Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/24**
(See policy history boxes for previous effective dates)

Title: Positron Emission Tomography (PET) for Oncologic Conditions

Description/Background

Positron emission tomography (PET) scans are based on the use of positron-emitting radionuclide tracers coupled to organic molecules, such as glucose, ammonia or water. The radionuclide tracers simultaneously emit two high-energy photons in opposite directions that can be simultaneously detected (referred to as coincidence detection) by a PET scanner, consisting of multiple stationary detectors that encircle the area of interest.

A variety of tracers are used for PET scanning, including oxygen-15, nitrogen-13, carbon-11, and fluorine-18. Because of their short half-life, some tracers must be made locally using an onsite cyclotron. The radiotracer most commonly used in oncology imaging has been fluorine-18 coupled with fluorodeoxyglucose (FDG), which has a metabolism related to glucose metabolism. FDG has been considered useful in cancer imaging since tumor cells show increased metabolism of glucose. The most common malignancies studied have been melanoma, lymphoma, lung, colorectal, and pancreatic cancer.

For this policy, PET scanning is discussed for the following four applications in oncology.

- Diagnosis. Diagnosis refers to use of PET as part of the testing used in establishing whether a patient has cancer.
- Staging. This refers to use of PET to determine the stage (extent) of the cancer at the time of diagnosis before any treatment is given. Imaging at this time is generally to determine whether the cancer is localized. This may also be referred to as initial staging.
- Restaging. This refers to imaging following treatment in two situations. Restaging is part of the evaluation of a patient in whom a disease recurrence is suspected based on signs and/or symptoms. Restaging also includes determining the extent of malignancy following completion of a full course of treatment.
- Surveillance. This refers to use of imaging in asymptomatic Individuals (Individuals without objective signs or symptoms of recurrent disease). This imaging is completed 6 months or more (12 months or more for lymphoma) following completion of treatment.

This policy only addresses the use of radiotracers detected with the use of dedicated PET scanners. Radiotracers such as FDG may be detected using single-photon emission computerized tomography (SPECT) cameras, a technique that may be referred to as FDG-SPECT imaging. The use of SPECT cameras for PET radiotracers presents unique issues of diagnostic performance and is not considered in this policy.

Regulatory Status

As of August 2022, the following radiopharmaceuticals have been granted FDA approval, to be used with PET for cancer-related indications (see Table 1). [1]

Table 1. Radiopharmaceuticals Approved for use with PET for Oncologic Applications

Radiopharmaceutical	Manufacturer	Name	Carcinoma-Related Indication With PET
Carbon-11 choline (C-11)	Various		Suspected prostate cancer recurrence based on elevated blood PSA after therapy and noninformative bone scintigraphy, CT, or MRI
Copper-64 dotatate	Curium	Detectnet™	Localization of somatostatin receptor-positive NETs in adult individuals
Fluorine-18 fluorodeoxyglucose (FDG)	Various		Suspected or existing diagnosis of cancer, all types
Fluorine-18 fluoroestradiol	Zionexa USA	Cerianna™	Detection of ER-positive lesions as an adjunct to biopsy in individuals with recurrent or metastatic breast cancer
Fluorine-18 fluciclovine	Blue Earth Diagnostics	Axumin™	Suspected prostate cancer recurrence based on elevated blood PSA levels after treatment
Gallium-68 dotatoc	UIHC - P E T Imaging Center		Localization of somatostatin receptor-positive NETs in adult and pediatric individuals
Gallium-68 dotatate	Advanced Accelerator Applications	NETSPOT™	Localization of somatostatin receptor-positive NETs in adult and pediatric individuals
Gallium-68 PSMA-11§	University of California, Los Angeles and the University of California, San Francisco		PSMA positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum PSA level
Piflufolastat fluorine-18	Progenics Pharmaceuticals, Inc	Pylarify®	PSMA positive lesions in men with prostate cancer with suspected metastasis who are

			candidates for initial definitive therapy or with suspected recurrence based on elevated serum PSA level

§ FDA-approval given to the University of California, Los Angeles and the University of California, San Francisco.
CT: computerized tomography; ER: estrogen receptor; MRI: magnetic resonance imaging; NET: neuroendocrine tumors; PET: positron emission tomography; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen.

Two kits used for the preparation of Gallium-68 PSMA-11 have received FDA approval: the Illuccix® (Telix Pharmaceuticals) kit, approved in December 2021; and the Locametz® (Advanced Accelerator Applications/Novartis) kit, approved in March 2022.[2,] The preparation kits are for use in individuals with PSMA-positive prostate cancer with suspected metastasis who are candidates for initial definitive therapy, or with suspected recurrence based on elevated serum PSA level. In addition, Locametz is approved for selection of patients with metastatic prostate cancer, for whom lutetium Lu-177 vipivotide tetraxetan (Pluvicto™; Novartis) PSMA-directed therapy is indicated.

Medical Policy Statement

The safety and effectiveness of PET scanning for selected oncologic applications have been established. It is a useful diagnostic option for individuals meeting patient selection criteria.

Inclusionary and Exclusionary Guidelines

General statements:

All inclusionary/exclusionary statements apply to both positron emission tomography (PET) scans and PET/computed tomography (CT) scans, i.e., PET scans with or without PET/CT fusion.

A PET or PET/CT may be appropriate for a patient with *known* diagnosis of a malignancy in order to determine the optimal anatomic site for a biopsy or other invasive diagnostic procedure if standard imaging is equivocal. It also may replace conventional imaging when conventional imaging would be inadequate for accurate staging, and when clinical management will depend upon the stage of disease. In general, for most solid tumors, a tissue diagnosis is made *prior* to the performance of PET scanning. PET scans following a tissue diagnosis are performed for staging, not diagnosis. If the results of the PET scan will not influence treatment decisions, these situations would be considered not medically necessary.

PET scans may be considered *appropriate* for the following oncologic conditions:

Anal Cancer

- **Inclusions:**
  - For the diagnosis when standard imaging cannot be performed or is nondiagnostic for metastatic disease.
  - Indicated in **EITHER** of the following:
    - Radiation planning for definitive treatment only
    - Standard imaging cannot be performed or is nondiagnostic for recurrent or progressive disease
  - For locally progressive or recurrent cancer with evidence of progression found on digital rectal exam.

- **Exclusions:**

- Conditions not listed above.

Bladder Cancer

- **Inclusions:**
  - Diagnostic workup:
    - evaluation of stage II or stage III bladder cancer prior to definitive treatment when standard imaging cannot be performed or is nondiagnostic for metastatic disease.
    - When bone metastasis is suspected based on signs and symptoms and standard imaging cannot be performed or is nondiagnostic.
  - Management:
    - standard imaging cannot be performed or is nondiagnostic for recurrent or progressive disease.
- **Exclusions:**
  - Conditions not listed above.

Bone Cancer/Sarcoma

- **Inclusions:**
  - Diagnostic workup:
  - Indicated in **ANY** of the following scenarios (all tumor types):
    - Initial work-up of Ewing sarcoma and osteosarcoma if curative treatment planned
    - Standard imaging cannot be performed or is nondiagnostic for metastatic disease
    - Standard imaging suggests a resectable solitary metastasis
    - Baseline study prior to neoadjuvant chemotherapy
  - Management:
    - Indicated following completion of neoadjuvant chemotherapy
    - Standard imaging cannot be performed or is nondiagnostic for recurrent or progressive disease
- Exclusions:
  - Conditions not listed above.

Brain Cancer

- **Inclusions:**
  - Diagnostic workup:
    - evaluation of possible systemic disease in proven CNS lymphoma.
  - For staging, where lesions metastatic from the brain are identified.
  - For restaging, to distinguish recurrent tumor from radiation necrosis.
- **Exclusions**:
  - Conditions not listed above.

Breast Cancer

- **Inclusions:**
  - Staging and restaging of breast cancer
  - Detecting locoregional or distant recurrence or metastasis (except axillary lymph nodes) when suspicion of disease is high and other imaging is inconclusive.
- **Exclusions:**
  - For the differential diagnosis in individuals with suspicious breast lesions or an indeterminate/low suspicion finding on mammography.
  - Staging axillary lymph nodes.
  - For predicting pathologic response to neoadjuvant therapy for locally advanced disease.

Cancer of Unknown Primary

- **Inclusions:**

- Individuals with an unknown primary who meet **ALL** of the following criteria:
  - In individuals with a single site of disease suspicious for cervical nodal metastases of unknown origin
  - In individuals with a single site of metastatic disease if therapy with a curative intent is planned
  - Individual has received a negative workup for a occult primary tumor
  - The PET scan will be used to rule out or detect additional sites of disease that would eliminate the rationale for local or regional treatment.

- **Exclusions:**
  - For individuals with an unknown primary, including, but not limited to the following:
    - As part of the initial workup of an unknown primary
    - As part of the workup of individuals with multiple sites of disease

Cervical Cancer

- **Inclusions:**
  - For the initial staging of individuals with locally advanced cervical cancer.
  - For the evaluation of known or suspected recurrence.
- **Exclusions:**
  - For the initial diagnosis of cervical cancer in all other situations.

Colorectal Cancer

- **Inclusions:**
  - Diagnostic workup:
    - Indicated when standing imaging (CT Chest, Abdomen and Pelvis) cannot be performed or is not diagnostic for surgically curable metastatic disease.
  - Management:
    - Indicated in ANY of the following scenarios:
      - CT is equivocal for metastatic disease and lesion(s) is/are greater than 1 cm in diameter.
      - CT demonstrates recurrence that is potentially curable with surgery.
      - CT does not demonstrate a focus of recurrence but carcinoembryonic antigen (CEA) level is rising.
      - Signs or symptoms are suggestive of recurrence and CT is contraindicated.
- **Exclusions:**
  - When used as a technique to assess the presence of scarring versus local bowel recurrence in individuals with previously resected colorectal cancer.
  - When used as a technique contributing to radiotherapy treatment planning.

Endometrial Cancer

- **Inclusions:**
  - Detection of lymph node metastases, and
  - Assessment of endometrial cancer recurrence.
- **Exclusions:**
  - Conditions not listed above

Esophageal Cancer

- **Inclusions:**
  - Staging and restaging of esophageal cancer,
  - Determining response to preoperative induction therapy.

- **Exclusions:**
  - Detection of primary esophageal cancer.

Gastric (Stomach) Cancer

- **Inclusions:**
  - Diagnosis, staging and restaging of gastric carcinoma if other imaging is inconclusive
  - Determining response to preoperative induction therapy.
- **Exclusions:**
  - Conditions not listed above.

Head and Neck Cancer

- **Inclusions:**
  - For the evaluation of the head and neck in the initial diagnosis of suspected head and neck cancer.
  - For the initial staging of the disease.
  - For restaging of residual or recurrent disease during follow up.
  - Treatment response evaluation.
- **Exclusions:**
  - Conditions not listed above.

Hepatobiliary Cancer

- **Inclusions:**
  - When standard imaging studies are equivocal or nondiagnostic regarding extent of disease.
  - When standard imaging prior to planned curative surgery has been performed and has not demonstrated metastatic disease.
- **Exclusions:**
  - Conditions not listed above.

Lung Cancer

- **Inclusions:**
  - Individuals with a solitary pulmonary nodule as a single-scan technique (not dual-time) to distinguish between benign and malignant disease when prior CT scan and chest x-ray findings are inconclusive or discordant,
  - To determine resectability for individuals with a presumed solitary metastatic lesion from lung cancer.
  - As a staging or restaging technique in those with known **non-small-cell** lung cancer.
  - PET scanning may be considered **established** in staging of small-cell lung cancer if limited stage is suspected based on standard imaging.
- **Exclusions:**
  - PET scanning in staging of small-cell lung cancer if extensive stage is established and in all other aspects of managing small-cell lung cancer.
  - Conditions not listed above.

Lymphoma, Including Hodgkin's Disease

- **Inclusions:**
  - PET scanning as a technique for staging lymphoma either during initial staging or for restaging at follow-up.
- **Exclusions:**
  - Conditions not listed above.

Melanoma

- **Inclusions:**
  - Assessing extranodal spread of malignant melanoma at initial staging or at restaging during follow-up treatment for advanced disease.

- **Exclusions:**
  - In managing stage 0, I or II melanoma.
  - When used as a technique to detect regional lymph node metastases in individuals with clinically localized melanoma who are candidates to undergo sentinel node biopsy.

Multiple Myeloma

- **Inclusions:**
  - For the initial and subsequent treatment strategy of multiple myeloma.
- **Exclusions**
  - N/A

Merkel Cell Carcinoma

- **Inclusions:**
  - As clinically indicated

Neuroendocrine Tumors

- **Inclusions:**
  - For the diagnosis, staging, restaging and monitoring of neuroendocrine tumors
- **Exclusions:**
  - Conditions not listed above.

Ovarian Cancer

- **Inclusions:**
  - Initial staging of ovarian cancer
  - For the evaluation of individuals with signs and/or symptoms of suspected ovarian cancer **recurrence** (restaging) when standard imaging, including CT scan, is inconclusive.
- **Exclusions:**
  - For the initial evaluation (not staging) of known or suspected ovarian cancer in all other situations

Pancreatic Cancer

- **Inclusions:**
  - For the initial diagnosis and staging of pancreatic cancer when other imaging and biopsy are inconclusive.
- **Exclusions:**
  - Evaluating other aspects of pancreatic cancer

Penile Cancer

- **Inclusions:**
  - Diagnostic workup:
    - Indicated in **EITHER** of the following scenarios:
      - Standard imaging cannot be performed or is nondiagnostic for metastatic disease.
      - Staging of penile cancer when pelvic lymph nodes are enlarged on CT or MRI and needle biopsy is not technically feasible.
  - Management:
    - Indicated in **ANY** of the following scenarios:
      - Radiation planning for preoperative or definitive treatment only.
      - Standard imaging cannot be performed or is nondiagnostic for recurrent or progressive disease.
      - Restaging of local recurrence when pelvic exenteration surgery is planned.
- **Exclusions:**
  - All other indications

Pleural, Thymus, Heart and Mediastinum Cancer

- **Inclusions:**
  - For surgical resection being considered and metastatic disease has not been detected by CT or MRI.
  - For surgical evaluation of malignant pleural mesothelioma (clinical stage I-IIIA and epithelioid histology), after CT chest and abdomen.
  - For restaging after induction chemotherapy if the patient is a surgical candidate.
  - For radiation planning for definitive treatment.
- **Exclusions:**
  - All other indications

Prostate Cancer

- **Inclusions:**
  - PET scanning with carbon 11 choline and fluorine18 fluciclovine for evaluating suspected or biochemically recurrent prostate cancer.
  - PSMA PET scanning with Gallium Ga-68 prostate-specific membrane antigen (PSMA)-11 and Piflufolastat fluorine-18 in individuals diagnosed with NCCN unfavorable intermediate-, high-, or very-high-risk prostate cancer for the following indications:
    1. as an alternative to standard imaging of bone and soft tissue for initial staging,
    2. for the detection of biochemically (elevated PSA) recurrent disease,
    3. as workup for progression with bone scan plus CT or MRI for the evaluation of bone, pelvis, and abdomen.
  - Individuals with metastatic prostate cancer for whom lutetium Lu-177 vipivotide tetraxetan PSMA-directed therapy is indicated.
- **Exclusions:**
  - PET scanning for all other indications.

Renal Cell Carcinoma

- **Inclusions:**
  - N/A
- **Exclusions:**
  - PET scanning is considered investigational in all aspects of managing renal cancer.

Soft Tissue Sarcoma

- **Inclusions:**
  - Diagnostic workup:
  - Indicated in **ANY** of the following scenarios (excluding desmoid tumors):
    - Standard imaging cannot be performed or is nondiagnostic for metastatic disease
    - Standard imaging suggests a resectable solitary metastasis
    - Baseline study prior to neoadjuvant chemotherapy
    - Initial staging for rhabdomyosarcoma
    - Determination of response to therapy, Gastrointestinal stromal tumor (GIST) for initial staging and re-staging when there is documented recurrence
  - Management:
    - Indicated following completion of neoadjuvant chemotherapy
    - Standard imaging cannot be performed or is nondiagnostic for recurrent or progressive disease
- **Exclusions:**
  - When used in evaluation of soft tissue sarcoma, including but not limited to the following applications:

- Distinguishing between low grade and high grade soft tissue sarcoma
- Detecting locoregional recurrence
- Detecting distant metastasis

Testicular Cancer

- **Inclusions:**
  - Diagnostic workup:
  - Indicated when standard imaging cannot be performed or is nondiagnostic for metastatic disease
  - Management:
  - Standard imaging cannot be performed or is nondiagnostic for recurrent or progressive Disease.
  - Residual mass greater than 3 cm and normal tumor markers after completion of chemotherapy.
- **Exclusions:**
  - All other indications.

Thyroid Cancer

Inclusions:

- For the initial treatment strategy of thyroid cancer types known not to concentrate radioactive iodine (RAI).
- For subsequent treatment strategy for differentiated thyroid cancer of follicular cell origin which is known to concentrate radioactive iodine (RAI), in the following situations:
  - When done following prior treatment with thyroidectomy and radioiodine ablation AND
  - With a current serum thyroglobulin > 10 ng/ml (except in the setting of documented anti-thyroglobulin antibodies,) AND
  - With a negative whole body RAI scan in the past.

- **Exclusions:**
  - For the evaluation of known or suspected differentiated or poorly differentiated thyroid cancer in all other situations.

Vaginal/Vulvar Cancers

- **Inclusions:**
  - Diagnostic workup:
    - Indicated in **EITHER** of the following scenarios:
      - Standard imaging cannot be performed or is nondiagnostic for metastatic disease.
  - Management:
    - Indicated in **ANY** of the following scenarios:
      - Radiation planning for preoperative or definitive treatment only.
      - Standard imaging cannot be performed or is nondiagnostic for recurrent or progressive disease.
      - Restaging of local recurrence when pelvic exenteration surgery is planned.
- **Exclusions:**
  - All other indications

Cancer Surveillance

- **Inclusions:**
  - N/A
- **Exclusions:**

- When used as a surveillance tool for individuals with cancer or with a history of cancer. A scan is considered surveillance if performed more than 6 months after completion of cancer therapy (12 months for lymphoma) in individuals without objective signs or symptoms suggestive of cancer recurrence.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

78608	78609	78811	78812	78813	78814
78815	78816	78999	G0253	A9593	A9594
A9595	A9800				

Other codes (investigational, not medically necessary, etc.):

G0219	G0252

Rationale

This policy is based on multiple evaluations of positron emission tomography (PET), including TEC Assessments, other systematic reviews, meta-analyses, decision analyses, and cost-effectiveness analyses.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

POSITRON EMISSION TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY PLUS COMPUTED TOMOGRAPHY

Clinical Context and Test Purpose

For this evidence review, PET and PET plus computed tomography (CT) scanning is discussed for the following 4 applications in oncology: diagnosis, staging, restaging, and surveillance. Diagnosis refers to the use of PET as part of the testing used in establishing whether a patient has cancer. Staging refers to the use of PET to determine the stage (extent)of cancer at the time of diagnosis before any treatment is given. Imaging at this time is generally to determine whether the cancer is localized. This also may be referred to as initial staging. Restaging refers to imaging after treatment in 2 situations. Restaging is part of the evaluation of a patient in whom disease recurrence is suspected based on signs and/or symptoms. Restaging also includes determining the extent of malignancy after completion of a full course of treatment. Surveillance refers to the use of imaging in asymptomatic individuals

(individuals without objective signs or symptoms of recurrent disease). This imaging is completed 6 months or more (≥12 months for lymphoma) after completion of treatment.

The question addressed in this evidence review is: Does use of PET or PET/CT improve the net health outcome in individuals with suspected, diagnosed, or treated with cancer compared to conventional imaging techniques?

The following **PICO** was used to select literature to inform this review.

Populations
The relevant populations of interest are;

- Individuals who are suspected of having cancer
- Individuals diagnosed with cancer and need information on the extent of the cancer (initial staging upon diagnosis confirmation or restaging following treatment)
- Individuals with cancer who have finished a round of treatment and may be at risk of recurrence.

Interventions
The test being considered is PET or PET/CT. A PET scan is a nuclear medicine 3-dimensional imaging technique. Radioactive tracers are ingested or injected, and radioactive emissions are detected by an imaging device, allowing observations on blood flow, oxygen use, and metabolic processes around the lesions. When CT is added to PET, the images are superimposed, providing additional anatomic information. The most common radioactive tracer used for oncologic applications is fluorine 18 (^{18}F) fluorodeoxyglucose (FDG). Radiation exposure from PET and PET/CT is considered moderate to high.

PET and PET/CT would be administered in a tertiary care center or a facility with the necessary equipment.

Comparators
The comparators of interest are conventional imaging techniques such as ultrasound, magnetic resonance imaging (MRI), and x-rays.

Outcomes
The general outcomes of interest are related to the clinical validity of PET and PET/CT in (1) diagnosing suspected cancers, (2) providing staging or restaging information, and (3) detecting recurrence following cancer treatment. Clinical utility is most often measured by sensitivity, specificity, positive predictive values (PPV) and negative predictive values. For the clinical utility of PET and PET/CT to be demonstrated, the tests would need to inform treatment decisions that would improve survival and quality of life.

Clinical validity can be measured as soon as results from PET or PET/CT can be compared with results from conventional imaging techniques. Outcomes for clinical utility are long-term, which, depending on the type of cancer, can range from months or a few years for less aggressive cancers to many years for less aggressive cancers.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess the clinical validity of PET and PET/CT, studies should report sensitivity, specificity, positive and negative predictive values. Additionally, studies reporting false-positive rates and false-negative rates are informative.
- To assess the clinical utility of PET and PET/CT, studies should demonstrate how results of these imaging techniques impacted treatment decisions and overall management of the patient.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The majority of evidence on the use of PET scanning in oncology focuses on clinical validity (sensitivity, specificity) and consists mostly of systematic reviews and meta-analyses. There are few rigorous studies assessing the impact of PET on clinical utility. A few of the studies that have reported on changes in staging and/or treatment that result from the PET scan do not evaluate whether these changes result in an improvement in the net health outcome. Due to the lack of direct evidence for clinical utility, evidence for clinical validity is presented first, followed by clinical guidelines, which help to outline the indications for which clinical utility is supported.

Review of Evidence

BLADDER CANCER

Systematic Review
A systematic review and meta-analysis (10 studies, total N=433) by Zhang et al (2015) evaluated the diagnostic accuracy of FDG-PET (^{18}F-FDG-PET) and ^{18}F-PET with CT (^{18}F-PET/CT) in individuals with urinary bladder cancer.[3] The 10 studies were assessed for quality using the 14-item Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Median QUADAS score was 9 (range, 7-10). Nine of the 10 studies used ^{18}F-PET/CT and 1 used ^{18}F-FDG-PET. Nine studies were retrospective and one prospective. Meta-analyses showed relatively high sensitivity (82%; 95% confidence interval [CI], 75% to 88%) and specificity (92%; 95% CI, 87% to 95%) in the diagnosis of bladder cancer, with the reference test of pathology results. The meta-analysis funnel plots showed some asymmetry, indicating a potential for publication bias.

Guidelines

American College of Radiology

In 2018, the American College of Radiology (ACR) issued an Appropriateness Criteria for pretreatment staging of muscle-invasive bladder cancer.[4] ACR stated that ^{18}F-PET/CT "may be appropriate" for the pretreatment staging of muscle-invasive bladder cancer. However, the ACR cites CT, MRI, and chest radiographs as the most appropriate imaging techniques for pretreatment staging.

In 2021, the ACR issued an Appropriateness Criteria for post-treatment surveillance of bladder cancer. For muscle-invasive bladder cancer, FDG-PET/CT may be appropriate for surveillance; however, the ACR states that chest radiograph, CT, and MRI are usually appropriate procedures.[5]

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines for bladder cancer (3.2023) state that FDG-PET/CT may be useful in assessing the presence of regional or distant metastases, though it is not the preferred imaging modality. [6] Recommendations for FDG-PET/CT in muscle-invasive bladder cancer include (all category 2B):

- For chest imaging:
  - Staging: "may be beneficial in selected patients with T2 (muscle-invasive disease) and in patients with ≥cT3 disease"
  - Follow-up with or without cystectomy: "may be performed if not previously done or if metastasis is suspected in selected patients"
  - Follow-up of cT4b and metastatic disease: "may be performed if not previously done or in high-risk patients in whom metastatic disease is suspected"

- For abdominal and pelvic imaging:
  - Staging: "may be useful in selected patients with ≥cT2 disease and may change management in patients with ≥cT3 disease"
  - Follow-up: "may be performed if not previously done or in high-risk patients in whom metastatic disease is suspected; this could also be used to guide biopsy in certain patients"

- Evaluation of suspected bone metastases
  - "Symptomatic, or high-risk patients, or those with laboratory indicators of bone metastasis may be imaged with MRI, FDG-PET/CT (category 2B), or bone scan. FDG-PET/CT (category 2B) may also be considered in cases when additional sites of extraosseous metastatic disease are suspected or previously documented."

However, the guidelines note that "PET/CT should not be used to delineate the anatomy of the upper urinary tract" or in patients with nonmuscle invasive bladder cancer.

Section Summary: Bladder Cancer

Evidence for the use of FDG-PET and FDG-PET/CT for the diagnosis and for the staging and restaging of muscle-invasive bladder cancer consists of a systematic review and meta-analysis of several studies. Pooled analyses have shown that PET/CT is effective in the staging of muscle-invasive bladder cancer. The evidence supports the use of FDG-PET/CT for the diagnosis and staging and restaging of muscle-invasive bladder cancer.

The evidence does not support the use of FDG-PET/CT for nonmuscle invasive bladder cancer.

Bone Sarcoma

Systematic Reviews

A meta-analysis (12 studies, N=375) by Zhang et al (2020) evaluated FDG-PET and FDG-PET/CT in the diagnosis and staging of chondrosarcoma, a common type of bone sarcoma.[7] Six studies used PET/CT, 5 studies used PET, and 1 study utilized both. For differentiating between chondrosarcoma and benign lesions, the pooled sensitivity and specificity of FDG-PET were 84% (95% CI, 46% to 97%) and 82% (95% CI, 55% to 94%), respectively. The sensitivity and specificity for FDG-PET/CT were also found to be high at 94% (95% CI, 86% to97%) and 89% (95% CI, 82% to 93%), respectively. There was substantial heterogeneity for sensitivity (*I2*, 86.90%; 95% CI, 76.8% to 97.0%) and specificity (*I2*, 70.32%; 95% CI, 42.57to 98.07%) among studies. Most included studies were retrospective (75%) and included small sample sizes (n=7 to 95), potentially introducing bias and variability.

A systematic review and meta-analysis (35 studies, total N=2171) by Liu et al (2015) evaluated FDG-PET and FDG-PET/CT in the diagnosis, staging, and recurrence assessment of bone sarcoma.[8] Most selected studies used PET/CT (n=29). Meta-analyses showed high sensitivity (96%; 95% confidence interval [CI], 93% to 98%) and specificity (79%; 95% CI, 63% to 90%) of 18F-FDG-PET and –PET/CT to differentiate primary bone sarcomas from benign lesions. For pooled results for detecting recurrence, sensitivity was 92% (95% CI, 85% to 97%) and specificity was 93% (95% CI, 88% to 96%). For pooled results for detecting distant metastases, sensitivity was 90% (95% CI, 86% to 93%) and specificity was 85% (95% CI, 81% to 87%). Subgroup analysis by specific metastatic site revealed that PET alone was less effective in detecting lung metastases than other metastatic sites (sensitivity, 71%; 95% CI, 52% to 86%; specificity, 92%; 95% CI, 87% to 96%).

A systematic review (13 studies, total N=342) and meta-analysis (5 studies, n=279) by Treglia et al (2012) examined the diagnostic accuracy of FDG-PET and FDG-PET/CT in Ewing sarcoma.[9] The meta-analysis showed high estimates of sensitivity and specificity for FDG-PET and FDG-PET/CT(pooled sensitivity, 96%; pooled specificity, 92%).

Guidelines

American College of Radiology

In 2020, the ACR issued an Appropriateness Criteria for primary bone tumors. [10] For suspected primary bone tumors with evidence of lesions on radiographs and indeterminate or aggressive appearance for malignancy, FDG-PET/CT of the whole body may be appropriate; MRI of area of interest with or without contrast was deemed usually appropriate. Use of FDG-PET/CT was considered usually not appropriate for other diagnostic and staging imaging procedures addressed in the guidance**.**

Current NCCN guidelines for bone cancer (v.1.2024) state that PET and CT may be considered for: [11]

- Diagnostic workup of individuals with suspected primary bone cancer, including chordoma, Ewing sarcoma, or osteosarcoma,
- Restaging in individuals with Ewing sarcoma or osteosarcoma, and
- Surveillance of individuals with Ewing sarcoma or osteosarcoma (category 2B).

Section Summary: Bone Sarcoma
Evidence for the use of FDG-PET and FDG-PET/CT for the diagnosis and for the staging and restaging of bone sarcoma consists of systematic reviews and meta-analyses. Pooled analyses have shown that PET is effective in the staging of bone sarcoma, including chondrosarcoma. Use of PET has also shown high sensitivities and specificities in detecting metastases in bone and lymph nodes but low sensitivity in detecting lung metastases. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis, staging, and restaging of bone sarcoma.

The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of bone sarcoma.

BRAIN TUMORS

FDG-PET and ^{18}F-FET-PET

Systematic Reviews
A systematic review and meta-analysis by Dunet et al (2016) included studies published through January 2015 in which Individuals with suspected primary or recurrent brain tumors underwent both fluorine 18 fluoro-ethyl-tyrosine PET (^{18}F-FET-PET) and ^{18}F-FDG-PET.[12] Four studies (total N=109 Individuals) met inclusion criteria. All 4 studies included in the meta-analysis had scores greater than 10 in the 15-point Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. ^{18}F-FET PET (pooled sensitivity, 94%; 95% CI, 79% to 98%; pooled specificity, 88%; 95% CI, 37% to 99%) performed better than ^{18}FFDG-PET (pooled sensitivity, 38%; 95% CI, 27% to 50%; pooled specificity, 86%; 95% CI, 31% to 99%) in the diagnosis of brain tumors. Target to background ratios of both FDG and FET were similar in detecting low- and high-grade gliomas.

A systematic review and meta-analysis including studies published through January 2011 addressed the use of FET in detecting primary brain tumors (Dunet et al, 2012).[13] Thirteen studies (total N=462 Individuals) were included in the systematic review and 5 (n=224 Individuals) were included in the meta-analysis. All 5 studies in the meta-analysis had scores above 10 on the 14-point QUADAS scale. The pooled sensitivity for ^{18}F-FET PET in detecting primary brain tumors was 82% (95% CI, 74% to 88%) and pooled specificity was 76% (95% CI, 44% to 92%). Other imaging modalities for diagnosing brain tumors were not included in this analysis, so no conclusions can be made about comparative effectiveness.

FDG-PET and ^{11}C Methionine PET

Systematic Reviews
A 2014 meta-analysis by Zhao et al compared the diagnostic performance of ^{18}F-FDG-PET with ^{11}C methionine PET in the detection of suspected primary brain tumors and suspected recurrence of brain tumors following treatment. The literature search included studies

published through February 2013. A total of 24 studies provided data on the use of ^{18}F-FDG-PET and 11 studies reported on the use of ^{11}C-methionine PET.[14] The pooled sensitivity and specificity of ^{18}F-FDG-PET in detecting primary or recurrent brain tumors were 71% (95% CI, 63% to 78%) and 77% (95% CI, 67% to 85%), respectively. Diagnostic performance was better with ^{11}C-methionine PET, with a pooled sensitivity and specificity of 91% (95% CI, 85% to 94%) and 86% (95% CI, 78% to 92%), respectively.

Another meta-analysis (Deng et al, 2013) assessed the ability of ^{11}C-methionine PET and MRI to detect glioma recurrence.[15] The literature search included articles through March 2012. All selected studies were retrospective cohorts, 11 using ^{11}C-methionine PET (n=244) and 7 using MRI (n=214). Meta-analyses found that the dynamic susceptibility contrast-enhanced MRI (pooled sensitivity, 88%; 95% CI, 82% to 93%; pooled specificity, 85%; 95% CI, 75% to 92%) performed similarly to ^{11}C methionine PET (pooled sensitivity, 87%; 95% CI, 81% to 92%; pooled specificity, 81%; 95% CI, 72% to 89%) in glioma Recurrence detection, with ^{11}C-methionine being slightly less specific.

Guidelines

Current NCCN guidelines for brain cancer (v.1.2023) include these statements:[16]

- PET can assess metabolism within the tumor and normal tissue by using radio-labeled tracers, which may be useful in differentiating tumor from radiation necrosis, may correlate with tumor grade, or provide an optimal area for biopsy.
- Limitations include the accuracy of interpretations and availability of equipment and isotopes.
- Close follow-up imaging, MR perfusion, MR spectroscopy, PET/CT imaging, and repeat surgery may be necessary if clinically indicated. Educate Individuals on the uncertainty of imaging as a whole, and the potential need for corollary testing to interpret scans.

Section Summary: Brain Tumors

Evidence for the use of PET to diagnose and stage brain cancer consists of several systematic reviews and meta-analyses. The diagnostic capabilities of PET vary depending on the radiotracer used. There was 1 direct comparison of radiotracers, with ^{18}F-FET-PET showing better diagnostic accuracy than FDG-PET. An indirect comparison between FDG-PET and ^{11}C-methionine PET showed that ^{11}C-methionine PET performed better, and another indirect comparison of ^{11}C methionine PET and MRI showed a comparable diagnostic capability between the 2 methods. The evidence supports the use of F-FDG-PET, ^{18}F-FET-PET, and ^{11}C-methionine PET for the diagnosis and staging and restaging of brain tumors cancer but does not support their use for surveillance.

The evidence does not support the use of FDG-PET, 18F-FET-PET, and 11C-methionine PET for surveillance of brain tumors.

BREAST CANCER

Breast Cancer Diagnosis

Systematic Reviews

Liang et al (2017) conducted a meta-analysis on the use of PET/CT to assess axillary lymph node metastasis.[17] Results from the meta-analyses of 14 studies using MRI and 10 studies using PET/CT showed that MRI had higher sensitivity in diagnosing axillary lymph node status.

In a meta-analysis of 8 studies (total N=873) on FDG-PET performed in women with newly discovered suspicious breast lesions, Caldarella et al (2014) reported pooled sensitivity and specificity of 85% (95% CI, 83% to 88%) and 79% (95% CI, 74% to 83%), respectively, on a per-lesion basis.[18] As previously noted, a false-negative rate of 15% (100% – sensitivity) may be considered unacceptable given the relative ease of breast biopsy.

A systematic review by Sloka et al (2007) on PET for staging axillary lymph nodes identified 20 studies.[19] Three of these 20 studies were rated high quality, indicating broad generalizability to a variety of individuals and no significant flaws in research methods. The remaining studies were less generalizable due to flaws in the methodology. Reviewers observed that there was great variability in estimates of sensitivity and specificity from the selected studies and that it was difficult to draw conclusions from the evidence.

A TEC Assessment (2001) focused on multiple applications of PET scanning in breast cancer, including characterizing breast lesions, staging axillary lymph nodes, detecting recurrence, and evaluating response to treatment.[20] A TEC Assessment (2003) reexamined all indications except for characterizing breast lesions.[21] The bulk of the data on FDG-PET for breast cancer focuses on its ability to characterize breast lesions further such that individuals could avoid biopsy of a mammographically indeterminate or suspicious lesion. The key statistic in this analysis is the false-negative rate because individuals with a false-negative result on a PET scan may inappropriately forgo a biopsy and subsequent treatment. The false-negative rate will vary with the underlying prevalence of the disease, but may range from 5.5% to 8.5%. Given the relative ease of breast biopsy, this false-negative rate may be considered unacceptable, and thus individuals may undergo biopsy regardless of the results of a PET scan.

Breast Cancer Staging

A meta-analysis by Han et al (2021) evaluated the impact of FDG-PET, PET/CT, and PET/MRI on staging and management during the initial staging of breast cancer. [22] A total of 29 studies (N=4276) were identified. The pooled results for all 3 imaging studies demonstrated that they led to a change in staging in 25% (95% CI, 21% to 30%) of individuals and a change in management in 18% (95% CI, 14% to 23%) of individuals.

A 2013 meta-analysis by Hong et al reported sensitivity and specificity of FDG-PET/CT in diagnosing distant metastases in breast cancer Individuals were .96 (95% confidence interval [CI], 0.90 to 0.98) and 0.95 (95% CI, 0.92 to 0.97) when 8 studies totaling 748 individuals were evaluated.[23] When the meta-analysis was completed on 6 comparative studies totaling 664 individuals, the sensitivity and specificity were 0.97 (95% CI, 0.84 to 0.99) and 0.95 (95% CI, 0.93 to 0.97), compared with 0.56 (95% CI, 0.38 to 0.74) and 0.91(95% CI, 0.78 to 0.97) with conventional imaging.

Rong et al in 2013 meta-analyzed 7 studies totaling 668 individuals and reported ^{18}F-FDG-PET/CT sensitivity and specificity were greater than bone scintigraphy for detecting bone metastasis in breast cancer individuals.[24] FDG-PET/CT sensitivity and specificity were 0.93 (95% CI, 0.82 to 0.98) and 0.99 (95% CI, 0.95 to 1.00), compared with 0.81 (95% CI, 0.58 to 0.93) and 0.96 (95% CI, 0.76 to 1.00) with bone scintigraphy.

A meta-analysis by Isasi et al (2005) focused on PET for detecting recurrence and metastases.[25] The analysis concluded that PET is a valuable tool; however, they did not compare PET performance with that of other diagnostic modalities, so it is unclear whether use of PET resulted in different management decisions and health outcomes.

The TEC Assessment (2003) described above in the Breast Cancer Diagnosis section concluded that the use of FDG-PET for staging axillary lymph nodes did not meet TEC criteria.[21]

Breast Cancer Restaging

A 2016 systematic review by Xiao et al evaluated the diagnostic efficacy of ^{18}F-FDG-PET and ^{18}F-FDGPET/CT in detecting breast cancer recurrence.[26] The literature search, conducted through January 2016, identified 26 studies (total N=1752 individuals) for inclusion in the analysis; 12 studies used PET and 14 studies used PET/CT. Fourteen studies had QUADAS scores greater than 10. Reasons for suspected recurrence in the 1752 individuals were: elevated tumor markers (57%), suspicion from conventional imaging modalities (34%), and suggestive clinical symptoms or physical examination results (9%). Pooled sensitivity and specificity for PET and PET/CT were 90% (95% CI, 88% to 90%) and 81% (95% CI, 78% to 84%), respectively. Subgroup analyses showed that PET/CT was more specific than PET alone in diagnosing recurrent breast cancer (p=0.035).

A systematic review by Liu et al (2016) compared FDG-PET or FDG-PET/CT with MRI in assessing pathologic complete response to neoadjuvant chemotherapy in Individuals with breast cancer.[27] The literature search, conducted through August 2015, identified 6 studies (total N=382) for inclusion. Quality assessment of the studies was deemed satisfactory using the QUADAS-2 scale. Meta-analysis results are presented in Table 2.

In another 2016 meta-analysis comparing 18F-FDG-PET with MRI and evaluating pathologic complete response to neoadjuvant chemotherapy (NAC) in individuals with breast cancer, Sheikhbahaei et al (2016) selected 10 studies for analysis.[28] The inclusion criteria differed slightly from Liu (2016). Liu et al required that both ^{18}F-FDG-PET and MRI be performed before and during (or after) NAC, while Sheikhbahaei did not require the scanning before NAC. Pooled sensitivities and specificities are listed in Table 2. Subgroup analysis was performed, by time of scanning (during NAC and after NAC was completed).

Other reviews, including Li et al (2018), have also compared MRI with PET or PET/CT in evaluating response to NAC.[29] Meta-analytic results are similar to previous studies and are presented in Table 2.

Table 2. Pooled Diagnostic Performance of ^{18}F-FDG-PET and MRI in Detection of Residual Disease after NAC for Breast Cancer[50]

Type of Imaging	No. of Studies (Individuals)	Sensitivity (95% CI), %	Specificity (95% CI), %
Li et al (2018)[29]			
MRI	13 (575)	88 (78 to 94)	69 (51 to 83)
FDG-PET or FDG-PET/CT	13 (618)	77 (58 to 90)	78 (63 to 88)
Xiao et al (2016)[26]			
FDG-PET or FDG-PET/CT	26 (1752)	90 (88 to 90)	81 (78 and 84)
Liu et al (2016)[27]			
MRI	6 (382)	86 (76 to 93)	72 (49 to 87)
FDG-PET or FDG-PET/CT	6 (382)	86 (76 to 93)	72 (49 to 87)
Sheikhbahaei et al (2016)[28]			
All studies			

MRI	10 (492)	88 (76 to 95)	55 (41 to 68)
FDG-PET or FDG-PET/CT	10 (535)	71 (52 to 85)	77 (58 to 89)
FDG-PET/CT	7 (385)	82 (62 to 92)	79 (52 to 93)
FDG-PET	3 (150)	43 (26 to 63)	73 (44 to 91)
During NAC			
MRI	3 (256)	89 (66 to 97)	42 (20 to 68)
FDG-PET/CT	3 (256)	91 (86 to 95)	69 (25 to 93)
After NAC completion			
MRI	7 (236)	88 (71 to 96)	63 (51 to 74)
FDG-PET or FDG-PET/CT	7 (279)	57 (40 to 71)	80 (65 to 90)
FDG-PET/CT	4 (129)	71 (42 to 89)	88 (73 to 95)

CI: confidence interval; CT: computed tomography; FDG: fluorine 18 fluorodeoxyglucose; MRI: magnetic resonance imaging; NAC: neoadjuvant chemotherapy; PET: positron emission tomography.

Two 2012 meta-analyses pooled studies on the use of FDG-PET to predict pathologic response to neoadjuvant therapy before surgery for locally advanced breast cancer. [30, 31] Both reviews reported similar pooled point estimates for sensitivity and specificity. Both concluded that PET had reasonably high sensitivity and relatively low specificity. Neither described how PET should be used to influence patient management decisions and therefore whether health outcomes would be changed relative to decisions not based on PET results. Thus, it is unclear whether PET improves outcomes for predicting pathologic response to neoadjuvant therapy for locally advanced breast cancer.

Guidelines

American College of Radiology

In 2017, the ACR issued an Appropriateness Criteria for the initial workup and surveillance for local recurrence and distant metastases in asymptomatic women with stage I breast cancer.[32] ACR noted that FDG-PET/CT is usually not appropriate during initial workup or surveillance of these Individuals, to rule out metastases.

National Comprehensive Cancer Network

Current NCCN guidelines on breast cancer (v.4.2023) include category 2B recommendation for FDG-PET/CT as an optional test in the workup of breast cancer.[33] The use of FDG-PET/CT is "most helpful in situations where standard staging studies are equivocal or suspicious. FDG-PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging studies." NCCN recommends against FDG-PET/CT for lower stage breast cancer (I, II, or operable III) due to high false-negative rates in detecting low-grade lesions or lesions less than 1 cm; low sensitivity in detecting axillary node metastasis; the low prior probability of detectable metastases in these individuals; and high false-positive rates.

The NCCN guidelines do not recommend routine use of PET in asymptomatic individuals for surveillance and follow-up after breast cancer treatment. When monitoring metastatic disease, the guidelines note that PET is “challenging because of the absence of a reproducible, validated, and widely accepted set of standards for disease activity assessment.”

Section Summary: Breast Cancer

Evidence for the use of PET or PET/CT in Individuals with breast cancer consists of TEC Assessments, systematic reviews, and meta-analyses. There is no evidence that PET is useful in diagnosing breast cancer. The false-negative rates of PET in Individuals with breast cancer are estimated to be between 5.5% and 8.5%, which can be considered unacceptable,

given that breast biopsy can provide more definitive results. Use of PET/CT might be useful in detecting metastases when results from other imaging techniques are inconclusive. The evidence supports the use of FDG-PET and FDG-PET/CT for staging and restaging only if standard staging methods are inconclusive.

The evidence does not support the use of FDG-PET and FDG-PET/CT for diagnosis, staging, and restaging when standard staging methods are conclusive.

The evidence does not support the use of FDG-PET or FDG-PET/CT for surveillance of breast cancer.

Cervical Cancer

Systematic Reviews
In a systematic review of 20 studies, Chu et al (2014) reported a pooled sensitivity and specificity for FDG-PET or FDG-PET/CT of 87% (95% CI, 80% to 92%) and 97% (95% CI, 96% to 98%), respectively, for distant metastasis in recurrent cervical cancer.[34] For local regional recurrence, pooled sensitivity and specificity were 82% (95% CI, 72% to 90%) and 98% (95% CI, 96% to 99%), respectively.

In a meta-analysis of 9 cervical cancer recurrence studies, Rong et al (2013) reported a sensitivity and a specificity for PET/CT of 94.8% (95% CI, 91.2% to 96.9%) and 86.9% (95% CI, 82.2% to 90.5%), respectively.[24] Reviewers found the quality of studies on recurrence was average with some limitations. For example, studies included mostly symptomatic women and did not differentiate between PET for diagnosis or surveillance.

An Agency for Healthcare Research and Quality (AHRQ) review (2008) identified several studies using FDG-PET or FDG-PET/CT to stage advanced cervical cancer and to detect and stage recurrent disease.[35] The report concluded that most studies supported enhanced diagnostic accuracy, which would improve the selection of appropriate treatment for individuals. For recurrent disease, PET identified additional sites of metastasis, which would alter treatment decisions in some cases. For example, in a study by Yen et al (2004) of 55 individuals whose recurrences were initially considered curable with radical surgical treatment, 27 instead underwent palliative therapy based on PET results.[36] An NCCN report conducted by conducted by Podoloff et al (2009) also identified several studies supporting the use of PET for initial staging and identifying and staging recurrent disease.[37]

Guidelines
Current NCCN guidelines on cervical cancer (v1.2024) state that PET/CT may be considered under the following conditions: [38]

- Part of the initial non-fertility and fertility-sparing workup for individuals with stage I cervical cancer.
- Part of the initial staging workup for detection of stage II, III, or IV metastatic disease.
- Follow-up/surveillance for stage I (only nonfertility sparing) through stage IV at 3 to 6 months after completion of therapy or if there is suspected recurrence or metastases.
- To assess response or determine future therapy in individuals with Stage IVB or cervical cancer recurrence.
- PET/CT should cover neck, chest, abdomen, pelvis, and groin.

Section Summary: Cervical Cancer

Evidence for the use of PET in Individuals with cervical cancer consists of systematic reviews and meta-analyses. Pooled results have shown that PET can be used for staging or restaging and detecting recurrent disease. The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis and staging and restaging of cervical cancer but does not support their use for surveillance.

Colorectal Cancer

CRC Diagnosis

Systematic Reviews

Mahmud et al (2017) conducted a systematic review comparing the use of FDG-PET and -FDG-PET/CT with conventional imaging techniques in the staging, treatment response, and follow-up of Individuals with rectal cancer.[39] The literature review, conducted through April 2016, identified 17 studies (total N=791) for the qualitative review, with 8 of those studies (n=428) included in the meta-analysis. The QUADAS-2 tool was used to assess study quality. A limitation of many of the studies was that there was either no blinding or unclear blinding used for assessing the index test or the reference standard. For the detection of a primary tumor, pooled sensitivity and specificity were 99% (95% CI, 97% to 100%) and 67% (95% CI, 50% to 82%), respectively. For the detection of inguinal lymph nodes, the pooled sensitivity and specificity were 93% (95% CI, 76% to 99%) and 76% (95% CI, 61% to 87%), respectively.

A systematic review by Jones et al (2015) compared the role of -FDG-PET and FDG-PET/CT with conventional imaging in the detection of primary nodal disease.[40] Twelve studies met inclusion criteria (total N=494). A meta-analysis for detecting primary disease in situ showed that PET and PET/CT had a higher sensitivity (99%; 95% CI, 96% to 100%) than CT alone (60%; 95% CI, 46% to 75%).

Two clinical applications of PET scanning were considered in a TEC Assessment (1999): (1) to detect hepatic or extrahepatic metastases and to assess their resectability in individuals with colorectal cancer (CRC), either as part of initial staging or after primary resection, and (2) to evaluate the presence of postoperative scar versus recurrent disease as a technique to determine the necessity of tissue biopsy.[41]
The body of evidence indicates that PET scanning adds useful information to conventional imaging in detecting hepatic and extrahepatic metastases. In particular, PET can detect additional metastases leading to more identification of non-resectable disease, allowing individuals to avoid surgery. The strongest evidence comes from a study that directly assessed the additional value of PET. In a group of 37 individuals thought to have solitary liver metastases by conventional imaging, PET correctly upstaged 4 individuals and falsely over staged 1. This and another study found that when PET results were discordant with conventional imaging results, PET was correct in 88% and 97% of individuals, respectively. When PET affected management decisions, it was more often used to recommend against surgery.

When used to distinguish between local recurrence and scarring, the comparison is between performing histological sampling in all individuals with a suspected local recurrence and avoiding sampling in individuals whose PET scans suggest the presence of postoperative scar. The key concern is whether the negative predictive value for PET is sufficiently high to influence decision making, specifically to avoid tissue biopsy when the PET scan is negative. The TEC Assessment found that studies available at that time suggested an 8% probability of

false-negative results, making it unlikely that individuals and physicians would forgo histologic sampling and delay potentially curative repeat resection.

Colorectal Cancer Staging

Systematic Reviews

Results from a meta-analysis of 10 studies by Albertsson et al (2018) found that PET/CT influenced treatment plans for anal cancer, though the impact on survival and quality of life could not be determined.[42]

A 2015 meta-analysis by Ye et al assessed the use of ^{18}F-FDG-PET/CT in preoperative TNM staging of CRC.[43] The literature search, conducted through July 2014, identified 28 studies for inclusion. Of the 28 studies, 12 assessed tumor detection rate; 4 evaluated T staging, 20 N staging, and 5 M staging; while 8 examined stage change. Using the QUADAS tool, all studies met 9 or more of the 14 criteria. Pooled diagnostic estimates are listed in Table 3.

Three systematic reviews published in 2014 included overlapping studies that assessed the predictive value of FDG-PET/CT in individuals with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy.[44,45,46] Various PET parameters were investigated (standardized uptake value, response index [percentage of the standardized uptake value decrease from baseline to post neoadjuvant treatment]), and cutoff values varied. Pooled sensitivities ranged from 74% to 82%, and pooled specificities ranged from 64% to 85%. The value of FDG-PET/CT in this setting has yet to be established.

Two systematic reviews were conducted to evaluate the use of PET/CT for radiotherapy planning in individuals with rectal cancer. Gwynne et al (2012) compared different imaging techniques for radiotherapy treatment planning and concluded that additional studies would be needed to validate the use of PET in this setting.[47]

Table 3. Pooled Diagnostic Performance of ^{18}F-FDG-PET, ^{18}F-FDG-PET/CT, and CT Alone in the Staging of Colorectal Cancer

Type of Imaging	No. of Studies	Diagnostic Threshold	Sensitivity (95% CI), %	Specificity (95% CI), %
T staging				
^{18}F-FDG-PET or –PET/CT	4	Yes	73 (65 to 81)	99 (98 to 99)
N staging				
^{18}F-FDG-PET or –PET/CT	20	Yes	62 (59 to 66)	70 (67 to 73)
^{18}F-FDG- PET/CT alone	12	Yes	70 (66 to 74)	63 (59 to 67
^{18}F-FDG-PET alone	8	No	36 (29 to 44)	93 (89 to 96)
CT alone	7	No	79 (75 to 80)	46 (41 to 51)
M staging				
^{18}F-FDG-PET or –PET/CT	5	No	91 (80 to 96)	95 (91 to 98)
CT alone	5	No	91 (87 to 94)	16 (8 to 27)

Adapted from Ye et al (2015).[40]
CI: confidence interval; CT: computed tomography; M staging: distant metastases; N staging: regional lymph nodes; PET: positron emission tomography; T staging: primary tumor

Colorectal Cancer Restaging

Systematic Reviews

A 2016 meta-analysis by Rymer et al evaluated use of ^{18}F-FDG-PET/CT in the assessment of the response of locally advanced rectal cancer to neoadjuvant chemoradiotherapy.[48] The literature search, conducted through April 2014, identified 10 studies (total N=538) for inclusion in the analysis. Selected studies were high quality, complying with an average 12.7 items on the 14-item QUADAS checklist. Tumors confirmed to have regressed following chemoradiotherapy (responders) had a higher response index with mean difference of 12% (95% CI, 7% to 18%) and a lower standardized uptake value of -2.5 (95% CI, -3.0 to -1.9%) compared with nonresponders.

A 2015 meta-analysis by Yu et al evaluated the diagnostic value of ^{18}F-FDG-PET/CT for detecting local recurrent colorectal cancer.[49] A literature search was conducted and identified 26 studies (total N=1794) for inclusion. Study quality was assessed using QUADAS. Pooled sensitivity and specificity were 95% (95% CI, 93% to 97%) and 93% (95% CI, 92% to 95%), respectively.

In 2015, Maffione et al conducted a systematic review of ^{18}F-FDG-PET for predicting response to neoadjuvant therapy in individuals with rectal cancer.[50] A literature search was conducted with 29 studies meeting inclusion criteria for the meta-analysis. The studies had QUADAS scores ranging from 8 to 14 (median, 12). The pooled sensitivity and specificity for ^{18}F-FDG-PET assessment of response to chemoradiotherapy in locally advanced rectal cancer were 73% (95% CI, 71% to 76%) and 77% (95% CI, 75% to 79%), respectively.

In a systematic review, Lu et al (2013) evaluated 510 individuals from 11 studies on ^{18}F-FDG-PET for colorectal cancer tumor recurrence detection in individuals with carcinoembryonic antigen (CEA) elevation.[51] Estimates for FDG-PET and PET/CT pooled sensitivity estimates were 90.3% (95% CI, 85.5% to 94.0%) and 94.1% (95% CI, 89.4% to 97.1%), while specificities were 80.0% (95% CI, 67.0% to 89.6%) and 77.2% (95% CI, 66.4% to 85.9%), respectively.

Colorectal Cancer Surveillance

Randomized Controlled Trials

Sobhani et al (2018) conducted an open-label RCT to determine whether adding 6 monthly FDG-PET/CT scans to usual surveillance (ie.,3 monthly physicals and tumor marker assays; 6 monthly liver ultrasounds and chest radiographs; 6 monthly CT scans) of individuals with CRC following surgery and/or chemotherapy improves health outcomes.[52] A total of 239 individuals in remission were enrolled, with 120 in the intervention arm and 119 in the control arm. After 3 years follow-up, the failure rate in the intervention group was 29% (31 unresectable recurrences, 4 deaths) and 24% in the control group (27 unresectable recurrences, 1 death), which was not a statistically significant difference.

Guidelines

American College of Radiology

In 2017, the ACR issued an Appropriateness Criteria for the pretreatment staging of CRC.[53] In the evaluation of distant metastases, the criteria stated that “routine use of PET/CT is likely not indicated; however, it may provide guidance in cases of advanced, bilobar liver disease to exclude extrahepatic metastases prior to surgical intent to cure.”

National Comprehensive Cancer Network
Current NCCN guidelines for colon cancer (v.3.2023) “strongly discourage the routine use of PET/CT scanning for staging, baseline imaging, or routine follow-up and recommend consideration of a preoperative PET/CT scan at baseline only if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease.”[54] For initial workup of nonmetastatic individuals, the guidelines state that PET/CT is not routinely indicated, and "PET/CT does not supplant a contrast-enhanced diagnostic CT or MR scan and should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or MR scan or in individuals with strong contraindications to IV [intravenous] contrast. "PET/CT can be considered in select individuals "considered for image-guided liver-directed therapies," "for assessment of response and liver recurrence after image-guided liver-directed therapies, or serial carcinoembryonic antigen elevation during follow-up." Otherwise, use of PET/CT is not recommended for surveillance. The NCCN has noted that PET/CT should not be used to assess response to chemotherapy. The NCCN was divided on the appropriateness of PET/CT when carcinoembryonic antigen level is rising; PET/CT might be considered when imaging study results (eg, a good quality CT scan) are normal.

Current NCCN guidelines for rectal cancer (v.5.2023) state that PET/CT is “not routinely indicated” and “should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or in individuals with strong contraindications to IV contrast.” [55] For certain individuals with potential surgically-curable MI disease, a PET/CT may be considered. Use of a PET/CT is not recommended for restaging or for surveillance. Use of PET/CT can be considered if serial carcinoembryonic antigen elevation occurs or if there is documented metachronous metastases.

Section Summary: Colorectal Cancer
Evidence for the detection of primary nodal disease, staging, restaging, and detecting recurrence of CRC consists of several meta-analyses and a RCT. A meta-analysis evaluating the diagnostic accuracy of PET or PET/CT found a high sensitivity but low specificity. Several pooled analyses evaluating staging or restaging using PET or PET/CT resulted in sensitivities and specificities ranging from 16% to 99%. The evidence for the use of PET or PET/CT did not show a benefit over the use of contrast CT in individuals with CRC. The RCT found no differences in outcomes when FDG-PET/CT was added to usual surveillance compared to usual surveillance only. The evidence does not support the use of FDG-PET and PET/CT for the diagnosis, staging and restaging, or surveillance of CRC.

ENDOMETRIAL CANCER

Systematic Review
In 2016, Bollineni et al published a systematic review and meta-analysis on the diagnostic value of ^{18}FFDG-PET for endometrial cancer.[56] Twenty-one studies were identified for inclusion in the meta-analysis: 13 on detection of lymph node metastases (n=861) and 8 on detection of endometrial cancer recurrence (n=378). Pooled sensitivity and specificity for 18F-FDG-PET for detecting lymph node metastases were 72% (95% CI, 63% to 80%) and 94% (95% CI, 93% to 96%), respectively. Pooled sensitivity and specificity for 18F-FDG-PET for

detecting endometrial cancer recurrence following primary surgical treatment were 95% (95% CI, 91% to 98%) and 91% (95% CI, 86% to 94%), respectively.

Guidelines

American College of Radiology
In 2020, the ACR issued Appropriateness Criteria for the pretreatment evaluation and follow-up of endometrial cancer. [57] Skull base to mid-thigh PET/CT may be appropriate for pretreatment evaluation for lymph node and distant metastases, is usually appropriate for initial staging for high-grade tumors, and is usually appropriate for evaluation of clinically suspected recurrence of endometrial cancer.

National Comprehensive Cancer Network
Current NCCN guidelines for endometrial cancer (v.1.2024) state that whole body PET/CT can be considered in the initial workup, in both nonfertility and fertility-sparing management, if metastases are suspected in select individuals (based on clinical symptoms, physical findings, or abnormal laboratory findings).[58] PET/CT may also be considered for individuals with suspected recurrence or metastases who are candidates for surgery/locoregional therapy. Following treatment, PET/CT can be considered in select individuals for surveillance, if clarification is needed and metastasis is suspected.

Section Summary: Endometrial Cancer
The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis, staging and restaging, or surveillance of endometrial cancer.

Esophageal Cancer
For initial diagnosis, PET is generally not considered for detecting primary esophageal tumors, and evidence is lacking in its ability to differentiate between esophageal cancer and benign conditions.
Systematic Reviews
Kroese et al (2018) conducted a systematic review of the use of FDG-PET and FDG-PET/CT for detecting interval metastases following neoadjuvant therapy in individuals with esophageal cancer.[59] The literature search identified 14 studies for inclusion. The QUADAS tool was used to assess quality, with most studies rated moderate. The pooled proportion of individuals with true distant metastases as detected by FDG-PET and FDG-PET/CT was 8% (95% CI, 5% to 13%). The pooled proportion of Individuals with false-positive distant findings was 5% (95% CI, 3% to 9%).

In 2016, Cong et al published a meta-analysis evaluating the predictive value of ^{18}F-FDG-PET and -PET/CT for tumor response during or after neoadjuvant chemoradiotherapy in individuals with esophageal cancer.[60] Four studies were identified (n=192) in which PET or PET/CT was performed during neoadjuvant chemoradiotherapy and 11 studies (n=490) in which PET or PET/CT was performed after neoadjuvant chemoradiotherapy. All studies scored between 9 and 12 using the QUADAS tool. Pooled sensitivity and specificity for PET and PET/CT performed during NRCT is 85% (95% CI, 76% to 91%) and 59% (95% CI, 48% to 69%), respectively. Pooled sensitivity and specificity for PET and PET/CT performed after neoadjuvant chemoradiotherapy were 67% (95% CI, 60% to 73%) and 69% (95% CI, 63% to 74%), respectively.

In 2015, Goense et al published a systematic review evaluating ^{18}F-FDG-PET and FDG-PET/CT for the detection of recurrent esophageal cancer after treatment with curative intent.[61] The literature search identified 8 studies (total N=486) for inclusion. The quality of the studies was considered reasonable using the QUADAS tool, with low risk of bias for a majority of the studies, and high risk of bias in a few studies for patient selection. Pooled estimates of sensitivity and specificity of ^{18}F-FDG-PET and -PET/CT combined were 96% (95% CI, 93% to 97%) and 78% (95% CI, 66% to 86%), respectively. Subgroup analysis by technique (PET alone and PET/CT) was not possible for sensitivity due to heterogeneity. Specificity subgroup analysis showed no statistical difference between PET alone and PET/CT in detecting recurrent esophageal cancer.

In a meta-analysis of 245 individuals with esophageal cancer from 6 studies, Shi et al (2013) reported that, for detection of regional nodal metastases, FDG-PET/CT had a sensitivity of 55% (95% CI, 34% to 74%) and specificity of 76% (95% CI, 66% to 83%), respectively.[62]

An NCCN report conducted by Podoloff et al (2009) found studies showing that PET is more sensitive than other diagnostic imaging in detecting stage IV disease with distant lymph node involvement.[37] A meta-analysis described in the report found a 67% pooled sensitivity, 97% specificity, and small added value after conventional staging in detecting distant metastasis.

Another use of PET in esophageal cancer is in determining whether to continue chemotherapy for potentially curative resection. The NCCN report by Podoloff described several studies in which response to chemotherapy, defined as a decline in standardized uptake values, correlated with long-term survival.[34] Individuals who do not respond to chemotherapy might benefit from this test by being spared futile and toxic chemotherapy. However, the treatment strategy of PET-directed chemotherapy does not appear to have been validated with RCTs showing improved net health outcome.

Guidelines

American College of Radiology

In 2022, the ACR issued Appropriateness Criteria for staging and follow-up of esophageal cancer. [63] Skull base to mid-thigh PET/CT is considered usually appropriate for pretreatment clinical staging, imaging during treatment, and for post-treatment imaging in individuals with or without suspected or known recurrence.

Current NCCN guidelines for esophageal cancer (v.3.2022) indicate that PET/CT can be considered under the following conditions: [64]

- Part of the initial workup if there is no evidence of M1 disease.
- To assess response to preoperative or definitive chemoradiation.
- For staging purposes, prior to surgery to obtain nodal distribution information.

The guidelines note that PET/CT for these indications is preferable to PET alone.

Section Summary: Esophageal Cancer

Evidence for PET or PET/CT to detect metastases, predict tumor response to treatment, or to detect recurrence in Individuals with esophageal cancer consists of meta-analyses. The meta-analyses have shown high sensitivity and specificity estimates for these indications. The

evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis and staging and restaging of esophageal cancer, but does not support their use for surveillance.

Gastric Cancer

Systematic Reviews

A 2016 systematic review by Li et al evaluated ^{18}F-FDG-PET and ^{18}F-FDG-PET/CT for detecting recurrent gastric cancer.[65] The literature search identified 14 studies (total N=828) to be included in the analysis. The analysis combined both imaging techniques; 3 studies used PET alone and 11 studies used PET/CT. Pooled sensitivity and specificity were 85% (95% CI, 75% to 92%) and 78% (95% CI, 72% to 84%), respectively.

In a 2013 meta-analysis, Zou and Zhou evaluated studies published through May 2013 and calculated the sensitivity and specificity of ^{18}F-FDG-PET/CT for detecting recurrence of gastric cancer after surgical resection.[61] Eight studies (total N=500) were eligible for the meta-analysis. The studies fulfilled 12 of the 14 QUADAS criteria for methodologic quality. Pooled sensitivity was 86% (95% CI, 71% to 94%) and pooled specificity was 88% (95% CI, 75% to 94.

A systematic review by Wu (2012) pooled 9 studies (total N=562) published through July 2011 that used ^{18}F-FDG-PET alone for evaluating recurrent gastric cancer.[67] Each selected study fulfilled at least 9 of the 14 criteria in the QUADAS tool for methodologic quality. Pooled sensitivity and specificity were 78% (95% CI, 68% to 86%) and 82% (95% CI, 76% to 87%), respectively. Reviewers concluded that PET/CT might be more effective than either PET alone or CT alone, but it was unclear what sources reviewers used for their estimates for PET/CT and CT alone.

Guidelines

Current NCCN guidelines for gastric cancer (v.2.2023) indicate that PET/CT (but not PET alone) can be used as part of an initial workup if there is no evidence of metastatic disease.[68] The guidelines note that the sensitivity of PET/CT is lower than for CT alone due to low tracer accumulation in diffuse and mucinous tumor types, but specificity is higher. Use of FDG-PET/CT adds value to the diagnostic workup with higher accuracy in staging (identifying tumor and pertinent nodal groups). The NCCN guidelines also indicate that PET/CT can be used to evaluate response to treatment, in cases of renal insufficiency or allergy to CT contrast. There is no discussion on the use of PET/CT for surveillance.

Section Summary: Gastric Cancer

Evidence for the use of PET to diagnose recurrent gastric cancer consists of meta-analyses. One meta-analysis evaluated ^{18}F-FDG-PET alone, one evaluated ^{18}F-FDG-PET/CT, and another combined the 2 techniques into a single estimate. Sensitivity estimates ranged from 78% to 85% and specificity estimates ranged from 78% to 88%. The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis and staging and restaging of esophageal cancer, but does not support their use for surveillance.

Head and Neck Cancer

Systematic Reviews

A 2016 meta-analysis by Chen et al compared MRI, CT, and ^{18}F-FDG-PET/CT in the detection of local and metastatic nasopharyngeal carcinomas.[69] A literature search identified 23 studies (total N=2413 Individuals) for inclusion. Table 4 lists the results of the meta-analysis.

Table 4. Pooled Diagnostic Performance of ^{18}F-FDG-PET/CT, Magnetic Resonance Imaging, and CT alone in the Detection of Nasopharyngeal Carcinomas[76]

Type of Imaging	No. of Studies (No. of Individuals)	Sensitivity (95% CI), %	Specificity (95% CI), %
T staging			
MRI	8 (984)	95 (93 to 97)	76 (71 to 80)
CT alone	4 (404)	84 (79 to 88)	80 (71 to 88)
N staging			
MRI	10 (750)	82 (79 to 84	71 (65 to 78)
CTR alone	4 (340)	92 (85 to 95)	93 (76 to 99)
^{18}F-FDG-PET/CT	10 (629)	88 (85 to 90)	95 (93 to 97)
M staging			
MRI	2 (261	53 (35 to 70)	99 (96 to 100)
CT alone	2 (98)	80 (44 to 97)	93 (86 to 97)
^{18}F-FDG-PET/CT	7 (1009)	82 (74 to 88)	98 (96 to 99)

Adapted from Chen et al (2016).69,CI: confidence interval; CT: computed tomography; FDG: fluorine 18 fluorodeoxyglucose; MRI: magnetic resonance imaging; M staging: distant metastases; MRI: magnetic resonance imaging; N staging: regional lymph nodes; PET: positron emission tomography; T staging: primary tumor.

A 2016 meta-analysis by Wei et al compared diagnostic capabilities of ^{18}F-FDG-PET/CT, MRI, and single-photon emission computed tomography in Individuals with residual or recurrent nasopharyngeal carcinoma.[70] The literature search identified 17 studies for inclusion.
All studies scored at least 9 of 14 in the QUADAS tool. Pooled sensitivity and specificity for ^{18}F-FDGPET/ CT (n=12 studies) were 90% (95% CI, 85% to 94%) and 93% (95% CI, 90% to 95%), respectively. Pooled sensitivity and specificity for single-photon emission computed tomography (n=8 studies) were 85% (95% CI, 77% to 92%) and 91% (95% CI, 85% to 95%), respectively. Pooled sensitivity and specificity for MRI (n=9 studies) were 77% (95% CI, 70% to 83%) and 76% (95% CI, 73% to 79%), respectively.

Two meta-analyses evaluated ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT in the detection of residual or recurrent head and neck cancer at various times following treatment.[71,72] Results from these analyses are summarized in Table 5.

Table 5. Pooled Diagnostic Performance of ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT in the Detection of Head and Neck Cancer

Indication	No. Studies (No. Individuals)	Sensitivity (95% CI), %	Specificity (95% CI), %
Cheung et al (2016)[66]			
Residual/recurrent at primary site	18 (805)	86 (80 to 91)	82 (79 to 85)
Residual/recurrent at neck nodes	15 (726)	72 (63 to 80)	88 (85 to 91)
Recurrent at distant metastases	3 (184)	85 (65 to 96)	95 (90 to 98)
Local residual/recurrent, <12 wk since therapy	NR	85 (75 to 92)	80 (76 to 83)
Local residual/recurrent, ≥12 wk since therapy	NR	87 (78 to 94)	88 (83 to 93)
Nodal residual/recurrent, <12wk since therapy	NR	67 (56 to 78)	86 (83 to 89)
Nodal residual/recurrent, ≥12 wk since therapy	NR	83 (61 to 95)	96 (90 to 99)
Sheikhbahaei et al (2015)[72]			
Local recurrence, ≥4 mo since therapy	10 (992)	91 (86 to 95)	89 (83 to 94)
Regional recurrence, ≥4 mo since therapy	8 (885)	88 (80 to 93)	95 (92 to 97)

Distant metastases/second primary, ≥4 mo since therapy	9 (958)	93 (86 to 96)	97 (95 to 98)
Overall diagnostic performance, 4-12 mo since therapy	11 (1003)	95 (91 to 97)	78 (70 to 84)
Overall diagnostic performance, ≥12 mo since therapy	7 (923)	92 (85 to 96)	91 (78 to 96)

CI: confidence interval; CT: computed tomography; NR: not reported; PET: positron emission tomography

A 2015 systematic review by Sheikhbahaei et al calculated the predictive value of intratherapy or post therapy ^{18}F-FDG-PET or PET/CT for overall survival (OS) and event-free survival.[72] The literature search, conducted through November 2014, identified 9 studies (n=600 Individuals) for inclusion in OS calculations and 8 studies (n=479 Individuals) for inclusion in event-free survival calculations. Individuals with a positive scan had significantly worse OS compared with Individuals with negative scans (hazard ratio, 3.5; 95% CI, 2.3% to 5.4%). The pooled hazard ratio for event-free survival was 4.7 (95% CI, 2.6 to 8.6). Two year and 3- to 5-year relative risks for death or recurrence or progression were calculated, based on timing of ^{18}F-FDG-PET or -PET/CT. Results are summarized in Table 6.

Table 6. Pooled Diagnostic Performance of ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT in the Detection of Head and Neck Cancer[68]

Outcome	No. Studies	2-Year RR (95% CI)	No. Studies	3 to 5 Year RR (95% CI)
Death				
Final ^{18}F-FDG-PET or –PET/CT	6	8.3 (3.8 to 18.0)	6	2.2 (1.6 to 3.2)
^{18}F-FDG-PET or –PET/CT, <12 wk post treatment	8	3.0 (1.9 to 4.6)	4	2.0 (1.3 to 3.2)
^{18}F-FDG-PET or –PET/CT, ≥12 wk post treatment	3	8.5 (4.0 to 18.3)	6	2.8 (1.9 to 4.0)
Recurrence or progression				
Final ^{18}F-FDG-PET or –PET/CT	6	5.2 (3.3 to 8.3)	5	2.6 (1.7 to 4.1)
^{18}F-FDG-PET or –PET/CT, <12 wk post treatment	9	3.2 (2.0 to 5.2)	6	4.3 (2.1 to 8.7)
^{18}F-FDG-PET or –PET/CT, ≥12 wk post treatment	2	3.2 (2.0 to 5.2)	2	2.2 (1.5 to 3.1)

CI: confidence interval; CT: computed tomography; PET: positron emission tomography; RR: relative risk

Four meta-analyses in 2013, 2014, and 2018 reported good sensitivities and specificities with FDG-PET/CT for diagnosing head and neck squamous cell cancers (better than CT and MRI), detecting head and neck cancer metastases (better than bone scintigraphy), and detecting recurrence. [74-77]

Additional meta-analyses by Li et al (2017)[78] and Lin et al (2017)[79] have reported that higher values of standard uptake value, metabolic tumor volume, and total lesion glycolysis from FDG-PET/CT might predict a poorer prognosis for individuals with nasopharyngeal cancer.

Among the 3 studies identified in the TEC Assessment (2000) that used other diagnostic modalities to identify a primary tumor in individuals with positive cervical lymph nodes, PET found more primary tumors than the other modalities in 2 studies and identified similar proportions in the third.[80] When data from these 3 studies were pooled, PET was found to identify a tumor in 38% of cases and other modalities in 21% of cases.

When PET was used to stage cervical lymph nodes initially, the addition of PET to other imaging modalities increased the proportion of individuals correctly staged, as confirmed histologically. When compared directly with other imaging modalities, pooled data from several studies has suggested that PET has a better diagnostic performance than CT and MRI. Of 8 studies focusing on the use of PET to detect residual or recurrent disease, 5 found PET to be more specific and sensitive, 2 reported mixed or equivalent results, and 1 reported worse results compared with CT.

A 2022 systematic review and meta-analysis by Zhu et al assessed the diagnostic accuracy of PET/CT and MRI for surveillance of treated head and neck squamous cell cancer. [81] The meta-analysis included 3 studies that included 176 individuals who underwent imaging 3 to 6 months post-treatment for assessment of potential recurrence or residual disease. For a positive imaging test, the reference standard was histological confirmation, and for a negative imaging test the reference standard was histological confirmation or clinical follow up for at least 6 months. Sensitivity of PET/CT was 68% (95% CI, 49% to 84%) and specificity was 89% (95% CI, 84% to 93%); corresponding values for MRI were 72% (95% CI, 54% to88%) and 85% (95% CI, 79% to 89%). The review concluded that evidence was insufficient to recommend either imaging modality over the other for surveillance of recurrent or residual head and neck cancer.

Guidelines
Current NCCN guidelines on head and neck cancer (v.1.2024) indicate that PET/CT can be appropriate for stage III or IV disease evaluation, for detection of metastases or recurrence, and for evaluation of response to treatment (at a minimum of 12 weeks post-treatment to reduce false-positive rate).[82] For surveillance of locoregionally advanced disease, an initial 3-monthPET/CT scan may be useful, but if the scan is negative, then further routine imaging is not supported in an asymptomatic patient.

Section Summary: Head and Neck Cancer
Evidence for the use of ^{18}F-FDG-PET/CT in the management of individuals with head and neck cancer consists of systematic reviews and meta-analyses. In individuals with head and neck cancers, PET or PET/CT is better able to detect local and metastatic disease than other imaging techniques. Evidence has also shown that ^{18}F-FDG-PET/CT may be useful in predicting response to therapy. The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis and staging and restaging of esophageal cancer, but does not support their use for surveillance.

Lung Cancer
Use of PET scanning may have a clinical role in individuals with solitary pulmonary lung nodules in whom the diagnosis is uncertain after CT scan and chest radiograph. Younger individuals who have no smoking history are at a relatively low risk for lung cancer, and in this setting, the NPV of a PET scan is relatively high. If presented with a negative PET scan and information about the very low probability of undetected malignancy, it is quite likely that some individuals would choose to avoid the harms of an invasive sampling procedure (i.e., biopsy). A 2012 meta-analysis on evaluating pulmonary nodules using dual-time PET (a second scan added after a delay) found that its additive value relative to a single PET scan is questionable.[83]

Non-Small Cell Lung Cancer
In individuals with known non-small cell lung cancer (NSCLC), the clinical value of PET scanning relates to improved staging information regarding the involvement of mediastinal

lymph nodes, which generally excludes individuals from surgical excision. The 1997 TEC Assessment cited a decision-analysis study that suggested that the use of CT plus PET scanning in staging the mediastinal lymph nodes resulted in fewer surgeries and an average gain in life expectancy of 2.96 days.[84] The gain in life expectancy suggests that avoidance of surgery was not harmful to the individuals.

Systematic Reviews

Brea et al (2018) conducted a systematic review comparing MRI, CT, FDG-PET, and FDG-PET/CT in differentiating metastatic and nonmetastatic lymph nodes.[85] A meta-analysis was not conducted. Reviewers reported that most studies showed MRI had higher sensitivities, specificities, and diagnostic accuracy than CT and PET in determining malignancy of lymph nodes in individuals with NSCLC.

A 2017 systematic review by Ruilong et al evaluated the diagnostic value of ^{18}F-FDG PET/CT for detecting solitary pulmonary nodules.[86] The literature search, conducted to May 2015, identified 12 studies (1297 individuals) for inclusion in the analysis. The pooled sensitivity and specificity of ^{18}F-FDGPET/CT to detect malignant pulmonary nodules were 82% (95% CI, 76% to 87%) and 81% (95% CI, 66% to 90%), respectively.

Li et al (2017) conducted a meta-analysis of studies that compared FDG-PET/CT with gadolinium-enhanced MRI in the detection of brain metastases in Individuals with NSCLC.[87] The literature search identified 5 studies (total N=941 Individuals) for inclusion. Study quality was assessed using criteria recommended by the Cochrane Methods Working Group, with scores ranging from 9 to 11 on the 12-point scale. Meta-analyses results are presented in Table 7.

He et al (2014) compared PET, PET/CT, and conventional imaging techniques for detecting recurrent lung cancer.[82] Table 7 summarizes the diagnostic performances of the different imaging techniques.

Other meta-analyses have reported good sensitivities and specificities in the detection of lung cancer metastases (Table 7). Seol et al (2021) investigated the diagnostic performance of FDG-PET or PET/CT for detection of occult lymph node metastases in individuals with NSCLC. [88] The literature search, conducted through March 2020, identified 14 studies (N=3535). The pooled sensitivity and specificity analyses had a high level of heterogeneity (*I2:* 81.5 and 93.7, respectively). Li et al (2017) conducted a meta-analysis of studies that compared FDG-PET/CT with gadolinium-enhanced MRI in the detection of brain metastases in individuals with NSCLC. [89] The literature search identified 5 studies (N=941) for inclusion. Study quality was assessed using criteria recommended by the Cochrane Methods Working Group, with scores ranging from 9 to 11 on the 12-point scale. A meta-analysis by Li et al (2013) calculated the sensitivity and specificity of PET/CT in the detection of distant metastases in individuals with lung cancer and with NSCLC (see Table 7). [90]

Table 7. Pooled Diagnostic Performance of Various Imaging Techniques in Individuals with Lung Cancer

Type of Imaging	Detection Measured	Sensitivity (95% CI), %	Specificity (95% CI), %	DOR (95% CI)
Ruilong et al (2017)[86.]	Solitary pulmonary nodules			
[1]FDG-PET/CT		82 (76 to 87)	81 (66 to 90)	18 (8 to 38)
Li et al (2017)[89.]	Brain metastases			
FDG-PET/CT		21 (13 to 32)	100 (99 to 100)	235 (31 to 1799)

Gadolinium MRI		77 (60 to 89)	99 (97 to 100)	657 (112 to 3841)
He et al (2014)[87.]	Recurrent NSCLC			
FDG-PET		94 (91 to 97)	84 (73 to 89)	65 (19 to 219)
FDG-PET/CT		90 (84 to 95)	90 (87 to 93)	79 (19 to 335)
CIT		78 (71 to 84)	80 (75 to 84)	13 (4 to 40)
Li et al (2013)[90.]	Distant metastases			
FDG-PET/CT		87 (55 to 98)	96 (93 to 98)	196 (22 to 1741)
Seol et (2021) [88]	Occult lymph node metastases			
		79 (70 to 86)	65 (57 to 72)	7 (5 to 10)

CI: confidence interval; CIT: conventional imaging technique; CT: computed tomography; DOR: diagnostic odds ratio; FDG: fluorine 18 fluorodeoxyglucose; MRI: magnetic resonance imaging; NSCLC: non-small-cell lung cancer; PET: positron emission tomography.

Guidelines

American College of Chest Physicians

The American College of Chest Physicians (2013) issued guidelines for the diagnosis and management of NSCLC.[91] The guidelines stated that RCTs support the use of PET or PET/CT scanning as a component of lung cancer treatment and recommended PET or PET/CT for staging, detection of metastases, and avoidance of noncurative surgical resections.

In 2019, the ACR issued Appropriateness Criteria for noninvasive clinical staging of primary lung cancer. [92] Skull base to mid-thigh PET/CT is recommended in initial clinical staging to evaluate for extrathoracic metastases in individuals with NSCLC.

National Comprehensive Cancer Network

Current NCCN guidelines for NSCLC (v.4.2023) indicate that PET/CT can be used in the staging of the disease, detection of metastases, treatment planning, and detection of disease recurrence.[93] The guidelines note that PET is “best performed before a diagnostic biopsy site is chosen in cases of high clinical suspicion for aggressive, advanced-stage tumors.” However, PET is not recommended for detection of brain metastasis from lung cancers. While PET/CT is not routinely recommended for surveillance after completion of definitive therapy, it may be considered to differentiate between true malignancies and benign conditions (e.g., atelectasis, consolidation, and radiation fibrosis), which may have been detected by CT imaging. If PET/CT detects recurrent disease, biopsy confirmation is necessary prior to initiating additional treatment because FDG remains avid up to 2 years.

Section Summary: Non-Small Cell Lung Cancer

Evidence for PET or PET/CT in individuals with NSCLC consists of meta-analyses. The meta-analyses have shown that use of PET or PET/CT in individuals with lung cancer can aid in the diagnosis, staging, as well as detecting metastases and recurrence. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis and staging and restaging of NSCLC. The evidence does not support the use of FDG-PET and FDG-PET/CT for surveillance of NSCLC.

Small-Cell Lung Cancer

Approximately 15% of all lung cancers are small-cell lung cancer (SCLC). Individuals with SCLC are typically defined as having either limited stage or extensive stage disease. Most Individuals diagnosed with SCLC have extensive stage disease, which is characterized by distant metastases, malignant pericardial or pleural effusions, and/or contralateral hilar lymph

node involvement. Limited stage SCLC is limited to the ipsilateral hemithorax and regional or mediastinal lymph nodes and can be encompassed in a safe radiotherapy field.

Systematic Reviews

A systematic review by Lu et al (2014) included 12 studies (total N=369) of F-FDG-PET/CT for staging SCLC.[94] Although estimated pooled sensitivity and pooled specificity were 98% (95% CI, 94% to 99%) and 98% (95% CI, 95% to 100%), respectively, included studies were small (median sample size, 22); of primarily fair to moderate quality; and heterogeneous in design (retrospective, prospective), PET parameter assessed, indication for PET, and reference standard used. It is not possible from the limited, poor quality evidence in this systematic review to determine whether the use of PET adds value relative to conventional staging tests for SCLC.

A systematic review by Ruben and Ball (2012) of staging SCLC found PET to be more effective than conventional staging methods; however, a limitation of this review is that the reviewers did not conduct a quality assessment of individual studies.[95]

Guidelines

American College of Radiology

In 2019, the ACR issued Appropriateness Criteria for noninvasive clinical staging of primary lung cancer. [92] Use of PET or PET/CT is recommended for initial clinical staging in individuals with clinical stage I or II limited stage SCLC being considered for curative treatment.

National Comprehensive Cancer Network

Current NCCN guidelines for SCLC (v.1.2024) indicate PET/CT can be used in the staging of disease if limited stage is suspected. If extensive stage is established, brain imaging, MRI (preferred), or CT with contrast is recommended. PET/CT “is not recommended for routine follow-up.”[96]

Section Summary: Small Cell Lung Cancer

Evidence for PET or PET/CT for individuals with SCLC consists of systematic reviews and meta-analyses. These reviews have shown potential benefits in using PET for staging, though the quality of the studies was low. The evidence supports the use of FDG-PET and FDG-PET/CT for the diagnosis, staging, and restaging of SCLC. Guidelines support the use of PET/CT if limited stage is suspected. If extensive stage is established, other imaging techniques (MRI or CT with contrast) are preferred.

The evidence does not support FDG-PET and FDG-PET/CT for surveillance of SCLC.

Lymphoma, Including Hodgkin Disease

Systematic Reviews

Of the 14 available studies reviewed in the 1999 TEC Assessment, three compared PET with anatomic imaging in initial staging and restaging of individuals with Hodgkin’s disease (HD) and non-Hodgkin lymphoma.[97] Two of these studies included data from both diseased and non-diseased sites for PET and CT. Both studies found PET to have better overall diagnostic accuracy than CT. The third study addressed detection of diseased sites only and found PET to have the same sensitivity as use of CT or MRI. Among the 6 studies that reported on concordance between PET and other imaging modalities, PET was discordant with other modalities in 11% to 50%, PET was correct among discordances in 40% to 75%. Use of PET

has been reported to affect patient management decisions in 8%–20% of individuals in five studies mainly by correctly upstaging disease, but also by correctly down staging disease. Thus, when PET is added to conventional imaging, it can provide useful information for selective effective and appropriate treatment for the correct stage of disease.

Lymphoma Diagnosis

Meta-analyses have reported good sensitivities and specificities with PET/CT in the detection of newly diagnosed Hodgkin lymphoma (2014) and diffuse large B cell lymphoma (2014).[98-100]

Lymphoma Restaging

A 2016 systematic review and meta-analysis by Adams and Kwee evaluated the proportion of false-positive lesions at interim and end-of-treatment as detected by ^{18}F-FDG-PET in individuals with lymphoma.[101] The literature search, conducted through January 2016, identified 11 studies (total N=139) for inclusion. Study quality was moderate, as assessed by the QUADAS-2 tool. The weighted summary proportion of false-positive results among all biopsied lesions both during and after completion of treatment was 56% (95% CI, 33% to 77%). Subgroup analyses found the ^{18}F-FDG-PET false positive proportions for: interim non-Hodgkin lymphoma (83%; 95% CI, 72% to 90%); end-of-treatment non-Hodgkin lymphoma (31%; 95% CI, 4% to 84%), and end-of-treatment Hodgkin lymphoma (23%; 95% CI, 5% to 65%). We found no studies calculating the false-positive rate for interim Hodgkin lymphoma.

A 2015 systematic review by Adams et al focused for the outcomes of individuals with Hodgkin lymphoma who had negative residual mass after treatment with ^{18}F-FDG-PET.[102] When a persistent mass is non-FDG-avid, the patient is considered to be in complete remission, though the significance of having a residual mass is unclear. The literature search, conducted through December 2014, identified 5 studies (total N=727) for inclusion. Follow-up of individuals in the studies ranged from 1 to 13 years. The pooled relapse proportion was 6.8% (95% CI, 2.6% to 12.5%).

Lymphoma Management

Systematic Reviews

A 2017 systematic review by Adams and Kwee evaluated the prognostic value of ^{18}F-FDG-PET in individuals with refractory or relapsed Hodgkin lymphoma considering autologous cell transplantation.[103] The literature search, conducted through May 2016, identified 11 studies (total N=664) for inclusion. In general, the overall quality of selected studies was poor, based on Quality in Prognosis Studies (QUIPS). Pooled sensitivity and specificity of pretransplant ^{18}F-FDG-PET for predicting treatment failure were 54% (95% CI, 44% to 63%) and 73% (95% CI, 67% to 79%), respectively. Pooled sensitivity and specificity of pretransplant ^{18}F-FDG-PET in predicting death after treatment were 55% (95% CI, 39% to 70%) and 69% (95% CI, 61% to 76%), respectively.

A 2016 meta-analysis by Adams and Kwee evaluated the prognostic value of ^{18}F-FDG-PET in individuals with aggressive non-Hodgkin lymphoma considering autologous cell transplantation.[104] The literature search, conducted through July 2015, identified 11 studies (total N=745) for inclusion. The overall quality of selected studies was moderate, based on QUIPS criteria. Individuals with positive pretransplant ^{18}F-FDG-PET results had progression-free survival (PFS) rates ranging from 0% to 52%. Individuals with negative pretransplant 18F-FDG-PET results had PFS rates ranging from 55% to 85%. OS was 17% to 77% in individuals

with positive ^{18}F-FDG-PET results and 78% to 100% in individuals with negative ^{18}F-FDGPET results. Based on 5 studies, pooled sensitivity and specificity of pretransplant ^{18}F-FDG-PET predicting treatment failure (defined as progressive, residual, or relapsed disease) were 67% (95% CI, 58% to 75%) and 71% (95% CI, 64% to 77%), respectively.

A 2015 systematic review by Zhu et al evaluated the prognostic value of ^{18}F-FDG-PET in individuals with diffuse B-cell lymphoma treated with rituximab-based immune chemotherapy.[105] The literature search identified 11 studies (N=1081) for inclusion. The pooled hazard ratio comparing PFS of individuals with positive interim ^{18}F-FDG-PET results and negative interim ^{18}F-FDG-PET results was 3.0 (95% CI, 2.3 to 3.9). Individuals with a negative interim ^{18}F-FDG-PET result had a higher complete remission rate than individuals with a positive interim ^{18}F-FDG-PET result (relative risk, 5.5; 95% CI, 2.6 to 11.8).

Randomized Controlled Trials

Borchmann et al (2017) reported on an open-label phase 3 RCT by the German Hodgkin Study Group, which randomized Individuals newly diagnosed with advanced Hodgkin lymphoma to different levels of eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), based on PET results.[106] After 2 cycles of eBEACOPP, PET-positive Individuals were randomized to 6 more cycles of eBEACOPP (n=217) or eBEACOPP plus rituximab (n=217). PET-negative Individuals were randomized to 6 more cycles of eBEACOPP (n=504) or 4 more cycles of eBEACOPP (n=501). Five-year PFS rates for the PET-positive 6-cycle eBEACOPP and 6-cycle eBEACOPP plus rituximab arms were 90% (95% CI, 85% to 94%) and 88% (95% CI, 83% to 93%), respectively. Five-year PFS rates for the PET-negative 6-cycle and 4-cycle arms were 91% (95% CI, 88% to 94%) and 92% (95% CI, 89% to 95%), respectively. Results showed that PET-negative Individuals can receive fewer cycles of treatment without a negative impact on PFS and that PET-positive individuals do not need an intensified treatment (addition of rituximab) to improve PFS.

Guidelines

Current NCCN guidelines for Hodgkin lymphoma (v.1.2024) [107] and non-Hodgkin lymphomas, including chronic lymphocytic leukemia/small lymphocytic lymphoma [v.1.2024], [108] B-cell lymphomas [v.6.2023], [109] primary cutaneous lymphomas [v.1.2023], [110] and T-cell lymphomas [v.1.2023]) [111] indicate that PET/CT (in some cases PET only) may be used in the diagnostic workup, staging, restaging, and evaluating treatment response. The guidelines recommend using the internationally recognized Deauville 5-point PET scale for initial staging and assessment of treatment response. The following PET/CT results are assigned the corresponding scores: 1=no uptake; 2=uptake ≤ mediastinum; 3=uptake > mediastinum but ≤liver; 4=uptake moderately higher than liver; and 5=uptake markedly higher than liver and/or new lesions. The Deauville PET scores can be used to determine the course of treatment. The guidelines note that if PET/CT detects 3 or more skeletal lesions, the marrow may be assumed to be involved and marrow biopsies are no longer indicated. The Hodgkin lymphoma guidelines also note "Surveillance PET should not be done routinely due to risks for false-positives. Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed." [107]

Section Summary: Lymphoma, Including Hodgkin Disease

Evidence for the use of ^{18}F-FDG-PET/CT in the management of individuals with lymphoma consists of systematic reviews, meta-analyses, and an RCT. In individuals with lymphoma, PET can provide information for staging or restaging. Evidence has also shown that ^{18}F-FDG-

PET/CT can be useful in predicting response to therapy in individuals with lymphoma. The evidence supports the use of ^{18}F-FDG-PET and ^{18}FPET/CT for the diagnosis and staging and restaging of Hodgkin lymphoma and non-Hodgkin lymphoma, but does not support their use for surveillance.

Melanoma
Surgical resection for melanoma is limited to those with local disease. Individuals with widespread disease are not candidates for resection. Frequently, there is microscopic spread to the proximal lymph nodes. Therefore, individuals with a high risk of nodal spread, as assessed by the thickness of the primary melanoma, may be candidates for lymph node sampling, termed sentinel node biopsy. Use of PET scanning has been investigated both as a technique to detect widespread disease as part of an initial staging procedure, and to evaluate the status of the local lymph nodes to determine the necessity of sentinel node biopsy.

To consider PET a useful alternative to sentinel node biopsy, it must have high sensitivity and specificity when either sentinel node biopsy or lymph node dissection serves as the reference standard. In the only study of this kind, PET had a sensitivity of only 17%, suggesting that PET rarely detects small metastases that can be discovered by sentinel node biopsy. Thus the TEC Assessment concluded that PET is not as beneficial as sentinel node biopsy in assessing regional lymph nodes.[112]

> "The intent of using PET to detect extranodal metastases is to aid in selecting treatment appropriate to the patient's extent of disease. For example, surgical resection is typically not appropriate for widespread disease. A prospective blinded study of 100 Individuals found that PET was much more sensitive and specific than conventional imaging. Another prospective study of 76 Individuals found that, compared to CT, PET had much higher sensitivity and equivalent specificity. A third comparative study of 35 Individuals found that PET was much more sensitive than CT. It may be inferred from these studies that PET was usually correct when discordant with other modalities. PET affects management in approximately 18% of Individuals."

Systematic Reviews
In a meta-analysis of 9 studies (total N=623), Rodriquez Rivera et al (2014) reported pooled sensitivity and specificity of FDG-PET for detecting systemic metastases in Individuals with stage III cutaneous melanoma of 0.89 (95% CI, 0.65 to 0.98) and 0.89 (95% CI, 0.77 to 0.95), respectively.[113]

Guidelines
Current NCCN guidelines for cutaneous melanoma (v.3.2023) indicate that PET/CT can be used for staging and restaging more advanced disease (e.g., stage III) in the presence of specific signs and symptoms.[114] Use of PET/CT is not recommended for stage I or II disease. Also, PET/CT listed as an option for surveillance screening for recurrence every 3 to 12 months (category 2B) at the physician's discretion. Because most recurrences occur within the first 3 years, routine screening for asymptomatic recurrence is not recommended beyond 3 to 5 years. The guidelines note that the safety of PET/CT is of concern due to cumulative radiation exposure.

Section Summary: Melanoma

Evidence for the use of ^{18}F-FDG-PET/CT in the management of individuals with melanoma consists of a TEC Assessment, systematic review, and meta-analysis. In individuals with melanoma, PET can provide information for staging or restaging in individuals with more advanced disease (stage III or higher). The evidence does not support the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis or staging and restaging of stage I or II melanoma. The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis and staging and restaging of stage III or IV melanoma. The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for surveillance of melanoma.

Multiple Myeloma and ^{18}F-FDG-PET and ^{18}F-FDG-PET/CT

Systematic Reviews

Lu et al (2012) included 14 studies (N=395 Individuals) and reported pooled estimates of sensitivity and specificity of 96% (95% CI, 80% to 100%) and 78% (95% CI, 40% to 95%), respectively, in the detection of extramedullary lesions in individuals with multiple myeloma.[115]

Van Lammeren-Venema et al (2012) included 18 studies (N=798) in a systematic review that compared FDG-PET with whole body x-ray in staging and response assessment of individuals with multiple myeloma.[116] Using the QUADAS tool to assess quality, the studies received a mean percentage of the maximum score of 61%. Reviewers reported that, in general, FDG-PET is more sensitive than whole body x-ray in detecting myeloma bone lesions.

Han et al (2021) conducted a meta-analysis to evaluate the prognostic value of FDG-PET/CT in newly diagnosed multiple myeloma patientsindividuals.[117] Eleven articles (N=1542)were included in the quantitative analysis. The prognostic performance of 3 PET findings were evaluated, extramedullary disease, >3 focal bone lesions, and high FDG uptake as measured by the maximum standardized uptake value (SUVmax) in the study. All 3 PET findings were significant predictors for a shorter PFS and OS. For detection of extramedullary disease, the pooled HR for PFS and OS were 2.12 (95% CI, 1.52 to 2.96) and 2.37 (95% CI, 1.77 to 3.16), respectively, with significant heterogeneity observed with PFS and publication bias with OS. For >3 focal lesions, the pooled HR for PFS and OS were 2.38 (95% CI, 1.84 to 3.07) and 3.29 (95% CI, 2.38 to 4.56), respectively. For high FDG uptake, the pooled HR for PFS and OS were 2.02 (95% CI, 1.51 to 2.68) and 2.28 (95% CI, 1.67 to 3.13), respectively.

A systematic review and meta-analysis conducted Rama et al (2022) compared the diagnostic accuracy of FDG-PET/CT and whole-body MRI for evaluation of multiple myeloma treatment response.[118] The review included 12 studies (N=373), 6 of which provided direct comparison of FDG-PET/CT and whole-body MRI. The remaining 6 studies assessed only whole-body MRI (4 studies) or FDG-PET/CT (2 studies). Risk of bias was assessed using the QUADAS-2 tool, and was generally low across the studies. A funnel plot analysis did not reveal evidence of publication bias for either FDG-PET/CT (p=.31) or whole-body MRI (p=.43). Based on pooled analysis, the sensitivity of FDG-PET/CT was 64% (95% CI, 45% to79%; $I2$=48%) and specificity was 82% (95% CI, 75% to 88%; $I2$=0%). MRI was more sensitive (87%; 95% CI, 75% to 93%) and less specific (57%; 95% CI, 37% to 76%; p=.01 vs. FDG-PET/CT specificity). Sensitivity and specificity of FDG-PET/CT (66% and 81%) and whole-body MRI (90% and 56%) were similar when limited to the 6 studies directly comparing the 2 imaging modalities, as

were corresponding AUC values (0.83 and 0.84). The clinical significance of these findings is unclear, and NCCN guidelines do not recommend either FDG-PET/CT or whole-body MRI for routine assessment of treatment response in multiple myeloma.

Comparative Studies

Mesguich et al (2020) prospectively compared FDG-PET/CT to whole body MRI, as a reference standard, for the initial staging of multiple myeloma. [119] The number of focal bone lesions detected and the diagnostic performance of FDG-PET/CT to diagnose diffuse bone marrow infiltration were assessed. Thirty individuals were included in the study. The mean number of focal bone lesions detected in the body was 16.7 and 23.9 for FDG-PET/CT and whole body MRI, respectively. The number of focal bone lesions detected was higher with MRI in the skull and spine; no significant differences were noted in number of bone lesions detected in the pelvis, sternum-ribs, upper limbs, and lower limbs. Both imaging modalities were interpreted as positive in 28 out of 30 individuals (100% agreement). For the diagnosis of diffuse bone marrow infiltration with FDG-PET/CT, the sensitivity, specificity and accuracy were 0.75, 0.79, and 0.77, respectively. Overall, whole body MRI detected more focal bone lesions, but there was no difference in the detection of bone disease on a per-patient basis.

Guidelines

Current NCCN guidelines for multiple myeloma (v.2.2024) recommend PET/CT as an imaging technique option for initial workup. The NCCN recommends using PET/CT for follow-up and surveillance as needed, if utilized for initial workup. Use of PET/CT is considered first choice during initial work up of solitary extraosseous plasmacytoma. [120] PET/CT may also be considered to detect disease progression.

Section Summary: Multiple Myeloma

Evidence for the use of PET or PET/CT in the management of individuals with multiple myeloma consists of systematic reviews and a meta-analysis. The evidence supports the use of ^{18}F-FDG-PET and ^{18}FPET/CT for the diagnosis, staging and restaging. The evidence does not support the use of FDG-PET and FDG-PET/CT for routine surveillance of multiple myeloma.

Neuroendocrine Tumors

Systematic Reviews

^{68}Ga-PET and ^{68}Ga-PET/CT

Barrio et al (2017) conducted a systematic review and meta-analysis on the impact of gallium 68 (^{68}Ga) PET/CT on management decisions in individuals with neuroendocrine tumors.[121] Reviewers selected 14 studies (N=1561). Change in management occurred in 44% of the individuals following ^{68}Ga-PET/CT. Clinical outcomes were not reported.

Deppen et al (2016) conducted a systematic review assessing the use of ^{68}Ga-PET/CT for the diagnosis and staging of gastroenteropancreatic neuroendocrine tumors.[122] Seventeen studies (total N=971) were included in the analysis. Comparators differed among the studies: octreotide and conventional imaging (3 studies), other radiopharmaceuticals without direct imaging comparators (5 studies), and conventional imaging (9 studies). Meta-analysis of the 9 studies that compared ^{68}Ga-PET/CT scanning with conventional imaging resulted in a sensitivity of 91% (95% CI, 81% to 96%) and a specificity of 91% (95% CI, 78% to 96%).

Two meta-analyses from Treglia et al (2012) addressed the use of PET in individuals with neuroendocrine tumors.[123,124] One report included individuals with thoracic and gastroenteropancreatic neuroendocrine tumors who had imaging with PET using ^{68}Ga-PET and ^{68}Ga-PET/CT.[123] Sixteen studies (total N=567) were included in the analysis. The studies were considered medium to high quality, based on an assessment using the QUADAS tool. Meta-analysis showed a sensitivity and specificity of 93% (95% CI, 91% to 95%) and 91% (95% CI, 82% to 97%), respectively, with histology and/or clinical or imaging follow-up as the reference standard in diagnostic accuracy.

^{18}F-DOPA PET and ^{18}F-DOPA PET/CT

The other meta-analysis included studies of individuals with paragangliomas scanned by PET with fluorine 18-dihydroxyphenylalanine (^{18}F-DOPA) PET and ^{18}F-DOPA PET/CT.[124] Eleven studies (total N=275 Individuals) were analyzed. The QUADAS tool was used to assess quality: 2 studies had a B rating, 4 a C rating, and 5 a D rating. Reference standards varied across studies, with 2 using MRI, 3 using histology on all Individuals, and the remaining using histology only when feasible. Meta-analysis showed a sensitivity and specificity of 91% (95% CI, 87% to 94%) and 79% (95% CI, 76% to 81%), respectively.

Prospective Studies

64Cu-PET and 64Cu-PET/CT

Delpassand et al (2020) conducted a phase 3, reader-masked, controlled trial to evaluate the sensitivity and specificity of copper 64 (64Cu) PET/CT for detecting neuroendocrine tumors.[125] Individuals with known or suspected disease, along with healthy volunteers, were recruited and results of imaging with 64Cu PET/CT was compared against a standard of truth, based on an alternative, established imaging modality. Three readers evaluated the sensitivity and specificity of 64Cu PET/CT compared with a standard truth in 63 evaluable individuals with known or suspected neuroendocrine tumors. The overall sensitivity and specificity based on the standard of truth was 100% and 96.8%, respectively. This translated toa PPV of 96.7%, a NPV of 100%, and an accuracy of 98.4%.

Johnbeck et al (2017) conducted a head-to-head trial comparing the diagnostic performance of 64Cu PET/CT to 68Ga-PET/CT in individuals with neuroendocrine tumors. Individuals(N=59) were prospectively enrolled and underwent both 64Cu PET/CT and 68Ga-PET/CT within 1 week. [126] Clinical follow-up was over 2 years, which allowed verification of discordant lesions (only found by 1 tracer) as either true- or false-positive findings. Overall, 701 PET-positive lesions were found by both tracers (concordant lesions), whereas an additional 68discordant lesions were found. Forty-two of the discordant lesions were found by 64Cu PET/CT, of which 33 were eventually confirmed to be true-positives. In contrast, 68Ga-PET/CT found 26 discordant lesions, of which 7 were confirmed as true-positives. The probability that a true-positive discordant lesion was detected by 64Cu PET/CT was 83% (95% CI, 67% to93%; p<.001 compared to 68Ga-PET/CT).

Guidelines

Current NCCN guidelines for neuroendocrine tumors (v.1.2023) have recommended somatostatin receptor-based imaging with PET/CT or PET/MRI, using somatostatin receptor PETtracers,68Ga-dotatate, 68Ga-dotatoc, or 64Cu-dotatate,to assess receptor status and presence of distant disease.[127] Somatostatin receptor imaging can assist in determining if a patient would benefit from receiving a somatostatin receptor-directed therapy. Use of FDG-PET may be considered to identify high-grade active disease in selected individuals when

high-grade neuroendocrine tumors or poorly differentiated carcinomas are documented or suspected or when disease is growing rapidly. For certain types of neuroendocrine tumors (eg, well-differentiated, grade 3), somatostatin receptor-based imaging with PET/CT or PET/MRI or FDG-PET/CT scans for surveillance are recommended as clinically indicated. Use of18F-DOPA PET/CT is not discussed in the guidelines.

Section Summary: Neuroendocrine Tumors
Evidence for the use of PET or PET/CT in the management of Individuals with neuroendocrine tumors consists of meta-analyses. Two different radiopharmaceuticals were used: FDG-PET/CT and ^{68}Ga-PET/CT. Meta-analyses of studies using ^{68}Ga-PET/CT as the radiotracer for diagnosis and staging of neuroendocrine tumors report relatively high sensitivities and specificities compared with conventional imaging techniques.

The evidence does not support the use of FDG-PET/CT for the diagnosis, staging, and restaging, or surveillance of neuroendocrine tumors.

The evidence does not support the use of FDG-PET/CT for surveillance of neuroendocrine tumors.

The evidence supports the use of ^{68}Ga-PET/CT for the diagnosis, staging, and restaging of neuroendocrine tumors.

The evidence does not support the use of ^{68}Ga-PET/CT for surveillance of neuroendocrine tumors.

Ovarian Cancer
For primary evaluation, i.e., in individuals with suspected ovarian cancer, the ability to rule out malignancy with a high NPV would change management by avoiding unnecessary exploratory surgery. However, available studies suggest that PET scan has poorer NPV compared to other options, including transvaginal ultrasound (TVUS), Doppler studies, or MRI. Adding PET scanning to TVUS or MRI did not improve results.

Positive predictive value (PPV) is of greatest importance in evaluating individuals with known ovarian cancer, either to detect disease recurrence or progression or monitor response to treatment.

Systematic Reviews
A 2017 meta-analysis by Xu et al evaluated the diagnostic value of PET and PET/CT for recurrent or metastatic ovarian cancer.[128] The literature search, conducted through August 2014, identified 64 studies for inclusion: 15 studies (n=657) using PET and 49 studies (n=3065) using PET/CT. The pooled sensitivity and specificity for PET were 89% (95% CI, 86% to 92%) and 90% (95% CI, 84% to 93%), respectively. The pooled sensitivity and specificity for PET/CT were 92% (95% CI, 90% to 93%) and 91% (95% CI, 89% to 93%), respectively. Subgroup analyses were conducted by study region (Asia, Europe, and America). For PET/CT, sensitivities in the Asia and Europe studies were significantly higher compared with the sensitivity in the America studies.

A meta-analysis by Limei et al (2013), included 28 studies (total N=1651) published through December 2012; it evaluated the diagnostic value of PET/CT in suspected recurrent ovarian cancer.[129] Using the Oxford Evidence rating system for quality, 7 studies were considered high quality and 21 were low quality. Reviewers found PET/CT was useful for detecting ovarian cancer recurrence, with pooled sensitivity and specificity of 89% and 75% for the high-quality studies and 89% and 93% for the low-quality studies, respectively.

An AHRQ systematic review conducted by Matchar et al (2004) suggested that PET might have value for detecting recurrence when cancer antigen 125 is elevated and conventional imaging does not clearly show recurrence, this had not been demonstrated in an adequately powered prospective study.[130] An AHRQ systematic review conducted by Ospina et al (2008) found that evidence supported the use of PET/CT for detecting recurrent ovarian cancer.[35] Evidence for initial diagnosis and staging of ovarian cancer was inconclusive.

Guidelines

American College of Radiology

In 2018, the ACR published Appropriateness Criteria (2018) on staging and follow-up of ovarian cancer have stated that PET/CT and MRI may be appropriate when lesions are indeterminate with contrast-enhanced CT.[131]

National Comprehensive Cancer Network

Current NCCN guidelines for ovarian cancer including fallopian tube cancer and primary peritoneal cancer (v.2.2023) indicate that PET/CT can be appropriate "for indeterminate lesions if results will alter management."[132] Use of PET/CT may be considered for monitoring individuals with stage II through IV ovarian cancer receiving primary chemotherapy if clinically indicated. PET/CT also can be considered if clinically indicated after complete remission, for follow-up and for monitoring for recurrence if cancer antigen 125 is rising or clinical relapse is suspected.

Section Summary: Ovarian Cancer

Evidence for PET and PET/CT for the initial diagnosis of ovarian cancer consists of a 2014 AHRQ systematic review, which reported that the evidence is inconclusive. Evidence for the use of PET and PET/CT for the detection of ovarian cancer recurrence included 2 meta-analyses and a 2008 AHRQ systematic review. Pooled sensitivities and specificities support the use of PET and PET/CT for the detection of recurrent ovarian cancer. The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis and staging and restaging of ovarian cancer, but does not support their use for surveillance.

Pancreatic Cancer

Systematic Reviews

A Cochrane review by Best et al (2017) compared the diagnostic accuracy of several imaging techniques (CT, MRI, PET, and endoscopic ultrasound) in detecting cancerous and precancerous lesions in the pancreas.[133] The literature review, conducted through July 2016, identified 54 studies total, 10 using PET. Assessment of the selected studies found none to have high methodologic quality. A meta-analysis of 3 studies reported a sensitivity and specificity in diagnosing pancreatic cancer of 92% (95% CI, 80% to 97%) and 65% (95% CI, 39% to 84%), respectively. The positive predictive value and NPV (calculated by BCBSA) were

89% and 71%, respectively. Reviewers could not adequately compare the various techniques due to the imprecision of estimates, poor quality of studies, and heterogeneity in categorizing lesions.

Wang et al (2017) conducted a meta-analysis comparing CT alone, PET alone, and PET/CT in the preoperative assessment of individuals with pancreatic cancer.[134] The literature review identified 13 studies (total N=1343). The Newcastle-Ottawa Scale was used to assess study quality, with scores ranging from 6 to 8 on the 9-point scale. PET alone was not superior to CT alone (pooled odds ratio [OR],1.0; 95% CI, 0.6 to 1.6) in detecting distant metastases. However, PET/CT was superior to CT alone (pooled OR=1.7; 95% CI, 1.3 to 2.1) in detecting distant metastases. Neither PET nor PET/CT was superior to CT alone in detecting lymph node invasion (pooled OR,1.0; 95% CI, 0.6 to 1.5).

In meta-analysis of 9 studies (total N=526), Rijkers et al (2014) reported pooled sensitivity and specificity of FDG-PET/CT for confirming suspected pancreatic cancer of 0.90 (95% CI, 0.87 to 0.93) and 0.76 (95% CI, 0.66 to 0.84), respectively.[135] A 2008 AHRQ review published and past NCCN guidelines for pancreatic carcinoma suggest that PET-CT may be useful for staging in certain individuals when the standard staging protocol is inconclusive.[32,34]

An AHRQ systematic review by Matchar et al (2004)[130] and the TEC Assessment (1999)[136] focused on 2 clinical applications of PET scanning in individuals with known or suspected pancreatic cancer: the use of PET to distinguish between benign or malignant pancreatic masses, and the use of PET as a staging technique in Individuals with known pancreatic cancer.

In terms of distinguishing between benign and malignant disease, the criterion standard is percutaneous or open biopsy. If PET were to be used to allow individuals with scans suggesting benign masses to avoid biopsy, a very high NPV would be required. The key statistic underlying the NPV is the false negative rate. Individuals with false negative results are incorrectly assumed to have benign disease, and are thus not promptly treated for pancreatic cancer. Based on the literature review, the negative predictive value ranged between 75% and 92%, depending on an underlying prevalence of disease ranging from 50%–75%. The TEC Assessment concluded that this level of diagnostic performance would not be adequate to recommend against biopsy. The 2004 AHRQ report found that PET was sometimes found to be more accurate than other modalities, but the meta-analysis stated that it is unclear whether PET's diagnostic performance surpasses decision thresholds for biopsy or laparotomy.[129] In both the TEC Assessment and AHRQ systematic review, there were inadequate data to permit conclusions regarding the role of PET scanning as a technique to stage known pancreatic cancer.

Observational Studies

Ghaneh et al (2018) conducted the largest study to date, measuring the incremental diagnostic value of PET/CT when added to a standard diagnostic workup with multidetector CT.[137] The study was a prospective nonrandomized study of 550 Individuals. Sensitivity and specificity were 88.5% and 70.6%, respectively, which was a significant improvement from CT alone. PET/CT also correctly changed staging in 56 Individuals, influenced management in 250 Individuals, and stopped resection in 58 Individuals scheduled for surgery.

Guidelines

Current NCCN guidelines for pancreatic cancer (v.2.2023) state “the role of PET/CT remains unclear… [PET/CT] may be considered after formal pancreatic CT protocol in high-risk Individuals to detect extra pancreatic metastasis. It is not a substitute for high-quality contrast-enhanced CT.”[138]

Section Summary: Pancreatic Cancer
Evidence for PET and PET/CT for the initial diagnosis of pancreatic cancer consists of a TEC Assessment, a Cochrane review, a meta-analysis, and a large observational study published subsequent to the reviews. The TEC Assessment reported that the NPVs in several studies were inadequate to influence the decision for a biopsy. Other reviews also noted limitations such as imprecise estimates and poor quality of studies. Studies published subsequent to the reviews also reported low NPVs. The large observational study, which assessed the incremental diagnostic value of PET/CT when added to standard workup with CT, showed significant improvements in sensitivity and specificity compared with CT alone.

The evidence supports the use of FDG-PET and FDG-PET/CT for suspected pancreatic cancer when results from other imaging techniques are inconclusive.

The evidence does not support the use of FDG-PET and FDG-PET/CT for the diagnosis, staging, and restaging, or surveillance of pancreatic cancer.

Penile Cancer

Systematic Reviews
Lee et al (2022) conducted a systematic review and meta-analysis of 5 prospective and 7 retrospective cohort studies (12 studies; N=479) published through August 2021 on the diagnostic accuracy of FDG-PET/CT for lymph node staging in penile cancer.[139] Histopathological analysis was the reference standard in all included studies; direct comparison of FDG-PET/CT with other imaging modalities was not reported. Most studies had low or unclear risk of bias across QUADAS-2 domains, and Deek's test for publication bias was not significant (p=.45). FDG-PET/CT was associated with a pooled sensitivity of 87% (95% CI, 79% to 92%) and a pooled specificity of 88% (95% CI, 79% to 93%). Heterogeneity was present for both sensitivity ($I2$=68%) and specificity ($I2$=85%) and meta-regression analysis could not account for the heterogeneity. The analysis found a positive likelihood ratio of 7.2(95% CI 3.9 to 13.1) and a negative likelihood ratio of 0.15 (95% CI 0.10 to 0.24). The pooled diagnostic odds ratio was 47 (95% CI, 19 to 116) and the AUC was 0.93 (95% CI, 0.90 to0.95). Subgroup analysis of diagnostic accuracy stratified according to inguinal or pelvic lymph nodes found similar sensitivities (84% and 89%) and specificities (79% and 83%) with no difference between groups in AUC (area difference -0.044; p=.34). Although the review showed that FDG-PET/CT had good diagnostic capability, this study is limited by the heterogeneity among the studies and the lack of comparison with other imaging modalities.

Comparative Studies
Jakobsen et al (2021) retrospectively evaluated the diagnostic accuracy of FDG-PET/CT compared to contrast-enhanced CT in the assessment of inguinal lymph node status, distant metastases and synchronous cancer at 2 medical centers.[140] Patients Individuals diagnosed with invasive penile squamous cell carcinoma who received a preoperative FDG-PET/CT were included. A radiologist, blinded to FDG-PET/CT results, analyzed and interpreted the CT part of the scan for suspicious findings. There were 171 patients individuals evaluated for distant metastases and synchronous incident cancers. Additionally, there were 286 groins in 143

patients individuals evaluated for lymph node metastases. For detection of lymph node metastases, 6 of the 171 groins read as negative by FDG-PET/CT were false positives (false negative rate of 11.5% per groin). For the diagnostic accuracy for inguinal lymph node status, with histopathology or complete clinical follow-up as reference, FDG PET/CT sensitivity and specificity was 85.4% and 57.8% per patient, respectively. For CT, sensitivity and specificity was 47.5% and 95.8% per patient, respectively.

Guidelines

Current NCCN guidelines for penile cancer (v.1.2024) states that PET/CT may be considered for cross-sectional imaging of the chest/abdomen/pelvis for staging or treatment response assessment in individuals with suspected inguinal lymph node positive disease. PET/CT can also be used to evaluate enlarged pelvic lymph nodes if percutaneous lymph node biopsy is not technically feasible.[141]

Section Summary: Penile Cancer

Evidence for the use of PET or PET/CT in the management of individuals with penile cancer consists of a systematic review and a retrospective comparative study. In individuals with suspected inguinal lymph node positive disease, PET/CT may offer increased sensitivity compared to CT alone for staging. Current NCCN guidelines note that PET/CT can be considered for staging or treatment response assessment in individuals with node positive disease.

The evidence does not support the use of FDG-PET and FDG-PET/CT for the diagnosis, staging, restaging, or surveillance of node negative penile cancer.

The evidence does support the use of FDG-PET and FDG-PET/CT for the staging and treatment response assessment of node positive penile cancer.

The evidence does not support the use of FDG-PET and FDG-PET/CT for the diagnosis or surveillance of node positive penile cancer.

Prostate Cancer

^{11}C-CHOLINE PET and ^{11}C-CHOLINE PET/CT, ^{18}F-Fluciclovine PET

Prostate Cancer Diagnosis

In 2016, Liu et al[142] and Ouyang et a[143] conducted meta-analyses comparing the diagnostic accuracy of 4 radiotracers (fluorine-^{18}fluorodeoxyglucose, carbon-11 choline [^{11}C-choline], fluorine ^{18}fluorocholine [^{18}F-FCH], and carbon-11 acetate) in detecting prostate cancer. The literature search by Liu et al, conducted through July 2015, identified 56 studies (total N=3586 Individuals) for inclusion. Using the QUADAS-2 system to evaluate study quality, the authors determined that the studies were reliable, with scores of 6 to 9 out of 10. Pooled estimates for the 4 types of PET are summarized below (see Table 8). The search by Ouyang et al included studies using elastography and was conducted through April 2015. Study quality was not addressed.

Biscontini et al (2021) conducted a meta-analyses to evaluate the diagnostic accuracy of 18 F-fluciclovine for the diagnosis of primary cancer, pre-operative lymph node staging, detection of recurrent disease, and for bone metastasis assessment. [144] Fifteen studies (N=697) were evaluated: 6 studies for diagnosis, 3 for staging, 6 for recurrence of disease, and1 for evaluation of bone metastasis. Pooled estimates for diagnosis are included in Table 8.

Table 8. Pooled Diagnostic Performance of Different Radiotracers in Detecting Prostate Cancer

Imaging Technique	No. of Studies	Sensitivity (95% CI), %	Specificity (95% CI), %	AUC (95% CI)
Liu et al (2016)				
^{11}C-choline PET/CT	31	81 (77 to 88)	82 (73 to 88)	0.89 (0.86 to 0.91)
^{18}F-FCH PET/CT	15	76 (49 to 91)	93 (84 to 97)	0.94 (0.92 to 0.96)
^{11}C-acetate PET/CT	5	79 (70 to 86)	59 (43 to 73)	0.78 (0.74 to 0.81)
^{18}F-FDG PET/CT	5	67 (55 to 77)	72 (50 to 87)	0.73 (0.69 to 0.77)
Ouyang et al (2016)				
Elastography[a]	26	76 (68 to 83)	78 (72 to 83)	0.84 (NR)
^{11}C-choline PET/CT	31	78 (72 to 84)	79 (71 to 82)	0.85 (NR)
^{18}F-FCH PET/CT	15	73 (54 to 87)	59 (41 to 75)	0.91 (NR)
^{11}C-acetate PET/CT	5	79 (68 to 86)	59 (41 to 75)	0.77 (NR)
F-FDG PET/CT	5	76 (68 to 83)	78 (72 to 83)	0.84 (NR)
Bisconti et al (2021)				
18F-fluciclovine	6	83 (80 to 86)	77 (74 to 80)	0.92 (NR)

11C-acetate: carbon 11 acetate; 11C-choline: carbon 11 choline; 18F-FCH: fluorine 18 fluorocholine; AUC: area under the curve; CI: confidence interval; CT: computed tomography; FDG: fluorine 18 fluorodeoxyglucose; NR: not reported; PET: positron emission tomography. a Includes transrectal real-time elastosonography and shear-wave elastography.

Prostate Cancer Staging and Restaging

Systematic Reviews

The meta-analysis by Biscontini et al (2021), described previously, assessed the accuracy of 18F-fluciclovine.[144] For pre-operative lymph node staging (3 studies), the pooled sensitivity and specificity was 57% (95% CI, 39% to 73%) and 99% (95% CI, 94% to 100%), respectively. For the detection of recurrent disease (6 studies), the pooled sensitivity and specificity was 68% (95% CI, 63% to 73%) and 68% (95% CI, 60% to 75%), respectively.

A 2016 meta-analysis by Fanti et al assessed ^{11}C-choline PET/CT accuracy in restaging of prostate cancer individuals with biochemical recurrence after initial treatment with curative intent.[145] The literature search, conducted through December 2014, identified 12 studies (total N=1270) for inclusion in the analysis. Pooled sensitivity and specificity was 89% (95% CI, 83% to 93%) and 89% (95% CI, 73% to 96%).

In a 2014 meta-analysis by von Eyben and Kairemo, the pooled sensitivity and specificity of ^{11}C-choline PET/CT for detecting prostate cancer recurrence in 609 individuals was 0.62 (95% CI, 0.51 to 0.66) and 0.92 (95% CI, 0.89 to 0.94), respectively.[146] In an evaluation of 280

individuals from head-to-head studies comparing choline PET/CT with bone scans, PET/CT identified metastasis significantly more often than bone scanning (127 [45%] vs. 46 [16%], respectively; odds ratio, 2.8; 95% CI, 1.9 to 4.1; p<0.001). The authors also reported results of the choline PET-CT changed treatment in 381 (41%) of 938 individuals. Complete prostate-specific antigen (PSA) response occurred in 101 of 404 (25%) individuals.

A 2013 systematic review by Umbehr et al investigated the use of ^{11}C-choline and ^{18}F-FCH-PET and -PET/CT in staging and restaging of prostate cancer. The literature search, conducted through July 2012, identified 10 studies (total N=637) to be included in the initial prostate cancer staging analysis; pooled sensitivity was 84% (95% CI, 68% to 93%) and specificity was 79% (95% CI, 53% to 93%).[147] Twelve studies (N=1055) were included in the restaging analysis; pooled sensitivity and specificity were 85% (95% CI, 79% to 89%) and88% (95% CI, 73% to 95%), respectively.

Mohsen et al (2013) conducted a systematic review of 23 studies on C-11-acetate PET imaging for primary or recurrent prostate cancer.[148] Pooled sensitivity for primary tumor evaluation was 0.75 ((95% CI, 0.83 to 0.98) and pooled specificity was 0.93 (95% CI, 0.83 to 0.98). Although study quality was considered poor, low sensitivities and specificities appear to limit the utility of ^{11}C-acetate imaging in prostate cancer. ^{11}C-acetate is not currently FDA-approved.

Other systematic reviews, including those by Sandgren et al (2017)[149] and Albisinni et al (2018),[150] have also reported that ^{11}C-choline PET/CT exhibits high sensitivity and specificity estimates in the staging and restaging of prostate cancer.

Prostate Cancer Management

Jani et al (2021) conducted a single-center, open-label, phase 2/3 randomized controlled trial that evaluated the benefit of 18F-fluciclovine-PET/CT in individuals who had undergone radical prostatectomy and were experiencing biochemical recurrence to guide final radiotherapy treatment decisions.[151] Individuals were randomly assigned in a 1:1 ratio to radiotherapy directed by conventional imaging only, or to radiotherapy directed by conventional imaging plus 18F-fluciclovine-PET/CT. All 81 individuals in the conventional imaging group received radiotherapy (56 to prostate bed alone and 25 to prostate bed and pelvic nodes). In the 18F-fluciclovine-PET/CT group, 76 (95%) of the 80 individuals received radiotherapy (41 to the prostate bed alone and 35 to the prostate bed and pelvic nodes). Median follow-up for the whole cohort was 3.52 years. Median survival was not reached in both groups. Three-year event-free survival was 63% (95% CI, 49.2 to 74) in the conventional imaging group compared with 75.5% (95% CI, 62.5 to 84.6 in the 18F-fluciclovine-PET/CT group (difference, 12.5 percentage points [95% CI, 4.3 to 20.8]; p=.0028).

Dreyfuss et al (2021) conducted a single-center retrospective evaluation of individuals with biochemical recurrence after primary treatment for prostate cancer who received imaging with18F-fluciclovine-PET/CT.[152] A total of 328 individuals were included resulting in 336 18F-fluciclovine PET/CT scans, which were classified as positive (65%), negative (25%), or equivocal(10%) based on radiology reports. Sensitivity and specificity were 93% (95% CI, 86% to 96%) and 63% (95% CI, 45% to 77%), respectively, using biopsy and other imaging as the

reference standard. Management recommendations after imaging was only available for 241 scans (72%). Of the evaluable scans, 73% had management changes with 18F-fluciclovine-PET/CT data with 58% of those recommendations involving treatment modality decisions.

Andriole et al (2018) presented results from the LOCATE trial.[153] The study population consisted of 213 men who had undergone curative intent treatment of histologically confirmed prostate cancer and were suspected to have recurrence based on rising PSA levels. Fluciclovine-avid lesions were detected in 122 (57%) Individuals. Compared with management plans specified by the treating physicians prior to the PET scans, 126 (59%) Individuals had a change in management. The most frequent change in management was from salvage or noncurative systemic therapy to watchful waiting (n=32) and from noncurative systemic therapy to salvage therapy (n=30).

In 2017, Akin-Akintayo et al evaluated the role of FACBC (anti–1-amino-3-[18F] fluorocyclobutane-1-carboxylic acid or fluciclovine) PET/CT in the management of post-prostatectomy Individuals with PSA failure being considered for salvage radiotherapy.[154] Forty-two Individuals who were initially planning radiotherapy due to post-prostatectomy PSA failure underwent fluciclovine PET/CT. Based on the PET/CT results, 17 (40.5%) Individuals changed a decision relating to the radiotherapy: 2 Individuals received hormonal therapy rather than radiotherapy when fluciclovine showed extrapelvic disease; 11 Individuals increased the radiotherapy field from prostate bed only to prostate plus pelvis; and 4 Individuals reduced the radiotherapy fields from prostate plus pelvis to prostate bed only.

In meta-analysis of 14 studies (total N=1667) of radiolabeled choline PET/CT for restaging prostate cancer, Treglia et al (2014) reported a maximum pooled sensitivity of 0.77 (95% CI, 0.71 to 0.82) in Individuals with PSA rate of increase greater than 2 ng/mL per year.[155] Pooled sensitivity was lower for Individuals with PSA rate of increase less than 2 ng/mL per year or with PSA doubling time of 6 months or less. In meta-analysis of 11 studies (total N=609) of radio-labelled choline PET/CT for staging or restaging prostate cancer, Von Eyben et al (2014) reported pooled sensitivity and specificity of 0.59 (95% CI, 0.51 to 0.66) and 0.92 (95% CI, 0.89 to 0.94), respectively.[128] Pooled PPV and NPV were 0.70 and 0.85, respectively.

Guidelines

American College of Radiology

In 2018, the ACR published an Appropriateness Criteria on posttreatment follow-up of Individuals with prostate cancer have stated that PET and PET/CT using ^{11}C-choline or ^{18}F-fluciclovine radiotracers is usually appropriate for Individuals with a clinical concern for residual or recurrent disease following radical prostatectomy, nonsurgical treatments, or systemic therapy.[156]

American Urological Association et al

Practice guidelines from the American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology (2021) recommend CT or MRI for cross-sectional imaging, along with bone scintigraphy, as the standard imaging approach for the post-treatment biochemical recurrence after exhaustion of local treatment.[157] Novel PET tracers (11C-choline, 18F-fluciclovine, prostate-specific membrane antigen [PSMA]-targeting radiotracers) "appear to show greater sensitivity than conventional imaging for the detection of prostate cancer recurrence and metastases at low PSA values (<2.0 ng/mL).

National Comprehensive Cancer Network
Current NCCN guidelines for prostate cancer (v.4.2023) indicate that ^{11}C-choline PET or 18F-fluciclovine PET/CT or PET/MRI may be used for detection of biochemically recurrent small-volume disease in soft tissues and in bone. [158] 18F-sodium fluoride PET/CT or PET/MRI may be considered for further bone assessment. Use of FDG-PET should not be used routinely for initial assessment due to limited evidence of clinical utility.

Subsection Summary: ^{11}C-Choline PET, ^{11}C-Choline PET/CT, ^{18}F-Fluciclovine PET, and ^{18}F-Fluciclovine PET/CT for Prostate Cancer
Evidence for the use of 11C-choline PET, 11C-choline PET/CT, 18F-fluciclovine PET, and 18F-fluciclovine PET/CT for diagnosis, staging, and restaging of prostate cancer, consists of meta-analyses, which have shown that the use of 11C-choline and 18F-fluciclovine radiotracers result in similar sensitivities and specificities. Prospective studies in men with biochemical recurrence after primary treatment have reported that a majority of management decisions were changed based on 18F-fluciclovine PET/CT. One of those studies evaluated the impact on clinical outcomes and reported an increase in 3-year event-free survival rates. Further study is needed to compare PET and PET/CT with other imaging techniques, such as MRI and radionuclide bone scan. The evidence supports the use of 11C-choline PET and PET/CT and 18F-fluciclovine PET and PET/CT for the diagnosis, staging, and restaging of prostate cancer.

The evidence does not support the use of ^{11}C-choline PET and PET/CT and ^{18}F-fluciclovine PET and PET/CT for surveillance of prostate cancer.

^{68}GA-PET, ^{68}GA-PET/CT, Piflufolastat-F18 PET, and Piflufolastat-F18 PET/CT
FDA-approved PSMA-targeting radiotracers for PET include 68Ga PSMA and piflufolastat-F18. The Albisinni et al (2018) [150] discussed in the ^{11}C-choline PET/CT section, and a systematic review by Eissa et al (2018)[159] noted that an advantage of using PSMA-targeting radiotracers compared with ^{11}C-choline and ^{18}F-fluciclovine is the potential to detect local and distant recurrences in Individuals with lower PSA levels (<0.5 ng/ml).

Prostate Cancer Diagnosis

Kawada et al (2022) conducted a systematic review on the diagnostic accuracy of PSMA PET for detection of clinically significant prostate cancer. [160] Five studies reporting data from497 individuals with suspected prostate cancer due to elevated PSA were included in the review; 2 studies included only biopsy-naïve individuals (N=333) while in the remaining 3studies participants had a prior negative biopsy. The median pre-imaging PSA was 8.0 ng/mL (range, 5.6 to 18 ng/mL). The prevalence of clinically significant prostate cancer, variably defined among the studies but generally requiring an International Society of Urologic pathology grade group ≥2, was 59% (range, 32% to 75%). 68GA was the imaging agent in 4 of the studies. Three of the studies (N=228) assessed PSMA PET, MRI, and PSMA PET/MRI and reported diagnostic measures for all 3 imaging modalities. In all studies, systemic and targeted biopsy was the reference standard. Risk of bias, assessed using the QUADAS-2 tool, was judged to be low in one study and moderate in the other studies.

Measures of diagnostic accuracy are reported in Table 9. Results were similar for PSMA PET and MRI, alone and in combination, with overlapping CIs, and were consistent when limited to 2 studies of biopsy-naïve individuals.

Table 9. Diagnostic Performance of Imaging Modalities in Detecting Clinically Significant Prostate Cancer

Imaging Technique for Targeted Biopsy	No. of Studies	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	DOR (95% CI)	AUC
Kawada et al 2022[]							
All studies PSMA PET	5	89 (85 to 93)	56 (29 to 80)	69 (58 to 79)	78 (50 to 93)	10.50 (2.59 to 42.57)	0.88
Studies comparing imaging techniques PSMA PET	3	90 (85 to 93)	39 (14 to 71)	68 (62 to 73)	72 (29 to 94)	5.16 (1.07 to 24.79)	0.88
MRI	3	84 (78 to 88)	53 (46 to 60)	70 (46 to 87)	76 (55 to 89)	6.40 (4.00 to 10.32)	0.81
PSMA PET/MRI	3	91 (77 to 97)	64 (40 to 82)	75 (56 to 87)	85 (62 to 95)	19.04 (9.54 to 38.02)	0.87

AUC: area under the curve; DOR: diagnostic odds ratio; MRI: magnetic resonance imaging; NPV: negative predictive value; PET: positron emission tomography; PPV: positive predictive value; PSMA: prostate-specific membrane antigen.

Prostate Cancer Staging

Stabile et al (2022)[161] and Wang et al (2021)[162] conducted systematic reviews on the use of PSMA PET for prostate cancer staging. The Stabile review included 27 studies (N=2832) assessing the diagnostic accuracy of PSMA PET/CT for prostate cancer staging in newly diagnosed individuals. Specifically, studies were included that reported on the predictive ability of PSMA PET for lymph node invasion. The mean PSA at baseline, reported in 14 studies, was 12.2 ng/mL. Among the studies, 9 included high-risk individuals, 1 included intermediate-risk individuals, 15 included individuals with mixed risk levels, and 2 did not report risk. 68GA was the imaging agent used in 22 of the studies. The reference standard was pelvic lymph node dissection in all of the included studies. Risk of bias was assessed using QUADAS-2 criteria; nearly all the studies had limitations resulting in unclear or high risk of bias ratings for 1 or more QUADAS-2 domain. Funnel plots and Egger's test found potential publication bias for sensitivity (p=.002) and negative predictive value (p=.02), but not for specificity (p=.1) or positive predictive value (p=.1).

Measures of diagnostic accuracy are reported in Table 10. Among the studies, the median prevalence of lymph node invasion was 26% (interquartile range [IQR], 20% to 34%; range 5% to 58%). Higher prevalence was associated with a significant decrease in negative predictive value (p=.04). Study authors stated that the clinical implication of these findings suggested that for individuals with a nomogram-calculated borderline risk of lymph node invasion and negative PSMA PET/CT, avoidance of pelvic lymph node dissection might be considered, while in individuals with higher-risk prostate cancer, avoidance of pelvic lymph node dissection should not be considered due to the decreased NPV in this risk group.

Wang et al (2021)[162] conducted a systematic review of 9 studies (N=640) comparing the diagnostic accuracy of 68GA PSMA PET/CT with multiparametric MRI for lymph node staging prior to prostatectomy in individuals with intermediate or high-risk prostate cancer. The reference standard was pelvic lymph node dissection. The median prevalence of pelvic lymph

node metastases was 25% (range, 4% to 58%). The median PSA ranged widely among 6 studies from 7.4 to 37.3 ng/mL and was not reported in the other 3 studies. Eight studies were retrospective, and the other was prospective; QUADAS-2 assessment of study quality found the majority of studies had low or unclear risk of bias for most domains. No publication bias was found for either 68GA PSMA PET/CT (p=.15) or multiparametric MRI (p=.87). Study results are summarized in Table 10. Sources of heterogeneity based on meta-regression analysis included pelvic lymph node metastases prevalence, PSA level, risk group, and reference standard for 68GA PSMA PET/CT and number of patients and PSA level for multiparametric MRI.

Table 10. Diagnostic Performance of Imaging Modalities for Prostate Cancer Staging

	No. of Studies	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	DOR (95% CI)	AUC (95% CI)
Stabile et al (2022)							
PSMA PET Overall	27	58 (50 to 66)	95 (93 to 97)	79 (72 to 85)	87 (84 to 89)	14.76 (to 19.00)	0.84 (0.87 to 0.81)
High-risk	9	54 (37 to 70)	95 (91 to 98)	77 (67 to 86)	83 (79 to 87)	18.97 (10.65 to 33.78)	-
Intermediate-risk	1	93 (76 to 100)	96 (86 to 100)	93 (76 to 100)	96 (86 to 100)	364 (21.12 to 6273)	-
Mixed-risk	15	58 (49 to 67)	94 (92 to 96)	77 (68 to 85)	88 (84 to 91)	13.58 (9.98 to 18.47)	-
p value for between risk group difference	-	.008	.9	.3	.04		
Wang et al (2021)[]							
PSMA PET	9	71 (48 to 86); I^2=75%	92 (88 to 95); I^2=54%	-	-	-	0.92 (0.89 to 0.94)
Multiparametric MRI	9	40 (16 to 71); I^2=5%	92 (80 to 97); I^2=91%	-	-	-	0.82 (0.79 to 0.86)

AUC: area under the curve; DOR: diagnostic odds ratio; MRI: magnetic resonance imaging; NPV: negative predictive value; PET: positron emission tomography; PPV: positive predictive value; PSMA: prostrate-specific membrane antigen.

Prostate Cancer Management

Systematic Reviews

Systematic reviews conducted by Mazrani et al (2022) [163] and Pozdnyakov et al (2022) [164] assessed the effect of PSMA PET imaging for detection of biochemical prostate cancer recurrence, change in management, and patient outcomes following PSMA PET. Study characteristics of the reviews are summarized in Table 11. In both reviews, 68GA was the imaging agent used in the majority of studies (80% [16/20] and 88% [30/34], respectively). Only 6 studies overlapped between the 2 reviews, potentially due to Mazrani et al limiting their inclusion criteria to prospective studies and differences in study search dates. Of note, the Fendler 2019 study (N=635) discussed below in the Prospective Studies section was included in both reviews, accounting for 30% of the total population in Mazrani and 17% of the total population in Pozdnyakov. Mazrani assessed the quality of the included studies using the QUADAS-2 tool. For most studies, risk of bias was determined to be high or unclear for the patient selection domain (17/20 studies) and for the reference standard domain(17/20 studies).

Study quality was assessed by Pozdnyakov using National Heart, Lung, and Blood Institute (NHLBI) criteria for observational and cohort studies. Studies were scored on a scale of 0 to 14, with higher scores reflecting a lower risk of bias. Scores for individual studies ranged from 1 to 11; the median score for the change in management studies was 8,and median score for clinical outcome studies was 9. A funnel plot analysis conducted by Pozdnyakov suggested the presence of publication bias (Egger's test p=.008).

Table 11. Characteristics of Systematic Reviews of PSMA PET Imaging for Prostate Cancer Management

Study	Dates	No. of Included Studies	Reference Standard	Participants	N (Range)	Study Design(s)
Mazrani et al 2022[,]	Through July 1, 2021	20	Conventional imaging or histopathology	Individuals with biochemical prostate cancer recurrence Mean PSA NR; range 0.2 to 14.9 ng/mL Initial prostate cancer treatment NR	2110 (30-635)	Prospective
				Individuals with biochemical prostate cancer recurrence		
Pozdnyakov et al 2022	Through October 1, 2020	34 for change in management 27 for clinical outcomes	NR	Median PSA 7.6 ng/mL at time of diagnosis and 1.3 ng/mL at time of PET imaging 63% had a Gleason score <7 Initial treatment: 56% radical prostatectomy, 24% radiotherapy plus radical prostatectomy, 18% radiotherapy only Androgen-deprivation therapy prior to PET imaging: 18%	3680 for change in management 2674 for clinical outcomes	Prospective or retrospective

NR: not reported; PET: positron emission tomography; PSA: prostate-specific antigen.

Study results are summarized in Table 12. The reviews found similar proportions of individuals with positive PSMA imaging and with a change in management based on PSMA PET imaging results. Meta-regression analysis conducted by Pozdnyakov [164], found increasing age (p=.0003), Gleason score ≥8 (p=.016), prior treatment with androgen-deprivation therapy(p<.001), initial treatment with radical prostatectomy (p=.003), and a higher PSA at initial diagnosis and the time of PET (p=.003 for both) all associated with PSMA positive imaging. Regarding change in management, PSMA positivity was the only variable with a significant association (p=.001). Twenty-seven of the studies (n=2674) included in Pozdnyakov review [163] reported clinical outcomes following PSMA PET imaging. In this subset of studies, individuals received treatment after PSMA PET with metastasis-directed radiotherapy (61%), standard salvage radiotherapy (26%), or surgical mastectomy (8.3%). Twenty percent also received adjunctive androgen-deprivation therapy. The median duration of follow-up was 16 months across the studies, but varied according to outcome from 11 months for complete biochemical response (9 studies), 20 months for biochemical recurrence-free survival (9 studies), and 24 months for overall survival (12 studies). Heterogeneity was 75% or higher for all outcomes. Additional analyses limited to data from individuals who underwent metastasis-directed treatment found similar results for biochemical recurrence-free survival (63.7%,95%

CI, 53.3% to 74.1%) and overall survival (96.9%, 95% CI, 95.1% to 98.8%); data on complete biochemical response were too limited in this population to pool.

Table 12. Results of Systematic Reviews of PSMA PET Imaging for Prostate Cancer Management

Study	Positive PSMA Imaging	Change in Management	Complete Biochemical Response	Biochemical Recurrence-Free Survival[a]	Overall Survival
Mazrani et al 2022,					
Total N	2210	330	Not reported	Not reported	Not reported
Proportion (n/N)	66.6% (1406/2110)	42.7% (141/330)	-	-	-
95% CI	-	-	-	-	-
I^2(p)	-	-	-	-	-
Podzdynakov et al 2022					
Total N	3680	Not reported	558	1057	1684
Proportion (n/N)	68.2%	56.4%	23.3%	60.2%	98.3%
95% CI	-	48.0% to 63.9%	14.6% to 32.0%	49.1% to 71.4%	97.2% to 99.4%
I^2(p)	-	96%	86%	94%	75%

a
PSA <0.2 ng/ml or <nadir

Prospective Studies

Prospective studies not included in one of the systematic reviews are summarized below. The exception is the Fendler 2019 study, which although included in both the Mazrani and Pozdnyakov reviews, is described separately as it is one of the largest studies published to date and was one of the studies upon which FDA approval of the Locametz 68GA preparation kit was based (see Prostate Cancer Treatment, below).

Hofman et al (2020) published results from the multicenter, randomized proPSMA trial (N=300) that evaluated the diagnostic utility of 68Ga-PSMA PET/CT as a replacement for conventional imaging in newly diagnosed individuals with prostate cancer and high-risk features.[165] Individuals were randomly assigned 1:1 to receive 68Ga-PSMA PET/CT or conventional imaging prior to radical prostatectomy or radiotherapy with curative intent. The primary outcome was accuracy for identifying either pelvic nodal or distant-metastatic disease. A reference standard was assessable for 98% of individuals, with 30% of the cohort positive for nodal or distant metastases. 68Ga-PSMA PET/CT had an improved sensitivity (85% vs. 38%) and specificity (98% vs. 91%) compared to conventional imaging. This translated to a greater AUC for accuracy with 68Ga-PSMA PET/CT (92% vs. 65% with conventional imaging; absolute difference, 27%; 95% CI, 23 to 31, p<.0001). A change in intended management was reported more frequently with 68Ga-PSMA PET/CT compared to conventional imaging (28% vs. 15%, p=.008).

Pienta et al (2021) published results from the prospective Phase 2/3, multi-center Study of 18-F-DCFPyL PET/CT imaging in individuals with prostate cancer: Examination of diagnostic accuracy (OSPREY) trial. [166] Two different cohorts were evaluated: individuals with high-risk prostate cancer undergoing radical prostatectomy with pelvic lymphadenectomy (cohort A) and individuals with suspected recurrent/metastatic prostate cancer on conventional imaging (cohort B). Both cohorts received conventional imaging at baseline and piflufolastat-F18 PET/CT 4 to 6 weeks later. In cohort A, 268 individuals with high-risk prostate cancer were evaluable to determine the diagnostic performance of piflufolastat-F18 PET/CT in detecting pelvic nodal metastases. The median specificity was 97.9% (95% CI, 94.5% to 99.4%) and

median sensitivity was 40.3% (95% CI, 28.1% to 52.5%). The sensitivity end point was not met, as the lower bounds of the 95% CI did not reach the pre-specified success threshold of 40%. In cohort B, 93 individuals were analyzed to assess the diagnostic performance for detecting sites of prostate cancer metastases or locoregional occurrence. Median sensitivity was 95.8% (95% CI, 87.8% to 99.0%) and median PPV was 81.9% (95% CI, 73.7% to 90.2%). Specificity was not reported.

Morris et al (2021) published results from the CONDOR trial, which was a prospective, multicenter, phase 3 study.[167] The performance of piflufolastat-F18 PET/CT in individuals with biochemical recurrence and uninformative conventional imaging (including 18F-fluciclovine or 11C-choline PET, CT, MRI, and/or whole-body bone scintigraphy) was evaluated. The primary endpoint was correct localization rate, a measure of PPV plus anatomic lesion colocalization based on histopathology, imaging findings, or therapy response. It was further defined as the percentage of individuals with a 1:1 correspondence between at least 1 lesion identified on piflufolastat-F18 PET/CT by central readers and the composite standard of truth. The FDA considered correct localization rate to functionally represent a patient-level PPV.[167] It also stated that due to high disease prevalence in individuals with biochemically recurrent prostate cancer, true negative regions are difficult to identify and would require long-term follow-up. Thus, specificity is not considered a practical endpoint in this patient population. However, "PPV can also provide some information related to false positive patients and is much more readily estimated."

The CONDOR trial included 208 individuals (median PSA of 0.8 ng/mL) who received piflufolastat-F18 PET/CT.[167] The correct localization rate across the 3 readers ranged from 84.8% to 87.0% (lower bound of 95% CI, 77.8 to 80.4), meeting the pre-specified success threshold of 20% for the lower bound of the 95% CI in the primary analysis, which excluded individuals with a negative PET result or if there was no reference standard data available for a PET-positive region. The detection rate rose with increasing PSA levels ranging from 36.2% (<0.5 ng/mL) to 96.7% (≥5 ng/mL). A change in intended management was reported in 63.9% (131/205) of evaluable individuals.

Hope et al (2021) included 764 individuals with intermediate or high-risk prostate cancer undergoing 68GA PSMA PET imaging, 277 of whom had subsequent radical prostatectomy and pelvic lymph node dissection.[169] The median PSA was 11.4 mg/ml, and 78% of the study population was high-risk, based on D'Amico risk classification. Compared with a histopathological reference standard, sensitivity of 68GA PSMA PET in this population was 40% (95% CI, 34% to 46%), specificity 95% (95% CI, 92% to 97%), PPV 75% (95% CI, 70% to 80%), and NPV 81% (95% CI, 76% to 85%).

Fendler et al (2019) conducted a prospective single-arm clinical trial to evaluate the accuracy of 68Ga-PSMA PET/CT in individuals with biochemically recurrent prostate cancer after prostatectomy, radiation therapy, or both.[170] The primary endpoint was PPV on a per-patient and per-region basis of 68Ga-PSMA PET for detection of tumor location. A total of 635 individuals were enrolled. On a per-patient basis, PPV was 84% (95% CI, 75% to 90%) by histopathologic validation (primary endpoint, n=87) and 92% (95% CI, 88% to 95%) by the composite reference standard (n=217). Detection rates significantly increased with increasing PSA levels.

Prostate Cancer Treatment
Individuals with previously treated metastatic castration-resistant prostate cancer (mCRPC) who are potential candidates for treatment with 177Lu-vipivotide tetraxetan (Pluvicto) should undergo PSMA PET imaging to appropriately select those individuals with PSMA-positive lesions. The Locametz 68GA preparation kit received FDA approval as a theranostic agent in conjunction with Pluvicto, although Pluvicto labeling indicates that other PSMA PET imaging agents may also be used for identification of PSMA-positive individuals. FDA approval of Locametz was based on the Hope et al (2021) [169] and Fendler et al (2019) [170] studies, described above.

Guidelines

National Comprehensive Cancer Network
NCCN guidelines for initial workup of suspected prostate cancer (v.1.2023) recommend multiparametric MRI prior to biopsy in certain individuals and include no recommendations on the use of PSMA PET or PET/CT. [171]

The current NCCN guidelines for prostate cancer (v.4.2023) [158] indicate that piflufolastat-F18 or 68Ga-PSMA PET/CT or PET/MRI imaging may be appropriate following equivocal standard imaging or as an alternative to standard imaging for initial staging of individuals who are symptomatic and/or with a life expectancy >5 years with unfavorable intermediate-, high-, or very high-risk disease, for the detection of biochemically recurrent disease following initial definitive therapy, and as part of a workup for progression in in individuals with N1 cancer on androgen deprivation therapy or localized cancer on observation. The guidelines include the following specific imaging recommendations:

- Bone imaging can be achieved by conventional technetium-99m-MDP bone scan.
  - Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 prostate-specific membrane antigen (PSMA)-11, or F-18piflufolastat PSMA can be considered for equivocal results on initial bone imaging.

- Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Mp MRI is preferred over CT for pelvic staging.

- Alternatively, Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging.
  - Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front- line imaging tool for these patients.

Imaging (including PSMA PET) is not recommended for individuals with asymptomatic very low, low, or favorable intermediate risk disease and life expectancy

Society of Nuclear Medicine and Molecular Imaging
The SNMMI has published appropriate use criteria (2022) for PSMA PET imaging. [172]
Panel recommendations for PSMA PET imaging are as follows, based on clinical scenarios and appropriate use scores (scale 1-9):

- Appropriate use scenarios (score 7-9)
  - Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer (score: 8)
  - Newly diagnosed unfavorable intermediate-, high-risk, or very-high-risk prostate cancer with negative/equivocal or oligometastatic disease on conventional imaging (score:8)
  - PSA persistence or PSA rise from undetectable level after radical prostatectomy (score: 9)
  - PSA rise above nadir after definitive radiotherapy (score: 9)
  - nmCRPC (M0) on conventional imaging (score: 7)

- Potentially appropriate use scenarios (score 4-6)
  - Newly diagnosed prostate cancer with widespread metastatic disease on conventional imaging (score 4)
  - PSA rise after focal therapy of the primary tumor (score 5)
  - Posttreatment PSA rise in the mCRPC setting (score 6)
  - Evaluation of response to therapy (score 5)

- Rarely appropriate use scenarios (score 1-3)
  - Patients with suspected prostate cancer (e.g., high/rising PSA levels, abnormal digital rectal examination results) evaluated for targeted biopsy and detection of intraprostatic tumor (score 3)
  - Patients with very-low, low-, and favorable intermediate-risk prostate cancer (score: 2)

American Society of Clinical Oncology
The American Society of Clinical Oncology (2021) recommends against the use of "PET, CT, and radionuclide bone scans, or newer imaging scans in the staging of early prostate cancer at low risk for metastasis." [173] The recommendations note that current evidence does not support the use of PSMA PET imaging modalities for staging newly diagnosed prostate cancer with low risk of distant metastasis based on clinicopathologic features (grade 1 disease, T1c/T2a disease, prostate-specific antigen (PSA) <10 ng/ml, Gleason score≤6).

American Urological Association et al
The American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO; 2022) [174] joint guideline on risk assessment, staging and risk-based management of clinically localized prostate cancer includes the following statements:

- Clinicians should not routinely perform abdomino-pelvic computed tomography (CT) scan or bone scan in asymptomatic patients with low- or intermediate-risk prostate cancer.(Expert Opinion)

- Clinicians should obtain a bone scan and either pelvic multi-parametric magnetic resonance imaging (mpMRI) or CT scan for patients with high-risk prostate cancer. (Strong Recommendation; Evidence Level: Grade B)
  - To evaluate for the presence of bone metastasis, conventional bone scan should be obtained as the initial staging study. As robust evidence to support an imaging

evaluation in unfavorable intermediate-risk disease remains lacking, the Panel offers that clinicians may consider obtaining staging imaging for patients within this risk classification.

- In patients with prostate cancer at high risk for metastatic disease with negative conventional imaging, clinicians may obtain molecular imaging to evaluate for metastases.(Expert Opinion)

The guideline notes "while data to date supporting a clinical benefit to novel imaging modalities for patients with negative conventional imaging remain quite limited, the Panel did conclude that clinicians may offer molecular imaging in patients at high risk for metastatic disease based on the demonstrated enhanced staging accuracy."

The guideline states that the systematic review used to provide evidence for the AUA/ASTRO guideline conducted literature searches through September 2021. Although the systematic review has not yet been published, the literature search end date was prior to the November 2021 publication of the Hope et al [169] prospective study (described above),which informed the updated NCCN treatment guideline. It is unclear how inclusion of the Hope et al results would impact the AUA/ASTRO guideline recommendations.

Subsection Summary: 68Ga-PSMA PET, 68Ga-PSMA PET/CT, Piflufolastat-F18 PET, and Piflufolastat-F18 PET/CT for Prostate Cancer

Evidence for the use of 68Ga-PSMA PET, 68Ga-PSMA PET/CT, piflufolastat-F18 PET, and piflufolastat-F18 PET/CT consists of systematic reviews and prospective, multicenter trials. A systematic review of studies conducted in individuals with suspected prostate cancer found similar sensitivity and specificity for PSMA PET and MRI for detection of clinically significant prostate cancer, but only 3 studies of 228 individuals were included in the analysis. The evidence does not support the use of PSMA PET for initial diagnosis of prostate cancer. Systematic reviews have found PSMA PET to have similar diagnostic accuracy across risk groups in newly diagnosed individuals, and to be similar to MRI for staging intermediate/high-risk prostate cancer. Systematic reviews of studies conducted in individuals with biochemical recurrence, found high proportions with positive PSMA PET imaging often leading to change in management. Individual prospective trials have generally found that PSMA-targeted radiotracers provide a high specificity for detecting pelvic lymph node or distant metastases in newly diagnosed individuals with high-risk disease and a clinically relevant PPV in individuals with biochemical recurrence. NCCN guidelines and SNMMI recommend the use of PSMA PET in specific clinical circumstances. The evidence supports the use of 68Ga-PET, 68Ga-PET/CT, piflufolastat-F18 PET, and piflufolastat-F18 PET/CT for staging, restaging, and surveillance of prostate cancer in selected individuals.

Renal Cell Carcinoma

Systematic Reviews

A 2017 systematic review by Ma et al evaluated the use of ^{18}FDG-PET or -PET/CT for restaging renal cell carcinoma.[175] The literature search identified 15 studies, mostly retrospective, for inclusion into a meta-analysis. Pooled estimates for sensitivity and specificity were 86% (95% CI, 88% to 93%) and 88% (95% CI, 84% to 91%), respectively. Reviewers concluded that PET showed potential for identifying metastatic or recurrent lesions in individuals with renal cell carcinoma, but that more prospective studies would be needed.

Guidelines
Current NCCN guidelines for RCC (v.1.2024) state that "The value of PET in RCC [renal cell carcinoma] remains to be determined. Currently, PET alone is not a tool that is standardly used to diagnose kidney cancer or follow for evidence of relapse after nephrectomy."[175]

Section Summary: Renal Cell Carcinoma
The evidence does not support the use of FDG-PET and FDG-PET/CT for the diagnosis, staging and restaging, or surveillance of RCC.

Soft Tissue Sarcoma

Systematic Reviews
A 2012 systematic review by Treglia et al evaluated PET for assessing response to imatinib and other treatments for gastrointestinal stromal tumors.[177] Reviewers selected 19 studies. They concluded there was sufficient evidence that PET/CT can be used to monitor response to imatinib treatment, and that the information can be used to adapt treatment strategies. However, the review had the following limitations: it lacked appraisal of the methodologic quality of individual studies and lacked comparison of decision making and outcomes between PET-guided management.

A 2002 AHRQ systematic review on use of PET for soft tissue sarcoma evaluated five applications: distinguishing between benign lesions and malignant soft tissue sarcoma, distinguishing between low-grade and high-grade soft tissue sarcoma, detecting locoregional recurrence, detecting distant metastases, and evaluating response to therapy.[178] The review found that PET has low diagnostic accuracy in distinguishing low-grade tumors from benign lesions; however, PET performed better at differentiating high- or intermediate-grade tumors from low-grade tumors; however, it is unclear whether this will have an impact on management decisions and health outcomes. Evidence is insufficient on the comparative diagnostic performance of PET and alternative diagnostic modalities in the diagnosis of soft tissue sarcoma, detection of locoregional recurrence, detection of distant metastasis, and evaluation of treatment response.

Guidelines
Current NCCN guidelines for soft tissue sarcoma (v.2.2023) state that PET/CT may be useful in staging, prognostication, grading, and determining response to chemotherapy.[179] The guidelines also state that PET can provide information on imatinib activity after 2 to 4 weeks of therapy when rapid reading of activity is considered necessary; however, long-term PET follow-up is rarely indicated. The guidelines also indicate that PET can be used to assess the progression of disease if results from other imaging techniques (CT or MRI) are inconclusive.

Section Summary: Soft Tissue Sarcoma

Evidence for the use of PET or PET/CT in Individuals with soft tissue sarcoma consists of 2 systematic reviews. Results of the ARHQ review showed that PET or PET/CT had low diagnostic accuracy. Another systematic review reported evidence supporting the use of PET/CT in monitoring response to imatinib treatment. The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis and staging and restaging of soft tissue sarcoma, but does not support their use for surveillance.

Testicular Cancer

Systematic Reviews
An AHRQ technology assessment conducted by Ospina et al (2008)[35] and studies evaluating residual masses in individuals after chemotherapy for seminoma[180] support the use of PET.

The 2004 AHRQ systematic review by Matchar et al found one prospective study and four retrospective studies that generally showed higher sensitivity and specificity for PET over CT. However, these studies were small in size and failed to report separate results for individuals with seminoma versus those with non-seminoma. Studies also failed to report separate results by clinical stage of disease.[130]

In addition, studies on PET's ability to discriminate viable tumor and necrosis/fibrosis after treatment of testicular cancer were flawed in two main ways. First, most studies did not compare the diagnostic accuracy of PET with other imaging modalities. Second, studies that did compare PET and CT did not state a clear threshold for a positive CT test, making study results difficult to interpret. Therefore, it is uncertain whether use of PET leads to different patient management decisions and health outcomes than other imaging modalities.

Guidelines
Current NCCN guidelines for testicular cancer (v.1.2023) support the use of PET to evaluate residual masses that are greater than 3 cm following primary treatment with chemotherapy (at ≥6 weeks posttreatment).[181] If a PET scan is negative, surveillance is recommended. If a PET scan is positive, resection or biopsy of residual mass is recommended. The guidelines warn that there is "limited predictive value for PET/CT scan for residual masses." Use of PET is not recommended for non-seminoma individuals.

Section Summary: Testicular Cancer
Evidence for the use of PET or PET/CT in individuals with testicular cancer consists of an AHRQ systematic review of small studies. Results showed that PET or PET/CT can be useful in evaluating residual masses following chemotherapy for seminoma. There is no evidence supporting the use of PET or PET/CT in non-seminoma individuals. The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis and staging and restaging of testicular cancer, but does not support their use for surveillance.

Thyroid Cancer

Differentiated
Schutz et al (2018) conducted a systematic review and meta-analysis of 29 prospective studies (22 differentiated, 7 medullary) investigating the staging, restaging, and recurrence of

thyroid cancer.[182] Meta-analyses showed higher sensitivity and specificity with PET compared with conventional imaging.

In 2016, Haslerud et al conducted a systematic review of studies using ^{18}F-FDG-PET to detect recurrent differentiated thyroid cancer in individuals who had undergone ablative therapy.[183] The literature search identified 34 studies (total N=2639) for inclusion: 17 using ^{18}F-FDG-PET/CT, 11 using ^{18}F-FDG-PET, and 6 using both methods. Study quality was assessed using the QUADAS tool. Pooled sensitivity and specificity for ^{18}F-FDG-PET/CT were 80% (95% CI, 74% to 86%) and 76% (95% CI, 63% to 85%), respectively. Pooled sensitivity and specificity for 18F-FDG-PET alone were 77% (95% CI, 63% to 86%) and 76% (95% CI, 60% to 87%), respectively. Combining all 34 studies in the meta-analysis resulted in a pooled sensitivity and specificity of 79% (95% CI, 74% to 84%) and 79% (95% CI, 71% to 85%), respectively.

The NCCN report conducted by Podoloff et al (2009) showed that PET could localize recurrent disease when other imaging tests are negative.[37] Additionally, PET was found to be prognostic in this setting, showing that more metabolically active lesions on PET were strongly correlated with reduced survival [184]

Medullary
A meta-analysis of studies on detecting recurrent or metastatic medullary thyroid carcinoma was conducted by Cheng et al (2012).[185] The literature search identified 15 studies to be included in the meta-analysis: 8 used ^{18}F-FDG-PET and 7 used ^{18}F-FDG-PET/CT. The pooled sensitivity for ^{18}F-FDG-PET alone in detecting recurrent or metastatic medullary thyroid cancer was 68% (95% CI, 64% to 72%). The pooled sensitivity for ^{18}F-FDG-PET/CT was 69% (95% CI, 64% to 74%).

Guidelines
Current NCCN guidelines (v.4.2023) for thyroid carcinoma continue to support the use of FDG-PET/CT in thyroid cancer evaluation, such as when iodine-131 imaging is negative and stimulated thyroglobulin is greater than 2 to 5 ng/ml.[186]

Section Summary: Thyroid Cancer
Evidence for the use of PET and PET/CT to diagnose recurrent differentiated and medullary thyroid cancer consists of systematic reviews and meta-analyses. Pooled sensitivity and specificity for ^{18}F-FDGPET and ^{18}F-FDG-PET/CT in detecting recurrent differentiated thyroid cancer were comparable, ranging from 76% to 80%. Pooled sensitivity for both PET and PET/CT in detecting recurrent medullary thyroid cancer were also comparable (68% to 69%). The evidence supports the use of ^{18}F-FDG-PET and ^{18}FPET/CT for the diagnosis and staging and restaging of thyroid cancer, but does not support their use for surveillance.

Cancer of Unknown Primary
Burglin et al (2017) conducted a systematic review and meta-analysis on the use of PET/CT for the detection of the primary tumor in individuals with extra cervicalmetastases.[187] The literature search identified 20 studies (total N=1942) published between 2005 and 2016 for inclusion. The QUADAS tool was used to assess the risk of bias. In regard to patient selection and reference standard, the risk of bias was low; however, the risk of bias was high or unclear for most studies in regard to flow and timing of the index test. The pooled detection rate was 41% (95% CI, 39% to 43%), with large heterogeneity among the studies.

A larger (N=2795) systematic review conducted by Woo et al (2021) included 38 cohort studies (29 of which were retrospective) published through February 2021 assessing the effect of FDG-PET or FDG-PET/CT on patient management. [188] Study quality was assessed using the QUADAS-2 tool; no studies were judged low risk of bias for all QUADAS-2 domains. A funnel plot analysis did not reveal publication bias (Egger's test p=.98). In pooled analysis, 35% (95% CI 31% to 40%) of individuals undergoing FDG-PET or FDG-PET/CT imaging had a change in management, although the proportions among the individual studies ranged widely from 0% to 73%, and heterogeneity was high when pooled ($I2$=82%). The reason for change in management was detection of the primary cancer site in 22% (95% CI, 19% to 28%) of individuals undergoing imaging, and detection of metastatic site(s) in 14% (95% CI10% to 19%).

No evidence was identified that evaluated the use of FDG-PET for surveillance of individuals with cancer of unknown primary.

Guidelines
Current NCCN guidelines for occult primary cancers (v.1.2024) state the PET has been useful in the diagnosis, staging, and restaging of many malignancies, so it may be warranted in some situations for cancers of unknown primary. [189] However, the exact role of PET/CT remains undetermined. The guideline does not recommend PET/CT for the initial evaluation of cancers of unknown primary individuals, but notes that it can be useful in certain cases, especially when considering local or regional therapy.

Section Summary: Cancer of Unknown Primary
The evidence supports the use of ^{18}F-FDG-PET and ^{18}F-PET/CT for the diagnosis, staging and restaging, and surveillance of cancer of unknown primary.

Cancer Surveillance
The clinical utility for PET scanning in surveillance, i.e., in performing follow-up PET scans in asymptomatic Individuals to detect early disease recurrence, is not well studied. (For this policy, a scan is considered a surveillance scan if performed more than 6 months following therapy, but 12 months for lymphoma.) The most 2009 NCCN Task Force report stated, “PET as a surveillance tool should only be used in clinical trials.” [37] In addition, NCCN guidelines for various malignancies often note that PET scans are not recommended in asymptomatic Individuals. For example, the NCCN guidelines for breast cancer comment that PET scans (as well as many other modalities) provide no advantage in survival or ability to palliate recurrent disease and are not recommended.[33]

Other Oncologic Applications
There are inadequate scientific data to permit conclusions regarding the role of PET scanning in other malignancies.

SUMMARY OF EVIDENCE

Bladder Cancer
For individuals who have suspected or diagnosed bladder cancer in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes a systematic review and meta-analysis. The relevant outcome is test validity. Pooled analyses

showed relatively high sensitivity and specificity. Clinical guidelines include PET and PET/CT as considerations in staging bladder cancer, though CT, magnetic resonance imaging, and chest radiographs are also appropriate techniques for staging purposes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic after completing bladder cancer treatment who receive FDG-PET or FDG-PET/CT, there is no evidence. The relevant outcome is test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Bone Sarcoma
For individuals who have suspected or diagnosed bone sarcoma and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, the evidence includes systematic reviews and meta-analyses of many studies. Relevant outcomes are test accuracy and test validity. Pooled analyses have shown that PET or PET/CT can effectively diagnose and stage bone cancer, including chondrosarcoma. Use of PET or PET/CT has high sensitivities and specificities in detecting metastases in bone and lymph nodes; however, the tests have low sensitivity in detecting lung metastases. Clinical guidelines include PET and CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic after completing bone sarcoma treatment who receive ^{18}F-FDGPET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Brain Tumors
For individuals who have diagnosed brain tumors and in need of staging or restaging information or who have suspected brain cancer or are asymptomatic after completing brain cancer treatment who receive ^{18}F-FDG-PET, ^{18}F-FET-PET, or ^{11}C-methionine PET, the evidence includes several systematic reviews and meta-analyses. Relevant outcomes are test accuracy and test validity. Pooled analyses have shown that PET or PET/CT can be effective in distinguishing brain tumors from normal tissue. Indirect comparisons between the radiotracers ^{11}C-methionine and ^{18}F-FDG have shown that ^{11}C-methionine may have better diagnostic performance. Clinical guidelines include PET to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic after completing brain cancer treatment who receive FDG-PET, fluorine 18 fluoro-ethyl-tyrosine-PET, or ^{11}C-methionine PET, the evidence includes systematic reviews and meta-analyses. The relevant outcome is test validity. Pooled analyses did not support the use of PET for surveillance of brain cancer following treatment. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Breast Cancer
For individuals who have diagnosed breast cancer and inconclusive results from other imaging techniques who receive adjunctive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT for stating or restaging, the evidence includes meta-analyses. Relevant outcomes are test accuracy and test validity. While studies included in the meta-analyses report variability in estimates of sensitivity and

specificity, ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT may be helpful in situations in which standard staging results are equivocal or suspicious, particularly in individuals with locally advanced or metastatic disease. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected or diagnosed breast cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, the evidence includes a TEC Assessment, several systematic reviews, and meta-analyses. Relevant outcomes are test accuracy and test validity. There is no evidence supporting the use of PET in diagnosing breast cancer. The false-negative rates (5.5%-8.5%) using PET in individuals with breast cancer can be considered unacceptable, given that breast biopsy can provide more definitive results. Us of PET/CT may be considered for detection of metastases only when results from other imaging techniques are inconclusive. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic after completing breast cancer treatment who receive ^{18}F-FDGPET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Cervical Cancer

For individuals who have diagnosed cervical cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes an Agency for Healthcare Research and Quality (AHRQ) report and a meta-analysis. Relevant outcomes are test accuracy and test validity. Pooled results show that PET can be used for staging or restaging and for detection of recurrent disease. Clinical guidelines include PET and CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected cervical cancer or who are asymptomatic after completing cervical cancer treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Colorectal Cancer

For individuals who have diagnosed colorectal cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes a TEC Assessment and several meta-analyses. Relevant outcomes are test accuracy and test validity. Several pooled analyses evaluating staging or restaging using PET or PET/CT resulted in wide ranges of sensitivities and specificities, from the low 60s to the high 90s. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have suspected colorectal cancer or who are asymptomatic after completing colorectal cancer treatment who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes a RCT. Relevant outcome is test validity. The RCT found no differences in outcomes when FDG-PET/CT was added to usual surveillance compared to usual surveillance only. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Endometrial Cancer

For individuals who have diagnosed endometrial cancer in need of staging or restaging information or who are asymptomatic after completing endometrial cancer treatment who receive ^{18}F-FDG-PET or ^{18}FPET/CT, the evidence includes a systematic review and meta-analysis. Relevant outcomes are test accuracy and test validity. Pooled estimates from the meta-analysis showed high sensitivities and specificities for ^{18}F-FDG-PET/CT in detecting lymph node metastases and endometrial cancer recurrence following treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Esophageal Cancer
For individuals who have diagnosed esophageal cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes several meta-analyses. Relevant outcomes are test accuracy and test validity. Pooled estimates have shown high sensitivities and specificities compared to other diagnostic imaging techniques. Clinical guidelines include PET and CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected esophageal cancer or who are asymptomatic after completing esophageal cancer treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, the evidence includes meta-analyses. Relevant outcomes are test accuracy and test validity. Pooled analyses showed adequate sensitivities but low specificities. The evidence is insufficient to determine the effects of the technology on health outcomes.

Gastric Cancer
For individuals who have suspected or diagnosed gastric cancer and in need of staging or restaging information, who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes several meta-analyses. Relevant outcomes are test accuracy and test validity. Pooled analyses, with sensitivities and specificities ranging from the high 70s to the high 80s, have shown that PET or PET/CT can inform staging or restaging of individuals with gastric cancer. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic after completing gastric cancer treatment who receive ^{18}F-FDGPET or ^{18}F-FDG-PET/CT, the evidence includes meta-analyses. Relevant outcomes are test accuracy and test validity. Pooled analyses showed low sensitivities and specificities. The evidence is insufficient to determine the effects of the technology on health outcomes.

Head and Neck Cancer
For individuals who have suspected or diagnosed head and neck cancer in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes a TEC Assessment and several meta-analyses. Relevant outcomes are test accuracy and test validity. In individuals with head and neck cancers, PET and PET/CT are better able to detect local and metastatic disease compared with other imaging techniques. Evidence has also shown that ^{18}F-FDG-PET/CT may be useful in predicting response to therapy. Two meta-analyses calculated the ability of ^{18}F-FDG-PET or PET/CT to detect residual or recurrent disease during various stages of treatment and another meta-analysis calculated the ability of positive PET or PET/CT results to predict overall survival and event-free survival. The

evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic after completing head and neck cancer treatment who receive ^{18}FFDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Non-Small-Cell Lung Cancer
For individuals who have suspected non-small-cell lung cancer and inconclusive results from other imaging techniques or who have diagnosed non-small cell lung cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes several meta-analyses. Relevant outcomes are test accuracy and test validity. Pooled analyses have shown that PET and PET/CT have better diagnostic performance compared with conventional imaging techniques. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected non-small-cell lung cancer or who are asymptomatic after completing non-small-cell lung cancer treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Small-Cell Lung Cancer
For individuals with diagnosed small-cell lung cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes a systematic review and a meta-analysis. Relevant outcomes are test accuracy and test validity. While the quality of the studies was considered low, PET and PET/CT can be considered for staging or restaging in individuals with small-cell lung cancer. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected small-cell lung cancer or who are asymptomatic after completing small-cell lung cancer treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Hodgkin and Non-Hodgkin Lymphoma
For individuals who have suspected or diagnosed Hodgkin and non-Hodgkin lymphoma in need of staging or restaging information who receive ^{18}F-FDG-PET or PET/CT, the evidence includes a TEC Assessment and several meta-analyses, and an RCT. Relevant outcomes are test accuracy and test validity. Both PET and PET/CT have been found to provide useful information in the management of Hodgkin and non-Hodgkin lymphoma. The Deauville 5-point scale was developed based on PET results and can be used for staging and treatment response for individuals with lymphoma. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic after completing Hodgkin lymphoma treatment who receive ^{18}FFDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic after completing non-Hodgkin lymphoma treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Melanoma
For individuals who have suspected or diagnosed stage I or II melanoma and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes a TEC Assessment. Relevant outcomes are test accuracy and test validity. Evidence has shown PET and PET/CT are not as beneficial as the reference standard (sentinel node biopsy) for assessing regional lymph nodes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have diagnosed advanced melanoma (stage III or IV) and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes a TEC Assessment and a meta-analysis. Relevant outcomes are test accuracy and test validity. Evidence has shown PET and PET/CT can detect systemic metastases in individuals with advanced melanoma. Clinical guidelines include PET/CT for staging or restaging stage III or IV disease and for surveillance. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic after completing melanoma treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, the evidence includes retrospective and observational studies. Relevant outcomes are test accuracy and test validity. At the discretion of the physician, imaging surveillance can be considered every 3 to 12 months. Since recurrences usually occur within 3 years, screening asymptomatic individuals beyond 3 to 5 years is not recommended. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Multiple Myeloma
For individuals who have suspected or diagnosed multiple myeloma in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes 2 systematic reviews, one of which conducted a meta-analysis. Relevant outcomes are test accuracy and test validity. The meta-analysis reported high sensitivity in detecting extramedullary lesions in individuals with multiple myeloma. The other systematic review compared FDG-PET with whole-body x-ray and reported that FDG-PET was more sensitive in detecting myeloma bone lesions. Clinical guidelines include PET/CT on the list of imaging techniques that may be useful for initial workup, as well as follow-up and surveillance as indicated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic after completing multiple myeloma treatment who receive ^{18}F-FDGPET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Neuroendocrine Tumors
For individuals who have suspected or diagnosed neuroendocrine tumors and in need of staging or restaging information or who are asymptomatic after completing neuroendocrine tumor treatment who receive FDG-PET or FDG-PET/CT, the evidence includes 2 meta-analyses. The relevant outcome is test validity. The evidence did not compare PET or PET/CT with other modalities and, therefore, did not provide comparative effectiveness information. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have suspected or diagnosed neuroendocrine tumors and in need of staging or restaging information who receive ^{68}Ga-PET or ^{68}Ga-PET/CT, the evidence includes several systematic reviews with meta-analyses. The relevant outcome is test validity. The meta-analyses showed relatively high sensitivities and specificities compared with other imaging techniques in the diagnosis and staging of neuroendocrine tumors. Clinical guidelines support the use of the ^{68}Ga radiotracer in the diagnosis and staging of neuroendocrine tumors. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic after completing neuroendocrine tumor treatment who receive ^{68}Ga-PET or ^{68}Ga-PET/CT, there is no evidence. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ovarian Cancer
For individuals who have diagnosed ovarian cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes an AHRQ systematic review and several meta-analyses. Relevant outcomes are test accuracy and test validity. Pooled sensitivities and specificities have supported the use of PET and PET/CT for the detection of recurrent ovarian cancer. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected ovarian cancer or who are asymptomatic after completing ovarian cancer treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Pancreatic Cancer
For individuals who have suspected or diagnosed pancreatic cancer and with inconclusive results from other imaging techniques who receive adjunctive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT for staging or restaging, the evidence includes a TEC Assessment and a systematic review. Relevant outcomes are test accuracy and test validity. The evidence has shown that PET and PET/CT do not have a high enough negative predictive value to surpass current standard decision thresholds. Therefore, PET or PET/CT should only be considered if results from standard staging methods are inconclusive. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected or diagnosed pancreatic cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes an AHRQ systematic review, a TEC Assessment, and a meta-analysis published after the review

and assessment. Relevant outcomes are test accuracy and test validity. The evidence has shown that PET and PET/CT do not have a high enough negative predictive value to surpass current standard decision thresholds. Therefore, PET or PET/CT should only be considered if results from standard staging methods are inconclusive. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic after completing pancreatic cancer treatment who receive ^{18}F-FDGPET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Penile Cancer
For individuals who have suspected or diagnosed penile cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes a systematic review. Relevant outcome is test validity. The evidence have shown that PET had a low sensitivity, and no comparisons were made with other modalities. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have suspected or diagnosed node positive penile cancer and in need of staging or restaging information who receive FDG-PET or FDG-PET/CT, the evidence includes a systematic review and a retrospective comparative study. Relevant outcome is test validity. In individuals with suspected inguinal lymph node positive disease, PET/CT may offer increased sensitivity compared to CT alone for staging. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing penile cancer treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Prostate Cancer
For individuals who have suspected or diagnosed prostate cancer and in need of staging or restaging information who receive ^{11}C-choline PET or ^{11}C-choline PET/CT, evidence includes several meta-analyses. Relevant outcomes are test accuracy and test validity. Meta-analyses have reported that use of 11C-choline and 18F-fluciclovine radiotracers result in similar sensitivities and specificities. Prospective studies in men with biochemical recurrence after primary treatment have reported that a majority of management decisions were changed based on 18F-fluciclovine PET/CT results among men with suspected recurrence. One of those studies evaluated the impact on clinical outcomes and reported an increase in 3-year event-free survival rates. Further study is needed to compare PET and PET/CT with other imaging techniques, such as MRI and radionuclide bone scan. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing prostate cancer treatment who receive ^{11}C-choline PET or ^{11}C-choline PET/CT, there is no evidence. Relevant outcomes is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have suspected prostate cancer who receive ^{68}Ga-prostate-specific membrane antigen (PSMA) PET, ^{68}Ga-PSMA PET/CT, piflufolastat-F^{18} PET, and piflufolastat-

F18 PET/CT, the evidence includes a systematic review. Relevant outcome is test validity. The systematic review found similar diagnostic accuracy for PSMA PET and MRI for detection of clinically significant prostate cancer, but evidence was too limited to draw conclusions as only 3 studies of 228 individuals were included in the analysis. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have diagnosed prostate cancer and in need of staging or restaging information who receive 68Ga-prostate-specific membrane antigen (PSMA) PET, 68Ga-PSMAPET/CT, piflufolastat-F18 PET, and piflufolastat-F18 PET/CT, the evidence includes systematic reviews and prospective, multicenter trials. Relevant outcome is test validity. Systematic reviews have found PSMA PET to have similar diagnostic accuracy across prostate cancer risk groups in newly diagnosed individuals, and to be similar to MRI for staging intermediate/high-risk prostate cancer. Systematic reviews of studies conducted in individuals with biochemical recurrence found high proportions with positive PSMA PET imaging, often leading to change in management. Individual prospective trials have generally found that PSMA PET provides a high specificity for detecting pelvic lymph node or distant metastases in newly diagnosed individuals with high-risk disease and a clinically relevant PPV in individuals with biochemical recurrence. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic after completing prostate cancer treatment who receive 68Ga-PSMA PET, 68Ga-PSMA PET/CT, piflufolastat-F18 PET, and piflufolastat-F18PET/CT, there is no evidence on clinical outcomes. Relevant outcome that has been studied is test validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Renal Cell Carcinoma

For individuals who are diagnosed renal cell carcinoma and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes a systematic review and meta-analysis. Relevant outcome is test validity. The review concluded that PET has the potential to detect metastatic or recurrent lesions in individuals with renal cell cancer but that additional prospective studies are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Soft Tissue Sarcoma

For individuals who have diagnosed soft tissue sarcoma and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes an AHRQ systematic review. Another systematic review evaluated PET for assessing response to imatinib. Relevant outcomes are test accuracy and test validity. The review reported that PET had low diagnostic accuracy and there was a lack of studies comparing PET with alternative diagnostic modalities. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with diagnosed soft tissue sarcoma and in need of rapid reading of activity following imatinib treatment who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes a systematic review. Relevant outcomes are test accuracy and test validity. The review concluded that PET/CT can be used to monitor treatment response to imatinib, which can lead to individually adapted treatment strategies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have soft tissue sarcoma or who are asymptomatic after completing soft tissue sarcoma treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, the evidence includes a systematic review. Relevant outcomes are test accuracy and test validity. The review concluded that there was insufficient evidence on the use of PET for detection of loco-regional recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes.

Testicular Cancer
For individuals with diagnosed testicular cancer in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes an AHRQ systematic review and assessment. Relevant outcomes are test accuracy and test validity. Results have shown that PET or PET/CT can evaluate residual masses following chemotherapy for seminoma. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. There is no evidence supporting the use of PET or PET/CT in non-seminoma individuals. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected testicular cancer or who are asymptomatic after completing testicular cancer treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Thyroid Cancer
For individuals with diagnosed thyroid cancer and in need of staging or restaging information who receive ^{18}F-FDG-PET or ^{18}F-PET/CT, the evidence includes systematic reviews and meta-analyses. Relevant outcomes are test accuracy and test validity. Pooled analyses have shown that PET or PET/CT can effectively detect recurrent differentiated thyroid cancer. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have suspected thyroid cancer or who are asymptomatic after completing thyroid cancer treatment who receive ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT, there is no evidence. Relevant outcomes are test accuracy and test validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Cancer of Unknown Primary and Single-Site Metastatic Disease
For individuals with cancer of unknown primary and single-site metastatic disease who receive ^{18}F-FDG-PET or ^{18}FPET/CT, the evidence includes a TEC Assessment. Relevant outcomes are test accuracy and test validity. Studies reviewed in the assessment showed that PET identified previously undetected metastases confirmed by biopsy. Additionally, PET can contribute to the management of individuals with unknown primary. Clinical guidelines include PET/CT to inform management decisions that may offer clinical benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Government Regulations
National:

National Coverage Determination for Positron Emission Tomography Scans (220.6). Publication No. 100-3. Effective on or after 04/10/2023 - **Retired.**

Indications and Limitations of Coverage

The following indications may be covered for PET under certain circumstances. Details of Medicare PET coverage are discussed later in this section. Unless otherwise indicated, the clinical conditions below are covered when PET utilizes FDG as a tracer.

APPENDIX

Appendix Table 1: Effect of Coverage Changes on Oncologic Uses of FDG-PET[89]

	Final Framework	
Solid Tumor Type	**Initial Treatment Strategy[a]**	**Subsequent Treatment Strategy[b]**
Colorectal	Cover	Cover
Esophagus	Cover	Cover
Head and neck (not thyroid or CNS)	Cover	Cover
Lymphoma	Cover	Cover
Non-small-cell lung	Cover	Cover
Ovary	Cover	Cover
Brain	Cover	CED
Cervix	Cover[c]	Cover
Small cell lung	Cover	CED
Soft tissue sarcoma	Cover	CED
Pancreas	Cover	CED
Testes	Cover	CED
Breast (female and male)	Cover[d]	Cover
Melanoma	Cover[e]	Cover
Prostate	NC	CED
Thyroid	Cover	Cover[f] or CED
All other solid tumors	Cover	CED
Myeloma	Cover	Cover
All other cancers not listed herein	CED	CED

Note: This manual section lists all Medicare-covered uses of PET scans. A particular use of PET scans is not covered unless this manual specifically provides that such use is covered. Although this section lists some non-covered uses of PET scans, it does not constitute an exhaustive list of all non-covered uses.

Clinical Condition	Effective Date	Coverage
Solitary Pulmonary Nodules (SPNs)	January 1, 1998	Characterization
Lung Cancer (Non Small Cell)	January 1, 1998	Initial staging
Lung Cancer (Non Small Cell)	July 1, 2001	Diagnosis, staging and restaging
Esophageal Cancer	July 1, 2001	Diagnosis, staging and restaging
Colorectal Cancer	July 1, 1999	Determining location of tumors if rising CEA level suggests recurrence
Colorectal Cancer	July 1, 2001	Diagnosis, staging and restaging
Lymphoma	July 1, 1999	Staging and restaging only when used as an alternative to Gallium scan
Lymphoma	July 1, 2001	Diagnosis, staging and restaging
Melanoma	July 1, 1999	Evaluating recurrence prior to surgery as an alternative to a Gallium scan
Melanoma	July 1, 2001	Diagnosis, staging and restaging; Non-covered for evaluating regional nodes
Breast Cancer	October 1, 2002	As an adjunct to standard imaging modalities for staging patients with distant metastasis or restaging patients with locoregional recurrence or metastasis; as an adjunct to standard imaging modalities for monitoring tumor response to treatment for women with locally advanced and metastatic breast cancer when a change in therapy is anticipated.
Head and Neck Cancers (excluding CNS and thyroid)	July 1, 2001	Diagnosis, staging and restaging
Thyroid Cancer	October 1, 2003	Restaging of recurrent or residual thyroid cancers of follicular cell origin that have been previously treated by thyroidectomy and radioiodine ablation and have a serum thyroglobulin >10ng/ml and negative I-131 whole body scan performed
Myocardial Viability	July 1, 2001 to September 30, 2002	Covered only following inconclusive SPECT
Myocardial Viability	October 1, 2001	Primary or initial diagnosis, or following an inconclusive SPECT prior to revascularization. SPECT may not be used following an inconclusive PET scan
Refractory Seizures	July 1, 2001	Covered for pre-surgical evaluation only
Perfusion of the heart using Rubidium 82* tracer	March 14, 1995	Covered for noninvasive imaging of the perfusion of the heart
Perfusion of the heart using ammonia N-13* tracer	October 1, 2003	Covered for noninvasive imaging of the perfusion of the heart

*Not FDG-PET

For complete listing, see https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=211&ncdver=2&bc=AAAAQAAAAEAAAA%3d%3d&.

Local:

There is no WPS LCD on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Positron Emission Tomography (PET Scans) for Cardiac Applications
- Positron Emission Tomography (PET Scans) for Miscellaneous Applications (Non-Cardiac, Non-Oncologic)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/12	12/13/11	12/21/11	Joint policy established. Information was pulled from previous consolidated policy "PET Scans." Added additional covered indications for PET scanning: certain gastric cancers, small cell lung cancer, anal cancer and neuroendocrine cancers
7/1/12	4/10/12	5/18/12	Added additional recommendations to policy based on input from American Imaging Management (AIM)
7/1/14	4/8/14	4/15/14	Routine update. Updated information from BCBSA and AIM. Updated Medicare information.
9/1/14	6/20/14	6/23/14	Updated Medicare section to reflect new Medicare coverage determination
11/1/14	8/21/14	8/25/14	Added codes for PET-CT fusion services 78814-6 and 78899
1/1/16	10/13/15	10/27/15	Routine update. No change in policy status.
1/1/17	10/11/16	10/11/16	Updated rationale and references. No change in policy status.
7/1/18	4/17/18	4/17/18	Changes to Inclusion/Exclusion sections; added Endometrial Ca and Renal Cell carcinoma; changes for Prostate Ca and Testicular Ca; eliminated "other Oncologic Applications"; added references 37, 41, 48-50, 59-63, 67, 69-70, 73, 76-80, 85, 94-98, 103, 109-110, 112, 115, 119-120 and 126.
7/1/19	4/16/19		Added bladder cancer, added language to the lung cancer and melanoma sections. Reformatted rationale section, added references 4, 25, 39, 49, 55, 72, 79, 98, 115, 121, 132, 134, 138, 140 and 149.
7/1/20	4/14/20		Added the following covered indications: hepatobiliary Cancer with indications according to AIM, Merkel Cell cancer, as clinically indicated, to

			Pleural, added Thymus, Heart and Mediastinum to pleural cancer and Added Vaginal/Vulvar cancers with AIM criteria. Updated references.
7/1/21	4/20/21		– Routine maintenance – References 158-162 added – References on NCCN updated – Policy statements unchanged. – These radiopharmaceutical codes A9591, A9592; and C9067 were determined to be payable in the system but will not be added to this policy. Rationale: many more radiopharmaceutical codes may be added and it will be too difficult to maintain on policy.
3/1/22	12/14/21		Added the following codes under established based on NCCN guideline: A9593 Gallium Ga-68 PSMA-11, diagnostic, (UCSF), 1 mCi eff 7/1/21 A9594 Gallium Ga-68 PSMA-11, diagnostic, (UCLA), 1 mCi eff 7/1/21 A9595 Piflufolastat f-18, diagnostic, 1 millicurie eff 1/1/22 Added the following language under Inclusions under Prostate Cancer: PET scanning with Gallium Ga-68 prostate-specific membrane antigen (PSMA)-11 and Piflufolastat fluorine-18 for the following indications: as an alternative to standard imaging of bone and soft tissue for initial staging, for the detection of biochemically (elevated PSA) recurrent disease, and as workup for progression with bone scan plus CT or MRI for the evaluation of bone, pelvis, and abdomen.
3/1/23	12/20/22		• Routine maintenance – BCBSA updated their policy on 9/2022. • Added new code A9800 EFD 10/1/2022 as EST. • The word patients changed to individuals. • The following oncologic conditions were updated with current AIM criteria eff

			11/2022 (see internal section on the back under Rationale for divergence to see what criteria was incorporated from AIM): o Anal Cancer o Bladder Cancer o Bone Cancer/Sarcoma o Brain Cancer o Colorectal Cancer o Head and Neck Cancer o Penile Cancer o Soft Tissue Sarcoma o Testicular Cancer o Vaginal/Vulvar Cancers • References updated. (ky)
3/1/24	1/5/24		• Routine maintenance • Vendor: Carelon Oncologic Imaging updated: draft 04-14-2024. • NCCN Updated • Removed coverage of renal cell carcinoma - under the Inclusions section. Added under Exclusions: Pet scan is considered investigational in all aspects of managing renal cancer. NCCN, Carelon, and BCBSA considers PET scanning investigational for renal cell carcinoma. • Removed staging of penile cancer when pelvic lymph nodes are enlarged on CT or MRI and needle biopsy is not technically feasible under vaginal/vulvar cancers. • The below following oncologic conditions were updated last year with AIM guidelines and changes were noted from Carelon's draft criteria effective 4/14/2024. o Anal Cancer o Bladder Cancer o Bone Cancer/Sarcoma (added under management: Standard imaging cannot be

			performed or is nondiagnostic for recurrent or progressive disease) o Brain Cancer o Colorectal Cancer o Head and Neck Cancer (updated to Treatment response evaluation) o Penile Cancer o Soft Tissue Sarcoma (added under management: Standard imaging cannot be performed or is nondiagnostic for recurrent or progressive disease) o Testicular Cancer o Vaginal/Vulvar Cancers • References updated (ky)

Next Review Date: 4th Qtr. 2024

Previous Joint BCBSM/BCN Consolidated Medical Policy History
(Positron Emission Tomography)

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/13/02	11/13/02	11/13/02	Joint policy established
3/1/07	12/28/06	9/18/09	Routine maintenance; new diagnoses added
11/1/08	8/19/08	10/30/08	Maintenance, combined PET for brain-non-oncologic and initial diagnosis of breast cancer with this policy; added PET for myocardial indications
5/1/09	2/10/09	2/10/09	Maintenance, initial diagnosis of breast cancer added as investigational to PET scan policy
9/1/09	6/16/09	6/16/09	Redefined criteria for PET myocardial perfusion
7/1/11	4/19/11	5/3/11	Additional references added. Clarified indications for PET for oncologic conditions.

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: 10/12/98	Revised: 5/8/01
BCBSM: 10/30/00	Revised: 12/4/00

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: POSITRON EMISSION TOMOGRAPHY (PET) FOR ONCOLOGIC CONDITIONS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.