

Sources and resources for oncologists to help answer the question: Is PET/CT appropriate for my patient?

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Abstract

Positron emission tomography (PET)/computed tomography (CT) -subsequently referred to as PET/CT is emerging as a critically important diagnostic tool in oncology. There has been a substantial increase in the utilization of this modality over the last decade. *The optimal imaging protocols are, however, still not established* which results in considerable confusion and uncertainty among referring physicians and providers. Oncologists, hematologists and other physicians managing oncologic patients frequently face the dilemma of whether or not to order a PET/CT scan for their patients. The large body of evidence from clinical research often overwhelms the ability of physicians to stay adequately informed on the disease specific performance of PET/CT. Moreover, regulatory agencies have changed their requirements for reimbursement of PET/CT scans in an effort to curtail health care expenditures. In this article we attempt to inform users and providers about the appropriate use of this technology.

Introduction

A PubMed search with the keywords "FDG PET" as of January 1st 2011 yielded 37574 publications. A more detailed chronological analysis lists 2 papers published in 1975, 5 in 1976, 8 in 1977, 1733 throughout the 80's, and an astonishing 4306 for the year 2010 alone reflecting the dramatically increasing utilization of this modality. Imaging with PET/CT is now an integral part of the management of many cancers. Yet, the appropriate application of PET/CT in oncology and its place in the diagnostic algorithm remain to be clearly defined. Therefore, the acceptance and application of PET/CT varies among countries and health care systems.

Oncological PET was introduced clinically in the early 1990s [1]. The development of combined PET/CT imaging systems in the late 1990s was an important step to increase the acceptance of PET among radiologists and oncologists. These "hybrid" scanners made it possible to obtain information regarding anatomy, function and molecular phenotype of cancers in a single imaging session [2]. The first clinical PET/CT scanners became operational in 2001 and since then, utilization rates have grown by more than 10% annually [3]. In many developed countries PET/CT is now available for detection, staging and evaluation of treatment response

for most cancers. Nevertheless, even in these countries, misconceptions and confusion are common among physicians ordering PET/CT studies for their patients.

Similarly, regulatory agencies now require imaging test to be highly accurate, cost-effective and to have a significant impact on patient management and outcome. Studies to address impact on outcome are still sparse.

The following article provides some of the sources that referring physicians can use to gain information about the appropriate use of PET/CT and discusses the role of PET/CT in decision making processes in oncology.

Indications and reimbursement policies

There is a disconnect between the actual clinical value of PET/CT in various cancers and the reimbursed indications. In theory, PET/CT should be reimbursed for all indications for which its usefulness has been shown. However, the imaging community has frequently failed to provide robust data to support the utility of PET/CT in the context of appropriateness and cost-effectiveness. These requirements have traditionally not been applied to diagnostic modalities such as CT or magnetic resonance imaging (MRI). However, given the dramatic changes in the economic environment PET/CT has been subjected to a much higher level of scrutiny. Consequently, reimbursement varies among countries and health care systems.

Accepted indications for ¹⁸F-FDG PET/CT in oncology

A vast number of frequently retrospective and single center prospective studies have analyzed the performance and effectiveness of PET/CT in a variety of cancers. Based on these data and the collective experience of expert physicians, as well as the consensus of expert panels, guidelines from various professional organizations for the use of PET/CT have been issued.

In 2007 the American College of Radiology (ACR) provided guidelines for the use of PET/CT in oncology with the intent to serve as an educational tool designed to assist practitioners in providing appropriate radiologic care for patients [4]. The key points and major indications for fluorine-18-fluorodesoxyglucose (¹⁸F-FDG-PET/CT) in oncology according to this publication are presented in Table 1. As

Table 1. Indications for PET/CT according to ACR guidelines include, but are not limited to, the following

1. Evaluating an abnormality detected by another imaging method to determine the level of metabolism and the likelihood of malignancy.
2. Searching for an unknown primary tumor when metastatic disease is discovered as the first manifestation of cancer.
3. Staging patients with known malignancy.
4. Monitoring the effect of therapy on known malignancies.
5. Determining if residual abnormalities on imaging studies following treatment represent tumor or post-treatment inflammation, fibrosis, or necrosis.
6. Detecting recurrence, especially in the presence of elevated tumor markers.
7. Assisting in treatment planning.

Table 2. Referral Criteria per the UK PET-CT Advisory Board

- *Lung cancer:* All patients suitable for radical treatment-surgery or radiotherapy. In patients post radical treatment with suspected disease relapse when detection of recurrence would affect management.
- *Colorectal cancer:* Patients considered for radical treatment with a prior history of colorectal cancer and proven or suspected disease relapse, and patients with synchronous metastases at presentation potentially suitable for resection.
- *Anal cancer:* All patients with anal cancer suitable for radical radiotherapy.
- *Gastrointestinal tumours:* All patients with GISTs unsuitable for complete surgical resection. Patients require a baseline and a post treatment (2 cycles or by local agreement) scan.
- *Malignant melanoma:* All patients with malignant melanoma relapse suitable for radical treatment.
- *Paraneoplastic syndrome:* In patients with paraneoplastic syndrome and an inconclusive or negative contrast enhanced multislice CT scan.
- *Head and neck cancer:* Patients with prior head and neck cancer and suspected disease relapse, and in patients with biopsy proven squamous cell carcinoma in cervical nodes and no identified primary tumour site.
- *Suspected tumour relapse when detection would alter therapy and outcome:* Patients with suspected tumour relapse not confirmed on conventional scanning, when detection would alter treatment and outcome.
- *Uterine carcinoma:* In patients with locally extensive uterine carcinoma (cervix/endometrium) which is potentially curable by exenterative surgery.
- *Cholangiocarcinoma, gallbladder carcinoma potentially curable by radical surgery:* In patients with intrahepatic cholangiocarcinoma or gallbladder carcinoma which is potentially curable by radical surgery.

can be seen in this table, these are general guidelines that are not specific for any cancer type. The authors suggest that “the ultimate judgment regarding the propriety of any specific procedure or course of action should be made by the physician or medical physicist in light of all the circumstances presented”.

In January of 2009 the “Committee for Indications for PET/CT” of the UK PET/CT Advisory Board of the British Nuclear Medicine Society (BNMS) issued its suggestions for the oncologic ¹⁸F-FDG PET/CT scan referral criteria [5]. Based on the available evidence the board specified which patient groups would benefit from PET/CT referrals whereby benefit is defined as improved disease assessment resulting in altered treatment and improved outcome. Table 2 lists these referral criteria. The National Comprehensive Cancer Network (NCCN) Task Force issued a report in 2009 on the clinical utility of PET/CT in a variety of tumor types [6]. The recommendations of this multidisciplinary expert panel are summarized in Table 3. A significant conclusion was that PET/CT is useful as an adjunct imaging technique in detecting unsuspected metastases, especially for excluding patients from futile, invasive treatment. An additional important message was that although the evidence indicated a limited efficacy for certain cancer types, the technology was mature enough and its general use in cancer sufficiently understood for physicians to be empowered to use it as they deemed most appropriate for individual patients. They suggested that more intelligent use will occur over

time as more evidence for PET/CT use in all types of cancer will be developing.

In 2010 the Royal College of Radiologists (RCR) issued guidance for the indications of PET/CT [7]. This guidance was intended to update physicians involved in the provision and reporting of PET/CT. This guidance refers to a broad spectrum of PET/CT indications including rare tumors, neurologic and cardiologic problems, fever of unknown origin and vasculitis, and provides an extensive list of key references for physicians to consult from.

The European Association of Nuclear Medicine (EANM) issued the 1st version of procedure guidelines for tumor PET/CT imaging in 2010 [8]. In this publication, the authors provide a brief summary of the indications based on the combination of expert experience and scientific literature. They also suggested a prior publication [9] for a more detailed reference pointing out that these indications are constantly changing and require updating with time.

In February of 2011 The Society of Nuclear Medicine (SNM) issued practice guidelines for the use of ¹⁸F-FDG PET/CT in oncology [10]. Here the recommendations and practice guidelines of SNM, National Comprehensive Cancer Network (NCCN), and other professional organizations regarding the use of ¹⁸F-FDG PET and PET/CT in oncology were summarized for the cancer indications approved by the Centers for Medicare and Medicaid Services (CMS). Also in 2011, the SNM issued the NCCN practice guideline summary for the utilization of PET and PET/CT [11].

Table 3. The National Comprehensive Cancer Network (NCCN) Task Force report on the role of PET in various cancer types**Diagnosis/Staging**

- *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 metastases
- *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

Restaging/Recurrence

- *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 ¹³¹I imaging is negative
MTC: restage when calcitonin > 1000pg/mL

Prognosis

- *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

Treatment planning and response monitoring

- *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

Reimbursable indications in oncology

There is very limited information available pertinent to the current status of the acceptable and reimbursable indications of oncologic PET/CT throughout the world. Several factors may account for this lack of information: One is the lack of sufficient published data. Another one is the dynamic growth of this modality resulting in constant changes with continuous incorporation of new indications that are difficult to track. This growth is related not only to the relatively recent introduction of PET/CT into clinical practice, but also to the extensive ongoing research on the use of ^{18}F -FDG and other radiopharmaceuticals.

Considering the complexity of the various health systems and the variable economic strengths of countries, a wide variety of legislative and reimbursement policies in different countries is not surprising. In many developing countries PET has not been introduced yet and therefore indications or reimbursement policies have not been established. Unfortunately, even for countries where PET/CT is available and established firm guidelines are lacking. The majority of available data on appropriateness and utilization of PET/CT were generated in the USA and Europe.

In 2010 Buck et al reviewed the economic evaluations of PET and PET/CT in oncology [12] and summarized those indications for which cost effectiveness had already been demonstrated. Moreover, other clinical indications for which diagnostic effectiveness but not cost-effectiveness had been demonstrated were listed. According to the authors, cost-effectiveness of PET/CT has been demonstrated for the staging of non-small cell lung cancer, the differential diagnosis of solitary pulmonary nodules, the restaging of Hodgkin disease and non-Hodgkin lymphoma, and the restaging of colorectal carcinoma. They also reported that PET/CT imaging is reimbursed in the USA for many other cancers and indications including the staging of gastrointestinal tract cancers, breast cancer, malignant lymphoma, melanoma, head and neck cancers, cervical cancer, myeloma and others. These reimbursement decisions were based on the diagnostic superiority of PET/CT over conventional imaging modalities while cost-effectiveness has not been demonstrated consistently. Finally, the authors emphasized the need for prospective, randomized clinical trials comprising high patient numbers to evaluate the clinical relevance and cost effectiveness of PET/CT in other cancers since these studies are increasingly requested by decision makers.

In the USA coverage and reimbursement policies have been dominated historically by the Centers for Medicare & Medicaid Services (CMS) for the Medicare program. Starting in January 2005, CMS coverage for PET/CT scans included diagnosis, staging, and restaging of esophageal, head and neck, NSCLC, colorectal cancers, lymphoma and melanoma (excluding regional lymph node evaluation). Reimbursement for PET/CT was also approved for specific indications in breast, cervical, and thyroid cancers. In 2009 CMS issued a new framework for ^{18}F -FDG PET coverage [13]. Here the CMS transitioned the prior framework-diagnosis, staging, restaging and monitoring response to treatment into two new categories: the initial treatment strategy and subsequent treatment strategy. In this new framework the colorectal, esophageal, head and neck, ovarian, non-small cell lung cancers and lymphoma are

covered for either indication, whereas for breast, cervical, thyroid cancers and melanoma there are a few certain limitations. Other indications including myeloma, cervical and ovarian cancer were added. The CMS coverage as of 2005 and 2009 for oncologic PET indications as listed in the Journal of the National Comprehensive Cancer Network [6] is depicted in Table 4. Among third-party payers, coverage for clinical use of PET in oncology in the USA varies significantly.

Within the above mentioned reimbursement policies, the CMS starting from 2005 incorporated a new approach to coverage policy called coverage with evidence development (CED) for selected promising technologies. The CED policy is a formal approach for coverage of evolving diagnostic and treatment methods, including PET/CT that would not otherwise meet CMS evidentiary standards. Non-covered indications that are eligible for CED get reimbursed through CMS provided that the referring physician completes certain questionnaires designed to determine the actual impact of PET/CT on patient management. Data across a wide range of cancers were collected by the National Oncologic PET/CT Registry (NOPR), a prospective internet-based registry designed to assess the impact of PET/CT on patient management [14]. The NOPR officially began accepting patient registrations on May 8, 2006. It is sponsored by the Academy of Molecular Imaging (AMI) and managed by the American College of Radiology (ACR). The rationale behind the NOPR was to determine if the results of PET scans influence physicians' intended plans of patient management, while imposing minimal restrictions on the use of such scans in the clinical setting [15]. In practical terms, this program evaluates a considerable number of cases of each of the non covered PET/CT indications to determine if PET/CT impacts patient management. The ultimate plan is for an official coverage decision to be made based on this data. The NOPR received input from, and was endorsed by the ACR, the American Society for Clinical Oncology (ASCO), and the SNM.

In an interesting analysis of the NOPR data (2008) by Hillner et al [16] the authors suggested that "physicians often change their intended management on the basis of PET/CT scan results across the full spectrum of its potential uses". These data that represented 22,975 studies (83.7% PET/CT) from 1,178 centers revealed that post-PET/CT strategies changed to wait and watch in 37% and to a different treatment strategy in 48%. According to the analyzed results, biopsy was avoided in approximately 70% of patients in whom a biopsy was planned prior to PET/CT. Overall, these results indicate that physicians changed their intended management in 36.5% of cases after PET/CT.

In a same year subsequent publication, Hillner et al presented the updated results of NOPR for 18 specific cancer types and indications for testing [17]. By this time data were available from 40,863 PET/CT studies done at 1,368 centers. The results suggested that the impact of PET/CT on physicians' intended management for patients with known cancer was significant and consistent across all studied cancer types. When intended management was classified as treatment or non-treatment, physicians changed their intended management in 38.0% of the cases. The change in intended management of treatment vs.

Table 4. Medicare coverage of PET/CT in cancer (In USA)

Cancer type	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	Cov.‡/ CED	»
Colorectal	Covered	Covered	Covered	»	Covered	»
Esophagus	»	»	»	»	»	»
Head and neck	»	»	»	»	»	»
Lymphoma	»	»	»	»	»	»
Melanoma	»	Covered§	»	»	»	»
Myeloma	CED	CED	CED	»	»	»
NSCLC	Covered	Covered§	Covered	»	»	»
Ovary	CED	CED	CED	»	»	»
Prostate	»	»	»	»	NC	CED
Thyroid	Covered	Covered	Covered¶	»	Covered	Cov.¶/CED
All other solid tumors	CED	CED	CED	»	»	CED

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).

Table 5. Ontario Health Insurance Plan (OHIP) list of covered oncologic indications for PET

Solitary Pulmonary Nodule (SPN): for which a diagnosis could not be established by a needle biopsy due to unsuccessful attempted needle biopsy; the SPN is inaccessible to needle biopsy; or the existence of a contra indication to the use of needle biopsy.

Thyroid cancer: where recurrent or persistent disease is suspected on the basis of an elevated and/or rising thyroglobulin but standard imaging studies are negative or equivocal.

Germ cell tumours: where recurrent disease is suspected on the basis of elevated tumour marker(s)–(beta human chorionic gonadotrophin (HCG) and/or alpha fetoprotein) and standard imaging tests are negative, or a mass persists after primary treatment for seminoma when curative surgical resection is being considered.

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

Lymphoma: for the evaluation of residual mass(es) following chemotherapy in a patient with Hodgkin’s or non Hodgkin’s lymphoma when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered; or for the assessment of response in early stage Hodgkin’s lymphoma following two (2) or three (3) cycles of chemotherapy when the chemotherapy is being considered as the definitive single modality therapy.

Non small cell lung cancer (NSCLC): For which curative surgical resection is being considered based on negative standard imaging tests; or; For clinical stage III NSCLC which is being considered for potentially curative combined modality therapy with radical radiotherapy and chemotherapy .

Limited disease small cell lung cancer: for evaluation and staging where combined modality therapy with chemotherapy and radiotherapy is being considered.

non-treatment was quite similar across different indications. Only in multiple myeloma did PET/CT have a consistently greater impact on intended management (48.7%). When the intended management plan before PET/CT was treatment, a change in the intent of curative vs. palliative treatment or a major change in the modality of treatment

occurred at similar frequencies across different cancer types. The authors concluded that the use of PET/CT in management for patients with known cancer should not be restricted by cancer type or testing indication.

There is an enormous amount of information collected by NOPR. It is estimated that during nearly four years of

operation, over 150,000 patients have undergone ^{18}F -FDG-PET/CT under NOPR [18]. Nevertheless, because the results of the NOPR are presented in aggregate by indication, not by tumor type or stage, it is difficult to estimate the clinical utility of PET/CT for specific clinical scenarios within each specific cancer indication [14, 19].

Reimbursement policies in countries other than the USA have not been published systematically. However, reimbursement varies from unrestricted coverage, based on the referring physician's decision in Norway, to the very limited coverage in other countries such as Germany and some southern European countries.

An interesting evidence-based approach was adopted by the Ontario (Canada) provincial government; after a systematic review of the literature, a provincial PET/CT evaluation program was launched for the indications where only weak evidence existed that PET/CT had a positive impact on clinical outcomes. Clinical trials were proposed and performed and the indications for which the clinical utility of PET/CT was clearly demonstrated through these trials were approved and incorporated into the Ontario Health Insurance Plan (OHIP) list of covered indications for PET/CT. Seven oncologic indications were covered [20]; including solitary pulmonary nodule, thyroid cancer, germ cell tumors, colorectal cancer, lymphoma, non-small cell lung cancer (NSCLC), and limited disease small cell lung cancer. The covered indications are listed in Table 5. Although the Ontario trials addressed important clinical management questions in a number of tumor types, there were many other cancers and clinical indications that were not adequately evaluated.

Discussion

The incorporation of oncologic PET into the health and economic systems of different countries is a challenging process and requires time, cooperation on the regional and national level, prospective research addressing multiple health and economic parameters, and certainly a true willingness of governments and health administrators to advance the quality of health care provided to individuals. If regulatory agencies, methodologists, economists, and physicians cooperate effectively, populations can benefit from PET/CT imaging. Countries that have been left behind in the advancement and exploitation of PET should use the experience and knowledge from other health care systems to modify and expand the use of oncologic PET.

Physicians around the world need to be willing and able to extract the pertinent information about the use of PET/CT from numerous sources. There are two effective tools that clinicians may use to arrive at the best management decisions for their patients. One is the easy, on-line access to up-to-date knowledge, publications, evidence-based management strategies and guidelines. The other one is the direct consultation of experienced and specialized imaging specialists like nuclear medicine physicians and radiologists. While the former requires the know-how and the acquired skills to differentiate between reliable and unreliable sources, the consultation of experts is straight-forward and can be accomplished by attending national and international meetings of leading experts in the field of imaging. There is an overwhelming quantity of both reliable and unreliable

information about the use of PET/CT in oncology. The appropriate use of this enormous pool of information depends on the experience, critical ability and "browsing" skills of individual physicians. It is hoped that the current overview will help to direct interested stakeholders to the most appropriate sources.

In conclusion, while the acceptance of PET/CT is increasing world-wide and its use continues to grow, physicians need to be capable of identifying emerging evidence to the best use of this imaging modality in cancer patients.

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