensitivity 83.3%, specificity 86.5%). The study supports the use of integrated imaging approaches to improve preoperative staging and potentially guide treatment strategies.
Fever of unknown origin								
Fathala et al, 2024 [13] Saudi Arabia	Single centre Retrospective cohort study **Objectives:** a) Evaluate the diagnostic performance of ^{18}F-FDG PET/CT in patients presenting with FUO. b) Determine the sensitivity, specificity, and predictive values of PET/CT in identifying the underlying causes of FUO.	105 patients with FUO Median (IQR) Age: 51 (31-65) years % male: 58.1%	^{18}FDG PET/CT	NR	Tissue biopsy, other diagnostic studies, laboratory tests and continued follow-up	Sens: 72%, Spec: 29%, PPV: 68%, NPV: 33%, Acc: 58%	NA	NA In summary: In this retrospective study of 105 patients with FUO, ^{18}F-FDG PET/CT identified the underlying cause in 49% of cases, with infections (51%), malignancies (35%), and inflammatory diseases (14%) being the most common etiology. The scan demonstrated a sensitivity of 72% and a positive predictive value of 68%, though specificity was low at 29%. While PET/CT proved valuable in detecting metabolically active foci, it also yielded a notable rate of false positives and negatives. Despite these limitations, the findings

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	c) Assess the clinical utility of PET/CT in a tertiary care setting in Saudi Arabia.							support the use of ^{18}F-FDG PET/CT as a helpful tool in the diagnostic workup of FUO, particularly in settings where conventional imaging is inconclusive.
Khan et al, 2024 [14] India	Single centre Ambispective (retrospective + prospective) observational study **Objective:** To evaluate the role of ^{18}F-FDG PET/CT in guiding diagnosis and biopsy site selection in patients with FUO.	573 patients with pyrexia of unknown origin Mean Age (SD): 39.40 (4.6) years % male: 41%	^{18}F-FDG PET/CT	NA	Histopathology and clinical follow-up	NA	NA	Contribution to diagnosis: PET/CT guided biopsy site in 104 patients; 36 (34.6%) had conclusive diagnoses. Overall, PET/CT contributed to diagnosis (via biopsy guidance or correct first differential) in 70 of 139 patients (50.05%). **In summary:** PET/CT helped expedite diagnosis, guide biopsy, and potentially reduce unnecessary investigations.
Kobayashi et al, 2024 [15] Japan	Single centre Retrospective case series **Objective:** To determine which patients with FUO/IUO can benefit most from the FDG-PET/CT approach.	45 patients, (21 with fever of unknown origin and 24 with inflammation of unknown origin) Median age (IQR) 74 (68–80) years % male: 40%	^{18}F-FDG PET/CT	CT MRI Ultrasound Endoscopy Serology and Histopathology	Histopathology, microbiology, clinical criteria, or follow-up	Sens: 90.6% Spec: 38.5% PPV: 78.4% NPV: 62.5%	NA	PET was helpful for final diagnosis: 64.4% (29/45 patients). PET/CT guided further diagnostic steps (e.g., biopsy) and informed treatment decisions. **In summary:** ^{18}F-FDG PET/CT was particularly effective in diagnosing IUO, with significantly higher diagnostic yield compared to FUO. It contributed to diagnosis in nearly two-thirds of patients and showed high sensitivity. The study supports integrating PET/CT into the diagnostic pathway for FUO/IUO, especially when conventional methods are inconclusive.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
Gastro-intestinal cancer								
Engel et al, 2024 [16] Switzerland	Single centre Retrospective cohort study **Objectives:** a) Compare the diagnostic accuracy of FDG-PET/CT versus conventional CT in staging lymph node involvement and distant metastases in CRC. b) Evaluate the impact of PET/CT on overall survival and cost-effectiveness in CRC staging.	539 patients with colorectal cancer staged (nodal n=471; distant metastases n=479) with PET/CT or CT Median age (IQR: Staged with PET: 69 (59-77 years) Staged without PET: 75 (66 to 83) years % male: 56.4%	PET/CT	CT	Histopathology	Nodal involvement: Sens: 66.7% (95% CI 62.4%–70.9%) Spec: 63.6% (95% CI 59.3%–68.0%) PPV: 51.8% Metastases detection: Sens:	Nodal involvement: Sens: 55.2% (95% CI 5.7%–59.7%) Spec: 67.0 % (95% CI 62.8%–71.3 %) PPV: 49.5% Metastases detection: Sens: 53.6% (95% CI 49.1%–58.1%)	Survival at 40 months: PET/CT: 47.9% CT: 26.3% Cox regression analysis: after adjustment for age as confounder the apparent survival advantage did not attain statistical significance. **In summary:** This retrospective cohort study of 539 colorectal cancer patients found that FDG-PET/CT significantly outperformed conventional CT in detecting both lymph node involvement and distant metastases, with sensitivities of 66.7% and 82.5% respectively (vs. 55.2% and 53.6% for CT). PET/CT provided added diagnostic value across colon and rectal cancer subgroups and showed a trend toward improved survival, though not statistically significant after adjusting for age. While PET/CT incurs higher upfront costs, its superior accuracy may reduce unnecessary treatments and improve staging precision, especially relevant in the context of evolving neoadjuvant therapies. These findings support considering PET/CT as a valuable adjunct in CRC staging.
Horvat et al, 2024 [17]	Single centre Retrospective study	28 patients with biopsy-proven anal	^{18}F FDG PET/CT	CT, MRI PET/CT was compared to MRI	Clinical follow-up	Tumour detection rate:	NA	More patient staged as T1 and T2 by PET/CT (16/28, 57%), compared to MRI

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
USA	**Objectives:** To investigate the differences in baseline staging of anal squamous cell carcinoma based on CT, MRI, and PET/CT, and the resultant impact on the radiation plan.	squamous cell carcinoma Median Age (range): 62 years [31–78] % male: 21%		and CT for staging and treatment planning		PET/CT: 96% (27/28)		(11/28, 39%) and CT (10/28, 36%) For stages T3 and T4: 39% were staged with PET/CT, 50% by MRI, and 43% by CT Radiologist diagnosed 14% more suspicious nodes on MRI (75%) vs. PET/CT (61%); p>0.999 **In summary**: Despite differences in T-category classification, treatment plans were largely consistent across modalities
Liang Z et al, 2024 [18] China	Single centre Prospective study (NCT05485792) **Objectives**: To compare the diagnostic performance of ^{18}F-FAPI-04 PET/CT and ^{18}F-FDG PET/CT in evaluating liver cancer lesions, and to explore correlations between PET parameters and immune-histochemical markers.	44 patients with liver cancer (28 hepatocellular carcinomas and 11 intrahepatic cholangiocarcinoma Mean Age (SD): 59.32 (12.00); range: 26–83 years % male: 91%	^{18}F-FAPI-04 PET/CT	^{18}F-FDG PET/CT	Histopathology	^{18}F-FAPI-04 PET/CT Lesion-based visual analysis Sens: 84.6% Spec: 60.0% Accu: 81.8%	^{18}F-FDG PET/CT Lesion-based visual analysis Sens: 76.9% Spec: 100% Accu: 79.5%	TN Staging Adjustments: 9 patients due to ^{18}F-FAPI-04 findings T stage upgrade: 8 patients N stage upgrade: 1 patient Treatment Modifications: Radiotherapy protocols adjusted in 4 patients because of distant metastases detection by ^{18}F-FAPI-04 **In summary:** ^{18}F-FAPI-04 showed higher sensitivity, and impact on clinical management greater than ^{18}F-FDG PET/CT
Mihailovic et al, 2024 [19] Serbia	Single centre Retrospective **Objectives:** To evaluate the diagnostic performance of F-^{18}FDG PET/CT in detecting recurrent CRC and compare it with CIM and tumour	134 patients with histologically confirmed CRC. Mean Age (SD): 69.6 (11.0); range 39–89 years % male: 45.8%	^{18}F-FDG-PET/CT used for the detection of recurrent CRC	CeCT and/or MRI	Histopathology in 27.8% of cases Clinical follow-up ≥6 months including tumour markers in 72.2% of cases	Sens: 94.4% Spec: 82.5% PPV: 78.5% NPV: 95.7% Accu: 87.3% AUC: 0.885 (95% CI: 0.824–0.946)	Conventional imaging Sens: 51.9% Spec: 98.8% PPV: 96.6% NPV: 75.2% Accu: 79.9% AUC: 0.753 (95% CI: 0.612–0.844)	PET/CT altered management in 26 patients with false-negative CIM: 22 received chemotherapy, 4 had surgery, and 3 had surgery followed by chemotherapy. **In summary:** ^{18}F FDG PET/CT demonstrated high diagnostic accuracy and

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	markers (CEA and CA 19-9).						Tumour markers: CEA Sens: 98.1% Spec: 15.0% PPV: 48.3% NPV: 92.3% Accu: 48.5% AUC: 0.844 (95% CI: 0.772–0.916) CA19-9 Sens: 44.4% Spec: 67.5% PPV: 48.0% NPV: 64.3% Accu: 58.2% AUC: 0.547 (95% CI: 0.442–0.652)	sensitivity for detecting recurrent CRC, outperforming conventional imaging and tumour markers. It significantly influenced patient management and should be considered for routine surveillance in patients with elevated tumour markers.
Zhang Xuneng et al, 2024 [21] China	Single centre Retrospective **Objectives:** a) To compare the diagnostic performance of ^{18}F-FAPI-42 PET/CT vs ^{18}F-FDG PET/CT for detecting PM in CRC. b) To evaluate the consistency of PET/CT-derived Peritoneal Cancer Index with intraoperative Peritoneal Cancer Index. c) To assess the ability of PET/CT to predict complete cytoreduction (CC-0).	48 patients with colorectal cancer and synchronous or metachronous PM Age ≥50 years: 47.9% <50 years: 52.1% % male: 45.8%	^{18}F-FAPI-42 PET/CT	^{18}F-FDG PET/CT	Histopathology and surgical exploration	Overall detection of PM: Sens: 82.1% Spec: 87.5% Accu: 84.6% NPV: 80.8% PPV: 88.5% Detection of PM by region: Right upper region Sens: 92.9% Epigastrium Sens: 92.9% Small intestine Sens: 59.3%	Overall detection of PM Sens: 61.1% Spec: 90% Accu: 74.5% NPV: 66.8% PPV: 87.6% Detection of PM by region: Right upper region Sens: 39.3% Epigastrium Sens: 42.6% Small intestine Sens: 3630%	No formal statistical comparison is provided **In summary:** ^{18}F-FAPI-42 PET/CT offers superior diagnostic accuracy for peritoneal metastases in colorectal cancer, especially in regions with high physiological FDG uptake.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	D) To analyze the impact on patient management and prognosis (OS and PFS).							
Zhang Xiao et al, 2024 [20] China	Single centre Prospective, prognostic (NCT05999227) **Objectives**: To evaluate and compare the diagnostic accuracy and the effectiveness of 3 imaging modalities: ^{68}Ga Ga-FAPI-04 PET/MRI, ^{18}F FDG PET/CT, CeMRI in predicting pCR after neoadjuvant short-course radiotherapy combined with immune-chemotherapy in patients with locally advanced rectal cancer.	20 treatment naïve, histologically confirmed patients with T3–4N0M0 or T1–4N1M0 rectal adenocarcinoma Mean age (SD): 60.20 (5.86); range: 49–70) years % male: 65%	^{68}Ga Ga-FAPI-04 PET/MRI and ^{18}F FDG PET/CT	CeMRI	Histopathology (resected specimens)	^{68}Ga Ga-FAPI-04 PET/MRI DSUL peak % (percentage change in the SUV normalized by lean body mass) >63.92 Sens: 77.78% Spec: 100% Cut-off: 63.92 AUC: 0.929 ^{18}F FDG PET/CT DMTV% (change in metabolic tumour volume): AUC: 0.798 Sens: 88.89% Spec: 81.82% DTLG% (change in total lesion glycolysis): AUC: 0.798 Sens: 88.89% Spec: 81.82%	CeMRI: Visual assessment AUC 0.778 Sens: 55.56%	pCR rate: 45% (9/20 patients) **In summary:** In patients with locally advanced rectal cancer undergoing short-course radiotherapy followed by immunochemotherapy, ^{68}Ga Ga-FAPI-04 PET/MRI demonstrated strong potential for predicting pCR. Among various imaging parameters, the DSUL peak % from baseline to post-treatment showed the highest specificity (100%) and strong predictive accuracy (AUC = 0.929). This suggests that ^{68}Ga Ga-FAPI-04 PET/MRI, particularly DSUL peak %, may help identify patients who could safely forgo surgery, supporting a watch-and-wait strategy after neoadjuvant therapy.
GU cancer								
Akcay et al, 2024 [22] Turkey	Single centre Retrospective cohort study **Objectives:** 1) to investigate the role of 68 Ga-Ga-PSMA-11 PET /CT imaging (PRIMARY score) in the diagnosis of clinically significant pCa	147 treatment-naive patients diagnosed with clinically significant pCa (ISUP) GG 1 and 2 pCa by biopsy (bISUP GG) and who underwent radical prostatectomy in different hospitals	68 Ga- Ga-PSMA-11 PET/CT	mpMRI	Histopathology (final pathology results)	<u>PRIMARY (bISUP GG 1), n=73</u> Sens: 76% (95% CI: 62%–87%) Spec: 58% (95% CI: 41%–74%) NPV: 64% (95% CI: 46%–80%) PPV: 71% (95% CI: 57%–83%)	<u>PIRADS (bISUP GG 1 and 2), n=101</u> Sens: 85% (95% CI: 74% to 92%) Spec: 26% (95% CI: 13% to 42%) NPV: 47% (95% CI: 26% to 69%)	NA **Importance:** Authors note that to their knowledge, this is the first study to evaluate PRIMARY scoring for differentiation of pCa using final pathology results instead of biopsy results. **In summary:**

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	(ISUP GG 2 and higher) in patients initially diagnosed with ISUP GG 1 and 2 after prostate biopsy.	Mean age 64 ± 7 years PSA median: 7.15 (CI 1.08-90.0)				<u>PRIMARY (bISUP GG1 and 2), n=114</u> Sens: 77% (95% CI: 67% to 85%) (p>0.05) Spec: 58% (95% CI: 41% to74%) (p<0.001) NPV: 49% (95% CI: 33% to 64%) (p>0.05) PPV: 83% (95% CI: 74% to 90%) (p<0.005) A moderate correlation was observed between PRIMARY scores and ISUP GG (Rho=0.54, p<0.001) but not between PI-RADS and ISUP GG (p=0.281). Comparatively, PRIMARY scoring was significantly more reliable than PI-RADS scoring in identifying pCa.	PPV: 68% (95% CI: 58% to 78%) No substantial correlation was found between PI-RADS and ISUP GG	^{68}Ga-Ga-PSMA-11 PET /CT imaging is promising for distinguishing high-risk pCa patients from those appropriate for active surveillance, potentially aiding in the identification of pCa.
Algin et al, 2023 [23] Turkey	Multicentre Retrospective cohort study **Objectives:** to investigate the impact of ^{68}Ga-PSMA PET/CT on OS and management in PCa	100 pCa patients who had 68Ga PSMA PET/CT for various purposes, including primary staging biochemical recurrence after definitive treatment or restaging and who had at least one CI examination (BS, CT or MRI) within 3	68Ga-PSMA PET/CT	Conventional imaging (CI) methods including magnetic resonance imaging (MRI) multi-parametric (35%), cross-sectional computed tomography (CT) thorax or abdomen, and bone scan (BS) (65%)	NA	Predictive Factors: both a PSA < 8 ng/ml and having a hormone-sensitive disease at the time of imaging were found to be statistically significant independent factors predicting	NA	**Change in Staging:** After 68Ga-PSMA PET/CT, the stage changed in 64 patients (64%). By the reason of 68Ga-PSMA PET/CT findings, treatment plans based on CI were changed in 73 patients (73%). **Change in Treatment** A statistically significant correlation between changes in staging and treatment

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
		months before ^{68}Ga-PSMA PET/CT Mean age: 66 years Range 46-87 years PSA: <8ng/mL 47% PSA: >8ng/mL 53%				change in staging with ^{68}Ga-PSMA PET/CT.		was found by using the phi correlation coefficient (phi) analysis (ϕ=0.638, p<0.0001). **Change in Survival** Between patients whose therapy was modified following ^{68}Ga-PSMA PET/CT and those whose treatment was not changed no difference in those (2- year overall survival 83% versus 75% p-0.059. In a subgroup analysis for hormone sensitive patients there was some important difference between those with and without treatment change (95% versus 81%, p=0.006). There was no difference in the subgroup with castration resistant disease who did or did not change treatment (median overall survival 17.9 versus 10.4 months, p=0.735) **In summary:** ^{68}Ga-PSMA PET/CT has the effect of changing the treatment in 73% of pCa patients. There is a positive correlation between the changes in staging and treatment. Survival of hormone sensitive patients has improved due to treatment changes based on PET/CT findings.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								The study authors believe this is the first study to link ^{68}Ga PSMA PET/CT to overall survival.
Bian et al, 2024 [24] China	Retrospective cohort **Objectives:** Overall purpose to evaluate the significance of ^{18}F-PSMA-1007 PET/CT in preoperative assessment of PCa patients in the PSA gray area (4 ng/mL to <10.0 ng/mL). More specifically to: a) Evaluate the diagnostic performance of ^{18}F-PSMA-1007 PET/CT in detecting extra-prostatic extension, lymph node metastasis, and bone metastasis in pCa patients with serum PSA levels in the "gray area" (4–10 ng/mL). b) Determine whether PET/CT imaging parameters, particularly SUVmax, offer superior predictive value	117 pCa patients Median age: 69.55 (SD 7.11) years Range: 55 to 84 years Total PSA value 6.72 ng/mL Range: 4 to 10 ng/mL	^{18}F-PSMA-1007 PET/CT	NR	Histopathology Histopathological analysis was taken as the reference for extra-prostatic extension and regional LN metastasis.	Diagnosis of regional LN metastases Sens: 100%, Spec: 97.35%, Acc 97.44% **N-Stage** **Sens** PET+ (7 patients) PPV: 57.14%, PET- (110 patients) NPV: 100%, Acc: 97.44% **M-stage** (determined by clinical follow-up) Sens 100.0% Spec: 97.35% Accu: 99.15 PET+ (7 patients) PPV: 85.71% PET- (110 patients) NPV: 100% <u>Diagnosis of bone metastasis</u> Sens: 100%, Spec: 97.35%, Acc: 99.15%	NA	^{18}F-PSMA-1007 PET/CT revealed abnormal pelvic lymph node uptake in 7 of 117 patients. **In summary:** This retrospective study assessed 117 pCa patients with PSA levels between 4–10 ng/mL using ^{18}F-PSMA-1007 PET/CT ((odds ratio, 1.114; 95% CI: 1.040 to 1.194; p=0.002). The predicted model's AUC curves were 75.4%. The results demonstrated that SUVmax was the only independent predictor of extra-prostatic extension, outperforming traditional clinical parameters such as PSA, PSA density, and prostate volume. PET/CT also showed high diagnostic accuracy for LN (99.05%) and bone metastases (99.15%), with excellent sensitivity and specificity. The authors believe that these findings suggest that ^{18}F-PSMA-1007 PET/CT is a valuable tool for preoperative staging in patients within the PSA gray zone (4–10 ng/mL), potentially guiding more precise treatment decisions.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	compared to conventional clinical indicators.							
Elsadawy et al, 2024 [25] Egypt	Multicentre Retrospective cohort study **Objectives:** a) Evaluate the diagnostic performance of ^{68}Ga-PSMA PET/CT in anatomical staging of pCa. b) Correlate PET/CT findings, including SUVmax, with histopathological zonal staging, Gleason score, and PSA levels.	40 patients with pathologically proven pCa Age range: 55.0 to 69.6 (SD 7.11) PSA: Median: 20.50 Range: 5.2 to 79.0)	^{68}Ga-PSMA PET/CT	Computer-enhanced CT	Histopathology	Detection of prostatic cancer lesions in ^{68}Ga PSMA PET/CT studies in different prostatic zones (right base, left base, right middle, left middle, right apex left apex); correlation between PSMA and biopsy findings: Sens: range 76.9% to 90.6%, Spec: range 85.7% to 100%, PPV: range 95.2% to 100% and NPV: range 50% to 81.3%	NR	NA **In summary:** This retrospective study of 40 patients with biopsy-proven pCa assessed the utility of ^{68}Ga-PSMA PET/CT in anatomical staging. The imaging demonstrated high sensitivity (76.9–90.6%) and specificity (85.7–100%) across prostate zones when compared with histopathological findings. There was correlation with PSA (r=42% p=0.02) and SUVmax (r=37%, p=0.03) to the Gleason score. SUVmax values were significantly higher in malignant (median SUVmax=20.06) versus benign tissue (median SUVmax=1.6, (p=0.001) and correlated strongly with both Gleason scores and PSA levels.
Ettema et al, 2024 [26] Netherlands	Multicentre Retrospective cohort study **Objectives:** a) To compare early oncological outcomes—specifically biochemical recurrence-free survival and biochemical	1337 pCa patients undergoing (RARP and (ePLND. From these 880 were matched for propensity scoring matching (for PSA value at diagnosis CT stage, (benign vs malign), and biopsy ISUP GG)	All of the following: ^{18}F-DCFPyL-PSMA, ^{18}F-PSMA-1007 and ^{18}F-JK-PSMA-7, or ^{68}Ga-Ga-PSMA-11 PSMA-PET/CT (n= 735, 55%)	Conventional imaging (historical cohort, i.e., staging according to European Association of Urology guidelines) (n=602, 45%)	Histopathology	NA	NA	**Changes in Survival:** Multivariable Cox regression showed: PSMA-PET/CT staging have longer biochemical recurrence (BCR)-free survival (BFS) than patients who do not (HR 0.70, 95% CI 0.55–0.89, p=0.0030). Other variables showing benefit from PET/CT staging included initial PSA, ISUP GG

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	persistence—in pCa patients staged with PSMA PET/CT versus conventional imaging prior to undergoing RARP and ePLND. b) To assess whether PSMA PET/CT staging independently influences patient selection and outcomes.	Historical cohort (n=602) comparator was staged without PSMA-PET/CT (from 2013 to 2016) Index group (n=735) staged with PSMA PET/CT (from 2016 to 2021) Median Age: PSMA cohort: 68 Historical cohort: 66 (61 to 49) Median PSA: Historical cohort 9.2 (6.5 to 14.7) PSMA PET 10.5 (6.9 to 20.0)	PSMA PET-MRI (4%)					biopsy, pT3a, pT3b-pT4. Positive pN1 And positive status of the surgical margins **Changes in Survival:** At 35 months (median, IQR 21–60) follow-up (PSMA cohort: 27 months, historical cohort: 60 months, 331/880 patients (38%) experienced BCR. PSMA cohort: 29% (126/440) Historical cohort: 47% (204/440) (chi-square test p<0.001). PSMA-PET/CT was associated with longer BFS: HR 0.78, 95% CI, 0.62–0.98, p=0.032). Biochemical persistence of PSA ≥0.1ng/ml (BCP) after RARP PSMA: 57 patients (13%) vs Historical control: 83 patients (19%), p=0.021, OR 0.64 [95% CI 0.44–0.92, p=0.016) **In summary:** This retrospective, propensity score–matched study of 880 patients found that those who underwent PSMA PET/CT staging prior to RARP and ePLND had significantly better early oncological outcomes than those staged with conventional imaging. Specifically, the PSMA cohort showed lower rates of biochemical recurrence (29% vs. 47%) and biochemical persistence (13% vs. 19%), with

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								multivariable analysis confirming PSMA PET/CT as an independent predictor of improved BFS (HR 0.70, p=0.003). These findings suggest that PSMA PET/CT enhances patient selection by more accurately identifying metastatic disease, thereby reducing unnecessary surgeries and improving early treatment outcomes in intermediate- and high-risk pCa.
Evangelista et al, 2024 [27] Italy	Multicentre Retrospective, analysis **Objectives:** a) To assess the diagnostic performance of radiolabeled PSMA PET/CT in staging intermediate-risk pCa distinguishing between favourable and unfavourable subgroups. b) To evaluate the impact of PSMA PET/CT findings on treatment decisions. c) To compare PSMA PET/CT with mpMRI in terms of lesion detection and staging accuracy.	181 patients diagnosed with intermediate risk pCa (both favourable and unfavourable) Median Age (IQR): 70 (48 -84) years Median PSA (IQR): 6.6 (1.17 to 20)	Radiolabeled PSMA PET/CT either ^{68}Ga-Ga-PSMA-11 or ^{18}FF-PSMA1007	mpMRI (a subgroup of 136 (75%) of patients)	Histopathology or clinical follow-up	PSMA/CT for N and M N overall Sens: 100% Spec: 99% (95% CI: 97% to 100 %) PPV: 87% (95% CI: 68% to 100%) NPV: 100% Accu: 99% (92% CI: 97% to 100%) M overall: Sens: 100% Spec: 95% (95% CI: 92% to 98%) PPV: 53% (95% CI: 20% to 86%) NPV: 100% Accu: 96% (95% CI: 92% to 98%)	NA	**Change in Management** The inclusion of PET/CT impacted clinical management in 13.3% of patients (n=24). PET/CT impacted the management of both favourable and unfavourable patients in similar proportions (12% vs 15%); Major changes in management: Unfavourable: n=8 (61.5%) Favourable: n=2 (18.2%), p<0.05 Major changes in management included a change from radiotherapy to systemic therapy or from surgery to systemic therapy. **In summary:** This multicentre retrospective study evaluated 181 patients with intermediate risk pCa who underwent PSMA PET/CT prior to treatment. The imaging detected nodal or distant metastases in 12.7%

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								of cases, with significantly higher positivity in the unfavourable subgroup. PSMA PET/CT influenced clinical management in 13.3% of patients, prompting major changes in 58% of those cases—primarily among unfavourable-risk patients. Diagnostic accuracy for LN and distant metastases exceeded 90%, and the primary score from PSMA PET/CT correlated better with metastatic risk than PI-RADS scores from mpMRI. These findings support the integration of PSMA PET/CT into initial staging workflows for intermediate-risk PCa, especially in patients with unfavourable features, to guide more precise treatment planning.
Fu et al, 2024 [28] China	Single centre Retrospective cohort study **Objectives:** a) To evaluate the diagnostic performance of ^{18}F-DCFPyL PET/CT imaging in patients with PI-RADS 3 or 4 lesions identified on mpMRI. b) To determine whether PET/CT can help distinguish benign from malignant prostate lesions and reduce the	30 patients presenting with prostate imaging reporting and data system (PI-RADS) 3/4 findings on MRI examinations Mean age: 69.1 years (range: 57–82) Mean PSA: 17.0 (1.61–100)	^{18}F-DCFPyL PET/CT	MRI	Histopathology	The optimal diagnostic threshold for SUVmax, determined by the Youden index, was 4.17. Using this threshold, the diagnostic properties of ^{18}F-DCFPyL PET/CT were: Sens: 92.3%, Spec: 88.2%, PPV: 85.7%, NPV: 93.8%, Accu: 90.0%.	NR	NA **In summary:** This single-centre retrospective study assessed 30 patients with PI-RADS 3/4 lesions on mpMRI using ^{18}F-DCFPyL PET/CT prior to biopsy. PET/CT visual analysis showed moderate diagnostic accuracy (76.5%), while semi-quantitative analysis using SUVmax ≥4.17 significantly improved sensitivity (92.3%) and overall accuracy (90%). Notably, PET/CT correctly identified benign lesions in 50% of cases, potentially avoiding unnecessary

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	need for unnecessary biopsies. c) To compare visual and semi-quantitative (SUVmax-based) analysis methods for PET/CT interpretation.							biopsies. All PI-RADS 4 lesions with high SUVmax were confirmed malignant, suggesting PET/CT may be particularly useful in this subgroup. The study supports integrating ^{18}F-DCFPyL PET/CT into pre-biopsy evaluation for PI-RADS 3/4 patients to enhance diagnostic precision and reduce procedural risks.
Furman et al, 2024 [29] Israel	Single centre Retrospective cohort study **Objectives:** a) To compare LN detection and distribution using conventional CT versus PSMA PET/CT in node-positive pCa patients. b) To assess how PSMA PET/CT findings influence radiotherapy planning, including field modifications and dose escalation. c) To identify potential predictors for exclusive nodal positivity on PSMA PET/CT.	95 patients with intermediate unfavourable and high-risk pCa. This analysis focused on those patients without distant metastases but positive regional and non-regional nodes up to the aortic bifurcation found on PSMA PET/CT prior to receiving primary radiotherapy and androgen deprivation therapy. Median age: 72 years (range: 51–87 years) Median PSA value at diagnosis: 14.5 ng/mL (range: 1.4–630 ng/mL)	^{18}F-PSMA-1007PET/CT or ^{68}Ga-PSMA	CeCT	NR	NA	NA	**Change in Staging** PSMA PET detected additional positive nodes in 46 patients (48.4%). Of these, 28 patients had nodes only detected on the PSMA. Among these patients, 5 (18%) had radiotherapy treatment fields changed, and 23 (83%) had a dose boost. The most common nodes only detected on PSMA PET were in the external iliac (27, 40%), internal iliac (13, 19%), obturator (11, 15%) stations. Staging shifted from N0 to N1 in 29% of patients. **In summary:** This single-centre retrospective study of 95 node-positive pCa patients evaluated the impact of PSMA PET/CT on radiotherapy planning. PSMA PET/CT identified additional positive LNs in 48% of cases, leading to a staging shift from N0 to N1 in 29% of patients. Among those with PSMA-only positive nodes,

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								radiotherapy fields were modified in 18% and dose boosts applied in 83%. Overall, PSMA PET/CT findings led to treatment field changes in 29% and dose modifications in 59% of the cohort. No clinical or pathological predictors were found for exclusive PSMA PET positivity. These findings support the routine integration of PSMA PET/CT into staging workflows to enhance radiotherapy precision and personalize treatment in node-positive pCa.
Garcia et al, 2024 [30] Spain	Single centre Prospective cohort **Objectives:** a) To analyze the efficacy of integrated assessment of ^{18}F-F-PSMA-1007 PET/MRI on the early detection of **local recurrence** for pCa patients with PSA levels **<0.5 ng/mL after radical prostatectomy**. b) To assess the location of recurrence so that therapy may be tailored to patient.	35 PCa patients with very low PSA levels (PSA<0.5 ng/mL) **after prostatectomy (low biochemical recurrence)** No demographics reported	^{18}F- F-PSMA-1007 PET	MRI	Clinical and imaging follow-up: Biochemical response (PSA reduction >50% after salvage treatment); imaging follow-up (ultrasound, bone scintigraphy, CT, MRI, and PET. Histology was not performed for ethical reasons.	Overall Detection Rate for Local Recurrence: PET/MRI was positive in 71.4% (25 out of 35 patients) with PSA < 0.5 ng/mL. Local Recurrence Detection: Detected in 42.9% of patients (15 out of 35). MRI alone was superior in 2 patients (5.7%). PET alone was superior in 3 patients (8.6%). Integrated PET/MRI improved detection in 5 patients (14.3%). Nodal and Distant Detection Rate (N1 + M1a): Combined	NA	**Change in Staging** Early and precise Location of Recurrence: Local only: 11 patients (44.0%) Pelvic LNs (N1): 10 patients (40.0%) Local recurrence + N1: 2 patients (8.0%) Local recurrence + N1 + distant LNs (M1a): 2 patients (8.0%) **In summary:** This single-centre prospective study implemented radio-guided radiotherapy in 80% of patients based on PET/MRI findings (11 with local recurrence and 9 with N1 involvement). Hormonal therapy was chosen in 20% due to widespread disease.

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						detection rate was 56%. Note: No bone or visceral metastases were detected, likely due to the low PSA levels.		
Giunta et al, 2024 [31] Italy	Single centre Prospective cohort (response monitoring with prognostic implications) **Objectives:** to assess the utility of response monitoring to enzalutamide by using ^{68}Ga-Ga-PSMA PET in metastatic castration-resistant pCa patients treated with enzalutamide as first-line therapy	69 men with metastatic castration-resistant pCa Median PSA (range) ng/mL: 2.57 (1.09 to 6.19)	^{68}Ga-Ga-PSMA-11 PET/CT	PSA response	NA	The concordance between PSMA PET and PSA response was 47.8%	NA	**Changes in Survival** ***PFS*** PFS in patients treated with enzalutamide: Median PFS: 37 months (95% CI: 26–66). PSA response associated with improved PFS overall (HR: 0.36; p=0.003). In PET-non-response patients, PSA response had a weak impact on PFS (HR: 0.48; p=0.075). In PET-responder patients, PSA response had no significant impact on PFS (HR: 0.52; p=0.406). OS: Median OS: 66 months (95% CI: 38–not reached). PSA response associated with improved OS (HR: 0.32; p=0.005). In PET-non-responder patients, PSA response significantly improved OS (HR: 0.36; p=0.033). In PET-responder patients, PSA response had no significant impact on OS (HR: 0.66; p=0.701). **In summary:** In this prospective single-centre study, PSMA PET was

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								more informative than PSA in predicting outcomes in patients treated with enzalutamide. In discordant cases (e.g., PET-R but PSA-NR), PET findings better predicted survival. Suggests PSMA PET may guide treatment decisions more effectively than PSA alone.
Harsini et al, 2024 [32] Canada	Multicentre trial in Vancouver area hospitals Post-hoc subgroup analysis of a prospective, non-randomized clinical trial (NCT02899312) **Objectives:** To assess the outcome of patients with BCR post radical prostatectomy who have negative - ^{18}F-DCFPyL PET/CT scan at relapse	101 patients with biochemical recurrence (PSA >0.4 ng/mL and rising) of pCa after radical prostatectomy who had a negative ^{18}F-DCFPyL PSMA PET/CT result. Patients were divided in two groups: surveillance (n=65) and salvage radiotherapy (n=36) Median age (range) whole group: 75 (55–92) years Median PSA at PSMA PET/CT scan whole group: 0.6 ng/mL (range: 0.4–11.5 ng/mL).	^{18}F-DCFPyL PSMA PET/CT	Surveillance only	Follow-up imaging (PSMA PET/CT, MRI, CT, bone scan)	All patients had negative PSMA PET/CT, so sensitivity/specificity were not directly assessed. However, 21% (21/101) of patients experienced clinical progression despite negative scans, indicating limitations in negative predictive value.	NA	**Changes in Survival** Freedom from Progression: sRT group: 3-year freedom from progression = 94% Surveillance group: 3-year freedom from progression = 71% Multivariate analysis: sRT significantly reduced risk of progression (HR = 0.20; p=0.03) ISUP Grade 5 significantly increased risk of progression (HR = 5.1; p=0.04) Overall Survival: 100% at last follow-up (no deaths reported) **In summary:** This study suggests that salvage radiotherapy is associated with a decreased or delayed clinical progression in patients with biochemical recurrence following radical prostatectomy who have negative PSMA PET/CT scan results. The analysis also underscores the prognostic significance of the initial ISUP grade, with ISUP grade 5 being

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								associated with worse outcomes.
Leow et al, 2024 [33] Australia	Multicentre Retrospective cohort **Objectives**: To compare outcomes of patients with pelvic node-positive pCa staged using PSMA PET versus conventional imaging, all treated with definitive androgen deprivation therapy (ADT) and radiation therapy.	76 patients with pelvic node-positive pCa, all treated with definitive androgen deprivation therapy (ADT) and RT Median Age overall: 74 (IQR 67 to 78) years Median iPSA ng/mL) overall: 13 (IQR 9 to 30)	^{68}Ga-PSMA PET (n=51 staged with PSMA PET)	Conventional imaging (n= 21 for conventional imaging staging)	NR	NA	NA	**Changes in Survival** Overall survival 4 years (multivariate analysis) PET: 93% Conventional staging: 76% HR = 5.81 (95% CI: 1.43–23.7, p=0.007). Biochemical failure-free survival at 4 years: PET: 72% Conventional Staging: 38% HR = 3.00 (95% CI: 1.43–6.29, p=0.004). **In summary:** In this multicentre retrospective cohort study PSMA PET identifies a more favourable cohort for curative treatment (suggesting PET identifies more accurately classifies patients to earlier stages). Supports curative-intent treatment for pelvic node-positive patients staged with PSMA PET.
Longoni et al, 2024 [34] Italy	Single centre Retrospective cohort **Objectives**: To evaluate the diagnostic performance of ^{18}F-FDG PET/CT for lymph node staging in bladder cancer patients undergoing radical	199 patients with muscle-invasive or high-risk bladder cancer and RC and PLND Mean age overall: 68 (IQR 62 to 74) years	^{18}F-FDG PET/CT	Standard cross-sectional CT imaging of the abdomen and pelvis	Histopathology	Per-patient analysis): Sens: 30% (95% CI: 19% to 44%) Spec: 91% (95% CI 85% to 95%) PPV: 57% (95% CI 37% to 75%) NPV:77% (95% CI: 70% to 83%) Accu: 74% (95% CI 0.66–0.79)	Per-patient analysis: Sens: 36% (95% CI: 23% to 50%) Spec: 87% (95% CI: 81% to 92%) PPV: 53% (95% CI: 36% to 69%)	NA **In summary:** This single centre retrospective cohort study, showed that PET/CT had high specificity and NPV, suggesting it may help rule out nodal disease. Low sensitivity can miss cases. Could aid in selecting patients for extended PLND or tailoring surgical approaches.

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	cystectomy (RC) and pelvic lymph node dissection (PLND), including those receiving neoadjuvant chemotherapy (NAC) or immunotherapy (NAI).					Per Region analysis Sens: 15% (95% CI 9% to 23%), Spec: 98% (95% CI: 97% to 98%) PPV: 40% (95% CI: 26% to 55%) NPV:92% (95% CI: 90% to 93%), Accu: 90% (95% CI: 88% to 90%)	NPV: 78% (95% CI: 70% to 84%) Accu: 0.73 (95% CI 0.67% to 0.80%) Per Region analysis Sens: 9% (95% CI 4% to 15%), Spec: 96% (95% CI: 95% to 97%) PPV: 20% (95% CI: 10% to 34%) NPV:91% (95% CI: 85% to 96%) Accu: 88% (95% CI: 86% to 90%)	However, due to low sensitivity, PET/CT alone is insufficient to guide treatment decisions. Authors recommend further cost-effectiveness analysis before routine implementation.
Mainta et al, 2024 [35] Switzerland	Single centre Retrospective cohort study **Objectives**: To evaluate the diagnostic performance of ^{68}Ga-Ga-PSMA-11 PET/CT for detecting bone metastases in prostate cancer (PCa) using standardized interpretation criteria (PSMA-RADS and PROMISE), and to assess how	118 patients with histology proven prostate adenocarcinoma Mean Age (range): 71 (66 to 76) years	^{68}Ga-Ga-PSMA-11 PET/CT used for detection and characterization of bone metastases in prostate cancer	Composite reference standard, taking into account prior or follow-up examinations, including CT, MRI, bone scintigraphy, and serum PSA levels (	Histopathology proven prostate adenocarcinoma Follow-up imaging PSA response to treatment Lesion stability or progression over ≥1 year	After exclusion of lesions already treated, lesions without follow-up, and lesions that remained inconclusive diagnostic accuracy metrics were calculated for PSMA-Rads vs PROMISE Lesion-level analysis (n= 265) PSMA-RADS-cutoff 3B	NR	NA Please note Figure 4 (Sandkey diagram) showing sequential combination of different criteria **In summary:** In this single centre retrospective cohort study, diagnostic performance is evaluated using 4 different criteria and one that combines several criteria. The sequential use of PSMA-RADS and PROMISE criteria significantly reduces diagnostic uncertainty.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	combining these criteria affects diagnostic clarity.					Sens: 100% (96.4–100) Spec: 63.6% (52.6–73.4) PPV: 80.4% (73.3–86) NPV: 100% (92–100) Acc: 85.4% PSMA-RADS-cutoff4 Sens: 40.5% (32.1–49.4) Spec: 100% (94.8–100) PPV: 100% (91.6–100) NPV: 53% (45.1–60.7) Acc: 64.4% PSMA-RADS-cutoff 4 with reassignment Sens: 59.5% (50.6–67.9) Spec: 100% (94.8–100) PPV: 100% (94.2–100) NPV: 62.4% (53.8–70.3) Acc: 75.8% PROMISE criteria Sens: 89.3% (82.4–93.8) Spec: 96.6% (89.7–99.1) PPV: 97.5% (92.3–99.3) NPV: 85.9% (77.1–91.8) Acc: 92.2% PSMA-RADS +		PSMA-RADS-3B lesions classified as positive by PROMISE were malignant in 95.5% of cases. However, 32.6% of PSMA-RADS-3B lesions classified as negative by PROMISE were still malignant, indicating the need for follow-up. ^{68}Ga-Ga-PSMA-11 PET/CT demonstrates high diagnostic accuracy for detecting bone metastases in prostate cancer. The sequential use of PSMA-RADS and PROMISE criteria improves interpretability by reducing equivocal findings, though some false negatives remain. This approach may enhance clinical decision-making, but further validation and integration into treatment algorithms are needed.

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						PROMISE Sens: 89.3% (82.4-93.8) Spec: 96.6% (89.7-99.1) PPV: 97.5% (92.3-99.3) NPV: 85.9% (77.1-91.8) Acc: 92.2%		
Ou et al, 2024 [36] USA	Single centre Retrospective cohort study **Objective**: To evaluate the diagnostic performance of PSMA-PET/CT for detecting bone metastases in prostate cancer using bone biopsy as the histopathologic reference standard.	80 men with prostate cancer Mean Age (SD): 68.4 (7.9) years Mean PSA ng/mL (SD): 14.3 (24.3)	^{18}F--^{18}F-piflufolastat. PET/CT	Bone biopsy	Percutaneous CT guided Bone biopsy Histopathology	Overall Concordance with PSMA PET/CT and bone biopsy: 69% (55/80 cases) PPV for osseous metastasis: 66% (53/80; 95% CI: 55 to 76) PPV by Biopsy Site: Spine: 82% (23/28) Pelvis: 72% (18/25) Ribs: 26% (5/19) SUVpeak was significantly higher in biopsy-positive lesions (mean 17.3) vs. negative (mean 5.4), $p < 0.0001$ SUVpeak-to-liver SUVmean ratio threshold of 1.7 yielded: Sens: 61% Spec: 92%	NR	NR **In summary:** PET/CT-guided biopsy may improve diagnostic yield. PSMA-PET/CT has a moderately high histopathologic concordance and positive predictive value for the diagnosis of osseous metastatic disease in prostate cancer. Rib lesions were frequently false positives, highlighting interpretive challenges. In keeping with prior investigations, a majority of biopsied rib lesions were negative for metastatic prostate cancer. SUV metrics may help distinguish benign from malignant lesions, potentially guiding biopsy decisions.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						SUVpeak threshold of 9.2 yielded: Sens: 59% Spec: 96%		
Özman et al, 2024 [37] Netherlands	Single centre Retrospective cohort **Objective**: To assess the diagnostic performance of PSMA PET/CT for lymph node metastases (LNM) in prostate cancer (PCa) and its prognostic value for biochemical recurrence after radical prostatectomy. Therefore, the aim of this study was (1) to explore factors affecting the LNM detection performance of PSMA PET/CT using robot-assisted ePLND outcomes as a reference and (2) to evaluate its prognostic value for biochemical recurrence after radical prostatectomy	583 patients who: (1) had biopsy-proven intermediate- or high-risk PCa according to the European Association of Urology classification (2) underwent robot-assisted radical prostatectomy (RARP) and (3) extended pelvic lymph node dissection (ePLND). Median age at diagnosis: 68.0 (IQR 64.0 to 72.0) years Median PSA ng/mL: 10.5 (IQR 7.0 to 20.0)	^{68}Ga Ga-PSMA-11 (n = 460) or ^{18}F DCFPyL (n = 123)	Clinically assessed	Histopathology of lymph nodes	Combined scans for 68Ga Ga-PSMA-11 and 18F DCFPyL Per patient analysis Sens: 26.3% (95% CI: 18.9–35.5) Spec: 93.9% (95%CI 84.9–100) PPV: 61.8% (95%CI 44.5–83.5) NPV: 77.1% (95%CI 69.7–85.1) Accu: 75.3% (95%CI 71.6–78.8 Diagnostic OR: 5.40 (95% CI: 3.24–7.45)	NA	**Changes in Survival** Biochemical Progression-Free Survival defined as at least two consecutive PSA serum levels > 0.2 ng/mL at least 3 months after RARP): 1-year: PSMA PET/CT-positive lymph nodes (miN1): 56.0% PSMA PET/CT-negative lymph nodes (miN0): 83.3% ($p < 0.001$) The miN0pN1 disease did not significantly affect biochemical progression free survival. The miN1pN1 disease (was independently associated with decreased biochemical progression free survival: HR: 2.1 (95% CI: 1.3-3.4, $p < 0.001$) in the post-surgery setting. . **In summary:** PSMA PET/CT has strong prognostic value. It can stratify patients pre- and post-surgery for recurrence risk. This may guide decisions on adjuvant therapy in high-risk patients. PSMA PET/CT has high specificity but low sensitivity for detecting lymph node metastases in

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								prostate cancer, especially for small tumour deposits. Its diagnostic performance improves significantly for metastases >5.5 mm. Despite limitations in sensitivity, PSMA PET/CT provides strong prognostic information and may help stratify patients for recurrence risk after surgery.
Pepe et al, 2024 [38] Italy	Single centre Prospective cohort study **Objective**: To evaluate the diagnostic accuracy of PSMA PET/CT in **pelvic nodal staging** of prostate cancer (PCa), using postoperative histopathology as the reference standard.	78 patients with biopsy proven, clinically significant prostate cancer (ISUP Grade Group ≥2 and have undergone a radical prostatectomy. Median age (range): 63 (46 to 75) years Median PSA (range): 12.5 (0.3 to 100) ng/mL	^{68}Ga-PSMA PET/CT or ^{18}F-PSMA PET/CT	Clinical assessment (digital rectal exam, GLEASON staging, NA	Histopathology of lymph nodes (post surgery)	Sens: 87.5% Spec: 96.8% PPV: 87.5% NPV: 96.7% Accu: 92.3%	NA	NR **In summary:** This single centre prospective cohort study shows PSMA PET/CT has high diagnostic accuracy for nodal staging in prostate cancer, particularly in intermediate-risk patients. However, its sensitivity decreases in high-risk and ductal adenocarcinoma cases, where ePLND remains necessary even if PET/CT is negative. The study supports the integration of PSMA PET/CT into staging workflows but emphasizes a multimodal approach for high-risk disease.
Rovera et al, 2024 [39] Italy	Single centre Prospective study **Objectives**: a) to compare the diagnostic performance of ^{68}Ga-PSMA-11 PET/CT with respect to	60 patients with histologically confirmed prostate cancer Median age: 73 (IQR 68-76) years	^{68}Ga-PSMA-11 PE/CT	CT BS	Histopathology (post-operative) (available in 32 patients)	PETS vs Histopathology **Accuracy pelvic lymph node staging** Per patient analysis Sens: 92.3% (95% CI 64.0–99.8)	Detection Rate with CT: N/M1 in 13.3% of patients Bone Scintigraphy:	**Changes in management:** PET/CT led to potential management changes in 28.8% (17/59) of patients, including: Switch to systemic therapy: 16.9% (10/59)

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	conventional imaging (computed tomography (CT) and bone scintigraphy (BS)) in the primary staging of high-risk prostate cancer patients and b) To validate PSMA-PET/CT accuracy in pelvic **nodal staging** in comparison with postoperative histopathology and assess PSMA-PET/CT's impact on patient management.	Prebiopsy PSA median: 10.10 (IQR 6.22 to 17.95) NB; Change in management criteria were specified a priori The change in management criteria were defined as follows: (a) switch to systemic therapy due to previously unknown metastatic involvement: (b) change in the lymphadenectomy template in patients who are candidates for surgical treatment: (c) modification of the RT treatment planning and/or hormonal treatment: (d) potential stereotactic ablative RT (SABR) treatment in the case of the novel identification of oligometastatic disease spread; and (e) identification of collateral PSMA-avid oncologic findings (unrelated to PCa).				Spec: 89.5% (95% 66.9–98.7) PPV: 85.7% (95% 61.6–95.7) NPV: 94.4% (95% CI 72.0–99.1) Accu: 90.6% (95% CI 75.0–98.0) Per region analysis Sens: 85.7% (95% CI 57.1–98.2) Spec: 89.5% (95% CI 78.1–96.7) PPV: 85.7% (95% CI 50.4–85.0) NPV: 94.4% Accu: 90.6% (95% CI 78.8–95.5) **Detection rates for PET -CT compared to CT:** Nodal (N1): 45% Distant metastases (M1a+M1b): 31.7% TNM upstaging: 45% of patients with new evidence of downstaging	Detected suspicious bone metastases in 16.7% of patients Only 4/10 confirmed; 5 were false positives Combined CT + BS: Detected N/M1 in 16.7% of patients PET vs. Conventional Imaging: PET detected N/M1 in 56.7% vs. 16.7% ($p < 0.001$)	Change in lymphadenectomy template: 5.1% (3/59) Consideration of SABR for oligometastatic disease: 5.1% (3/59) Identification of incidental malignancy: 1.7% (1/59) **Biochemical Response Post-Surgery**: In patients with concordant PET and conventional imaging: 73.9% achieved complete biochemical response In patients with additional metastases on PET: 83.3% had biochemical persistence **In summary:** This prospective study evaluated 60 high-risk, hormone-sensitive prostate cancer patients undergoing **primary staging** with both conventional imaging (CT and bone scintigraphy) and ^{68}Ga-PSMA-11 PET/CT. PSMA PET/CT significantly outperformed conventional imaging, detecting nodal or distant metastases in 56.7% of patients versus 16.7% with conventional methods. PET/CT led to TNM upstaging in 45% of cases and influenced management decisions in 28.8%, including shifts to systemic therapy, changes in surgical planning, and consideration of stereotactic radiotherapy. Compared to histopathology, PSMA PET/CT showed high accuracy (90.6%) for pelvic nodal staging. These findings support the integration of

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								PSMA PET/CT into the primary staging workflow for high-risk prostate cancer, offering superior diagnostic performance and meaningful clinical impact.
Simsek et al, 2024 [40] Turkey	Single centre Retrospective cohort study **Objectives:** To compare the diagnostic accuracy of ^{68}Ga-PSMA I&T PET/CT, multiparametric MRI (mpMRI), and their combination in localizing prostate cancer lesions, using histopathology as the reference.	72 men with localized prostate cancer Mean age (range): 64.83 (46 to 82)	^{68}Ga-PSMA I&T PET/CT	mpMRI	Histopathology from radical prostatectomy specimens.	PSMA PET/CT vs Histopathology Sens: 63.6% Spec: 81.3% PPV: 81.0% NPV: 64.3% Accu: 71.5% ISUP Grade 1 Sens: 47.1% Spec: 83.0% PPV: 67.2% NPV: 72.1% ISUP GRADE 2-3 Sens: 62.4% Spec: 82.2% PPV: 82.8% NPV: 61.4% ISUP Grade 4-5 Sens: 74.1% Spec: 76.6% PPV: 85.1% NPV: 62.2%	mpMRI Sens: 67.6% Spec: 86.3% PPV: 86.0% NPV: 68.2% Accu: 75.9% ISUP Grade 1 Sens: 66.2% Spec: 83.9% PPV: 71.4% NPV: 80.3% ISUP GRADE 2-3 Sens: 62.2% Spec: 86.8% PPV: 87.0% NPV: 63.8% ISUP Grade 4-5 Sens: 74.8% Spec: 83.3% PPV: 92.0% NPV: 66.0% Combined modality Sens: 84.1% Spec: 73.1% PPV: 79.4% NPV: ISUP Grade 1 Sens:80.9% Spec: 71.4% PPV: 63.2% NPV: 86.0%	NA **In summary:** Combined mpMRI + PSMA PET/CT improves lesion localization, especially in ISUP grade 2–3 tumours. May reduce the need for repeat biopsies in active surveillance patients. Offers an alternative for patients unsuitable for MRI. Supports more precise treatment planning.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
							ISUP GRADE 2-3 Sens: 84.1% Spec: 73.6% PPV: 81.4% NPV: 77.1% ISUP Grade 4-5 Sens: 85.6% Spec: 74.0% PPV: 85.6% NPV: 74.0%	
Soeterik et al, 2024 [41] Multinational (Netherlands, Germany, Italy, USA, and Hong Kong, China)	Multicentre Retrospective **Objectives**: a)To assess the diagnostic accuracy of PSMA PET/CT, MRI, and their combination in detecting EPE, and SVI. b)To evaluate whether combining PSMA PET/CT with MRI improves local staging in pCa patients undergoing RP	550 patients with histopathologically confirmed pCa Median Age: 66 (IQR 62-67) years Median PSA: 9.7 (IQR 6.5-16.2) ng/mL	^{68}Ga- Ga-PSMA-11 PET/CT (59%) or ^{18}F PSMA-1007 PET/CT (35%) or ^{18}F JK-PSMA-7 PET/CT (4%) or ^{18}F DCFPyL PSMA PET/CT (1%)	mpMRI or biparametric MRI Direct rectal exam	Histopathology	EPE Detection (Patient-Level): Sens: 41% Spec: 83% PPV: 73% NPV: 56% AUC: 62% SVI Detection (Patient-Level): Sens: 44% Spec: 96% PPV: 75% NPV: 87% AUC: 70%	MRI EPE Detection (Patient-Level): Sens: 60% Spec: 77% PPV: 75% NPV: 64% AUC: 69% SVI Detection (Patient-Level): Sens: 36% Spec: 96% PPV: 71% NPV: 85% AUC: 66% Combined Modality Performance (MRI + PSMA PET/CT) EPE Detection: Sens: 73% (↑) Spec: 67% (↓) PPV: 71% NPV: 69% AUC: 70%	NR **In summary:** This large multicentre retrospective study evaluated the diagnostic accuracy of PSMA PET/CT and MRI in staging pCa prior to radical prostatectomy. MRI outperformed PSMA PET/CT in detecting EPE, while both modalities showed similar performance for SVI. Importantly, combining PSMA PET/CT with MRI significantly improved sensitivity and negative predictive value for both EPE and SVI, albeit at the cost of reduced specificity. These findings support the use of both imaging modalities together to enhance local staging and guide treatment decisions, particularly in high-risk pCa patients.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
							SVI Detection: Sens: 60% (↑) Spec: 93% (↓) PPV: 69% NPV: 90% AUC: 76%	
Spena et al, 2024 [42] Italy	Single centre Retrospective cohort study **Objectives**: To evaluate the diagnostic accuracy of ^{68}Ga-PSMA PET/CT in detecting LN metastases in intermediate/high-risk PCa patients. To assess whether PET/CT can reduce unnecessary PLND by accurately identifying LN involvement preoperatively.	50 patients with intermediate or high-risk pCa Mean age (SD): 63.3 (8.2) years Median iPSA ng/mL: 7.7	^{68}Ga-PSMA PET/CT	CT MRI	Histopathology (ePLND)	PET-PSMA Prevalence ePLND positive) 16% (95% CI: 7.17% to 29.11%) Sens: 25% (2/8) — 95% CI: 3.19% - 65.09%Spec: 88.1% (37/42) — 95% CI: 74.37% - 96.02% PPV: 28.6% (2/7) — 95% CI: 3.67% - 70.96% NPV: 86.0% (37/43) — 95% CI: 72.07% - 94.70% Accu: 78.0% (39/50) — 95% CI: 64.04% - 88.47% *Note*: 95% CI from personal communication with author	NA	NA **In summary:** While PET/CT demonstrated high specificity (88.1%) and NPV (86%), its sensitivity was low (25%), limiting its ability to reliably detect LN metastases. The findings suggest that although PET/CT may help exclude nodal disease, it cannot replace ePLND for accurate staging. PET/CT may better reflect intraprostatic tumour burden, as shown by its correlation with PSA and tumour volume.
Vigna-Taglianti et al, 2024 [43] (Italy)	Retrospective **Objectives**: To assess the diagnostic accuracy of ^{68}Ga-PSMA PET/CT in detecting prostate cancer **recurrence** in patients with early biochemical	70 men with biochemical recurrence after radical prostatectomy or radiotherapy Mean age (SD): 71.1 years (5.1) range 59 to 84 years	^{68}Ga-PSMA PET/CT	None	Clinical follow-up (PSA response 3 months after SRT)	Overall: Sens: 78% Spec: Not computed due to absence of true negatives Accu: 76% Prostatic Fossa Subgroup: Sens: 72% Accu: 72%	NA	NA **In summary:** Using PSA response after salvage radiotherapy as a surrogate reference, the study found that PET/CT had overall moderate sens (78%) and accu (76%). However, sens dropped to 62% in patients with PSA ≤ 1 ng/mL, highlighting a

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	failure after primary treatment. To evaluate whether SRT outcomes (PSA response) can serve as a surrogate reference standard for PET scan accuracy.	Mean PSA pre radiation therapy (SD): 0.81 ng/mL (0.91) range (0.2 to5.99)				Prostatic Fossa Subgroup with PSA ≤ 1 ng/mL: Sens: 62% Accu: 62% Pelvic Node Recurrence Subgroup: Accu: 92%		substantial false-negative rate in this subgroup. The findings **suggest that negative PET scans at low PSA levels should not preclude SRT**, and that PET/CT may be more reliable at higher PSA levels or in nodal recurrence. These results support a **nuanced**, PSA-guided approach to interpreting PSMA PET/CT in early recurrence settings.
Wang et al, 2024 [44] China	Retrospective Cohort study **Objectives**: To evaluate the diagnostic value of ^{68}Ga-PSMA PET/CT in detecting: a) intracapsular pCa; b) PPC (i.e., ISUP Grade Group ≥ 3), c) intracapsular pCa in patients without extracapsular invasion or distant metastasis.	221 patients with suspected pCa; 48 benign lesions, 173 malignant lesions, of which 81 with PPC Demographics not reported	^{68}Ga-PSMA PET/CT	NA	Histopathology (at diagnosis from transrectal ultrasound-guided needle biopsy or radical prostatectomy specimens)	All patients PC SUVmax Cut-off: 7.95 Sens: 81% Spec: 83% PPV: 95% NPV: 55% IHPC (Intermediate-High Risk) SUVmax Cut-off: 8.54 Sens: 90% Spec: 76% PPV: 85% NPV: 82% PPC SUVmax Cut-off: 13.94 Sens 78% Spec: 85% PPV: 75% NPV: 87% SUVmax and ISUP Grade Group were positively correlated (r = 0.54, p<0.01).	NA	NR **In summary**: ^{68}Ga-PSMA PET/CT is highly specific and has strong negative predictive value for detecting intracapsular poor prognosis prostate cancer. It is less reliable for detecting low-risk pCa, potentially missing early-stage, low-grade tumours. SUVmax is a useful quantitative marker for risk stratification. PET/CT may complement MRI, especially when MRI is inconclusive or unavailable.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
Wong et al, 2024 [45] Australia	Multicentre Prospective Cohort Study **Objectives**: To compare the diagnostic accuracy of: ^{18}F DCFPyL PSMA-PET/CT and Multiparametric MRI (mpMRI) for detecting prostate cancer and clinically significant prostate cancer (csPCa) at biopsy.	236 Patients clinically suspected of prostate cancer (48 benign and 173 malignant) Age median 65.3 (IQR 58.9 to 69.8) years Median PSA ng/ mL: 6.3 (IQR 4.8 to 8.7	^{18}F DCFPyL PSMA-PET/CT	mpMRI Combined modalities	Histopathology from targeted and systematic prostate biopsy	Sens: 73.9% (95% CI 64.7% to 81.8%), Spec: 52.1% (95% CI 40.0% to 63.9%), NPV: 56.7% (95% CI 44.0% to 68.8%), AUC Accu: 0.63 (95% CI 0.56 to 0.70). Diagnostic accuracy to detect clinically significant pCa at biopsy AUC: 0.62 (95% CI 0.55-0.69) (p=0.27)	mpMRI Sens: 78.4% (95% CI 69.6%, 85.6%) Spec: 72.6% 95% CI 60.9%, 82.4%), NPV: 68.8% % (95% CI 57.3%, 78.9%) AUC Accu: 0.76 (95% CI 0.69, 0.82). Combined modalities: Sens: 98.8% 95% CI 93.5 to 100%) Spec: Lower% NPV: 96.0% (95% CI 79.6 to 99.9%), Diagnostic acc to detect clinically significant pCa at biopsy mpMRI AUC: 0.72 (95% CI 0.67-0.78) Combined: AUC: 0.61 (95% CI 057-0.66) (p=0.01)	NA **In summary:** mpMRI remains superior for initial diagnosis of clinically significant prostate cancer; PSMA-PET/CT may be useful: in patients unable to undergo mpMRI, and when mpMRI is negative but clinical suspicion remains high. Combined imaging may help avoid unnecessary biopsies in select cases.
Ye et al, 2024 [46] China	Single centre Retrospective cohort study **Objectives:** To compare the diagnostic efficacy of ^{18}F-	41 patients with suspected pCa Median age (range): 70 years (52 to 85)	^{18}F-PSMA-1007 PET/CT	mpMRI	Histopathology	Sens: 95.1% PPV: 100% Accu: 95.1%	Sens: 82.9% PPV: 100% Accu: 82.9%	NA **In summary**: ^{18}F PSMA-1007 PET/CT demonstrated superior sensitivity and diagnostic accuracy compared to MRI in

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	PSMA-1007 PET/CT and pelvic MRI in primary prostate cancer; correlate methods with histopathological parameters, and serum PSA levels	Median PSA (range) ng/mL: 136 (2.5 to 2330)						detecting primary prostate cancer. The study supports the use of PET/CT, particularly in patients with low or ambiguous MRI findings (PI-RADS ≤ 3), to improve diagnostic precision and potentially guide biopsy decisions.
Gyneco-logical cancer								
Hong et al, 2024 [47] China	Single centre Prospective diagnostic accuracy study **Objectives:** to investigate the value of **combined** MRI, enhanced CT and ^{18}F-FDG PET/CT in the diagnosis of and metastasis after surgery for ovarian cancer.	95 patients with a history of ovarian cancer surgery No demographics provided.	^{18}F-FDG PET/CT	MRI, enhanced CT PET/CT was compared to MRI and enhanced CT individually and in combination	Histopathology from reoperation, multiple imaging modalities, and clinical follow-up.	Sens: 90.14 Spec: 70.83 Acc: 85.26 PPV: 90.14 NPV: 70.83 AUC (ROC): 0.805 (95% CI: 0.689-0.921, p < 0.001)	MRI Sens: 87.32% Spec: 45.83% Acc: 76.84% PPV: 82.67% NPV: 55.00% Enhanced CT Sens: 85.92% Spec: 41.67% Acc: 74.74% PPV: 81.33% NPV: 50.00% Combined (All): Sens: 97.18% Spec: 95.83% Acc: 96.84% In summary: Combined imaging improved detection of recurrent or metastatic lesions relative to each imaging technology alone (p<0.05)	NA **In summary**: Combining MRI, enhanced CT, and ^{18}F-FDG PET/CT improves the accuracy of detecting recurrent and metastatic lesions in ovarian cancer patients' post-surgery relative to each imaging technology alone (P<0.05). This multimodal approach may enable earlier and more reliable diagnosis, potentially guiding better treatment decisions and improving patient outcomes.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
Lee et al, 2024 [49] Hong Kong ChinaMRI, contrast CT or intraoperative exam.	Single centre Historical retrospective cohort and a Prospective cohort **Objectives**: To compare the diagnostic accuracy of ^{18}F-FDG PET/CT and ceCT in detecting residual disease after **neoadjuvant chemotherapy** in advanced ovarian cancer. To assess the relationship between metabolic uptake and histopathological response.	23 patients in historical retrospective cohort and 46 patients in prospective cohort; patients newly diagnosed with stage III–IV ovarian cancer scheduled for neoadjuvant chemotherapy Prospective validation Cohort: Mean Age (SD): 58 (13) years Historical control: 59 (9) years	^{18}F-FDG PET/CT	contrast-enhanced CT (CeCT)	Histopathology	Historical observational retrospective cohort (overall) Acc: 0.82% Sens: 0.38% Spec: 0.97% PPV: 0.79% NPV: 0.82% Prospective validation cohort (overall) Acc: 0.87% Sens: 0.48% Spec: 0.98% PPV: 0.84% NPV: 0.88%	Historical observational retrospective cohort (overall) Acc: 0.86% Sens: 0.64% Spec: 0.93% PPV: 0.75% NPV: 0.89% Prospective validation cohort (overall) Acc: 0.89% Sens: 0.66% Spec: 0.95% PPV: 0.77% NPV: 0.91%	NA **In summary:** Both modalities had low sensitivity in detecting disease in specific regions (e.g., right subdiaphragmatic space, omentum, bowel mesentery). PET/CT did not provide additional value over ceCT for surgical planning after neoadjuvant chemotherapy. Higher omental SUVmax was associated with histopathological non-response (CRS 1/2), suggesting potential prognostic value.
Malenkovic et al, 2024 [50] Serbia	Single centre Retrospective Cohort study **Objectives**: To evaluate the effectiveness of ^{18}F-FDG–PET–CT in **preoperative staging** of cervical cancer, particularly in assessing operability and LN metastases, compared to intraoperative examination,	62 patients with cervical cancer Age at onset Mean (SD): 49.3 (9.6) years; range: 32 to 76 years	^{18}F-FDG–PET/CT used for pre-operative staging	Intraoperative exam	Histopathology	**Primary tumour detection**: Sens: 86.8% Spec: 100% Accu: 88.7% PPV: 100% NPV: 56.2% **LN metastases detection**: Sens: 53.8% Spec: 89.8%; *p<0.001 Accu: 82.2%; p=0.002 PPV: 58.3% NPV: 88.8%	Primary Tumour detection Sens: 98.1% Spec: 33.3% Accu: 88.7% PPV: 89.7% NPV: 75.0% **LN metastases detection:** Sens: 76.9% Spec: 63.3%* Accu: 66.1%** PPV: 35.7% NPV: 91.2%	NA **In summary:** The authors believe that PET/CT may reduce over-staging and improve preoperative planning. High specificity of PET/CT for primary tumour and lymph node detection supports its use in ruling out disease and guiding surgical decisions.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	using histopathology as the reference standard.							
Virili et al, 2024 [48] Australia	Multicentre Prospective, non-randomized, Phase II (IMAGE trial) (NCT02258165) **Objectives:** a) To compare the diagnostic accuracy of **gated** ^{18}F-FDG PET/CT versus standard contrast-enhanced CT in detecting thoracic and extra-abdominal metastases in newly diagnosed advanced epithelial ovarian cancer. b) To assess changes in International Federation of Gynecology and Obstetrics (FIGO) **staging due to PET/CT** findings. c) To evaluate the impact of PET/CT on clinical management decisions.	67 patients (after excluding 17 with non-epithelial histology) with newly diagnosed, advanced epithelial ovarian cancer Age mean (SD): 64.8 (11)	Gated ^{18}F-FDG PET/CT	CeCT (chest. Abdomen and pelvis);	Histopathology or Clinical follow-up	Diagnostic Accuracy by Site (7.5 min scan): Lung: 99% Liver: 89% Pleura: 83% Extra-abdominal lymph nodes: 42% Other extra-abdominal sites: 89% Overall (PET/CT vs CT): Sens: 77% Spec: 37% PPV: 44% NPV: 53% Accu: 40%	Baseline CT Findings: Distant metastases detected in 36% Inconclusive in 12% Compared to PET/CT: PET/CT detected more pleural, mediastinal, hilar, and supraclavicular nodes CT missed many of these findings, specifically: Pleural Involvement Detected by CT: 10 patients (15%) Detected by 7.5 min PET/CT: 12 patients (18%) Hilar Nodes Detected by CT: 0 patients Detected by 7.5 min PET/CT: 6 patients (9%) Mediastinal Nodes	**Changes in Staging** FIGO Stage Changes (Post 7.5 min PET/CT): Upstaged: 46% (from stage III to IV) Down staged: 8% Conventional CT scan staging had 33% provisionally as stage IV at baseline **Change in Treatment Plan:** Only 5% of patients had a change in management: 2 patients: surgery → chemotherapy 1 patient: chemotherapy → surgery **Change in Survival** NR **In summary:** Compared to standard CT, PET/CT improved detection of thoracic and extra-abdominal metastases, leading to upstaging in nearly half of the patients. However, this enhanced staging translated into a change in clinical management in only 5% of cases. The study highlights the high diagnostic accuracy of gated PET/CT for pleural, liver, and lung metastases, but limited impact on treatment decisions in a setting where neoadjuvant chemotherapy is commonly used. These findings suggest that while PET/CT improves staging precision, its

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
							Detected by CT: 4 patients (6%) Detected by 7.5 min PET/CT: 15 patients (22%) Supraclavicular Nodes Detected by CT: 1 patient (2%) Detected by 7.5 min PET/CT: 7 patients (11%)	influence on management may be context dependent.
Head and Neck cancer								
Banjare et al, 2024 [51] India	Single centre Prospective cross-sectional study **Objectives:** To determine the role of FDG-PET CT in the evaluation of the extent of the primary lesion, nodal staging and distant metastases	50 patients with cytological and histologically proven naive cases of squamous cell carcinoma of the oral cavity, age >18 years Mean Age (SD): 49.7 (11.2) years; range 41–60 years. % male: 78%	^{18}F-FDG-PET CT done within 2 weeks Of ceCT/ MRI SUVMax compared to histological positive nodes	Clinical examination, cytology and imaging tests like ceCT scans, ultrasound, and ceMRI	Histology report after survey Histological positive nodes	NA	NA	**Changes in Staging** FDG PET CT scan induced a pronounced upstaging in 36% (n=18) of cases. Conversely, a distinct subset of cases experienced downstaging by 16% (n=8). Intriguingly, nearly half of the cases (48%) exhibited congruent staging results as determined by conventional CT scans FDG PET CT scans led to significant upstaging in 7 (14%) of cases and downstaging in another 7 (14%). However, 36 (72%) of cases showed consistent staging compared to the initial assessment. **In summary:** This prospective study evaluated the utility of ^{18}F-FDG PET/CT in the **pretreatment staging** of 50

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								patients with histologically confirmed oral squamous cell carcinoma. Compared to conventional imaging (CT/MRI), FDG PET/CT led to upstaging in 36% of T-stage and N-stage cases and identified distant metastases in 20% of patients, doubling the detection rate compared to standard imaging. Importantly, PET/CT SUVmax values >2.5 were significantly associated with histopathological positive lymph nodes ($p < 0.001$), suggesting a strong correlation between metabolic activity and nodal metastasis. The findings support the integration of FDG PET/CT into routine staging workflows for oral cancer, particularly for more accurate assessment of nodal and distant disease and to guide treatment planning.
Cailleteau et al, 2024 [58]	Single centre Retrospective Analysis **Objectives:** a) To evaluate the diagnostic performance of dual-phase ^{18}F-FDG PET combined with mpMRI in differentiating cerebral	23 patients >18 years old who had undergone a dual-phase ^{18}F-FDG PET-mpMRI due to **inconclusive findings** on prior MRI regarding the differentiation between brain tumour radionecrosis and **recurrence**.	Dual phase ^{18}F-FDG PET-mpMRI	mpMRI Inconclusive mpMRI findings post-radiotherapy whose results were deemed to not differentiate radionecrosis and recurrence.	Histopathology of radionecrosis or a composite criterion at 3 months	Qualitative Analysis (diagnosis made by the dual interpretation of the nuclear medicine physician and radiologist using: Out of the 22 evaluable lesions Sens: 85.7% (95% CI [65.7 to 100%]),	NA	NA **In summary:** This retrospective study assessed 24 brain lesions in 23 patients using dual-phase ^{18}F-FDG PET-mpMRI to distinguish radionecrosis from tumour recurrence post-cranial radiotherapy. Using the contralateral frontal lobe improved specificity to 63%.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	radionecrosis from local tumour recurrence following cranial radiotherapy. b) Compare qualitative and semi-quantitative analysis methods, including the Horky retention index, using different reference regions. c) Assess the feasibility and clinical utility of this combined imaging approach in routine practice.	Median Age (Range): 60.5 (29-74) years % male: 43%				Spec: 75% (95% CI 33.3 to 100%]). Semi-quantitative analysis (based on contralateral background noise): Sens: 100% Spec: 50% (95% CI: 0.152-0.848		Notably, diagnostic performance was highest for metastatic lesions, with both sensitivity and specificity reaching 100%. The integration of PET and mpMRI enabled precise lesion characterization, especially in cases where conventional MRI was inconclusive. These findings support the routine use of dual-phase ^{18}F-FDG PET-mpMRI for improved diagnostic accuracy in post-radiotherapy brain lesion assessment, particularly for metastases.
Chan et al, 2024 [52] Taiwan	Single centre Prospective cohort study **Objectives:** a) To evaluate the diagnostic performance of ^{18}F-FET PET/CT in identifying brain tumours in an Asian patient cohort with indeterminate MRI findings. b) To compare the accuracy of ^{18}F-FET PET/CT with ^{18}F-FDG PET/CT. c) To assess the utility of semiquantitative parameters such as TBR, Time to Peak and dynamic	33 patients with primary or recurrent brain tumours on MRI or undergoing restaging for glioma The patients underwent both ^{18}F-FET and ^{18}F-FDG PET/CT Mean age (SD) years: 54 (14) % male: 64%	^{18}F-FDG PET/CT SUV in the tumour or the TBR	^{18}F-FET PET As a radiolabeled amino acid analogue, ^{18}F-FET offers advantages over the traditional ^{18}F-FDG PET, particularly in distinguishing tumours from inflammation [11, 12]	Histopathology or follow-up MRI	^{18}F-FDG PET/CT Sen: 73.1% Spe: 71.4% Acc: 72.7% PPV: 90.5% NPV: 41.7%	^{18}F-FET PET Sen: 96.2%* Spe: 85.7% Acc: 93.9%** PPV: 96.2% NPV: 85.7% ^{18}F-FET PET/CT vs. 18F-FET PET *(p=0.031) **(p=0.030)	NA **In summary:** This prospective study of 33 patients with suspected brain tumours or glioma recurrence demonstrated that ^{18}F-FET PET/CT significantly outperforms ^{18}F-FDG PET/CT in diagnostic accuracy (93.9% vs. 72.7%) and sensitivity (96.2% vs. 73.1%). The use of TBR mean values further enhanced diagnostic performance, achieving 100% sensitivity and NPV. Similarly, dynamic curve pattern showed 100% specificity and 100% PPV Other dynamic imaging features such as Time to Peak also contributed to high PPV.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	curve patterns in improving diagnostic accuracy compared to visual interpretation.							Importantly, ^{18}F-FET PET/CT effectively differentiated tumour recurrence from post-treatment changes and benign lesions, making it a valuable adjunct to MRI in cases with inconclusive findings. The study supports broader clinical adoption of ^{18}F-FET PET/CT in neuro-oncology, especially in Asian populations. Note: "Gliomas in East Asian populations differ in epidemiology and genomic characteristics compared to those in other ancestry groups"
Clement et al, 2024 [57] France	Single centre Retrospective cohort study **Objectives:** a) To evaluate the diagnostic performance of ^{18}F-FDG PET/CT in detecting **SCR** of head and neck squamous cell carcinoma during post-treatment follow-up. b) To assess how diagnostic performance varies with time since treatment. c) To identify predictive factors associated with SCR detection using PET/CT.	852 adult patients with newly diagnosed with head and neck squamous cell carcinoma who received curative treatment between 2006 and 2021. Mean age (range): 63 (32 to 94) % male: 82%	^{18}F-FDG PET/CT	All patients' follow-up consisted of a conventional work-up according to guidelines, including clinical examinations every 2 months during the first year, every 3 months during the second year, every 4 months during the third year, every 6 months during the fourth and fifth years, and then annually. As recommended, 18F-FDG PET/CT was performed 3 months after	Histologic sampling, or by morphologic or metabolic progression on subsequent imaging within 3 months	The overall diagnostic performance of ^{18}F-FDG PET/CT PPV: 88%, NPV: 98%, Sens: 98%, Spec: 89%, Accu: 93% The overall detection rate of sub clinical recurrence by ^{18}F-FDG PET/CT was 14.7% (126/852). Of the 852 patients, 26% (221/852) had a recurrence of head and neck cancer, of which 57% (126/221)	NA	**In summary:** In this large retrospective study of 852 asymptomatic patients with head and neck squamous cell carcinoma, 2566 ^{18}F-FDG PET/CT scans were analyzed to assess their utility in detecting subclinical recurrence (SCR) and metachronous cancers. PET/CT demonstrated high diagnostic performance, with sensitivity and negative predictive value of 98%, specificity of 89%, and overall accuracy of 93%. Most SCRs (84%) were detected within the first two years post-treatment. Advanced tumour stage, PET-based upstaging at initial assessment, and higher body mass index were

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				radiotherapy for patients with node-positive disease to assess the necessity of neck dissection.		were detected by ^{18}F-FDG PET/CT.		independently associated with increased SCR detection. The study supports routine use of ^{18}F-FDG PET/CT in follow-up, particularly within the first two years, to improve early detection and enable curative intervention for recurrent disease.
Cobes et al, 2023 [59] France	Single centre Retrospective cohort study **Objectives:** a) To investigate the correlation between ^{18}F-FDOPA PET uptake and histomolecular characteristics, particularly LAT1 expression, in recurrent high-grade gliomas. b) To assess the impact of ^{18}F-FDOPA uptake and LAT1 expression on progression-free and overall survival in patients previously treated with chemoradiation.	39 patients with recurrent high-grade glioma, who underwent ^{18}F-FDOPA PET followed by brain surgery within 6 months following PET, between February 2016 and October 2020 Median age all patients (range): 57 (33 to 87) years % male all patients: 67%	^{18}F-FDOPA PET/CT or ^{18}F-FDOPA PET/MRI	NR	Histological examination	NA	NA	**Change in Survival** The median follow-up time was 16 months (range, 4–58 months) In the isocitrate dehydrogenase (IDH)-mutant gliomas subgroup, a threshold >100 (median) for the LAT1 score was a predictor of longer progression free survival. (19 vs. 7 months, p< 0.005). The analysis of overall survival showed a persistent trend, (p=0.06). **In summary:** This retrospective study analyzed 39 patients with recurrent high-grade gliomas who underwent ^{18}F-FDOPA PET imaging followed by surgical resection. The authors believe their study is the first to suggest a link between LAT1 expression and IDH mutation status. The study found that IDH-mutant gliomas exhibited significantly higher ^{18}F-FDOPA uptake (TBRmax) and LAT1 expression compared

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								to IDH-wildtype glioblastomas. While no linear correlation was found between LAT1 expression and PET uptake across all subtypes, higher TBRmax was linked to elevated LAT1 levels. These findings suggest that LAT1 expression may contribute to 18F-FDOPA uptake and could serve as a prognostic marker in recurrent gliomas. The study supports further exploration of LAT1 as a therapeutic target and the role of amino acid PET tracers in post-treatment glioma evaluation.
De Koster, 2024 [53] Netherlands	Multicentre Prospective, triple-blinded, randomized controlled (Evaluation of Cytological indeterminate Thyroid nodules before Surgery (EfFECTS) trial NCT02208544) **Objectives:** a) To evaluate and compare the diagnostic performance of MD and ^{18}F FDG-PET/CT in patients with cytologically indeterminate thyroid nodules (Bethesda III/IV).	132 patients with a Bethesda III/IV thyroid nodule Mean Age (SD): 54.4 (13.7) years % male: 19%	^{18}F-FDG-PET/CT	MD which included total nucleic acid (DNA and RNA) was isolated from tumour cells scraped off cytology slides or from micro-dissected cytology cell blocks	Histopathology or active surveillance in case thyroid surgery was not performed	Concordance MD and [^{18}F] FDG-PET/CT were concordant in 63% (72/115) of cases (Table 4) Diagnostic Accuracy MD on cytology (n = 115), assuming nodules under active surveillance are benign Sens: 93% [95% CI 78% to 99%] Spec: 41% [95% CI 31% to 52%] PPV: 36% [95% CI 25% to 48%] NPV: 95% [95% CI 82% to 99%] MD on cytology (n = 92), surgically	MD was successful on cytology in 115 (87%) patients MD on cytology (n = 115), assuming nodules under active surveillance are benign: Sens: 80% [95% CI 61%-92%] Spec: 69% [95% CI 59%-79%] PPV: 48% [95% CI 34%-63%] NPV: 91% [95% CI 81%-97%]	NR **In summary:** In this prospective multicenter study of 132 patients with indeterminate thyroid nodules, both molecular diagnostics (MD) and [^{18}F] FDG-PET/CT demonstrated high NPV—91% and 95%, respectively—making them effective rule-out tools. However, their PPV was limited (48% for MD, 36% for PET/CT); this was especially noted in oncocytic nodules where PET/CT had a benign call rate of only 3%. **Combining both tests improved specificity but added limited clinical value in most cases**. In nononcocytic nodules, sequential testing may be considered when MD is

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	b) To assess the value of combining both techniques in clinical decision-making. c) To explore whether specific molecular alterations explain 18F FDG uptake in benign thyroid nodules. Note supplementary file for flowchart of test processes. Figure S3 shows flow algorithm for test use.					confirmed cases benign Sens: 93% [95% CI 78% to 99%] Spec: 24% [95% CI 14% to 37%] PPV: 36% [95% CI 26% to 49%] NPV: 95% [95% CI 64% to 99%] Combined modalities: Double negative test (defined as negative MD in combination with a negative [^{18}F] FDG-PET/CT (MD-/[^{18}F] FDG-)): Sens: 95% Spec: 44% Double positive test (defined double-positive test (MD+/[^{18}F] FDG+); in these scenarios, all other combinations of test results were considered test positive or test negative, respectively): Sens: 68% Spec: 86%	MD on cytology (n = 92), surgically confirmed cases benign Sens: 80% [95% CI 61%-92%] Spec: 66% [95% CI 53%-78%] PPV: 53% [95% CI 38%-68%] NPV: 87% [95% CI 74%-95%]	negative to safely avoid surgery. In oncocytic nodules, MD including copy number alteration analysis appears more promising than PET/CT. The study supports a tailored, cost-conscious approach to preoperative evaluation, emphasizing MD as the preferred first-line test in most settings.
Gupta R et al, 2024 [54] India	Single centre Prospective cohort study **Objectives:**	80 Patients with Head and Neck Tumours Mean Age (SD): 55.2 (10.4) years	PET/CT	Other imaging modalities (CT, functional MRI, MR spectroscopy, OCT)	Histopathology	PET Sens: 95% Spec: 88% Acc: 91.5% PPV: 96% NPV: 85%	CT Sens: 85% Spec: 80% Acc: 82.5% PPV: 88% NPV: 75%	NA **In summary:** This prospective study evaluated the diagnostic

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	To assess the diagnostic accuracy and clinical utility of advanced imaging modalities, including CT, functional MRI, MR spectroscopy, PET-CT, and OCT, in managing head and neck malignancies.	% male: 62.5%					MRI/MR Sens: 90% Spec: 85% Acc: 87.5% PPV: 92% NPV: 80% OCT Sens: 92 Spec: 95 Acc: 93.5 PPV: 97 NPV: 90	performance of advanced imaging modalities—CT, functional MRI, MR spectroscopy, PET-CT, and OCT—in 80 patients with suspected or confirmed head and neck malignancies. PET-CT demonstrated the highest sensitivity (95%) and positive predictive value (96%) for detecting metastases, while OCT showed the highest specificity (95%) and overall accuracy (93.5%) for early tumour detection. Radiological evaluations led to accurate staging in 93.8% of cases and influenced treatment plans in 25% of patients. Integration of multimodal imaging significantly enhanced diagnostic precision, staging accuracy, and early metastasis detection, underscoring its critical role in personalized treatment planning for head and neck cancers.
Henriksen et al, 2024 [55] Denmark	Single centre Phase II, open-label, prospective translational study **Objectives:** a) To evaluate the utility of [^{18}F] FET PET and contrast-enhanced MRI for early response assessment in patients with recurrent high-grade astrocytic glioma treated	20 patients with first recurrence of nonresectable high-grade astrocytic glioma WHO grade IV Demographics not reported	^{18}F-FET PET/MRI	CeMRI	Clinical follow-up (OS >11 months)	ROC AUC for Predicting Response (OS > 11 months): PRM plus (volume of tumour suggesting progression): 0.843 (cutoff: 4.0 mL, sensitivity: 80%, specificity: 100%) Change in tumour to background ratio, maximum) ΔTBR max: 0.814	MRI RANO Classification : Not predictive of response (ROC AUC = 0.671, p=0.188) Borderline association with OS (p=0.140 for PD vs. non-PD)	**Change in Survival** OS: Responders (OS > 11 months): Median OS = 15.4 months Nonresponders: Median OS = 4.8 months PET Metrics Predictive of overall survival: PRM plus, PRM net, MTV at follow-up and the largest predictor, ΔTBR max (OS HR: 2.807 (95% CI: 1.173–4.714)

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	with a **combination of nivolumab (PD-1 inhibitor) and bevacizumab** (VEGF inhibitor). b) To identify imaging biomarkers— specifically PET-derived metrics such as: MTV, TBR (TBR mean and TBR max) PRM metrics — that can predict treatment response and OS. c) To compare the predictive value of standard MRI-based RANO 2.0 criteria and PET-based PET RANO 1.0 criteria for assessing treatment response and survival outcomes. d) To explore whether PRM analysis of ^{18}F-FET PET provides additional value over conventional whole-tumour PET metrics in identifying responders (defined as OS > 11 months).					(cutoff: −0.53, sens: 70%, spec: 100%) (A decrease in TBR indicates a favourable treatment response). MTV at follow-up: 0.771 (cut-off: 18.3 mL). A smaller MTV at follow-up or a decrease in MRV indicates a favourable treatment response). PET Response Assessment in Neuro-Oncology (RANO) Classification: Borderline predictive of OS (p=0.056 for progressive disease vs. non-progressive disease)	Contrast-enhancing volume: Decreased in both responders and nonresponders Not predictive of response	MRI Metrics: Not predictive of overall survival or response **In summary:** The study indicates that [^{18}F] FET PET is superior to contrast-enhanced MRI for early response assessment in patients with recurrent high-grade astrocytic glioma treated with nivolumab and bevacizumab This may guide treatment continuation or discontinuation decisions.
Koroglu et al, 2024 [60] Turkey	Single centre Retrospective study **Objectives**:	50 patients with head and neck squamous cell carcinoma. PET/CT	^{18}F-FDG PET/CT	NA	Histopathology Results after neck dissection,	All time intervals Sens: 77.5% Spec: 71.7% PPV: 73.8% NPV: 75.6%	NA	NA **In summary:** The study suggests that PET/CT is most reliable

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	To assess the diagnostic performance of ^{18}F-FDG PET/CT in detecting cervical lymph node metastases in head and neck squamous cell carcinoma. To evaluate how the time interval between PET/CT and surgery affects its accuracy.	was performed prior to surgery Mean Age (SD): 59.08 (11.32) and range 29 to 84 years			17 (34%) patients had stage N0, three (6%) had stage N1, two (4%) had stage N2a, 16 (32%) had stage N2b, seven (14%) had stage N2c, and five (10%) had stage N3b	Acc: 74.6% By time interval: 0-2 weeks Sens: 100% Spec: 90% PPV: 92.8% NPV: 199% Acc: 95.6% 0-3 weeks Sens: 95% Spec: 82.3% PPV: 86.3% NPV: 93.3% Acc: 89.1% 0-4 weeks Sens: 90.9% Spec: 80% PPV: 80% NPV: 90.9% Acc: 85.1% 0-5 weeks Sens: 82.1% Spec: 70.3% PPV: 74.1% NPV: 79.1% Acc: 76.3% 0-6 weeks Sens: 78.7% Spec: 71.4% PPV: 76.4% NPV: 74.1% Acc: 75.4%		when performed within 2 weeks before surgery, and its diagnostic value diminishes significantly after 4 weeks, which could influence surgical planning and timing. PET/CT resulted in 66% accurate staging, 16% over-staging, and 18% low staging in determining the N of patients who underwent surgery within 4 weeks after imaging.
Li Y et al, 2024 [56] China	Single centre Prospective Cohort study **Objectives**: To evaluate the diagnostic performance of Intravoxel incoherent motion	62 patients with nasopharyngeal carcinoma Median Age (range): 54 (30-77) years % male: 79.0%	^{18}F NaF PET/CT	Intravoxel incoherent motion diffusion-weighted imaging; conventional MRI	Histopathology	Sens: 80.1% Spec: 90.4% AUC: 0.852 (95% CI: 0.812–0.887)	Conventional MRI Sens: 91.2% Spec: 91.7% AUC: 0.914 (95% CI: 0.881–0.941), Intravoxel incoherent	NA **In summary:** In patients with nasopharyngeal carcinoma, the combination of intravoxel incoherent motion diffusion-weighted imaging and conventional MRI demonstrated superior

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	diffusion-weighted imaging combined with conventional MRI versus ^{18}F-NaF PET/CT in detecting skull base invasion in nasopharyngeal carcinoma.						motion diffusion-weighted imaging plus conventional MRI Sens: 92.6% Spec: 96.8% AUC: 0.947, (95% CI: 0.919–0.967)	diagnostic performance for detecting skull base invasion compared to [^{18}F] NaF PET/CT. Intravoxel incoherent motion diffusion-weighted imaging plus conventional MRI outperforming PET/CT in detecting skull base invasion in critical substructures such as the petrous part of the temporal bone, pterygopalatine fossa, and foramen ovale. This combined imaging approach offers a non-invasive, radiation-free, and highly accurate method for skull base invasion assessment, supporting its clinical utility in staging, treatment planning, and prognosis evaluation in nasopharyngeal carcinoma.
Liang M et al, 2024 [61] China	Single centre Retrospective cohort study **Objectives**: To evaluate the supplementary diagnostic value of ^{18}F-NaF PET/CT in detecting skull-base bone invasion in nasopharyngeal carcinoma patients, compared to MRI alone	164 patients with nasopharyngeal carcinoma Mean Age (SD): 50.13 (11.95) % male: 76%	^{18}F-NaF PET/CT	MRI PET/CT + MRI	Clinical follow-up at 17 months	Patient level analysis (n=164): Sens: 100% (95% CI: 1.000–1.000) Spec: 93.1% (95% CI: 0.875–0.986) Acc: 97% (95% CI: 0.945–0.994) PPV: 94.8% (95% CI: 0.902–0.989) NPV: 100% (95% CI: 1.000–1.000) Lesion-level analysis (n=329): Sens: 99.6% (95% CI: 0.989–1.000) Spec: 75.9% (95% CI: 0.638–0.862) Acc: 95.4% (95% CI: 0.933–0.973)	Patient level analysis MRI Sens: 90.0% (95% CI: 0.837–0.957) Spec: 98.6% (95% CI: 0.958–1.000) Acc: 93.9% (95% CI: 0.902–0.97) PPV: 98.8% (95% CI: 0.964–1.000) NPV: 88.7% (95% CI: 0.824–0.947) PET/CT + MRI	NA **In summary:** In patients with nasopharyngeal carcinoma, the combined use of ^{18}F NaF PET/CT and MRI improved the detection of skull-base bone invasion compared to MRI alone. The integrated approach achieved 100% sensitivity and 98.8% accuracy at the patient level, and 100% sensitivity and 98.5% accuracy at the lesion level. This enhanced diagnostic performance supports the use of ^{18}F NaF PET/CT as a valuable supplement to MRI,

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						PPV: 95.1% (95% CI: 0.931–0.971) NPV: 97.8% (95% CI: 0.925–1.000)	Sens: 100% (95% CI: 1.000–1.000) Spec: 97.2% (95% CI: 0.931–1.000) Acc: 98.8% (95% CI: 0.97–1.000) PPV: 97.9% (95% CI: 0.948–1.000) NPV: 100% (95% CI: 1.000–1.000) Acc for PET/CT vs MRI p=0.034 Lesion-level analysis MRI Sens: 88.2% (95% CI: 0.845–0.919) Spec: 93.1% (95% CI: 0.862–0.983) Acc: 89.1% (95% CI: 0.854–0.924) PPV: 98.4% (95% CI: 0.968–0.996) NPV: 62.8% (95% CI: 0.553–0.713) Acc PET/CT vs MRI p < 0.001 PET/CT + MRI Sens: 100% (95% CI: 1.000–1.000)	particularly for identifying small or complex bone lesions, and may improve staging accuracy and treatment planning in nasopharyngeal carcinoma.

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							Spec: 91.4% (95% CI: 0.845–0.983) Acc: 98.5% (95% CI: 0.970–0.997) PPV: 98.2% (95% CI: 0.964–0.996) 1.000) NPV: 100% (95% CI: 1.000–1.000)	
Navran et al, 2024 [62] Netherlands	Single centre Retrospective cohort study **Objectives**: To assess the impact of incorporating FDG-PET/CT into post-treatment response evaluation for head and neck squamous cell carcinoma 3 months after chemotherapy/ radiotherapy), particularly in guiding the need for salvage neck dissection.	908 patients with node-positive head and neck squamous cell carcinoma treated with chemo/ radiotherapy Median Age: 62 years % male: 71%	^{18}F-FDG PET/CT	MRI/CT + ultrasound-guided fine needle aspiration received 3 months after chemotherapy. Pretreatment evaluation also included physical examination, laryngoscope, chest x-ray.	Histopathology	Sens: 77% (95% CI: 59–90%) Spec: 92% (95% CI: 78–98%) PPV: 89% (95% CI: 71–98%) NPV: 97.5%	Sens: 58% (95% CI: 42–72%) Spec: 79% (95% CI: 67–88%) PPV: 65% (95% CI: 48–79%) NPV: 75%	**Change in Treatment** Reduction in Unnecessary salvage neck dissections: FDG-PET/CT use led to a 22% reduction in unnecessary salvage neck dissection. Improved Selection: In the later study period (with more PET use), 53% of salvage neck dissections revealed pRND vs. 31% in the earlier period (p=0.008). **Change of Survival** At a median follow-up of 43 months: 5-Year Outcomes: Regional Recurrence-Free Survival: 88% disease-free survival: 55% Overall survival: 59% cancer-specific survival: 73% Impact of pRND: Significantly worse regional recurrence free survival, disease free survival, OS, and cancer-specific survival in patients with pRND (all p<0.01). pRND was an independent predictor of poor outcomes

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								in multivariable Cox regression. **In summary:** FDG-PET/CT outperformed conventional imaging (MRI/CT + ultrasound-fine needle aspiration) in identifying patients with residual neck disease after (chemo)radiotherapy for head and neck squamous cell carcinoma. Its use improved patient selection for salvage neck dissection, reduced unnecessary surgeries, and maintained excellent oncologic outcomes in patients with complete metabolic response.
Patel et al, 2024 [63] USA	Multicentre Retrospective cohort study **Objective**: To compare the diagnostic performance of four surveillance modalities—endoscopy, CT, PET/CT, and MRI—in detecting recurrence of sinonasal squamous cell carcinoma.	105 patients with histologically confirmed sinonasal squamous cell carcinoma Mean Age (SD): 62.3 (12.1) years	^{18}F-FDG PET/CT Used as a standardized surveillance once a year	Endoscopy CT MRI	Histopathology	Sens: 95.2% (95% CI: 91.7- 98.7) Spec: 90.8% (95% CI: 86.0, 95.6) PPV: 64.5% (95% CI: 56.6 - 72.4) NPV: >97% (95% CI: 95.1 - 100.1)	Endoscopy: Sens:18.5% (95% CI: 15.7-21.3) Spec: 99.2% (95% CI: 98.6-99.8) PPV: 45.5% (95% CI: 41.9-49.1) NPV: 97.0% (95% CI: 95.8, 98.2) CT: Sens: 75% (95% CI: 67.7-82.3) Spec: 100% (95% CI: 100.0- 100.0) PPV: 100% (95% CI: 100.0- 100.0)	NA **In Summary:** PET/CT is the most sensitive modality for detecting sinonasal squamous cell carcinoma recurrence, while endoscopy offers high specificity and NPV. NPV were almost identical across modalities and was >97% and suggests that all tests are highly reliable to confirm the absence of sinonasal squamous cell carcinoma recurrence. A multimodal surveillance strategy tailored to patient risk factors is recommended, especially beyond the 6-month post-treatment period suggested by current guidelines.

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							NPV: 97.6% (95% CI: 94.9 - 100.3) MRI: Sens: 72.4% (95% CI: 68.1 - 76.7) Spec: 97.1% (95% CI: 95.5 - 98.7) PPV: 65.6% (95% CI: 61.0 - 70.2) NPV: 97.9% (95% CI: 96.5 - 99.3)	
Sharma et al, 2024 [64] USA	Single centre Retrospective chart review **Objective**: to describe the management and outcomes of patients with persistent lymphadenopathy after primary chemoradiation for head and neck squamous cell carcinoma based on post-treatment PET/CT results.	63 patients with head and neck squamous cell carcinoma treated with primary concurrent chemoradiation Mean age (SD) at diagnosis: 60.23 (9.18) years % male: 84.1%	^{18}F-FDG PET/CT	Clinical observation and/or neck dissection	Histopathology or clinical follow-up	Sens: 54.5% Spec: 68.3% PPV: 48.0% NPV: 73.7% Study shows flow diagram of patients stratified by positive and negative PET results for nodes	64.7% of patients who underwent neck dissection had residual cancer All 11 biopsied patients had findings concerning malignancy	**Change in Treatment** 61.9% managed conservatively (observation) 27.0% underwent neck dissection 11.1% received palliative care PET-positive patients were significantly more likely to undergo surgery (p=0.042) **Change in Survival** OS rate: 60.3% No statistically significant difference in OS between PET-positive and PET-negative patients (p=0.081) **In summary:** This retrospective study evaluated 63 patients with head and neck squamous cell carcinoma who had persistent cervical lymphadenopathy after chemoradiation and

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								underwent post-treatment ^{18}F-FDG PET/CT. The study found that PET/CT had a lower-than-expected positive predictive value (48%) and negative predictive value (74%) for detecting residual neck disease in this subset. Most patients (62%) were managed conservatively, and PET-positive patients were more likely to undergo neck dissection. Biopsy findings were significantly associated with worse overall survival, as were larger post-treatment nodes and late-stage disease. The findings suggest that while PET/CT remains a valuable tool, its predictive accuracy is reduced in patients with persistent lymphadenopathy, and clinical decisions should be guided by a combination of imaging, biopsy, and clinical judgment.
Van Nuffel et al, 2024 [65] Belgium	Single centre Retrospective cohort study **Objectives**: To evaluate the role of ^{18}F-FDG PET/CT in detecting: a. Recurrences (local, regional, distant) b. Secondary primary malignancies	132 patients with curatively treated oropharyngeal or hypopharyngeal squamous cell carcinoma Median Age (range): 59 (41-79) years % male: 67.4%	^{18}F-FDG PET/CT	Clinical examination (clinical and fiber-optic endoscopy) MRI CT Ultrasound No direct comparator imaging modality was statistically compared.	Histopathology or radiological progression within 6 months	Spec: 85–100% NPV: 83–100% Sens and PPV: Variable (56–100% and 20–100%, respectively) Accu: Reached 100% after 3.5 years post-treatment	Clinical Examination: Detected 17 of 40 locoregional recurrences Detected only 1 of 17 distant metastases	**Change in Survival** No important survival difference for locoregional recurrences detected by PET/CT vs clinical exam. Significant survival benefit (median 18.5 vs 4.9 months, $p<0.05$) for asymptomatic patients with distant metastases detected by PET/CT compared to symptomatic patients Detection of Secondary Primary Malignancies:

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	To assess the diagnostic accuracy of PET/CT over time To explore the impact of PET/CT-detected asymptomatic metastases on survival							33 detected; 48% first identified by PET/CT Estimated incidence: ~5% per year **In summary:** The results showed low sensitivity (33.3%) but high specificity (93.3%), highlighting the limitations of FDG PET/CT in detecting sclerotic bone metastases, which are more common in invasive lobular carcinoma (ILC). The study suggests that alternative imaging modalities, such as ^{18}F-FES or ^{68}Ga-FAPI PET/CT, may offer improved detection in this patient population. These findings underscore the need for tailored imaging strategies in ILC and support further research into more effective molecular imaging techniques.
Zhang Z et al, 2024 [66] Austria/ China	Single centre Retrospective Cohort study **Objectives**: Evaluate the diagnostic value of ^{18}F F-DOPA PET/CT in MTC Assess its prognostic value Determine optimal cut-off values for calcitonin (basal calcitonin and stimulated calcitonin) and	109 patients with thyroid cancer: 50 with primary MTC, and 59 with recurrent MTC. Subtypes: hereditary MTC (n=12) Sporadic MTC (n=97)	^{18}F-F-DOPA PET/CT	NA	Histopathology or follow-up	Patient-Level Sens: 95% Spec: 93% Accu: 94% Lesion-Level Overall Sens: 65% Spec: 99% Accu: 72% For LN metastases: Sens: 54% Spec: 98% Accu: 59%	NA	NA **In summary:** ^{18}F F-DOPA PET/CT is highly effective for diagnosing and prognosticating MTC, especially in recurrent cases. It shows excellent patient-level diagnostic accuracy and strong prognostic value through MTV and SUVmean. It may be less sensitive for small lymph node or lung metastases. PET/CT positivity and high MTV are associated with

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	CEA for PET positivity Explore the correlation between PET parameters and survival					For distant metastases: Sens: 88% Spec: 100% Accu: 92%		worse survival in recurrent MTC. SUVmean in certain organs may serve as novel prognostic biomarkers.
Hemato-logical cancer								
Doma et al, 2024 [68] Slovenia	Single centre Retrospective cohort study **Objectives:** a) To evaluate the diagnostic performance of ^{18}F-FDG PET/CT compared to bone marrow biopsy in detecting bone marrow involvement in patients with stage II–IV DLBCL. b) To assess the concordance between PET/CT and bone marrow biopsy findings. c) To determine the prognostic impact of bone marrow involvement on OS.	145 Patients with histological confirmation of DLBCL; stage II to IV disease Median Age (range): 65 (20-79) years % male: 55.9%	^{18}F-FDG PET/CT	NR	Invasive bone marrow biopsy	Concordance Concordant results between PET/CT and bone marrow biopsy were observed in 115 (79.3%) patients; in 102 (70.3%) negative and 13 (9.0%) positive. Discordant results were seen in 30 (20.7%) patients; in 25 (17.2%) with true positive PET/CT and false negative bone marrow biopsy and in 5 (3.4%) with false negative PET/CT and true positive bone marrow biopsy. Diagnostic Accuracy DLBCL bone marrow involvement was detected in 38 patients (26.2%) by PET/CT	DLBCL bone marrow involvement was detected in 18 patients (12.4%) by bone marrow biopsy Bone marrow biopsy for the detection of DLBCL bone marrow involvement: Sens: 41.9% (95% Cl; 27.0–57.9), Spec: 100% (95% Cl; 84.6–100), PPV: 100% (95% Cl; 0–0), NPV: 46.8% (9 5% Cl; 40.6–53.1), and Acc: 61.5% (95% Cl; 48.6–73.3).	NR **In summary:** In this retrospective study of 145 patients with stage II–IV DLBCL, 18F-FDG PET/CT demonstrated superior diagnostic performance over bone marrow biopsy for detecting bone marrow involvement, with sensitivity, specificity, and accuracy of 88.4%, 100%, and 96.5%, respectively. Bone marrow biopsy showed lower sensitivity (41.9%) and accuracy (61.5%). PET/CT identified more cases of bone marrow involvement (26.2%) than bone marrow biopsy (12.4%), and combining both methods increased detection to 29.7%. Importantly, bone marrow involvement status did not significantly affect 5-yearyear OS, which remained high across all groups (82% overall). These findings support the use of PET/CT as a non-invasive, accurate alternative to bone marrow biopsy for staging DLBCL, with limited prognostic impact of bone

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						^{18}F-FDG PET/CT for the detection of DLBCL bone marrow involvement: Sens: 88.4% (95% CI; 74.9–96.1), Spec: 100% (95% CI; 96.4–100), PPV: 100% (95% CI; 0–0), NPV: 95.3% (95% CI; 89.9–97.9) and Acc: 96.5% (95% CI; 92.1–98.9).		marrow involvement on survival in this cohort.
Gupta DK et al, 2024 [71] India	Single centre Retrospective cohort study comparing two groups of patients **Objectives:** to determine the significance of PET-CT (SUVmax 5.0 or above) in determining remission or pathological status in patients with lymphoma	1) Group A: 40 patients with lymphoma (21 Hodgkin lymphoma, 19 Non-Hodgkin's lymphoma) in the post-chemotherapy setting. 2) Group B: 40 non-lymphoma patients with similar FDG uptake (SUVmax ≥ 5.0) in Waldeyer's Ring or neck Group A: Age categories: < 18: 35% 19 to 45 yrs: 40% > 45 yrs: 25% % male: 62.5% Group B: Age range: 30 to 70 years % male: 27.5%	^{18}F-FDG PET/CT	Group A: Histopathology Group B: Clinical correlation	Histopathology (Group A)	Sens: 90% Spec: 10% AUC: 0.478 (95% CI: 0.350 to 0.605)	All 40 patients had FDG-avid lesions with SUVmax ≥ 5.0. None were found suspicious for malignancy upon thorough clinical evaluation. No invasive procedures were performed. No false negatives were reported, suggesting high NPV in this context In summary: Clinical correlation alone, without	**Change in Staging** Only 6 out of 40 lymphoma patients (15%) had histologically confirmed relapse. 34 patients had reactive hyperplasia despite high SUVmax. None of the 40 non-lymphoma patients required biopsy or further intervention after clinical correlation. **In summary:** Routine biopsy for all FDG-avid lesions post-chemotherapy is not recommended unless accompanied by a suspicious clinical picture of asymmetry, significant lymph node involvement with FDG avid uptake and counterpart findings on CT.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
							biopsy, was sufficient to rule out malignancy in all control patients, supporting its utility in avoiding unnecessary invasive procedures when the clinical picture is not suspicious	
Huang et al, 2024 [69] China	Retrospective observational study **Objectives:** To research diagnostic and prognostic values of ^{18}F FDG PET/CT in patients with DLBCL.	98 patients with newly diagnosed DLBCL Age: >65yrs: 57% <65yrs: 43% % male: NR	^{18}F-FDG PET/CT	B-scan ultrasonography for initial staging and lesion detection	Histopathology and clinical follow-up	271 of 286 lesions determined by PET/CT Sens: 94.75%	239 of 286 lesions determined by B-scan ultrasonography Sens: 83.56%	**Change in survival** 3-year progression free survival rate: 66.32% 3-year overall survival rate: NR **In summary:** ^{18}F-FDG PET/CT demonstrated superior diagnostic sensitivity and staging accuracy compared to B-scan ultrasonography in DLBCL. PET/CT metabolic parameters (especially MTV and TLG) were strong predictors of recurrence, progression, and survival, supporting its role in both diagnosis and prognosis evaluation.
Shi et al, 2024 [70] China	Retrospective cohort study **Objective**: To evaluate the diagnostic and prognostic value of CT, ultrasound, PET/CT, combined imaging in the detection	76 patients with pathologically confirmed lymphoma PET group (n=22) Mean Age (SD): 53.7 (6.9) years Range: 40 to 79 years	^{18}F-FDG PET/CT (n=22)	CT (n=18) Ultrasound (n=19) Combination (PET/CT +CT+ ultrasound) (n=33)	Histopathology	Sens: 91.7% Spec: 81.2% PPV: 85.9% NPV: 58.9% AUC: 0.793 (p=0.002)	CT Sens: 85.3% Spec: 42.0% PPV: 82.4% Ultrasound Sens: 83.2% Spec: 41.0% PPV: 80.1% Combination	NR **In summary:** PET/CT, especially when combined with CT and ultrasound, provides improved diagnostic accuracy and prognostic value in lymphoma. It is particularly effective in early detection and staging,

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	and staging of lymphoma	CT group (n=18): Mean Age (SD): 51.5 (7.5) years Range: 38 to 74 years Ultrasound group (n=19): Mean Age (SD): 50.8 (8.1) years Range: 41 to 70 years Combination group (n=33): Mean Age (SD): 50.8 (8.1) years Range: 41 to 70 years					Sens: 93.6% Spec: 89.7% PPV: 95.7%	though cost and radiation exposure remain limitations.
Singla et al, 2024 [67] India	Prospective study **Objectives:** To assess the concordance between ^{18}F-FDG PET/CT and bone marrow biopsy in detecting bone marrow involvement in newly diagnosed lymphoma patients. To evaluate diagnostic performance metrics of PET/CT compared to bone marrow biopsy.	75 newly diagnosed, adult lymphoma patients Demographics not reported	^{18}F-FDG PET/CT	NA	Bone marrow biopsy	Overall Concordance with bone marrow biopsy: 88% Overall (n = 75): Sens: 69.2% Spec: 93.4% PPV: 69.2% NPV: 93.4% Accu: 89.1% By Subtype: *Hodgkin lymphoma (n=12):* Concordance: 92% Sens: 100% Spec: 88.9% PPV: 75.0% NPV: 100% Accu: 91.7% *Non-Hodgkin lymphoma (n=63):* Concordance: 93% Sens: 54.6% Spec: 94.2% PPV: 66.7% NPV: 90.7%	NA	NR **In summary:** PET/CT demonstrated high concordance (88%) with bone marrow biopsy overall, with particularly strong performance in Hodgkin lymphoma, high-grade non-Hodgkin lymphoma, and T-cell non-Hodgkin lymphoma.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						Accu: 87.3% *High-grade Non-Hodgkin lymphoma (n=53):* Concordance: 91% Sens: 50% Spec: 95.7% PPV: 60.0% NPV: 93.8% Accu: 90.6% *Low-grade Non-Hodgkin lymphoma (n=10):* Concordance: 70% Sens: 60% Spec: 80% PPV: 75% NPV: 66.7% Accu: 70% *DLCBL (n=39)* Concordance: 92% Sens: 66.7% Spec: 94.4% PPV: 50.0% NPV: 97.1% Accu: 92.3% *T-cell Non Hodgkin lymphoma (n=9):* Concordance: 100% Sens: 66.7% Spec: 94.4% PPV: 50.0% NPV: 97.1% Accu: 92.3%		
Infection and inflammation								

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
Becker et al, 2024 [72] Denmark	Retrospective Chart Analysis **Objectives:** the application of ^{18}F-FDG-PET/CT in a diverse clinical population of in-patients with suspected infection not defined by stringent FUO-criteria.	77 patients ≥18 years old with suspected infection of inflammation of unknown origin referred for [^{18}F] FDG-PET/CT scan in search of an infection source Mean Age (range): 68 (21-94) years % male: 69%	^{18}F-FDG-PET/CT	CT (n=70) ceCT (n=6) Low-dose CT (n=1)	NA	Overall True positives: 27 (35%) True negatives (20 (26%)	NA	**Change in Treatment** ^{18}F FDG PET/CT was considered helpful in the diagnostic process in a total of 47 of 77 (61%) cases. Overall, 27 (35%) were true positives, 20 (26%) were true negatives, and [^{18}F] FDG-PET/CT led to a direct change in antibiotic management in 20 of 77 (26%) cases. **In summary:** Results were comparable to findings in more classic FUO. ^{18}F-FDG-PET/CT was clinically helpful in 61% of cases but also prompted many additional examinations with relatively few clinically important findings. Note that in the subgroup of participants who did not have prior CT/MR imaging, there was a lower proportion of true positives (when expecting the detection rate to be higher). White blood cell count was a predictor of true positive outcome. CT and ^{18}F-FDG-PET/CT were discordant in 31% of cases, especially in cases of endocarditis and spondylodiscitis.
Fischer et al, 2024 [73] Switzerland	Case-Control Study (Retrospective study)	28 melanoma patients, divided equally between those with immunotherapy-	FDG PET/CT (likely ^{18}F)	NA	MRI	Diagnostic properties of FDG PET/CT for diagnosing hypophysitis using		**Changes in Classification** Applying the TBR threshold of 2.41, 8 out of 9 (88.9%) patients receiving combined ipilimumab/nivolumab were

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	Objectives: a) To evaluate the diagnostic accuracy of ^{18}F-FDG PET/CT in detecting immune checkpoint inhibitor-induced hypophysitis in patients with metastatic melanoma. b) To determine whether a specific pituitary TBR threshold on PET/CT could serve as an early indicator of hypophysitis.	induce hypophysitis and matched controls. Only studies from within 50 days before and 8 days after diagnosis of hypophysitis Mean Age (range) Cases: 69.6 (46.2 - 76.6) years Mean Age (range) Controls: 66.4 (45.1 -79.5) years %male Cases: 57.1% %male Control: 57.1%				a TBR threshold of 2.41: Sens: 72.7% Spec: 90.9% AUC: 0.769 (95% CI 0.542 – 0.994)		correctly classified, whereas the patients under pembrolizumab monotherapy were missed. **In summary:** This case-control study assessed 28 patients with metastatic melanoma undergoing immune checkpoint inhibitor therapy, comparing 14 patients with confirmed immune checkpoint inhibitor -induced hypophysitis to 14 matched controls. The study found that a pituitary TBR ≥2.41 on ^{18}F-FDG PET/CT—calculated as the SUVmax of the pituitary gland divided by the SUVmean of the blood pool—achieved 72.7% sensitivity and 90.9% specificity for detecting hypophysitis. Notably, elevated TBR values were observed up to 50 days before clinical diagnosis, suggesting PET/CT may enable earlier detection than MRI, which was abnormal in only 60% of cases. These findings support the potential role of FDG PET/CT as a non-invasive adjunct for early identification of immune checkpoint inhibitor -induced hypophysitis, particularly in patients receiving combination immune checkpoint inhibitor therapy.
Hurstel et al, 2024 [74] France	Retrospective head-to-head diagnostic accuracy study	17 patients with necrotizing otitis externa	^{18}F-FDG PET/CT at initial diagnosis and	Technetium-99m-hexamethylpropyleneamine oxime leukocyte	Clinical, otoscopic and biological data	Decision cut-offs were selected when the product of sensitivity and	Post 6 weeks antibiotic therapy (1.19 Threshold)	**Change in Recovery** 13 patients recovered; 4 did not

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	Objectives: To evaluate and directly compare the diagnostic performances of 18-Fluoro-^{18}F-FDG PET and labeled leukocyte scintigraphy to monitor treatment responses in necrotizing otitis externa	Mean Age (range): 72.0 (62.5 – 78.0) years % male: 71%	after the end of antibiotic therapy (6 weeks) and after leukocyte scintigraphy	scintigraphy (^{99}mTc-HMPAO-LS) at the end of antibiotic therapy	follow-up at 3 months	specificity reached its maximum to predict patient recovery. Initial SUVmax lesion at diagnosis (4.73 threshold) Sens: 69% Spec: 100% Acc: 76% PPV: 50% NPV: 100% Final SUVmax lesion (4.10 threshold) Sens: 100% Spec: 100% Acc: 100% PPV: 100% NPV: 100% Final SUVmax lesion (2.10 threshold) Sens: 85% Spec: 100% Acc: 88% PPV: 67% NPV: 100%	Sens: 85% Spec: 100% Acc: 88% PPV: 67% NPV: 100%	**Predictors of recovery** Comparing the initial PET with the final PET and the kinetics between the 2 time points, the ^{18}F-FDG PET scans (as well as planar or tomographic leukocyte scintigraphy) performed at 4 and 24 hours and the respective kinetics between these 2 ^{18}F FDG PET scan showed a maximal AUC of 1.0 [1.0;1.0] to predict patient recovery. See Supplemental Table 1 and 2 (for 14 patients who discontinued antibiotic therapy at least 1 week prior to leukocyte scintigraphy) detailing other predictors of recovery. **In summary:** PET can guide early discontinuation or extension of antibiotic therapy. ^{18}F-FDG PET demonstrated superior diagnostic accuracy (100%) over leukocyte scintigraphy for evaluating treatment response in necrotizing otitis externa.
Pisani et al, 2024 [75] Italy	Retrospective cohort study **Objective**: To evaluate the diagnostic performance of ^{18}F-FDG PET/CT in detecting infections related to cardiac implantable electronic devices, including	48 patients with suspicion of infections related to cardiac implantable electronic devices Mean age (range): 67 (26 – 88) years % male: 79%	^{18}F-FDG PET/CT	Transthoracic echocardiography Transesophageal echocardiography	Microbiological culture of explanted devices (in 30 patients) Clinical follow-up and modified Duke's criteria (in 18 patients)	Sens: 96.2% (95% CI: 80.36–99.90%) Spec: 81.8% (95% CI: 59.72–94.81%) PPV: 86.2% (95% CI: 71.97–93.83%) NPV: 94.7% (95% CI: 72.28–99.20%) Accu: 89.6% (95% CI: 77.34–96.53%)	NR	NA **In summary:** ^{18}F-FDG PET/CT is a highly sensitive and reasonably specific tool for diagnosing infections related to cardiac implantable electronic devices. It is particularly valuable when echocardiography is inconclusive.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	both the reliability of the qualitative analysis and semi-quantitative parameters and the comparison of the variability of the relative ranges of values. Also the validity of adequate dietary preparation of patients preparatory to the suppression of cardiac glucose metabolism in order to guarantee analyses							Proper dietary preparation (myocardial suppression dietary protocol) enhances image quality and diagnostic reliability (adherence markedly increased from 2021 and 2022). The method supports early and accurate diagnosis, guiding appropriate therapeutic strategies.
Shen et al, 2024 [76] China	Single centre Prospective cohort study **Objective**: To evaluate the clinical utility of semi-quantitative ^{18}F-FDG PET/CT parameters—standardized SUVmax, SULmax, MLV, and TLG—in the diagnosis and pathological classification of hepatic echinococcosis, specifically distinguishing between: Hepatic cystic echinococcosis Hepatic alveolar echinococcosis	20 patients with 36 hepatic echinococcosis lesions Age range: 14 – 67 years % male: 55%	^{18}F-FDG PET/CT	Pre PET: imaging and laboratory examination Concurrent with PET: ultrasound, CT angiography, MRI	Histopathology	SUVmax: Cutoff: 2.09 AUC: 0.986 (0.965–0.989) Sens: 91.7% Spec:90.1% SULmax: Cutoff: 2.67 AUC: 0.993 (0.975–1.00) Sens: 87.5% Spec:91.7% MLV: Cutoff: 27.12 AUC: 0.847 (0.722–0.973) Sens: 66.7% Spec:83.3% TLG: Cutoff: 18.79	NA	NR **In summary:** This study by Shen et al. (2024) evaluated the clinical utility of semi-quantitative ^{18}F-FDG PET/CT parameters—SUVmax, SULmax, MLV) and TLG—in differentiating hepatic alveolar echinococcosis from hepatic cystic echinococcosis. Among 20 patients with 36 lesions, SUVmax, SULmax, MLV, and TLG were significantly higher in hepatic alveolar echinococcosis than in hepatic cystic echinococcosis. In contrast lesion size showed no significant difference.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						AUC: 0.938 (0.851–1.00) Sens: 85.6% Spec:90.9%		These parameters demonstrated high diagnostic accuracy (AUCs up to 0.99), highlighting their value in improving classification and guiding treatment strategies for hepatic echinococcosis.
Lung/ Thoracic cancer								
Altaf et al, 2024 [77] UK	Single centre Retrospective cross-sectional study **Objectives:** to determine the usefulness of the FDG-PET/CT scan in detecting sub-centimeter mediastinal lymph node involvement in lung cancer patients by taking histopathology as the gold standard.	42 patients suffering from NSCLC having avid sub-centimeter nodes on FDG-PET/CT Age intervals number: (56-60) = 6 (61-65): 7 (66-70): 8 (71-75): 7 (76-80): 7 (81-85): 7 % male: 76.2%	^{18}F-FDG-PET/CT	NR	histopathology	Sens: 95%, Spec: 68%, PPV: 73%, NPV: 94%, and Accu: 80.9% Diagnosis of optimal nodal metabolic activity (SUVmax) AUC (standard error): 0.837 (0.062) Diagnostic ability of optimal notal size (MM) AUC: 0.714; standard error: 0.083	NA	**Changes in Survival** Patients undergoing PET/CT plus MRI had longer overall survival compared with those who received CT only (or plus MRI) in solid nodules ≥8.0 mm & sub-solid nodules ≥10.0 mm (HR, 0.44; 95%CI, 0.27–0.72; p<0.001). **In summary:** FDG-PET/CT was proven to have high sensitivity and accuracy but a low specificity rate to detect nodal involvement in lung cancer patients
Feng et al, 2024 [78] China	Single centre Retrospective cohort study **Objective:** To evaluate the necessity and prognostic value of PET/CT and brain MRI in detecting metastases among patients with clinical T1-category lung cancer.	4264 T-1 stage lung cancer patients: of these patients, 1683 underwent PET/CT plus MRI, 2581 had either CT plus MRI or CT only. Median age (IQR) ALL Metastases: 60 (52 to 66) years Median Age (IQR) ALL No Metastases: 59 (51 to 66) years	^{18}F-FDG PET/CT plus MRI	CT plus MRI or CT only	Histology	NA	NA	**Change in Survival** Patients undergoing PET/CT plus MRI had longer OS compared with those who received CT only (or plus MRI) in solid nodules **≥8.0 mm & sub-solid nodules ≥10.0 mm** (HR, 0.44; 95%CI, 0.27–0.72; p<0.001). In **solid nodules ≥8.0 mm** (HR, 0.12; 95%CI, 0.03–0.49; p<0.001).

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	Specifically, it stratified patients by tumour size and morphology (solid vs. sub-solid nodules) to determine optimal imaging thresholds and assess the impact of metabolic PET/CT parameters on OS.	% male ALL metastases: 35.7% % male ALL No metastases: 64.3%						In **sub-solid nodules ≥10.0 mm** (HR, 0.61; 95%CI, 0.35–1.05; p=0.075). No difference in OS was observed in **solid nodules<8.0 mm & sub-solid nodules<10.0 mm** (p=0.478). In solid nodules <8.0 mm (p=0.527); and in sub-solid nodules<10.0 mm (p=0.637) **In summary**: PET/CT and brain MRI may be unnecessary in clinical T1 lung cancer patients with solid nodules <8 mm or sub-solid nodules <10 mm due to negligible metastatic risk but remain essential for larger nodules where imaging significantly improves prognosis and guides treatment.
Gkika et al, 2024 [79] Germany	Multicentre Secondary analysis of the PET-Plan (ARO-2009–09; NCT00697333) randomized controlled trial **Objectives:** to evaluate the impact of mediastinal tumour burden and lymphatic spread in patients with locally advanced NSCLC The original trial focus' on a	172 patients with unresectable, locally advanced NSCLC	^{18}F-FDG PET/CT This study compares outcomes between these two strategies: No Intervention Arm A; Irradiation of all tumour manifestations detectable by CT and/or FDG PET including a part of	Arm A (Conventional): Targeting all CT-positive lymph nodes (short axis >10 mm), even if PET-negative, plus ENI.	histologically or cytologically proven, unresectable stage II or III NSCLC	NA	NA	**Change in survival** All patients: higher number of PET-positive lymph nodes was associated with: Trend to worse OS (HR = 1.09; 95% CI: 0.99–1.18, p=0.05). Worse PFS (HR = 1.12; 95% CI: 1.04–1.20; p=0.003). In the PET-based arm (Arm B), higher RT dose to PET-positive lymph nodes improved freedom from local progression (HR = 0.45; p=0.01), but not OS or PFS. Change in patient management outcomes:

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	randomized comparison of conventional radiotherapy planning with irradiation of macroscopic tumour and lymph nodes together with prophylactic target volumes versus. irradiation only of FDG-positive lesions.		eventual atelectasis and the whole affected lymph node stations by 60 - 74 Gy/2 Gy) irradiation of elective lymph node stations up to 50 Gy/2 Gy Arm B (PET-based): Irradiation of all tumour manifestations detectable by FDG PET including the whole affected lymph node stations by 60 - 74 Gy/2 Gy That is restriction of restriction of radiotherapy to FDG-PET positive areas only Restriction of radiotherapy target volumes to areas positive in FDG PET					PET-based planning allowed for: More focused radiation Higher dose escalation to involved nodes. Improved freedom from local progression without compromising OS or PFS. Key outcome differences: freedom from local progression improved in PET-based arm with higher radiation dose. No OS or PFS benefit from ENI or higher radiation dose in conventional arm. **In summary:** Mediastinal tumour burden and lymphatic involvement patterns influence outcome in patients treated with definitive chemo-radiotherapy for locally advanced NSCLC. Higher dose to LNs did not improve OS, but did improve freedom from local progression in patients treated with PET-based dose-escalated radiotherapy.
Graabak et al, 2024 [80] Norway	Multicentre Retrospective analysis (comparative analysis of 2 cohorts) of a	149 patients with limited-stage small cell lung cancer were randomly assigned to thoracic	^{18}F-FDG PET/CT	CT/ENI group (n=73) (HAST Phase II randomized controlled trial): CT-based staging.	NR	NA	NA	**Changes in Harm** Radiotoxicity: Fewer treatment-related deaths (1 vs. 3). PET-CT/SNI significantly reduced acute toxicity.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	subset of patients from 2 randomized controlled trials (One trial not registered and **NCT02041845)** **Objectives:** to compare survival and radiotoxicity between patients who received twice-daily thoracic radiotherapy of 45 Gy/30 fractions in the THORA AND HAST randomized controlled trials to provide more data on the potential clinical impact of PET-CT for staging and target volume definition in limited stage small cell lung cancer	radiotherapy of 45 Gy/30 fractions in the two trials comparing single to twice daily doses. The 2 studies were: HAST trial (CT-based staging with ENI. THORA trial (PET-CT-based staging with SNI.		ENI including lymph node stations 4–7 bilaterally. PET-CT/SNI group (n=76) (THORA Phase II randomized controlled trial): PET-CT-based staging. SNI limited to PET-positive lesions.				Patients in the PET-CT/SNI group reported a clinically significant lower mean score of dysphagia at the end of thoracic radiotherapy (45 versus 72). They also reported less dysphagia at weeks 12, 18, and 52, less dyspnea at weeks 18 and 52. **Quality of Life**: Clinically significant improvements in dysphagia, dyspnea, and global quality of life at various time points. **Changes in Survival**: No significant difference in: Median OS (24 vs 25 months; HR = 0.90; [95% CI: 0.62–1.30]; p=0.59). Median PFS (PET-CT/SNI: 11 vs. CT/ENI: 11 months; HR = 0.80; [95% CI: 0.55–1.15]; p=0.23). 5-year OS (30% vs. 23%; p=0.34). Multivariable analysis confirmed no OS benefit from PET-CT/SNI. (PET/CT/SNI vs CT/ENI; HR = 0.93, [95% CI: 0.63–1.38], p=0.73) or in 5-year OS (OR = 0.73, [95% CI: 0.33–1.63], p=0.44). **In summary:** PET for staging and radiotherapy planning reduces radiotoxicity and improves patient-reported outcomes. Does not improve survival outcomes (OS or PFS)

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
								compared to CT-based staging with ENI.
Haidey et al, 2024 [81] Canada	Multicentre Retrospective observational cross-sectional study **Objectives:** To determine the benefit of an FDG PET/CT scan prior to CT-guided lung biopsy on the rate of diagnosis, rate of complication, and the identification of potentially safer biopsy sites.	547 adult patients who underwent percutaneous CT-guided lung biopsy for lung nodules (<3 cm) and lung masses (≥3 cm) 8 weeks prior to biopsy (n=296) OR 8 weeks after biopsy (n=76) OR no PET scan performed 8 weeks prior or 8 weeks after (i.e. not within time range) (n=175) Men (n=251): Mean age (range): 70.7 (30 to 92) years Women (n=296): Mean age (Range): 69.3 (18 to 91) years	^{18}F-FDG PET/CT	CT-guided percutaneous lung biopsy without prior PET/CT	Histopathology from biopsy and surgical pathology reports used to determine diagnostic yield	Overall diagnostic rate with PET/CT) **prior to** CT guided biopsy: 257/296 (86.8%) Diagnostic rate for lung masses **(≥3 cm)**: With PET/CT: 139/153 (90.8%) Without PET/CT prior to biopsy: 105/ 131 (80.2%) Absolute increase for PET-CT prior to biopsy: 10.6% (p<0.05) Diagnostic rate for lung masses (<3cm) the overall diagnostic rate was for lung nodules (<3 cm) was 214/263 (81.4%). There was no significant difference between those that had a pre-biopsy PET/CT compared with those that did not get a PET-CT scan (p=0.601) ++++++++++++++ Overall diagnostic rate for PET/CT	Overall diagnostic rate for CT guided percutaneous biopsy 458/547 (83.7%)	**Changes in Harm** Overall post biopsy pneumothorax: 237/ 547 (43.3%) with 62/547 (11.3%) requiring chest tube. No difference between rate of pneumothorax, chest tube or hospital admission rate between those having PET/CT prior to biopsy (n=296) versus those that did not have PET/CT prior to biopsy (n=251). Alternate Safer Biopsy Sites Identified (in post-biopsy PET/CT group): Definitely safer: 28.9% Possibly safer: 32.9% Complications rates: Pneumothorax: 43.3% (no significant difference with PET/CT) Chest tube insertion: 11.3% Hospitalization: 13.9% Change in Management: NR Authors hypothesize that changes in the Impact of PET/CT: Could reduce need for repeat biopsy by increasing diagnostic yield. Could reduce biopsy-related complications by identifying safer biopsy sites. **Changes in survival:** NR **In summary:** Performing PET/CT before CT-guided lung biopsy improves diagnostic yield—

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						received post biopsy (n=76): have safer sites of disease amenable to biopsy 32/76 (42.1%) lesions classified as definitely lower risk to biopsy than CT guided 22/76 (28.9%)		especially for lung masses ≥3 cm—and frequently identifies safer alternative biopsy sites, potentially reducing complications and hospitalizations.
Hu et al, 2024 [82] China	Single centre Retrospective study **Objectives:** To evaluate the diagnostic performance of PET/CT metabolic parameters in differentiating benign or malignant cardiac or pericardial masses. Benign Group (n=18): Mean age (SD): 46 (18) years % male: 44.4% Malignant Group (n=23): Mean age (SD): 52 (17) years % male: 60.9%	41 patients with suspected cardiac or pericardiac masses	^{18}F-FDG PET/CT	None	Histopathology Imaging follow-up ≥2 years	SUVmax Cut-off value: 4.93 Sens: 91.3% Spec: 94.4% Accu: 92.7% AUC: 93.2% SUVmean Cut-off value: 3.73 Sens: 95.7% Spec: 94.4% Accu: 95.1% AUC: 94.1% MTV Cut-off value: 16.05 Sens: 91.3% Spec: 94.4% Accu: 92.7% AUC: 93.7%	NA	NA In summary: ^{18}F-FDG PET/CT metabolic parameters provide a reliable semi-quantitative method to differentiate benign from malignant cardiac and pericardial masses. Among these, SUV mean and MTV offer the highest diagnostic accuracy and should be prioritized in clinical evaluation. This approach enhances pre-treatment planning and may guide appropriate therapeutic strategies, especially in cases where conventional imaging is inconclusive.
Kessler et al, 2024 [83] Germany	Single centre Subgroup analysis of an ongoing Prospective registry study (NCT04571086)	41 patients with suspected or confirmed mesothelioma	^{68}Ga-FAPI46 PET/CT or ^{18}F-FDG PET/CT	CeCT	Confirmed reference standard per person and per region:	**Detection Rate** ^{68}Ga-FDP146: n= 144/252 lesions 57.1%)	**Detection Rate** CeCT: n= 128/252 lesions (50.8%)	NR **In summary:** These findings suggest that ^{68}Ga-FAPI46 PET/CT is a valuable diagnostic

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	Objectives: a) To investigate the association of histopathologic fibroblast-activation-protein expression and ^{68}Ga-FAPI46 PET uptake intensity in various tumour entities. b) To analyze the ^{68}Ga-FAPI46 PET/CT diagnostic performance) and detection rates of ^{68}Ga-FAP146 PET/CT in comparison to established imaging modalities (^{18}F-FDG PET/CT and Ce-CT).		Note: Detection rate defined as the number and proportion of patients with PET-positive results overall, per region, and per patient, independently of the reference standard or validation		1)Histopathology examination (n=41) and when feasible FAP immunohistochemistry (n=22) from surgeries and biopsies) within 4 weeks of ^{68}Ga-FAP146 PET/CT 2)Composite reference standard: pathology and imaging-based lesion follow-up)	^{18}F-FDG: n= 219/252 lesions **(86.8%);** P-0.0001 (higher detection than ^{68}Ga-FPT146 or ceCT) **Diagnostics PET vs histopathology:** **Diagnostics per patient** ^{68}Ga-FAP146 (95% CI) Sens: 100% (90.6-100.0) Spec: 25.0% (1.3-69.9) PPV: 92.5% (80.1-97.4) NPV: 100.0 (5.2-100.0) Accu: 92.7 (80.1-98.5) ^{18}F-FDG (95% CI) Sens: 97.3% (86.2-99.9) Spec: 50.0 (8.9-91.1) PPV: 94.7 (82.7-99.1) NPV: 66.7 (11.9-98.3) Accu: 92.3 (79.1-98.4) **Diagnostics per region**: ^{68}Ga-FDP146 (95% CI): Sens 98.0% (89.5-99.9)	No significant difference (^{68}Ga-FAP146/CT vs ^{18}F-FDG/CT vs ceCT) in detection was observed on a per-patient (P 5 0.3) or per-region (P 5 0.06) basis.	tool for mesothelioma, potentially superior to ^{18}F-FDG PET/CT in certain clinical scenarios. It may also serve as a non-invasive method to assess fibroblast-activation-protein expression, supporting future fibroblast-activation-protein -targeted therapeutic strategies.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						Spec: 81.1% (65.8–90.5) PPV: 87.5% (76.4–93.8) NPV: 96.8 (83.8–99.8) Accu: 90.8 (82.7–96.0) ^{18}F-FDG (95% CI): Sens: 95.9% (86.3–99.3) Spec: 36.8% (23.4–52.7) PPV: 66.2% (54.6–76.1) NPV: 87.5 (64.0–97.8) Accu: 70.11 (59.4–79.5)		
Kong et al, 2024 [84] China USA	Multicentre Phase II randomized controlled trial conducted in US and Canada (NCT01507428) **Objectives**: To evaluate whether PET-guided radiotherapy i.e., dose escalation to residual metabolically active tumour - improves outcomes compared with standard radiotherapy	138 patients with unresectable stage III NSCLC; 127 in analysis, 43 standard non-adaptive radiotherapy and 84 guided adaptive chemoradiotherapy Median age Standard radiotherapy (range): 64 (47 to 82) Median Age Adaptive radiotherapy (range): 65 (24 to 78) % male standard radiotherapy: 58.1%	^{18}F-FDG PET/CT guided therapy Standard chemoradiotherapy (50 Gy/weeks) and continue standard chemoradiotherapy (10 Gy/1wk) Accelerated chemoradiotherapy (46.2 Gy/ 4 weeks) and adapted chemoradiotherapy (up to 34.2 Gy/ 2 weeks)	NA	NA	NA	NA	**Change in Survival** Freedom from locoregional progression at 2 years: Standard radiotherapy: 59.5% vs Adaptive radiotherapy 54.6% (p=0.66) PFS: Median: 12.2 months (standard) vs 13.8 months (adaptive) 2-year PFS: 27.6% (standard) vs 33.9% (adaptive) (p=0.46) OS (median): Standard radiotherapy: 35.5 months (95% CI: 21.8 to 49.0) vs Adaptive radiotherapy: 31.2 months (95% CI: 21.5 to 46.8), HR 1.06 (95% CI: 0.66 to 1.71), p=0.80 (log-rank test)

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
		% male adaptive radiotherapy: 42.9%						3-year OS: 49.1% (Standard) vs 47.5% adaptive (p=0.80) Change in Harms: No significant increase in grade ≥3 toxicities in adaptive arm. Grade ≥2 esophagitis Standard: 31.0% (13/42) vs Adaptive 42.5% (34/80) radiotherapy, p=0.21 **In summary:** Mid-treatment PET-guided adaptive radiotherapy was feasible and safe but did not improve locoregional control, PFS, or OS compared to standard radiotherapy. The study does not support proceeding to a phase III trial with this regimen.
Moon et al, 2024 [85] Korea	Multicentre Retrospective **Objectives**: To evaluate and compare the diagnostic performance of ^{18}F-FDG PET/CT and CT in differentiating invasive adenocarcinoma from adenocarcinoma in situ and minimally invasive adenocarcinoma among pure ground-glass nodules in patients with lung cancer.	38 patients with 40 pathologically confirmed pure ground-glass nodule. Median age (IQR): 64 (59-68) years % male: 34%	^{18}F-FDG-PET/CT	CT	Histopathology	<u>Visual ^{18}F-FDG</u> Positivity: Sens: 88.0% Spec: 66.7% PPV: 81.5% NPV: 76.9% AUC: 0.773 p=0.001 <u>SUVmax ≥ 1.06:</u> Sens: 76.0% Spec: 66.7% PPV: 79.2% NPV: 62.5% AUC: 0.717 p=0.018 <u>SUVmaxTF ≥ 2.00:</u> Sens: 92.0% Spec: 60.0% AUC: 0.723p=0.013	<u>CT Size ≥ 15 mm:</u> Sens: 80.0% Spec: 60.0% AUC: 0.693 P=0.029 Diagnostic performance (ROC AUC) of CT size in differentiating invasive adenocarcinoma from adenocarcinoma in situ / minimally invasive adenocarcinoma, p=0.029	NA **In summary:** ^{18}F-FDG PET/CT is more effective than CT alone in distinguishing invasive adenocarcinomas from less aggressive subtypes among pure ground-glass nodules, supporting its use in guiding management decisions for these lung lesions.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						Multivariate analyses showed that the visual [^{18}F]FDG uptake positivity and sex were the only two independent factors for predicting invasive adenocarcinoma (p=0.008 and 0.042, respectively).		
Mu et al, 2024 [86] China	Single centre Retrospective study **Objectives**: To evaluate the diagnostic accuracy of ^{18}F-FAPI PET/CT in detecting primary tumours and mediastinal lymph node metastases in NSCLC, using histopathology as the reference standard, and to compare it with ^{18}F-FDG PET/CT.	19 patients with NSCLC	^{18}F-FAPI-42PET/CT Used to detect primary tumours and mediastinal lymph node metastases	^{18}F-FDG PET/CT	Histopathology	Primary tumour detection rate: FAPI-FDG PET/CT: 100% (n=13) ^{18}F-FDG PET/CT detection rate: 69.1% (n=13) Mediastinal Lymph Node Detection range for different F-FAPI (n=19 and n=13) (Per-Station Basis) Sens: range 83.3-85.7% Spec: range 97.7-98.3% Accu: range 95.9-97.1% PPV: range 83.3-85.7% NPV: range 97.7-98.3% Nodal Staging Accuracy	Primary tumour detection: 94.7% detection rate (18/19) Mediastinal Lymph Node Detection (Per-Station Basis) Sens: 83.3% Spec: 46.5% Accu: 51.0% PPV: 17.8% NPV: 95.2% Nodal Staging Accuracy Correct in 42% (5/12 patients)	NA **In summary:** ^{18}F-FAPI PET/CT demonstrated superior diagnostic accuracy over ^{18}F-FDG PET/CT in detecting mediastinal lymph node metastases in NSCLC, with significantly fewer false positives. It may serve as a valuable tool in preoperative staging, potentially reducing the need for invasive confirmation procedures.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						Correct in 88% (16/18 patients)		
Park et al, 2024 [87] Korea	Multicentre Retrospective cohort study **Objective**: To evaluate the impact of the timing of F-18 FDG PET/CT on biopsy site selection, complication rates, and diagnostic yield in patients with stage IV lung cancer.	1297 newly diagnosed patients with pathologically confirmed stage IV lung cancer. Patients were divided into 2 groups: Upfront PET/CT (before biopsy site selection) (n=5110/1297, 39.3%) Delayed PET/CT (after biopsy site selection) (787/1297, 60.7%) Mean age (SD): 71.4 (10.2) years % male: 71%	^{18}F-FDG PET/CT	Chest CT or ultrasound guided Percutaneous needle Biopsy Post biopsy evaluation to assess for adverse events using CT or ultrasounds.	Histopathology and clinical follow-up	Diagnostic success rate (92.7% vs. 93.8%, p=0.540) were not different between the upfront PET/CT group and the delayed PET/CT group	NA	**Changes in Harm** Major complications occurred significantly more frequently in patients of the delayed PET/CT group (2.9%; 23/787) compared to those in the upfront PET/CT group (1.0%, 5/510) (p=0.031). Minor complications: no significant difference (13.3%, 68/510 vs. 13.0%, 102/787, p=0.912)). All complications (14.3%, 73/510 vs. 15.9%, 125/787, p=0.491) . **Changes in Management** Biopsy site selection: Upfront PET/CT led to more non-lung target biopsies (46.1% vs. 32.9%, p<0.001). **In summary:** Upfront F-18 FDG PET/CT influences biopsy site selection in stage IV lung cancer, favouring non-lung targets and reducing major complications without compromising diagnostic yield. It supports safer diagnostic strategies and may guide optimal biopsy planning.
Zanoni et al, 2024 [88] Italy	Single centre Prospective, exploratory **Objectives:** To evaluate the diagnostic	64 adult patients with suspected lung cancer and only 50 underwent thoracic surgery; the current	^{68}Ga Ga-FAPI-46 PET/CT.	^{18}F FDG PET/CT	Histopathology	Per Patient (visual assessment) T stage Sens: 95% Spec: 67% Accu: 92%	Per Patient (visual assessment) T stage Sens: 84% Spec: 50% Accu: 80%	NA **In summary:** FAPI PET/CT showed slightly better overall diagnostic performance, particularly in terms of specificity and

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	performance of ^{68}Ga Ga-FAPI-46 PET/CT for T (tumour) and N (nodal) staging in patients with suspected or confirmed lung cancer undergoing surgery.	analyses focus on the 50 patients). All patients were already scheduled for conventional staging flow chart (including ^{18}F-FDG/CT with no changes in management deriving from FAPI results (clinicians and patients blind to FAPI results). In patients undergoing surgery FAPI/CT findings were validated by pathology and 1-year conventional follow-up				PPV: 95% NPV: 67% N stage Sens: 50% Spec: 88% Accu: 78% PPV: 60% NPV: 83%	PPV: 93% NPV: 30% N stage Sens: 67% Spec: 74% Accu: 72% PPV: 47% NPV: 86%	accuracy for nodal staging on a region-based level. However, its sensitivity for detecting nodal metastases remained suboptimal. While FAPI reduced false positives compared to FDG, especially in inflammatory conditions, it did not yet demonstrate sufficient reliability to replace invasive staging procedures.
Melanoma/ Dermatological cancer								
Gideonse et al. 2024 [89] Denmark	Retrospective, registry-based study using the Danish Metastatic Melanoma Database (DAMMED) **Objectives:** To determine the organ-specific accuracy of ^{18}F-FDG-PET/CT in identifying immune-related adverse events in patients with high-risk (stage III/IV) surgically resected melanoma	123 patients with who had undergone radical resection for high-risk (stage III or IV) melanoma and were treated with an adjuvant immune checkpoint inhibitors. Mean Age (range): 62 (17 to 83) years %male: 60.2%	^{18}F-FDG-PET/CT	NR	Clinical information on immune-related adverse events obtained from medical records	Accuracy of PET to diagnose immune-related adverse events Thyroid gland Sens: 92% (95% CI: 62–99%) Spec: 95% (95% 89–98%) PPV: 65% (95% CI: 0.38–0.86) NPV: 99% (95% CI 0.95–1) Heart Sens: 50% (95% CI 13–99%) Spec: 97% (95% CI: 92-99%)	NA	NA **In summary:** The authors conclude that ^{18}F-FDG-PET/CT generally had moderate to high sensitivity (except for skin and heart) and specificities in diagnosing immune-related adverse events in patients receiving adjuvant immune checkpoint inhibitor. They also indicate that this could be suggested to be systematically assessed and then findings reported in scan reports.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	treated with an adjuvant immune checkpoint inhibitor and to determine the incidence of immune-related adverse events within the first year after starting treatment					PPV: 20% (95% CI: (0.01–0.72) NPV: 99% (95% CI: 0.95-1) Lungs Sens: 75% (95% CI: 19–99%) Spec: 90% (95% CI: 83–95%) PPV: 20% (95% CI: 0.04-0.48) NPV: 99% (95% CI: 0.95-1) Intestines Sens: 100% (95% CI: 75–100%) Spec: 86% (95% CI: 77–91%) PPV: 45% NPV: 100% Muscles and Joints Sens: 71% (95% CI: 48–89%) Spec: 83% (95% CI: 75–90%) PPV: 47% (95% CI: 0.29–0.65) NPV: 93% ((95% CI: 0.86–0.98) Skin Sens: 19% (95% CI: 7–39%) Spec: 95% (95% CI: 88–98%) PPV: 50% ((95% CI 0.19–0.81) NPV: 81% (95% CI: (0.73–0.88)		

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
Pancreatic cancer								
Abdelkawi et al, 2024 [90] Egypt	Retrospective cohort study **Objectives:** To evaluate the value of ^{68}Ga-DOTATATE PET/CT in the diagnosis and localization of insulinomas, whether sporadic, malignant or MEN-1-associated insulinoma.	43 patients, having clinical (symptomatic hypoglycemia) and/or laboratory suspicion of having insuliinoma (72 h fasting test with serum insulin ≥18 pmol/L), with available pre-operative ^{68}Ga-DOTATATE PET/CT and CE-CT, and diagnosed with insulinoma confirmed by post-operative histopathology. Mean age total sample: 34.86 (SD 11.36) % male total sample: 53.5%	^{68}Ga-DOTATATE PET/CT	CeCT	Post-operative Histopathology	Overall Sensitivity: 87.5 % Specificity: 37.5 % PPV: 90.74 % NPV: 30 % Benign sporadic insulinomas Sensitivity: 88.1 % Specificity: 20 % PPV: 90.24 % NPV: 16.67 % Malignant Insulinomas Sensitivity: 77.78 % Specificity: 100 % PPV: 100 % NPV: 33.33 % MEN-1 syndrome associated insulinomas Sensitivity: 100 % Specificity: 50 % PPV: 83.33 % NPV: 100 %	Overall Sensitivity: 80.36 % Specificity: 50 % PPV: 93.75 % NPV: 21.43 % Benign sporadic insulinomas Sensitivity: 80.95 % Specificity: 0 % PPV: 94.44 % NPV: 0 % Malignant Insulinomas Sensitivity: 77.78 % Specificity: 100 % PPV: 100 % NPV: 50 % MEN-1 syndrome associated insulinomas Sensitivity: 80 % Specificity: 50 % PPV: 80 % NPV: 50 %	NA **In summary:** ^{68}Ga-DOTATATE PET/CT is a non-invasive imaging modality that can identify most insulinomas. However, it offers limited additional information if the tumour is localized by other imaging studies. It may be best suited as an adjunct test when imaging studies fail to localize a tumour in insulinoma patients.
Pediatric cancer								
Milosevic et al, 2024 [93] Serbia	Single centre Retrospective cohort study **Objectives**:	61 pediatric patients with Hodgkin lymphoma Mean age total group: 14.2 years (SD 2.4 to 17.8	^{18}F-FDG-PET/CT (post 2003) (n= 34)	CT-based protocols (pre-2003) (n=27)	Clinical follow-up	NR	NR	**Change in Treatment** PET/CT-based assessment reduced frequency of radiotherapy exposure compared to conventional CT imaging (32% vs 52%) and

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	To evaluate whether ^{18}F-FDG-PET/CT assessment at interim and end-of-treatment timepoints reduces unnecessary exposure to radiotherapy compared to conventional CT in pediatric cancer lymphoma.	% male total group: 54%						it helped tailor treatment based on metabolic response. Unnecessary radiation exposure decreased by 20% **Survival** OS rate: PET: 100%; CT-based protocols: 96% PFS rate: PET 92.6%; CT: 94.1% **In summary:** In pediatric patients with Hodgkin lymphoma, the use of ^{18}F FDG-PET/CT for interim and end-of-treatment evaluation significantly reduced the need for radiotherapy compared to conventional CT-based protocols (32% vs. 52%). This reduction did not compromise OS or event-free survival, which remained high in both groups. The findings support ^{18}F FDG-PET/CT as a valuable tool for more precise treatment response assessment, enabling tailored therapy that minimizes unnecessary radiation exposure and its associated long-term toxicities.
Sarcoma								
Jehanno et al, 2024 [94] France	Prospective Phase II study a substudy from the COMBINAIR3 multicentre clinical trial (NCT03011528)	42 patients with histologically confirmed very high-risk (primary extra-pulmonary metastases) Ewing sarcoma	^{18}F-FDG PET/CT	BMAB	cytological/histological BMAB	In 24 patients without bone marrow metastases who were true negatives PET showed:	Bone marrow aspiration showed 77% with negative BMAB also	Changes in Treatment NR **Survival** R.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
	prospectively enrolled 45 pediatric and adult patients (2 to 50 years), across 15 French centres from 2016 to 2021, with histologically confirmed Ewing tumour, harboring a specific transcript and with primary extra-pulmonary metastases. **Objective**: To compare the diagnostic performance of 18F-FDG PET/CT versus BMAB in detecting bone marrow involvement in patients with very high-risk Ewing sarcoma.	Median age at diagnosis: 14.6 years (range 6–47 years) % male: 66.7%				Spec: 100% (95% CI [85.7–100%] In 18 patients positive for bone marrow metastasis (including 3 patients with negative PET/CT and positive BMAB results) Sens: 83.3% (95% CI [58.6%--96.4%]) Overall, PET/CT PET/CT classified 15 patients as bone marrow infiltration but BMAB classified only 8 as having infiltration; the remaining 7 false negatives from BMAB were confirmed with other imaging to have bone marrow infiltration (Figure 2). Correctly classified 92.8% of patients (exact 95% CI [80.5–98.5%]) and reaching 100% accuracy when considering patients identified with bone involvement.	had negative PET/CT; 73% positive BMAB cases had positive BM infiltration on PET/CT	**In summary:** In this prospective multicentre study, PET/CT proved highly effective and more accurate than BMAB for detecting bone marrow involvement in very high-risk Ewing sarcoma. This would support its use as a non-invasive alternative to the need for routine BMAB in metastatic cases.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
						Accu: 100% (95% CI: [91.6 to 100%])		
Other Cancers								
Chang et al, 2024 [91] China	Prospective cohort study **Objectives:** To compare the diagnostic performance and cost-effectiveness of ^{18}F-FDG PET/CT versus CT in determining optimal bone biopsy sites in patients with suspected bone metastases. The study also sought to evaluate whether combining metabolic imaging (SUVmax) with serum alkaline phosphatase levels could improve diagnostic accuracy for malignant bone lesions.	273 patients >18 years old with bone metastases and Karnofsky performance status >60 Pet/CT group n= 136 CT group n=137 Mean age PET: 57.11 (SD 14.96) years Mean Age CT: 58.39 (SD 11.11) % Male PET: 65.7% % Male CT: 55.1%	^{18}F-FDG PET/ CT	CT	Histology (bone biopsy)	^{18}F-FDG PET/CT From 136 biopsies 81 patients with malignant bone metastases; 56 patients with benign bone lesions ^{18}F-FDG PET/CT detected 80 out of 81 actual malignant metastases; misinterpreted 3 benign lesions as malignant bone metastases. Sens*: 98.8% (95%CI 93.3-99.9%) Spec**: 94.6% (95%CI 85.1-98.9%). Acc***: 97.1% *^{18}F-FDG PET/CT vs. CT for the detection of malignant bone metastases: p=0.0394. **p=0.1134. ***p=0.0232	CT: From 136 biopsies, 89 were malignant bone metastases; 47 were benign bone lesions. CT detected 83 out of 90 malignant metastases and misinterpreted 6 benign lesions as malignant bone metastases. Sens*: 92.2% (95%CI 84.6-96.8%) Spec**: 86.9% (95%CI 73.7-95.1%) Acc***: 90.4%	Rate of a second biopsy because of an unsatisfactory biopsy: ^{18}F-FDG PET/CT: 2.19%, CT: 5.15%; p=0.031. The diagnostic time caused by the second biopsy: ^{18}F-FDG PET/CT 18.33±2.08 days: CT 21.28±1.25 days, p=0.021 **In summary:** ^{18}F-FDG PET/CT outperformed CT in guiding bone biopsy by demonstrating significantly higher diagnostic accuracy (97.1% vs. 90.4%) and sensitivity (98.8% vs. 92.2%), while reducing the need for second biopsies and shortening diagnostic time. It also proved more cost-effective overall. Combining SUVmax > 6.3 with alkaline phosphatase > 103 U/L further enhanced diagnostic precision, supporting the use of PET/CT as the preferred imaging modality for biopsy planning in suspected bone metastases.

Citation	Study Design - Objectives	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance	Change in Patient Management
Habouzit et al, 2024 [92] France	Retrospective cohort study **Objectives:** a) To evaluate how lesion size, PET/CT camera type, and patient-related covariates (e.g., body mass index, blood glucose level, liver density) influence the per-lesion sensitivity of ^{18}F-FDG PET/CT in detecting liver metastases (LMs). b) To assess the overall per-lesion diagnostic performance (sensitivity, specificity, PPV, NPV) of ^{18}F-FDG PET/CT for liver metastases.	192 patients with 330 suspected liver lesions (235 metastases and 95 benign) who underwent ^{18}F-FDG PET/CT scans Median age: 68.0 (28.0–91.0) years. % Male: 55.7%	^{18}F-FDG PET/CT	NR	Histopathology and imaging follow-up	Overall diagnostic performance: sens: 86% (95% CI: 0.80, 0.92) spec: 79% (95% CI: 0.71–0.87), PPV: 91% (95% CI : 0.87, 0.95), NPV: 69% (95% CI: 0.61, 0.78) Influence of covariates on PET sensitivity: PET camera type (TOF vs non-TOF PET/CT): 0.91% (95% CI 0.87, 0.95) **Lesion Size**: Lesions <10 mm had significantly lower sensitivity (56% 95% CI: 0.56 (0.41, 0.71)) compared to ≥10 mm (93% (95% CI 0.88, 0.98)), *p*< 0.001. **Body Mass Index**: A 5 kg/m^2 increase in BMI led to a 5% (95% CI 7% to 2%) reduction in sensitivity (*p*< 0.001). **Non-significant Factors**: Age, sex, blood glucose level <11 mmol/L, and liver density did not significantly affect sensitivity (p>0.05).	NA	NA **In summary:** ^{18}F-FDG PET/CT is a highly effective imaging modality for detecting liver metastases. However, its sensitivity is notably reduced in: Patients with higher body mass index, Lesions smaller than 10 mm, Scans performed with non-TOF PET/CT systems. These findings highlight the importance of considering technical and patient-related factors when interpreting PET/CT results and suggest potential areas for protocol optimization and future research to enhance diagnostic accuracy.

Abbreviations: Accu=accuracy; AUC=area under the curve; BCR=biochemical recurrence; BFS=BCR-free survival; BMAB=bone marrow aspiration and biopsy; Ce=contrast-enhanced; CEA=carcinoembryonic antigen; CI=confidence interval; CIM=conventional imaging modalities; CRC=colorectal cancer; CT=computed tomography; CUP=cancer of unknown primary; DCFPyl=Piflufolastat F-18; DLCBL=diffuse large B-cell lymphoma; DSUL=decrease in SUV corrected for lean body mass; EPE=extraprostatic extension; ENI=elective nodal irradiation; ePLND=extended pelvic lymph node dissection; ER=estrogen receptor; FAPI=fibroblast activation protein inhibitor; FDG=fluorodeoxyglucose; FES=^{18}F-fluoro-17β-estradiol; FET=fluoroethyltyrosine; FUO=fever of unknown origin; HER2=human epidermal growth factor receptor-2; HR=hazard ratio; ILC=invasive lobular carcinoma; IQR=interquartile range; ISUP GG=International Society of Urological Pathology Grade Group; IUO=inflammation of unknown origin; LABC=locally advanced breast cancer; LAT1=L-amino acid transporter 1; LBR-MRFDG=lesion/background ratio of MRFDG; LN=lymph node; MD=molecular diagnostics; MLV=metabolic lesion volume; mpMRI=multiparametric MRI; MRFDG=metabolic rate of FDG; MRI=magnetic resonance imaging; MTC=medullary thyroid cancer; MTV=metabolically active tumour volume; NA=not available; NAB=National Alzheimer Bank; NPV=negative predictive value; NR=not reported; NSCLC=non-small-cell lung cancer; OCT=optical coherence tomography; OS=overall survival; pCa=prostate cancer; pCR=pathologic complete response; PE=peritoneal metastases; PERCIST=PET Response Criteria in Solid Tumors; PET=positron electron tomography; PFS=progression=free survival; PI-RADS=Prostate Imaging Reporting & Data System; PLND=pelvic lymph node dissections; PPC=intracapsular pCa with poor prognosis; PPV=positive predictive value; PRM=parametric response mapping; pRND=pathology confirmed residual neck disease; PSA=prostate-specific antigen; RARP=robot-assisted radical prostatectomy; RP=radical prostatectomy; RECIST=Response Evaluation Criteria in Solid Tumors; SBI=skull bone invasion; SCR=subclinical recurrence; SD=standard deviation; Sens=sensitivity; SLNB=frozen biopsy of sentinel lymphadenectomy; SNI=selective nodal irradiation; Spec=specificity; SRT=salvage radiotherapy; SULmax=maximum standardized uptake value corrected for lean body mass; SUV=standardized uptake value; SUVmax=maximum SUV; SVI=seminal vesicle invasion; TBR=tumour-to-background ratio; TLG=total lesion glycolysis; UICC=Union for International Cancer Control staging

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