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NCCN Task Force Report: Clinical Utility of PET in a Variety of Tumor Types

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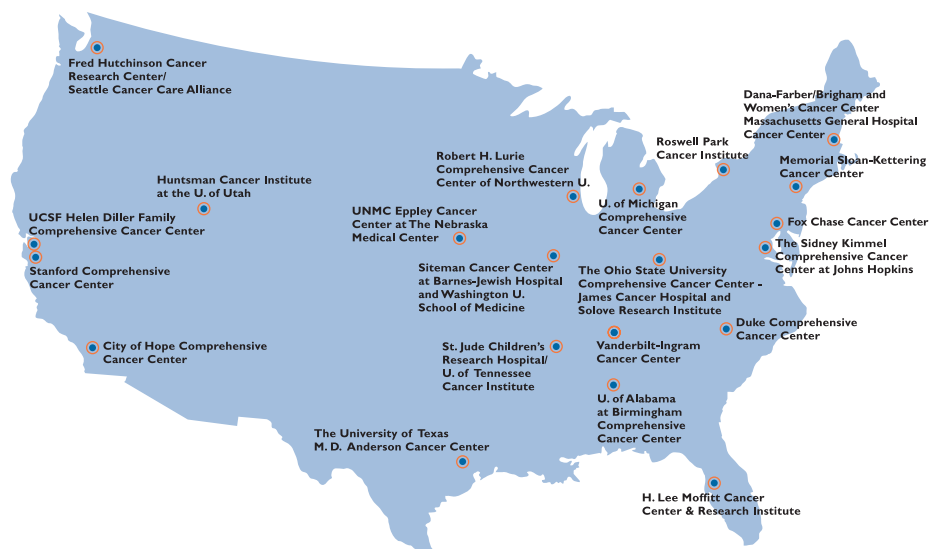
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Target Audience

This educational program is designed to meet the needs of oncologists, advanced practice nurses, and other clinical professionals who treat and manage patients with cancer.

Educational Objectives

After completion of this CME activity, participants should be able to:

- Describe the various context-specific applications of PET scanning in oncology.
- Identify important general and technical precautions to be observed when applying the technology.
- Make disease-specific recommendations on the use of PET scanning for initial or subsequent treatment evaluations in patients with different types of cancer.
- Summarize the strengths and limitations of data collected and analyzed by the National Oncologic PET Registry.

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Participants are encouraged to consult the package inserts for updated information and changes regarding indications, dosages, and contraindications. This recommendation is particularly important with new or infrequently used products.

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Participants will read all portions of this monograph, including all tables, figures, and references. A post-test and an evaluation form follow this activity, both of which require completion. To receive your continuing education certificate, you will need a score of at least 70% on the post-test. The post-test and evaluation form must be completed and returned by June 26, 2010. It should take approximately 1.0 hour to complete this activity as designed.

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NCCN Task Force: Clinical Utility of PET in a Variety of Tumor Types

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Key Words

PET, PET/CT, genitourinary cancers, gynecological cancers, pancreatic cancer, liver cancer, biliary tract cancer, sarcoma, thyroid cancer, brain cancer, small cell lung cancer, myeloma, gastric cancer, esophageal cancer

Abstract

Use of PET is widespread and increasing in the United States, mainly for oncologic applications. In November 2006, the National Comprehensive Cancer Network (NCCN) gathered a panel of experts to review the literature and develop clinical recommendations for using PET scans in lymphoma and non-small cell lung, breast, and colorectal cancers. However, because its use is not restricted to these diseases, and evidence is accumulating for its application in other types of cancers, NCCN convened a second meeting in December 2008 to expand on the initial report. A multidisciplinary panel met to discuss the current data on PET application for various tumor types, including genitourinary, gynecologic, pancreatic, hepatobiliary, thyroid, brain, small cell lung, gastric, and esophageal cancers, and sarcoma and myeloma. This report summarizes the proceedings of this meeting, including discussions of the background of PET, the role of PET in oncology, principles of PET use, emerging applications, and possible future developments. (*JNCCN* 2009;7[Suppl 2]:1–23)

Use of PET is widespread and increasing in the United States, mainly for oncologic applications, and especially in lymphoma and non-small cell lung (NSCLC), breast, and colorectal cancers. In November 2006, the NCCN gathered a panel of experts to review the literature and develop clinical recommendations for using PET scans in these malignancies.¹ However, because PET use is not restricted to these diseases and evidence is accumulating for its application in other types of cancers, NCCN convened a second meeting in December 2008 to expand on the initial report. A panel of radiologists, surgeons, radiation oncologists, nuclear medicine

physicians, medical oncologists, and general internists discussed the current data on PET use in various tumor types, including genitourinary, gynecologic, pancreatic, hepatobiliary, thyroid, brain, small cell lung, gastric, and esophageal cancers, sarcoma, and myeloma. This supplement summarizes the proceedings of this meeting.

In this report, the term *PET* refers to either PET or PET/CT, unless otherwise specified. In addition, the radiopharmaceutical used for PET is fluorine-18–labeled fluoro-deoxyglucose (¹⁸F-FDG), unless otherwise specified.

What is PET and How Does it Work?

Imaging can be broadly subdivided into anatomic and molecular methods. CT and MRI are anatomic imaging methods, whereas PET and some forms of MRI are considered molecular imaging methods. PET/CT, which is the fusion or “coregistration” of PET and CT images taken sequentially in the same scanning session, provides the advantage of combined anatomic and molecular images.

PET imaging is based on a unique physical process involving the interaction between an electron and a positron arising from the decay of a positron-emitting radioisotope. This process, known as *annihilation*, produces two 511-KeV photons emitted at 180° that can be simultaneously detected (*coincidence detection*) by a PET scanner consisting of multiple stationary detectors encircling the patient. PET images are reconstructed from large numbers of detected coincident events and represent the radiotracer distribution in the body.

¹⁸F-FDG is a glucose analogue and the most common tracer used clinically for PET. Because F-18 has a half-life of approximately 110 minutes, FDG can be transported easily to sites remote from its production.

Transport of glucose and FDG from the bloodstream into the cell is mediated by facilitative glucose transporters (especially GLUT-1). FDG is phosphorylated into FDG-6-phosphate (FDG-6P) by hexokinase, paralleling the conversion of glucose into glucose-6-phosphate in the glycolytic pathway. However, the substitution of fluorine for the 2-hydroxyl group of glucose blocks further metabolism of FDG, leaving FDG-6P trapped in the cell. The level of FDG uptake reflects the rate of FDG-6P trapping (Figure 1). Like most other imaging techniques, PET is minimally invasive.

Standardized Uptake Value

A semiquantitative measure, the standardized uptake value (SUV), is most commonly used to assess the uptake of the tracer to control for variations in body weight. Because of controversy regarding the best methodology for assigning measurement regions in tumor images, the maximum SUV (SUV_{max}) is generally a better parameter than the average SUV. The SUV is calculated using the following formula:

$$\frac{\text{Activity per unit volume}}{\text{Injected activity/body weight}}$$

PET and PET/CT

An estimated 1800 PET and PET/CT scanners are currently available in the United States, with approximately 80% of these PET/CT. The original impetus for combining PET/CT scans was to improve attenuation correction and throughput associated

with the CT scan. However, PET/CT scans provide more specific anatomic correlation than PET alone, and this technology has been widely adopted. Although studies directly comparing PET/CT with PET are still limited and much of the older literature centers on PET, clinicians generally feel comfortable in extrapolating PET findings to PET/CT. A rapid conversion to PET/CT has clearly occurred, and this technique has become the new standard. In specific clinical situations, PET/CT has been reported to be an improvement over PET alone.²⁻⁸ For example, a study of 260 patients with cancer showed that the accuracy of PET/CT in tumor staging (84%) was superior to side-by-side PET + CT, CT alone, or PET alone (76%, 63%, and 64%, respectively).⁹

Notably, the CT component of a PET/CT is often performed without contrast material administration and using lower-dose technique than conventional diagnostic CT. Hence, if a diagnostic CT is indicated, patients often must undergo a separate scan. For example, patients who are potential candidates for liver resection will typically undergo an initial diagnostic CT to evaluate the vascular anatomy of the liver, and then be referred for PET/CT to evaluate for extrahepatic metastases. In most current PET/CT scanners, the CT component is comparable to that in stand-alone CT devices and capable of providing high-quality diagnostic CT images. Therefore, in some institutions, when patients require a diagnostic CT concurrently with PET/CT, it can be performed as the CT component of the PET/CT examination or immediately after the PET/CT in the same scanner but using optimized diagnostic CT scan technique and contrast material.

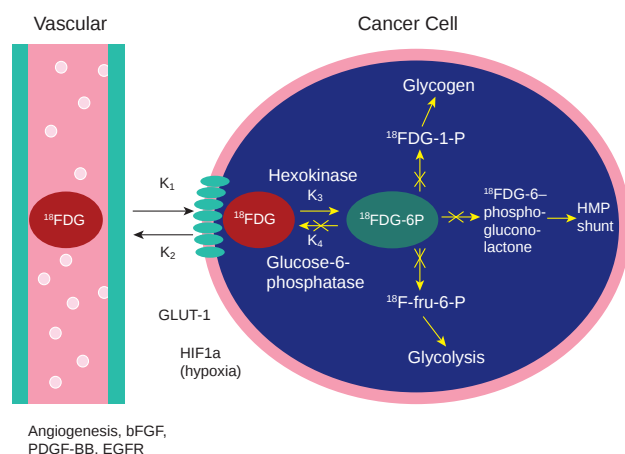


Figure 1 FDG uptake in a cancer cell.

Source: Podoloff DA, Advani RH, Allred C, et al. NCCN Task Force Report: Positron Emission Tomography (PET)/Computed Tomography (CT) Scanning in Cancer. *J Natl Compr Canc Netw* 2007;5(Suppl 1):S1-S22.

Role of PET in Oncology

The oncologic applications of PET scanning are based on increased FDG uptake by most malignant tumors. The Warburg effect, which is when cancer cells have abnormally accelerated rates of glycolysis in the presence of oxygen, was first observed in the 1930s.¹⁰ Glucose metabolism is the culmination of many different molecular pathways, and interrupting any of these components can result in glycolysis interruption and a change in the FDG-PET scan.¹¹⁻¹³ Therefore, FDG can be viewed as a downstream biomarker. Glycolysis can be stimulated by several oncogenic biologic factors associated with tumor

progression or proliferation, such as the multifunctional Akt signaling pathway.¹⁴ Additionally, elevated expression of GLUT proteins has been described in many cancers, which can further enhance FDG uptake.¹⁵ However, various benign pathologies, such as trauma, infection, noninfectious inflammatory diseases, and some benign tumors, can cause false-positive PET findings.

Evidence shows that elevated FDG uptake is associated with poor prognosis in various cancers with widely varying biology and treatment.^{16–19} For instance, a retrospective review of 400 patients with iodine-refractory thyroid cancer indicates that those with positive PET scans have significantly worse survival than those with negative scans ($P < .001$).¹⁹

National Oncologic PET Registry and Research Issues

Coverage for clinical use of PET in oncology varies among third-party payers, but development of coverage policies has been dominated historically by the Centers for Medicare & Medicaid Services (CMS) for the Medicare program. Starting from January 2005, PET scans were covered by Medicare (Table 1) for diagnosis, staging, and restaging for esophageal, head and neck, NSCLC, and colorectal cancers, and lymphoma and melanoma (excluding regional lymph node evaluation). Reimbursement for PET also was approved for specific indications in breast, cervical, and thyroid cancers. Coverage for all other cancers and indications (except those explicitly non-covered) required participation in the Coverage with Evidence Development (CED) program. In response to this CMS policy, the Academy of Molecular Imaging in collaboration with the American College of Radiology Imaging Network developed a CED program known as the National Oncologic PET Registry (NOPR). Partly due to data gathered by the NOPR, in April 2009 CMS announced a new coverage framework for PET to combine diagnosis and staging into “initial treatment strategy,” and restaging and treatment monitoring into “subsequent treatment strategy” (Table 1).²⁰ This new national coverage determination expanded coverage to lift the CED requirement for initial treatment evaluation for nearly all tumors, while maintaining data collection for subsequent treatment evaluations for a range of solid tumors.

Open since May 2006, the NOPR is a nationwide prospective medical registry designed to sys-

tematically collect clinical and demographic data on the usefulness and impact of PET in previously noncovered cancer types and indications.²¹ The main goal of the NOPR is to evaluate the impact of PET on physicians’ plans for patient management. Providers are required to submit data from pre- and post-PET physician questionnaires to the NOPR as a condition of reimbursement for the PET study.

At the end of its first year of operation, the NOPR published results from nearly 23,000 scans performed in more than 21,000 patients at 1178 centers.²² Of these, 24% were for cancer diagnosis, 28% for initial staging, 24% for restaging after treatment, and 24% for evaluation of suspected recurrence. Studies performed for treatment monitoring during cancer therapy were excluded from this analysis. The investigators reported that PET resulted in a change in intended management (classified as treatment or nontreatment) in 36.5% of cases.

In a subsequent study, the NOPR investigators reported on the impact of PET in patients with pathologically proven cancer of known origin to evaluate whether important differences were present as a function of cancer type. This study included results from nearly 41,000 scans performed in more than 34,000 patients at 1368 centers.²³ Of these, 35% were for initial staging, 36% for restaging after treatment, and 29% for evaluation of recurrence. The investigators reported that PET resulted in a change in intended management in 38.0% of cases overall; results were provided for 18 specific cancer types, and ranged from 31.4% for non-melanoma skin cancer to 48.7% for myeloma (Table 2). Most of these changes were from nontreatment to treatment (30%) rather than vice versa (8%), perhaps because of PET’s capacity to detect unsuspected lesions. In many cases, additional imaging such as CT or MRI was indicated as the initial management plan, and this may have caused overestimation of the impact of PET. To account for this, an imaging-adjusted impact was calculated by excluding these cases from the numerator but leaving them in the denominator (i.e., assuming no benefit from PET in these cases). This adjusted impact ranged from 9.6% for non-melanoma skin cancers to 16.2% for ovarian cancer (overall, 14.7%). The true impact is likely between the unadjusted and adjusted rates.

Notably, although the greatest number of scans was performed for prostate cancer, this is attributable

Table 1 Medicare Coverage of PET in Cancer

Cancer Type	Previous Framework (as of January 2005)				New Framework (as of April 2009)	
	Diagnosis	Initial Staging	Restaging (and Suspected Recurrence)	Treatment Monitoring	Initial Treatment Strategy Evaluation	Subsequent Treatment Strategy Evaluation
Breast	NC	Covered*	Covered	Covered	Covered [†]	Covered
Cervix	CED	Covered [‡] /CED	CED	CED	Covered [‡] /CED	Covered
Colorectal	Covered	Covered	Covered	CED	Covered	Covered
Esophagus	Covered	Covered	Covered	CED	Covered	Covered
Head and neck	Covered	Covered	Covered	CED	Covered	Covered
Lymphoma	Covered	Covered	Covered	CED	Covered	Covered
Melanoma	Covered	Covered [§]	Covered	CED	Covered [§]	Covered
Myeloma	CED	CED	CED	CED	Covered	Covered
NSCLC	Covered	Covered	Covered	CED	Covered	Covered
Ovary	CED	CED	CED	CED	Covered	Covered
Prostate	CED	CED	CED	CED	NC	CED
Thyroid	Covered	Covered	Covered [¶]	CED	Covered	Covered [¶] /CED
All other solid tumors	CED	CED	CED	CED	Covered	CED

Abbreviations: CED, coverage with evidence development; NC, non-covered; NSCLC, non-small cell lung cancer.

*Non-covered for initial staging of axillary lymph nodes.

[†]Non-covered for diagnosis and/or initial staging of axillary lymph nodes. Covered for staging of metastatic disease.

[‡]Covered for initial staging with negative conventional imaging for extrapelvic metastasis. All other uses are CED.

[§]Non-covered for initial staging of regional lymph nodes. Other uses for initial staging are covered.

[¶]Covered for restaging of previously treated cancers of follicular cell origin with negative I-131 whole-body scintigraphy and rising thyroglobulin (> 10 ng/mL).

to the high incidence (and prevalence) of the disease rather than a high frequency of PET use. Adjusting for disease rate, the use per incident cancer was only 3% for prostate cancer compared with 38% for ovarian. It is thought-provoking that the NOPR finds little variation in impact across cancer types despite apparent variation in clinical value. One possible explanation is that physicians are selective and only order PET when it is most likely to be useful. For example, prostate cancer is known to generally have low FDG avidity until it becomes castrate-refractory; thus, physicians may be using PET only in selected cases to help resolve clinical dilemmas. However, this lack of variation in impact may also reflect physician overconfidence and misconception about the usefulness of PET.

The NOPR has an impressive population size (> 130,000 cases as of March 2009, with approximately 88% consenting for research use of data) collected from a large fraction (approximately 80%) of PET facilities nationwide. Data were analyzed and reported in a timely manner, which heightened

their relevance amidst rapid advances in imaging technologies. Such rapidity and breadth is difficult to achieve in a prospective randomized trial. Despite these strengths, however, several confounding factors and limitations are present.²⁴ In contrast to randomized studies, a registry analysis is observational by nature, with inevitable potential bias. For example, physicians who participated may have the preconception that PET will change their clinical decisions. Furthermore, no control group was present to compare the impact of PET with that of current standard tests. Because data were derived from self-completed questionnaires, accuracy will vary, and whether the intended change will result in an actual change in management remains unknown.

A recent series of Australian studies^{25–28} undertook a similar questionnaire format but with additional follow-up of 12 months on 4 cancers currently reimbursed by Medicare (head and neck, lymphoma, colorectal, esophageal). They reported that treatment plans were implemented in more than 90% of cases. The NOPR investigators seek to adopt

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this approach and relate their findings to CMS billing records to assess the impact of PET on actual management change.

More importantly, even when management is changed, whether this change will benefit the patient remains to be elucidated. As Mol et al.²⁹ pointed out, the practical value of a diagnostic test such as PET ultimately relies on how it affects health measures, including survival, quality of life, toxicity, and symptom relief, through its impact on treatment decisions. Most research has focused on assessing the test characteristics of PET (i.e., sensitivity, specificity, and accuracy). However, the clinical context can undermine the usefulness of even a highly accurate scan. For example, therapeutic options may be limited for some advanced cancers, and sensitive or early detection of residual disease will not result in improved outcome; it may even cause unnecessary or prolonged anxiety in some patients. Although the NOPR looked beyond test characteristics, an impact on intended or actual change in management may not always translate to clinical advantage, particularly when consensus is lacking on the optimal management of the disease. The difficulty in assessing the indirect impact of any diagnostic test on outcome is a general problem in oncology given the complex nature of cancer and the individualized factors that can contribute to treatment response.

Prospective trials randomizing patients to undergo or skip PET are still the most direct ways to justify the clinical role of this technique. Admittedly, rigorous research data usually are not available even for existing conventional tests. Nonetheless, an increasing number of randomized studies have recently shown the clinical impact of PET imaging.

One established area is the use of PET in selecting patients with suspected NSCLC for curative surgery that was reportedly unsuccessful in up to 50% cases. Van Tinteren et al.³⁰ randomized 188 patients to conventional workup with or without PET before surgery. The PET arm showed a much lower rate of futile thoracotomy (21%) compared with the control (41%). Another recently completed randomized study on 337 patients echoed these findings.³¹ In another trial on NSCLC that randomly assigned 465 patients to either traditional workup or up-front PET,³² initial PET resulted in fewer invasive procedures without compromising staging accuracy or raising costs.

Table 2 Impact of PET on Intended Management of the Top 10 Cancers in the National Oncologic PET Registry

Cancer	No. of Scans	% Change in Intended Treatment	% Imaging-Adjusted Impact
Prostate	5309	35.1	15.0
Ovary	4509	41.4	16.2
Bladder	3578	37.9	15.4
Pancreas	3314	39.0	14.8
Stomach	3025	36.9	14.5
Small cell lung	2983	41.2	13.1
Kidney	2877	35.8	16.0
Uterus	2869	36.5	15.1
Myeloma	1784	48.7	11.5
Connective tissue	1350	36.4	13.6

Adapted from Hillner BE, Siegel BA, Shields AF, et al. Relationship between cancer type and impact of PET and PET/CT on intended management: findings of the national oncologic PET registry. *J Nucl Med* 2008;49:1928–1935.

Ideally, more sufficiently powered trials will be conducted for other cancer types and to address questions other than those pertaining to the surgical setting. For example, a French group randomized 130 patients who had undergone curative therapy for colorectal cancer to either conventional or PET-based follow-up.³³ They reported that follow-up with PET allowed earlier detection of recurrence (12.1 vs. 15.4 months; $P = .01$) and improved cure after surgery compared with conventional follow-up (10 vs. 2 patients). However, randomized studies such as these may be difficult to undertake for an imaging technique because of potential ethical issues and physician preconceptions.

Alternatively, PET and treatment can be performed on all patients, and PET findings compared with the treatment outcome. This design has been incorporated within a Dutch multicenter randomized study on surgery with or without preoperative neoadjuvant chemoradiation in esophageal cancer.³⁴ In the neoadjuvant arm, PET and CT will be performed before and during chemoradiotherapy. All patients complete therapy and surgery regardless of results. Subsequent analysis will then seek to compare the capacity of PET and CT for predicting non-response to chemoradiation. Furthermore, survival

and costs associated with PET or CT will be compared with those for patients who had no imaging prediction. This trial design may be more helpful in validating PET use in oncology than one that's truly randomized.

Issues and Concerns in Clinical Usefulness

PET is a noninvasive and sensitive imaging method for detecting metabolic changes in cancer. However, it is also expensive and has limitations, such as false-positive results from tracer uptake in normal tissues and benign lesions. As with any other advanced technology, challenges and concerns inevitably arise with the ever-increasing use of PET in the clinical setting. In particular, protocols of PET imaging have not yet been standardized, and both the method of performing PET and interpretation of the findings vary among cancer centers and clinical sites. The panel agreed that health care professionals considering PET must be alert to several important issues applicable to all types of cancers (Table 3).

Optimal and appropriate use of PET requires meticulous attention to technique. Proper patient preparation is essential, because PET is a sensitive measure of real-time metabolism of the body.³⁵ Care should be taken to minimize tracer uptake in normal tissues while maintaining uptake in target tumor tis-

sues. Patients must fast for 4 to 6 hours (Figure 2, top panel) and avoid strenuous exercise for 24 hours to reduce uptake in skeletal muscle. They should also be adequately hydrated to facilitate clearance of excreted FDG from the urinary tract. Because various benign features (e.g., some benign tumors, inflammatory and infectious lesions) and normal tissues (e.g., brain, gastrointestinal, and genitourinary tracts) can also accumulate FDG, physicians must take these into account when analyzing imaging results.

Patient history is equally important. For example, scanning conditions and medications may need to be adjusted for patients with diabetes undergoing PET; both hyperglycemia and insulin effects can lead to reduced tumor FDG uptake. Physicians must note other concurrent medications, such as granulocyte colony-stimulating factor, hormonal therapy, and chemotherapy, that may also influence scan findings.

Physicians ordering a PET/CT must be aware that it does not replace a diagnostic CT scan (Figure 2, bottom panel). The CT component of a PET/CT adds anatomic accuracy to molecular imaging compared with PET alone, but the PET component of a PET/CT does not make it superior to a diagnostic CT. Compared with a diagnostic CT, very small lesions may be missed on PET/CT because of the omission of contrast material or lack of full inspiration of the CT component. For example, micronodular metastasis to the lungs, common in patients with thyroid cancer, may only be detectable with a breath-holding diagnostic CT with full inspiration. PET/CT and diagnostic CT serve different purposes and indications cannot be applied interchangeably.

Panelists expressed concerns about the potential overuse of PET. Physicians should avoid ordering scans routinely if results are not likely to influence management. For example, in patients with widespread metastasis, finding additional scattered sites of disease using whole-body PET usually will have no impact on treatment decisions; thus, PET should not be performed simply to refine the assessment of disease extent. However, PET may be appropriate in these cases for a different purpose, such as establishing a baseline for treatment monitoring before starting an expensive therapy.

The NOPR reported a surprisingly high rate of cancellation of planned biopsy (75%) after PET.²² Physicians also expressed that PET results allowed them to avoid additional procedures or tests in 77%

Table 3 Principles of PET Interpretation and Use in Oncology

- PET/CT has an additive anatomic component and is generally considered more informative than PET alone.
- PET/CT and diagnostic CT are tests that serve different purposes. Patients must undergo separate scans where indicated; however, these may be performed on the same PET/CT scanner with the diagnostic CT performed as the CT component of PET/CT or immediately after PET/CT.
- PET is best used as an adjunct in diagnosis and has not been shown to be a definitive test by itself. PET should not be performed if results are not anticipated to change management.
- PET must not be used in lieu of a biopsy to establish a diagnosis of cancer.
- Extrapolation of evidence from the advanced setting to early-stage disease should be avoided.
- No patient should be denied potentially curative therapy based on PET or any other imaging findings alone. Patients with stable disease should not undergo therapy based on PET findings alone.
- PET as a surveillance tool should only be used in clinical trials.

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of the cases. Although these observations may potentially reflect a positive impact in avoiding the risks and costs of biopsies and other procedures, they can also indicate overconfidence in PET findings among the general medical community, and that many physicians see PET as the final arbiter that completes patient evaluation and decides treatment. Likewise, the lack of variation in apparent impact on management decisions across various different tumors can be interpreted as either high selectivity on the physicians' part in applying PET scans or overestimation of the significance of PET.

However, although PET is an established technology past the experimental stage, its clinical role in many cancers is still evolving and its usefulness can vary widely among different types of cancer. Most evidence indicates that PET is best used as an adjunctive imaging technique to conventional tests. Biopsy remains the gold standard in confirming tumor presence and must not be conveniently avoided or replaced by PET. Decisions of treatment or nontreatment should always be based on the combination of test results and the patient's overall situation, rather than PET findings alone. Specifically, PET results should not be the sole reason for deciding against potentially curative therapy. Similarly, a single positive PET finding is not sufficient to initiate therapy if patients seem to have stable disease otherwise.

Physicians also should be aware that data supporting a definitive role for PET in disease surveillance are still lacking, and therefore exploratory use should be restricted to well-designed clinical trials. Care should also be taken to distinguish evidence supporting its use in late- versus early-stage disease. A prime example is breast cancer, for which PET is sensitive in detecting recurrent and metastatic disease but insufficient to replace surgical staging of the axilla in early-stage disease.³⁶ Physicians should therefore avoid inappropriate extrapolation of data that may result in overuse of PET.

Undeniably, PET is emerging as a very useful test that can improve decision-making in oncology. However, potential abuse or misuse can also arise with its increasingly widespread use. In this respect, large registries like the NOPR provide timely data that allow monitoring of general conception and practice patterns in the medical community. Physician education regarding the appropriate use of PET is critical to maximize the value of this technology.

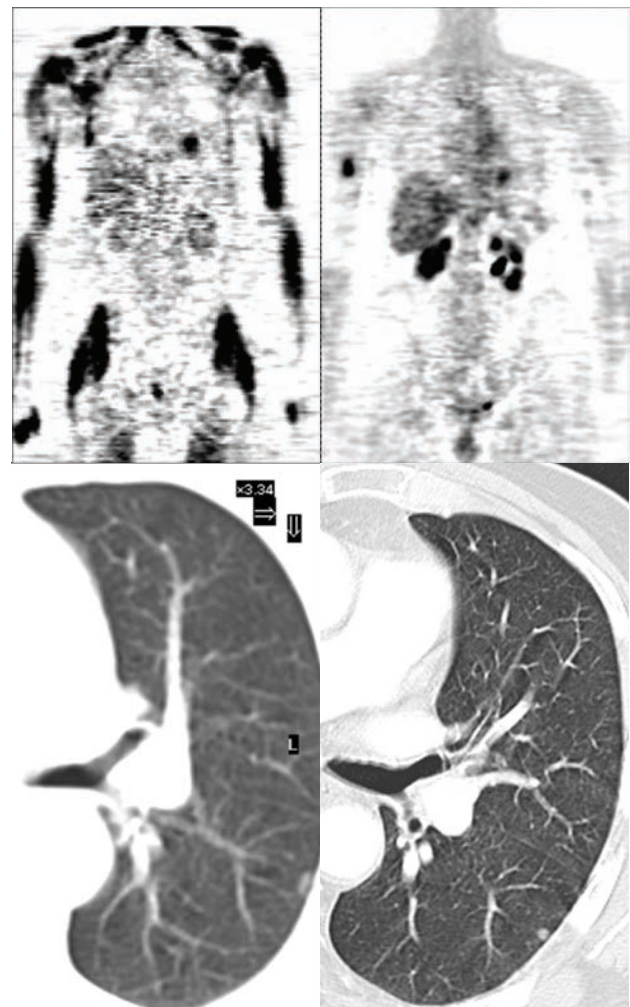


Figure 2 Potential misinterpretation and limitation of PET. (Top) PET scan on a patient is dramatically different after eating (left, note avidity of muscles) from that after proper fasting (right). (Bottom) The mid-inspiration CT component of PET/CT (left) provides less detail than a diagnostic CT with full inspiration (right). Contrast is used for both images.

Brain Cancer

Despite early exploration of PET imaging in brain cancers, the literature still reflects a paucity of definitive data on its clinical efficacy. Historically, PET has been used in grading and prognosis, with high FDG uptake generally correlating with higher grade and shorter survival.^{37–39} Most brain tumors can be effectively visualized with MRI, but PET may be useful in nonenhancing tumors. In a study of 28 patients with low-grade gliomas, increasing FDG avidity, as opposed to low avidity, indicated anaplastic transformation and predicted poor outcome (2-year survival, 33% vs. 100%).³⁸

The treatment paradigm has recently shifted toward concomitant use of radiation and temozolomide for glioblastoma.⁴⁰ Pseudo-progression and radiation injury can occur with concurrent radiation + temozolomide use, which can obscure MRI findings and hinder response assessment.⁴¹ FDG-PET has a relatively high sensitivity (80%–86%) for distinguishing radiation injury from high-grade tumor recurrence; the specificity ranges from 80% to 100% in 7 studies totaling 241 patients, although in 2 smaller studies of 19 and 20 patients, respectively, it was only in the 40% to 63% range.⁴² Correlation with MRI findings is critical for optimal interpretation of PET images.^{43–45} Causes of false-negative PET studies include recent radiation therapy, low histologic grade, and small tumor volume. False-positive PET findings may occur in inflammatory processes and subclinical seizure activity. Technical improvements have shown some success, such as delaying time to imaging,⁴⁶ MRI correlation, and the development of amino acid tracers (which currently are only for investigational use).⁴⁷

PET also has an emerging role in radiotherapy; it has been used to delineate tumor activity and target volume for radiation planning in gliomas.^{48,49} Latest research interest is turning toward PET verification of dose distribution in the growing field of proton beam therapy (Figure 3).^{50–52}

Conclusions

MRI is still the gold standard for diagnosing and staging brain cancers, but PET may be useful in identifying nonenhancing, low-grade gliomas undergoing malignant conversion. A negative PET scan is helpful in excluding recurrent anaplastic astrocytoma and glioblastoma multiforme. PET is useful for differentiating radiation effect from tumor recurrence, is a good predictor of survival in high-grade recurrent gliomas, and can guide biopsy to the site of maximum uptake. PET shows promise in aiding radiation planning and dose confirmation. With the rapid expansion of proton beam treatment centers, PET may become more commonly used as an *in vivo* dosimetric tool for radiation therapy.

Gastric/Esophageal Cancer

Although the incidence of gastric cancer is declining, that of esophageal adenocarcinoma is increasing, particularly for tumors of the distal esophagus and gastroesophageal junction. Results are mixed on di-

agnostic PET imaging in gastric cancer, with as much as half of primary tumors being FDG-negative.^{53–56} Nonetheless, in patients with FDG-avid tumors, PET may detect metastatic disease not identified by other imaging modalities. In contrast, 95% of primary esophageal tumors were FDG-avid.⁵⁷ PET is much more sensitive than CT and endoscopic ultrasonography in detecting stage IV disease (74% vs. 47%) with distant lymph node involvement. Meta-analyses attributed to PET a 67% pooled sensitivity, 97% specificity, and small added value after conventional staging in detecting distant metastasis.^{58,59} Based on its efficacy, PET is approved by Medicare for both initial and subsequent treatment strategy evaluation of esophageal cancer.

Recent research has generated strong interest in the ability of PET to assess response and predict outcome to neoadjuvant therapy.⁶⁰ In 2 studies involving 36 and 39 patients with esophageal cancer, response to preoperative chemoradiation as defined by PET was strongly correlated with prognosis.^{61,62} Response assessment seems most valuable for induction chemotherapy in patients eligible for potentially curative resection. Among patients with gastric cancer undergoing preoperative neoadjuvant chemotherapy, Ott et al.⁶³ showed a superior 90% 2-year survival in those experiencing PET-defined response (> 35% decline in SUV) compared with 25% in those experiencing no response. Response can be predicted with PET as early as 14 days into treatment. Because more than 60% of patients have unresponsive disease, they may be spared further unnecessary toxic therapy after early assessment with PET.

The same group reported similar findings in esophageal cancer, with PET unresponsiveness correlating to shorter time to progression and overall survival.⁶⁴ They further investigated 119 patients in the MUNICON trial to assess a PET response-guided therapeutic algorithm.⁶⁵ Patients for whom PET showed no response to platinum- and fluorouracil-based induction chemotherapy at day 14 were sent for immediate surgery, whereas those who did show response completed 3 months of therapy before resection. Again, a median follow-up of 2.3 years showed dramatic survival benefit for responders (hazard ratio, 2.13; $P < .015$). Notably, in patients experiencing no response, this trial showed that stopping chemotherapy early did not seem to reduce long-term survival compared with continuing treatment in the previous

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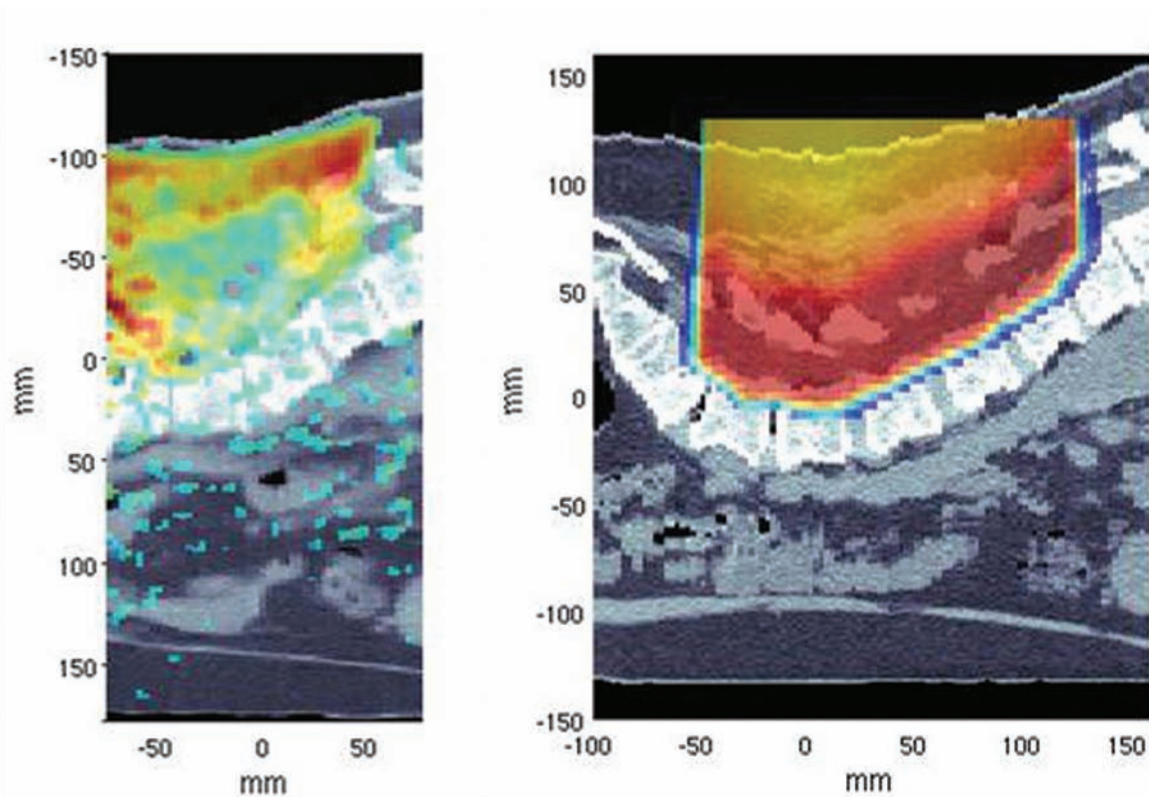


Figure 3 PET verification of radiation dose distribution in brain tumor. The PET/CT measurement (left) is comparable to the planned dose (right).

trial. Additionally, early PET-defined response corresponded with a high rate of histologic remission. An ongoing phase II study⁶⁶ is adopting a similar PET-based approach in predicting the efficacy of induction chemotherapy followed by chemoradiation before surgery on potentially resectable esophageal and gastro-esophageal junction cancers.

Conclusions

The role of PET in the primary imaging of gastric cancer remains to be established, but it is valuable in detecting advanced disease for gastric and esophageal cancer. Recent evidence shows that PET provides an exciting opportunity to accurately predict early which patients for whom induction therapy is likely to fail, thereby sparing them from futile, toxic treatment and directing them to potentially helpful salvage therapies.

Genitourinary Cancers

A major challenge for PET in genitourinary oncology is the physiologic urinary excretion of FDG,

which can significantly mask detection of localized prostate and bladder cancers. Urinary activity, however, can be minimized by good hydration, use of diuretics, and bladder catheterization. Another problem is the variable FDG uptake among genitourinary malignancies (e.g., low glycolysis of prostate tumor cells). Other tracers are being investigated to overcome these problems.

Diagnosis and Initial Staging

Because studies have not shown FDG to be reliable for diagnosing or initial staging of prostate cancers, Medicare has recently determined that PET is not covered for these purposes. Reports show significant overlap between benign prostatic hyperplasia, malignant tumor, local recurrence, and postoperative scarring.^{67,68} Sensitivity may be as low as 4% because of urinary excretion of FDG.⁶⁹ Similarly, urinary excretion limits diagnostic use of FDG in bladder and kidney cancers, unless diuretics and/or bladder catheterization are used to minimize physiologic activity. Although FDG-PET exhibited equally high specificity (100%) as abdominal CT in kidney cancer, it had much lower sensitivity than CT (60% vs. 92%).⁷⁰

Other potentially more helpful tracers are being studied. For example, a small study of 18 patients showed ^{11}C -choline uptake in all primary bladder tumors tested.⁷¹

Restaging and Metastasis Detection

FDG-PET has limited usefulness in detecting prostate cancer metastasis, except in castration-resistant disease, in which several panelists report from their experience at large cancer institutions that FDG-PET has high sensitivity for detecting distant metastases.⁷² Furthermore, in this subset of patients, FDG-PET has prognostic significance and may alter treatment intensity and duration. Although FDG-PET is possibly more useful in the distant metastatic setting,⁷³ with a low false-positive rate, a negative scan does not exclude metastatic disease. For example, a study of 24 patients showed that FDG-PET had higher specificity but lower sensitivity than bone scintigraphy.⁷⁴

Few studies are available on the usefulness of PET in restaging bladder cancer recurrence, but evidence suggests a role in detecting metastasis. In a study of 27 patients using histopathologic findings as reference, ^{11}C -choline was more accurate than CT in detecting lymph node metastasis.⁷⁵ In another study, FDG-PET was complementary to CT in finding positive lymph nodes in invasive bladder cancer.⁷⁶ Use of diuretics was reported to improve detection of locally recurrent disease.⁷⁷ However, the sensitivity of FDG-PET may decline in patients who have undergone chemotherapy.⁷⁸

Studies in kidney cancer have been focused on FDG. FDG-PET was used by Safaei et al.⁷⁹ to correctly restage 32 of 36 patients (89%) with advanced disease. FDG-PET was also more specific in visualizing distant metastasis than bone scintigraphy and chest CT in trials, including 18 to 66 patients, although sensitivity was variable (64%–100%).^{70,80,81}

Conclusions

Evidence supporting a routine role for FDG-PET in genitourinary cancers is lacking. However, FDG-PET may be indicated in castration-resistant metastatic prostate cancer, in which it has been reported to have high sensitivity for detecting distant metastasis. FDG-PET may also be considered in detecting metastasis in kidney cancer and muscle-invasive bladder cancer. Currently, FDG-PET should only be considered as an adjunct to, and not a replacement for, other con-

ventional imaging techniques (i.e., MRI/magnetic resonance spectroscopy, CT, and bone scintigraphy). Although ^{11}C -choline is generally considered more reliable than FDG in restaging localized disease in prostate and bladder cancers, it has limited broader application because of its short half-life and investigational status (see section on “Emerging Applications and Future Direction”). Because of its high specificity but low sensitivity, PET may be most useful in resolving diagnostic dilemmas in advanced disease.

Gynecologic Cancers

Research on PET usefulness in detecting gynecologic malignancies has not been extensive, with most data involving cervical cancer and the fewest involving uterine endometrial cancer. The role of PET in ovarian, cervical, and uterine cancers differs because of the varying nature and course of these diseases.

Diagnosis and Initial Staging

Based on findings that PET is superior in evaluating lymph nodes, in 2005 CMS approved coverage of PET for initial staging in patients with cervical cancer for whom conventional imaging methods (CT or MRI) showed no evidence of extrapelvic metastasis. In a larger study of 135 patients with locally advanced or recurrent cervical cancer, PET has greater sensitivity than MRI/CT for detecting pelvic (88% vs. 75%) and para-aortic (95% vs. 72%) lymph node involvement.⁸² Lin et al.⁸³ performed PET on 50 patients with negative abdominal CT scans and found that 12 had para-aortic lymph nodal metastasis, confirmed with histology. Additionally, PET has prognostic value in cervical cancer; patients with high pretreatment tumor SUV have worse disease-free survival rates.⁸⁴

Diagnostic use of PET in suspected ovarian cancer has been investigated in a prospective study by Risum et al.⁸⁵ In this study, PET scans were performed within 2 weeks before standard debulking surgery in 101 patients with a suspicious pelvic mass. The authors reported a high diagnostic sensitivity and specificity of 100% and 93%, respectively, although 7 PET-negative borderline ovarian cancers were categorized as benign. However, unlike cervical cancer, the usual late presentation of ovarian cancer generally limits the practical value of PET in initial evaluation. More than 80% of the cases are found at stage III or IV, with patients typically presenting

with extensive symptoms. In the remaining 15% to 20% of patients with clinical stage I or II disease, upstaging after surgical exploration primarily detects small volume involvement (< 1 cm) in para-aortic nodes, which is undetectable using current PET technology. Most patients require up-front debulking surgery, which minimizes the value of imaging for diagnostic and staging purposes.

Although uterine cancer is usually diagnosed at an early stage, it has the same tendency as ovarian cancer to spread as small nodal deposits for which PET has very low sensitivity. In a study of 30 patients, Suzuki et al.⁸⁶ found that preoperative FDG-PET detected none of 5 cases of lymph node involvement of 0.6 cm or less. PET was more sensitive than CT or MRI in visualizing non-nodal extrauterine lesions or the primary lesion^{86,87} but, similar to ovarian cancer, the problem is that up-front surgery is indicated for staging and treatment of uterine cancer. PET imaging does not currently preclude the need for surgical staging.

Recurrence

PET has significant value in diagnosing recurrent cervical cancer and restaging after chemoradiation.⁸⁸ In contrast to patients with ovarian or uterine cancers, those with cervical cancer experiencing a pelvic recurrence without extrapelvic disease have nearly a one third chance of long-term disease-free survival with pelvic exenteration. Because this is a highly invasive procedure, determining the presence of extrapelvic metastasis is important before making a clinical decision. In studies examining recurrence detection, the sensitivity and specificity of PET ranged from 76% to 100% and 57% to 100%, respectively.⁸⁹ Alteration in treatment plans based on PET results has been reported. Yen et al.⁹⁰ found that of the 55 patients whose recurrences were initially considered potentially curable, 36 (66%) experienced treatment modifications after PET, with 27 undergoing palliative therapy instead of aggressive surgical treatment, which would not be beneficial in patients with distant metastatic disease (Figure 4). In a more recent prospective study of 20 patients with recurrence, PET was 100% sensitive and 73% specific in detecting extrapelvic metastasis, which would obviate recommendations for pelvic exenteration.⁹¹

Several trials have shown PET's ability to detect recurrence in ovarian cancer. One larger study of 90 patients showed that FDG-PET was superior to con-

ventional imaging in verifying recurrence in patients, followed by CA-125.⁹² In combination, PET and CA-125 have 98% sensitivity. Similar results were found in a small trial of 22 patients with negative or indeterminate CT scans, in whom PET has very high overall sensitivity and specificity (95% and 100%, respectively) for assessment.⁹³ The use of PET seems to have a significant impact on clinical decision-making, resulting in changes in management strategies for 44% to 58% of patients.^{94,95} The question remains as to whether these changes are beneficial in the recurrence setting, given the lack of consensus on the best management. CMS recently approved coverage of PET for both initial and subsequent treatment strategy evaluation of ovarian cancer.

Data are scarce for uterine cancer. In one study of 90 women, Kitajima et al.⁵ found that PET had better sensitivity and specificity than CT for assessing recurrence of uterine cancer. A change of management based on PET findings was also reported for 42% of the patients. Another study reported that 70% of the 33 PET scans performed after recurrence/salvage therapy had a positive impact on management.⁸⁷

Conclusions

Among gynecologic malignancies, PET efficacy is best supported for initial staging of patients with cervical cancer who are to undergo chemoradiation. Approximately 7% are upstaged to stage IVb because PET detects unsuspected metastases in supraclavicular lymph nodes. PET also delineates involved pelvic and para-aortic nodes, which is essential for proper radiation therapy planning. PET is also useful in the recurrent setting, in which some patients may benefit by avoiding unnecessary invasive surgery.

The technology assessment performed for CMS by the University of Alberta Evidence-Based Practice Center showed substantial usefulness of PET in ovarian cancer.⁹⁶ In uterine cancer, the reported impact of PET on disease management is not as substantial. Although PET has been shown to have improved sensitivity and specificity compared with conventional imaging, it does not preclude the standard recommendation for initial surgery. PET may be helpful in confirming recurrence of ovarian cancer in patients with elevated CA-125 levels, when the information would change subsequent diagnostic evaluation and/or management. Additionally, current PET technology is inadequate in detecting small nodal metastasis common in these patients.

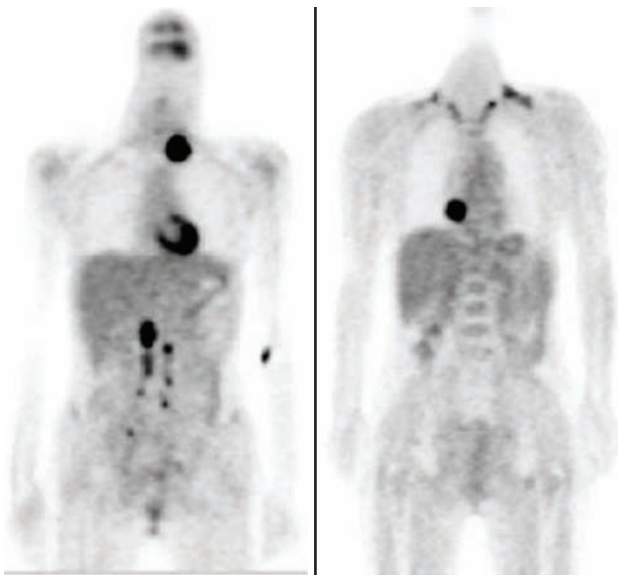


Figure 4 Efficacy of PET in recurrent cervical cancer. (Left) Three months after chemoradiation, a left neck mass was palpated in this patient. MRI and CT showed no definite abnormal findings, but PET suggested nodal metastases confirmed by histopathology. She received palliation treatment instead of salvage radiation. (Right) Six months after chemoradiation, elevated tumor marker level was noted in this patient. Again, MRI and CT were negative, whereas PET disclosed lung metastasis. She received pneumonectomy and was well for 1 year. Source: Yen TC, See LC, Chang TC, et al. Defining the priority of using 18F-FDG PET for recurrent cervical cancer. *J Nucl Med* 2004;45:1632–1639.

Myeloma

In multiple myeloma, imaging studies are critical to identify lytic bone lesions that may indicate active disease requiring treatment, but established techniques such as radiography (skeletal survey) and MRI have their limitations. Recently, increasing interest has been shown in exploring the diagnostic/staging value of PET compared with conventional imaging. PET was consistently found to be more sensitive than radiography in finding bone lesions. Additional lesions were reported in 23% to 57% of patients examined, frequently resulting in upstaging and change in management.^{97–100} In other studies involving 16 to 33 patients, MRI was able to detect much spinal disease not seen on PET, but the much larger field of view allowed PET to visualize lesions in other areas undetectable with MRI.^{100–102} Clearly, PET would be most useful when used in combination with other imaging tests, especially MRI.

A prognostic value has also been attributed to PET. Durie et al.¹⁰³ reported a consistent correlation

of PET negativity to indolent plasma cell disease. PET also showed extramedullary uptake in 23% of patients experiencing relapse, which is associated with a poor prognosis. However, whether PET adds independently to prognosis when powerful prognostic factors such as cytogenetic abnormalities are also considered remains unknown.

Conclusions

PET is an informative test that has a potential complementary role to conventional imaging in the diagnosis and staging of multiple myeloma. CMS recently approved coverage of PET for both initial and subsequent treatment strategy evaluation of myeloma. One key area for research is to investigate the correlation of FDG avidity with local disease activity using biopsy.

Pancreatic and Hepatobiliary Cancers

PET use is evolving in pancreatic and hepatobiliary malignancies. These cancers generally have a poor prognosis, with surgery the only potentially curative treatment. However, only a minority of patients are eligible for resection, and recurrence is common and typically incurable. These stark realities guide evaluation of PET efficacy in these diseases.

Diagnosis and Initial Staging

In pancreatic cancer, studies of 34 to 106 patients have consistently shown diagnostic accuracy for PET, which surpasses that of CT.^{2,96,104,105} In particular, PET can differentiate malignant tumors from benign cysts or pancreatitis with 84% to 94% accuracy.^{105,106} Because a diagnostic biopsy is performed for most patients, the clinical efficacy of FDG-PET/CT for diagnosis is questionable. However, although biopsy may provide a tissue diagnosis, this technique is associated with significant sampling error.^{107,108} FDG-PET/CT may represent a useful add-on diagnostic tool in the evaluation of patients with suspected pancreatic cancer, especially when CT and biopsy results are inconclusive.¹⁰⁹

PET may be more useful in staging. A recent study of 82 patients showed an improved detection sensitivity for metastases when combining PET/CT with standard CT (combined, 87%; PET/CT, 61%; CT, 57%).¹¹⁰ Detection of additional metastases resulted in a management change in 11% to 16% of patients.^{110,111}

In the fewer studies available for the less-common biliary tract (gallbladder and bile duct) malignancies, PET was generally found to be effective in visualizing primary tumors and distant metastasis,^{112–115} although false-positives were concerning for patients with cholangitis or biliary stents.¹¹⁶ Similar to pancreatic cancer, PET findings caused a change in primary treatment in 17% to 30% of patients because it detected unsuspected metastases.^{112,114,116,117}

The clinical picture may be different for hepatocellular cancer. The primary tumor generally has lower, more variable avidity for FDG, although PET is still effective in detecting 86% of metastatic lesions.^{118,119} PET may have an increasing role in assessing the impact of liver-directed therapies, which are notoriously difficult to judge with conventional CT imaging. Wudel et al.¹¹⁹ reported that FDG-PET added clinically significant information in 26 of 91 patients (28%) as a result of metastasis detection and response assessment of hepatic-directed therapy.

Recurrence and Other Applications

Several studies have investigated PET for recurrence detection, but its usefulness may be limited because few options are available when these cancers recur. Thus, early detection of an incurable recurrent malignancy with limited treatment options is unlikely to impact patient management. A study of 31 patients with pancreatic cancer showed that PET was more sensitive than CT/MRI for local recurrence but significantly less sensitive for liver metastases.¹²⁰ In a study of patients with biliary cancer, PET identified recurrence in 86% of patients but altered treatment in only 9%.¹¹² For hepatocellular carcinoma, Chen et al.¹²¹ reported a 73% PET sensitivity in detecting recurrence in patients with rising alpha-fetoprotein but otherwise normal conventional examinations. Thus, PET may have higher value in assessing recurrence or persistent disease in patients with hepatocellular cancer, because additional liver-directed treatments may be considered.

PET probably has prognostic significance. Seo et al.¹¹⁷ reported a lower disease-free survival for patients with cholangiocarcinoma cancer undergoing resection with high versus low SUV. Similarly in hepatocellular cancer, PET positivity was associated with shorter survival after liver transplantation¹²² or resection.¹²³ Smaller reports suggest a potential role for PET in response monitoring,^{104,124} particularly for liver-directed therapy in patients with hepatocellular

lar cancer,^{125–127} but more study and more-effective treatments are required to show clear benefit.

Conclusions

PET is most promising as an adjunct to standard staging tests for maximum metastasis detection to prevent unnecessary surgery. Although most primary pancreatic and biliary tract tumors are FDG-avid, hepatocellular cancers are not as much. In hepatocellular cancer, PET may have an expanded role in recurrence assessment and evaluation of response to liver-directed therapy, because additional treatment options may be available for localized disease. FDG-PET/CT imaging may represent a useful adjunctive diagnostic tool for evaluating patients with suspected pancreatic cancer, especially when CT and biopsy results are inconclusive. Improved detection of recurrence in pancreatic and biliary cancers is less likely to be of clinical benefit. Similarly, PET is unlikely to be used for response assessment in pancreatic and biliary cancers, given the limited efficacy of available treatments.

Sarcoma

Data on the use of PET to distinguish between benign masses and sarcomas are variable, depending on the definition of malignancy and the type of sarcoma examined.^{128,129} With respect to staging, FDG-PET is clearly inadequate (sensitivity, 50%–87%) in detecting lung involvement compared with chest CT (75%–100%), but whole-body PET is useful in detecting extrapulmonary metastasis.^{130,131} PET is particularly helpful in Ewing's sarcoma. FDG-PET alone detected osseous metastasis at a much higher sensitivity (100%) than conventional bone scintigraphy (68%).¹³² The hybrid PET/CT technique seems to further improve sensitivity in the staging of Ewing's sarcoma.⁴

Most sarcomas respond poorly to therapy. In recent years, however, targeted agents such as imatinib and sunitinib have shown dramatic, albeit often temporary, tumor control for gastrointestinal stromal tumors (GISTs).^{133,134} The assessment of response to these agents is where PET proved to be a valuable tool. Figure 5 illustrates the rapid change in tumor metabolism shown by PET, without a corresponding change in lesion size on CT.¹³⁵ FDG uptake significantly decreased in responsive tumors as early as 24 hours after the first dose of imatinib,¹³³ and PET was

much more accurate than CT in diagnosing response by 1 month (85% vs. 44%).¹³⁶ Likewise, FDG-PET sensitively showed on and off tumor response to sunitinib as patients with imatinib-resistant GISTs underwent treatment cycles.¹³⁷

Additionally, Prior et al.¹³⁸ reported a significant correlation between SUV at week 4 and progression-free survival in a study of 23 patients on sunitinib. For borderline resectable tumors, timely treatment response assessment can be the key to choosing between a less-invasive local excision and major surgery associated with high morbidity. This issue is critical when the tumor is located in the gastroesophageal junction, periampullary regions, and rectal/prostate areas.

Conclusions

PET may help complement conventional imaging in clarifying the disease stage of sarcomas, particularly in Ewing's sarcoma. PET imaging has an exciting role in monitoring response of GISTs to targeted agents. Rapid assessment using PET may allow a valuable window of opportunity for important surgical decisions, especially for borderline resectable tumors in specific locations.

Small Cell Lung Cancer

Evidence of benefit from PET use in small cell lung cancer (SCLC) mainly came from small studies focused on staging, which often included heterogeneous populations and used suboptimal conventional imaging algorithms for comparison. These studies included 18 to 120 patients with a cumulative staging concordance of 87% (range, 73%–100%) between PET and conventional imaging.^{139–147} Based on PET findings, approximately 15% of patients were upstaged from limited to extensive disease and 5% were downstaged. Because SCLC is an aggressive disease, it generally has high FDG uptake, leading to a sensitivity of nearly 100% for primary tumors. For most metastatic sites, PET was superior to standard imaging techniques with sensitivity of 97% to 100% and specificity of 78% to 96%. However, PET was inadequate in detecting brain metastases (sensitivity, approximately 45%) compared with cranial MRI or CT.^{139,140,143,147} NSCLC is more frequently associated with hypermetabolic metastatic brain lesions than SCLC (80% vs. 26.7%).¹⁴⁸

Changes in management based on PET staging

were reported in 16% to 38% of patients in 3 studies (vs. 41% reported by NOPR²³), primarily because of alterations in the radiotherapy field.^{139,143,147}

Data on other applications such as prognosis and response monitoring are based on small numbers of patients. One retrospective analysis showed that patients with positive PET findings had worse 2-year survival rates than those with negative findings (23% vs. 67%; $P = .01$) and that SUV_{max} inversely correlated with survival.¹⁴⁹ This information, however, is unlikely to have a significant impact on disease management.

Conclusions

Rigorous prospective research is still needed to determine the overall efficacy of PET in SCLC. PET seems to improve staging accuracy, although pathologic confirmation is still required for lesions that are upstaged. PET also seems to improve detection of intrathoracic sites of disease that can impact radiation planning in patients with limited-stage disease. However, PET is not adequate for detecting brain metastases.

Thyroid Cancer

The incidence of thyroid cancer has risen 2.4-fold over the past 30 years due to an increased detection of small papillary thyroid cancers, which represent 87% of all cases.^{150,151} These variants, together with the follicular and Hurtle cell subtypes, are classified as differentiated thyroid cancer (DTC), which has been the main research focus of PET in thyroid cancer. Medullary thyroid cancer (MTC), encompassing approximately 3% of cases, has a less than well-defined role for PET than DTC.

Diagnosis and Initial Staging

Emerging evidence shows PET provides effective diagnostic imaging for Hurtle cell thyroid cancer, which generally has low avidity to I-131.^{152,153} More generally, incidental focally high thyroid FDG uptake has been well documented in large studies, reporting 1.1% to 2.9% incidence in 1330 to 8800 individuals.¹⁵⁴ A significant number of these—14% to 47%, depending on the fraction of suspected lesions subjected to tissue biopsy—were confirmed to be thyroid cancer. In comparison, conventional imaging detected a higher rate of incidental nodules but lower rate of malignancy.¹⁵⁵ Hypermetabolic thy-

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roid “incidentalomas” identified with PET should be further evaluated using thyroid ultrasonography and fine needle aspiration. However, because of lower cost and higher sensitivity, thyroid ultrasonography is the preferred modality for the initial evaluation of a thyroid nodule.

PET is less useful in MTC, but the sensitivity is 70% when calcitonin levels are greater than 1000 pg/mL.¹⁵⁶ A larger study of 55 patients showed that PET was inferior to either ultrasonography, CT, or MRI for detecting disease at individual common metastatic sites, including neck, lung, mediastinum, liver, and bone.¹⁵⁷

Recurrence and Prognosis

FDG-PET sensitivity for recurrent DTC varied widely, from 45% to 100%, improving at higher serum thyroglobulin (Tg) levels and in patients with more extensive metastatic disease.¹⁵⁸ Because Tg is already a good marker for recurrence, the value of PET in this setting is generally restricted to localizing the residual disease, especially when I-131 scintigraphy is negative. Stimulation of thyroid stimulating hormone moderately increases the sensitivity for detecting FDG-positive lesions.¹⁵⁹

In the posttreatment setting, PET has profound prognostic impact based on the fact that PET-positive lesions are probably most metabolically active and aggressive. In a retrospective review of 400 patients who underwent PET (50% with metastasis), Robbins et al.¹⁹ found that only old age and positive PET findings continue to be strong predictors of short survival after multivariate analysis. Similarly, Wang et al.¹⁶⁰ report volume of FDG-avid disease to be the single strongest prognostic factor. Moreover, of the 58 patients with distant metastasis, those who had positive PET findings had a significantly shorter survival than the group with negative findings.

Notably, FDG avidity and concomitant loss of I-131 uptake is known to be associated with dedifferentiation,¹⁶¹ and several studies have used PET to detect metastasis in patients with negative I-131 scintigraphy and elevated Tg (Figure 6).^{162,163} Together, these findings favor PET use in selecting patients within this group who may require more vigilant follow-up or systemic therapy beyond radioactive iodine. For poorly DTC or anaplastic thyroid cancer (ATC), FDG-PET may improve metastasis detection and alter therapy.¹⁶⁴ Because of the generally poor prognosis of patients with ATC, no correlations be-

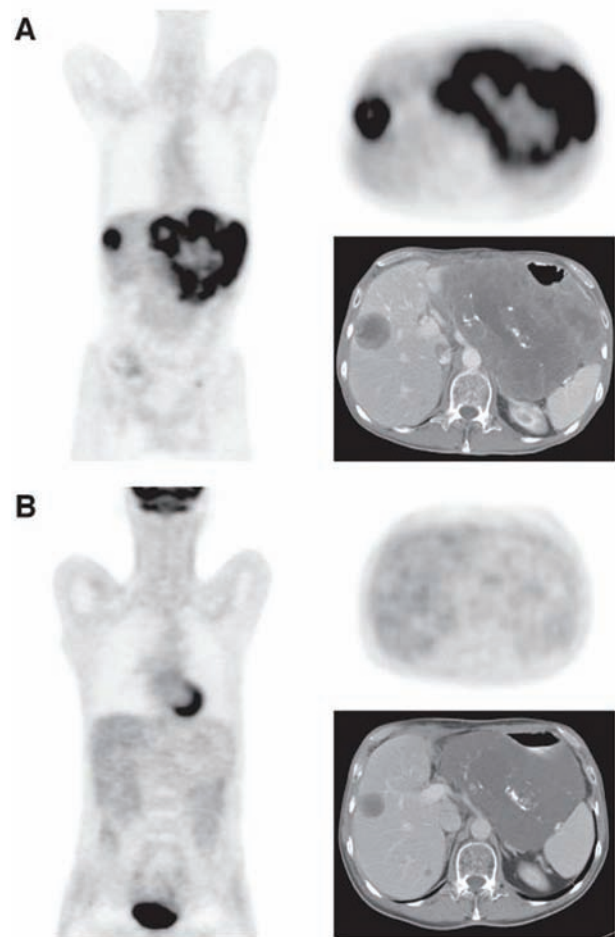


Figure 5 PET can provide rapid evaluation of tumor response to targeted agents in sarcoma. Comparing scans of a patient before (A) and 1 month after (B) imatinib therapy, PET/axial PET slices showed dramatic shrinkage of the tumor mass, whereas the corresponding axial CTs (inset panels) showed no apparent treatment effect.

Source: Van den Abbeele AD. The lessons of GIST—PET and PET/CT: a new paradigm for imaging. *Oncologist* 2008;13(Suppl 2):8–13.

tween PET findings and prognosis are available. PET received CMS approval of coverage in 2003 for restaging patients with previously treated thyroid cancer of follicular cell origin, elevated Tg (> 10 ng/mL), and negative whole-body I-131 scintigraphy.

Conclusions

The role of PET is limited for MTC, but expanding in DTC. Incidental discovery of focal FDG avidity may be helpful in identifying potentially malignant thyroid nodules for diagnosis, but cost and sensitivity preclude its use as a frontline diagnostic tool. Research data best support using FDG-PET in established intermediate- and high-risk patients with DTC and those

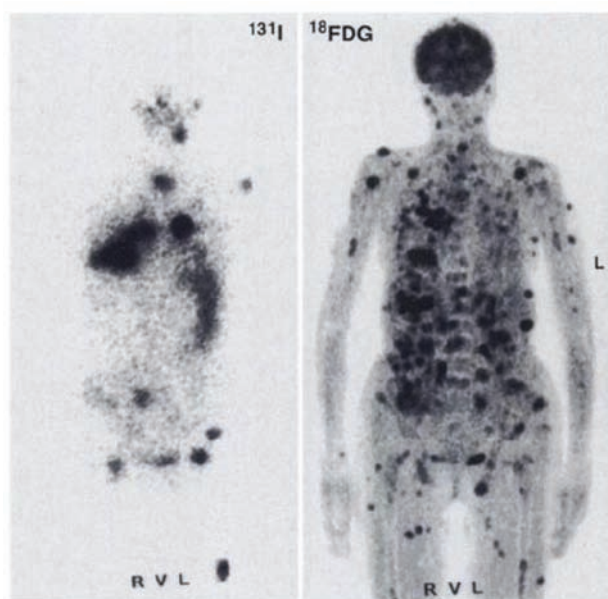


Figure 6 ^{131}I -negative thyroid cancer metastases are often FDG-avid. In contrast to ^{131}I scan (left), FDG-PET scan (right) revealed extensive metastasis in this patient.

Source: Feine U, Lietzenmayer R, Hanke JP, et al. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. *J Nucl Med* 1996;37:1468–1472.

with ATC. PET is a powerful prognostic indicator in the metastatic setting. One emerging use is in assessing patients with high Tg and negative I-131 imaging, where a positive PET may be indicative of dedifferentiation associated with tumor aggressiveness, calling for modification in treatment plans.

Conclusions

Table 4 summarizes the panel conclusions on PET use in different cancers based on a review of the literature. These are based on lower-level evidence and panel consensus was reached, corresponding to 2A category of NCCN recommendations. PET is generally useful as an adjunctive imaging technique in detecting unsuspected metastasis. This information is especially valuable in deselecting patients from futile, invasive treatment, such as pelvic exenteration in cervical cancer. PET also shows promise in assessing treatment response in gastric/esophageal cancer and GIST. Notably, however, PET has been found to be inadequate for disease detection in certain settings (e.g., brain metastasis of SCLC).

In some cases, panelists found the practical value of PET to be limited by the clinical circumstance.

For example, although PET can sensitively detect primary and recurrent ovarian tumors, its use is low in practice because initial debulking surgery is recommended for most patients and opinions differ on the best management for recurrent disease. However, the technology assessment performed for CMS by the University of Alberta Evidence-Based Practice Center showed substantial efficacy of PET in ovarian cancer.⁹⁶ The results of this technology report indicate that FDG-PET, especially when combined with CT, is a potentially useful tool for detecting recurrent ovarian tumors. A negative CA-125 and FDG-PET/CT is considered to rule out recurrent ovarian cancer and, in this clinical setting, can substitute for CT.

The essential message is that although the evidence is imperfect (and definitely indicates limited efficacy for certain cancers), the technology is now mature enough and its general use in cancer understood sufficiently for physicians to be empowered to use it as they think best for individual patients. More intelligent use will occur over time as more evidence for PET use in all types of cancer is developed. The continued development of new evidence by the NOPR should help accomplish this goal.

Emerging Applications and Future Directions

Interest in measuring metabolic change to evaluate therapeutic success has recently increased. PET is an area of active research, as an early surrogate biomarker based on the fact that alterations in glucose metabolism and thus FDG uptake in cancer tissues may sensitively reflect response to treatment before a gross reduction in tumor measurements. This can be especially useful in avoiding substantial side effects of futile therapy or allowing a timely switch to another potentially more effective treatment. Esophageal cancer and GIST are 2 examples discussed earlier, with several current trials using PET for response assessment. Similar trials are ongoing in a vast array of other cancers, including brain, breast, cervical, colorectal, head and neck, kidney, lung, and nasopharyngeal cancers and lymphoma and sarcoma. More research effort is needed to correlate PET findings to patient outcome for this application. Standardized protocols and evaluation criteria for specific diseases, such as those developed for lymphoma,¹⁶⁵ are also necessary to ensure reporting of quality data.

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Table 4 Role of PET in Various Types of Cancer*

Diagnosis/Staging	Restaging/Recurrence
- Brain: may identify anaplastic transformation in nonenhancing, low-grade gliomas - Gastric/esophageal: - Gastric: not for diagnosis; potential use for metastasis detection - Esophageal: detection of advanced disease - Genitourinary: FDG not for diagnosis; potential for adjunctive detection of metastasis - Gynecologic: - Cervical: detect nodal involvement - Ovarian/uterine: limited use - Myeloma: potential adjunct to MRI for detecting extraspinal lesions - Pancreatic/hepatobiliary: - Pancreatic/biliary tract: for diagnosis when other imaging and biopsy are nondiagnostic, and adjunct in metastasis detection - Liver: adjunct in metastasis detection, not for primary diagnosis - Sarcoma: - Ewing's sarcoma: adjunct in staging - Others: detecting extrapulmonary metastasis, not for lung involvement - SCLC: potential adjunct in nodal/distant metastasis detection, but not for brain metastasis - Thyroid: - DTC: incidental discovery of suspicious nodes - MTC: limited use	- Brain: differentiation of recurrence from radiation necrosis - Gastric/esophageal: - Gastric: unclear - Esophageal: distant lymph node detection - Genitourinary: limited use for local recurrence, possible use in detecting metastasis - Gynecologic: - Cervical: restaging to detect residual disease after chemoradiation, presurgical detection of extra-pelvic disease (deselection for surgery) - Ovarian: restage when CA-125 is elevated and CT normal - Uterine: unclear - Myeloma: potential adjunct to MRI for detecting extraspinal lesions - Pancreatic/hepatobiliary: - Pancreatic/biliary tract: limited use - Liver: potential use in assessing recurrent/persistent disease - Sarcoma: unclear - SCLC: unclear - Thyroid: - DTC: detection of suspected recurrence when Tg is elevated and whole-body I-131 imaging is negative - MTC: restage when calcitonin > 1000 pg/mL
Prognosis	Treatment Planning and Response Monitoring
- Brain: possible negative correlation with survival - Gastric/esophageal: negative correlation with chemoradiation/radiation outcome - Genitourinary: unclear - Gynecologic: - Cervical: negative correlation with survival - Myeloma: possible negative correlation with survival - Pancreatic/hepatobiliary: negative correlation with survival - Sarcoma: - GIST: negative correlation with targeted therapy outcome - SCLC: unclear - Thyroid: - DTC: negative correlation with survival - MTC: unclear	- Brain: potential use in radiation planning and dose verification - Gastric/esophageal: response assessment for preoperative induction therapy - Genitourinary: unclear - Gynecologic: unclear - Myeloma: unclear - Pancreatic/hepatobiliary: - Pancreatic/biliary tract: limited use - Liver: potential response assessment to liver-directed therapies - Sarcoma: - GIST: response assessment for targeted therapy - SCLC: may modify radiation field - Thyroid: unclear

Abbreviations: DTC, differentiated thyroid cancer; GIST, gastrointestinal stromal tumor; MTC, medullary thyroid cancer; SCLC, small cell lung cancer.

*Based on lower-level evidence (lack of randomized studies) with panel consensus, corresponding to the 2A category of NCCN recommendations.

Determining whether PET-guided adaptive treatment paradigms will lead to improved patient outcomes will likely require prospective, randomized, controlled trials.

A supplemental NOPR report discussed data collected on 10,497 PET scans performed for treatment monitoring, mainly for chemotherapy alone (82%).¹⁶⁶ Overall, PET led to an intended change of

therapy or modification in current treatment scheme (dose or duration) for 43% of patients. An intended change was recorded more often when PET findings suggested a worse or unchanged prognosis (78% vs. 40%). The highest percentage use of PET in this data set was for ovarian cancer (14% of all cases), which further shows its popular use for this cancer among the community and indicates the need for better research validation.

The role of PET in aiding other procedures is emerging. The latest evolution of image-guided radiation therapy involves the incorporation of PET scans in a 3-dimensional radiation planning process to maximize target dose while minimizing effects on surrounding tissue. For example, Esthappan et al.¹⁶⁷ described the use of PET to accurately guide intensity-modulated radiotherapy to positive para-aortic lymph nodes in patients with cervical cancer. PET has also been suggested as a tool to guide biopsy to the most biologically significant tumor area, based on the fact that aggressive cancer cells are often metabolically active and hence highly FDG-avid. This is currently under investigation for cancers with high tissue heterogeneity, such as lymphoma and sarcoma. Another application of PET with FDG and ¹¹C-methionine is in selecting the best biopsy site for diagnosis and PET-guided therapy.¹⁶⁸

Research is ongoing on new tracers that reflect other molecular processes, with ¹⁸F-fluorothymidine (FLT) being a common example.¹⁶⁹ ¹⁸F-FLT is a thymidine analog and a marker for cell proliferation. Studies using FLT to monitor therapeutic response are showing encouraging results.

Another promising tracer is ¹⁸F-misonidazole (FMISO) for detecting tumor hypoxia, a key mechanism in radioresistance. In a substudy of a larger trial randomizing patients with head and neck cancer to standard radiochemotherapy with or without the hypoxia-induced drug tirapazamine, 45 subjects underwent FMISO-PET before and during treatment.¹⁷⁰ The authors reported that hypoxia as shown by FMISO-PET in the no-tirapazamine arm is associated with an increased risk for locoregional failure.

The American College of Radiology Imaging Network is initiating 2 trials that use PET to image hypoxia. These and other studies may further expand potential application of PET in oncology. Another example, ¹¹C-choline, is a tracer that has low urinary excretion and has been found to be more sensitive

than FDG for detecting prostate and urinary tract cancers. Its uptake in malignant cells largely reflects the increased cell membrane synthesis in proliferating tumors. However, it has the significant limitation of a short half-life of 20 minutes, which limits its usefulness in centers with cyclotrons. Similar tracers labeled with ¹⁸F are under development.

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Post-test

Please circle the correct answer on the enclosed answer sheet.

1. Which of the following statements is TRUE regarding PET/CT scans?
 - a. PET/CT is not used as widely as PET alone.
 - b. PET/CT imaging improves the sensitivity of PET scans.
 - c. A diagnostic CT scan is always included in a PET/CT scan.
 - d. PET/CT requires a contrast medium.
2. Which of the following statements is/are TRUE regarding the NOPR?
 - a. The NOPR is a medical registry that collects data on the impact of PET, as part of the Coverage with Evidence Development program of CMS.
 - b. PET resulted in a change in intended management for 38% of cases in the NOPR.
 - c. The NOPR does not directly measure the impact of PET on clinical outcome.
 - d. All are true.
3. Which of the following is/are TRUE regarding the correct use of PET?
 - a. Meticulous patient preparation is essential.
 - b. PET should not be performed if results will have no impact on subsequent management.
 - c. A PET/CT scan does not replace a diagnostic CT scan.
 - d. All are true.
4. ^{18}F -FDG is a reliable tracer for visualization of tumors in the genitourinary tract.
 - a. True
 - b. False
5. Current applications of PET in gynecologic cancers include:
 - a. diagnosing ovarian cancer to avoid up-front debulking surgery.
 - b. identifying small nodal deposits in patients with uterine cancer.
 - c. detecting extra-pelvic metastasis to deselect patients from pelvic exenteration.
6. For patients with myeloma, PET is sensitive in detecting bone lesions, and MRI is sensitive in detecting spinal involvement.
 - a. True
 - b. False
7. Which of the following statements is FALSE regarding PET in pancreatic/hepatobiliary cancers?
 - a. PET shows high sensitivity in detection of metastases for pancreatic cancer.
 - b. False positive results can occur for patients with biliary stents or cholangitis.
 - c. Hepatocellular tumors are more FDG-avid than pancreatic tumors.
 - d. Detection of recurrence by PET may be useful in hepatocellular cancer as additional therapeutic options are available.
8. Which of the following is NOT an application of PET in thyroid cancer?
 - a. PET performed for other purposes that leads to incidental discovery of potentially malignant thyroid nodules
 - b. Detection of metastatic MTC
 - c. Restaging of previously treated patients with elevated Tg but negative I-131
 - d. Diagnosis of Hurthle cell cancer
9. PET is a promising tool for treatment monitoring in:
 - a. GISTs.
 - b. glioma.
 - c. myeloma.
 - d. uterine cancer.
10. Which of the following statements is/are TRUE regarding future developments of PET?
 - a. ^{18}F -FDG may achieve widespread use for diagnosis of prostate cancer.
 - b. ^{11}C -choline will likely replace ^{18}F -FDG in detecting ^{131}I -positive recurrent thyroid cancer.
 - c. ^{18}F -FLT may be used to detect proliferation.
 - d. All are true.

Post-Test Answer Sheet

Please circle one answer per question. A score of at least 70% on the post-test is required.

- | | | | | | | | | | |
|----|---|---|---|---|-----|---|---|---|---|
| 1. | a | b | c | d | 6. | a | b | | |
| 2. | a | b | c | d | 7. | a | b | c | d |
| 3. | a | b | c | d | 8. | a | b | c | d |
| 4. | a | b | | | 9. | a | b | c | d |
| 5. | a | b | c | | 10. | a | b | c | d |

The activity content helped me to achieve the following objectives:

(1 = Strongly disagree; 3 = Not sure; 5 = Strongly agree)

Describe the various context-specific applications of PET scanning in oncology.

1 2 3 4 5

Identify important general and technical precautions to be observed when applying the technology.

1 2 3 4 5

Make disease-specific recommendations on the use of PET scanning for initial or subsequent treatment evaluations in patients with different types of cancer.

1 2 3 4 5

Summarize the strengths and limitations of data collected and analyzed by the National Oncologic PET Registry.

1 2 3 4 5

Please indicate the extent to which you agree or disagree with the following statements:

You were satisfied with the overall quality of this activity.

Strongly agree Agree Undecided Disagree Strongly disagree

Participation in this activity changed your knowledge/attitudes

Strongly agree Agree Undecided Disagree Strongly disagree

You will make a change in your practice as a result of participation in this activity.

Strongly agree Agree Undecided Disagree Strongly disagree

The activity presented scientifically rigorous, unbiased, and balanced information.

Strongly agree Agree Undecided Disagree Strongly disagree

Individual presentations were free of commercial bias.

Strongly agree Agree Undecided Disagree Strongly disagree

**NCCN Task Force Report:
Clinical Utility of PET in a
Variety of Tumor Types**

Release Date: June 26, 2009
Expiration Date: June 26, 2010

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I certify that I have participated in this activity as designed.

Signature _____ Date _____

TO RECEIVE CREDIT, YOU MUST SUBMIT THIS FORM BY JUNE 26, 2010.

