




Imaging Recommendations for Positron Emission Tomography (PET) in Oncology

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Abstract

Cancer is one of the leading causes of morbidity and mortality. Imaging studies are central to the initial staging and follow-up management of cancers. In the past, oncologists have largely relied on anatomical imaging for staging, restaging, and therapy monitoring. The introduction of positron emission tomography-computed tomography (PET-CT) and its availability has transformed the practice of cancer imaging. PET-CT is an imaging technique that provides complementary information to imaging by CT or magnetic resonance imaging alone as it incorporates functional imaging to the anatomic information. It actually embeds tumor biology on the anatomical image. There are significant contributions of the CT component in adding value to the strength of PET-CT. PET-CT is useful for initial staging of cancers. It is particularly useful in detection of distant metastases, in assessing response to therapy and in detection of recurrence. Its utility in restaging and follow-up of cancers is now well established. Its role varies across different primary cancer sites. To cover the role of PET-CT in all cancer types is neither the intention nor feasible in a single article. In this article, an attempt will be made to highlight the generic concepts of PET-CT imaging and its role in primary staging and post-therapy follow-up across some common malignancies. Its pitfalls and limitations will also be discussed.

Keywords

- ▶ imaging
- ▶ oncology
- ▶ PET-CT

Principles of PET-CT Scanning

Cancer cells proliferate and grow by rapidly metabolizing glucose to lactate. Increased glucose uptake in cancer cells is the key to positron emission tomography-computed tomog-

raphy (PET-CT) imaging.^{1,2} However, you need to identify a glucose analogue that will follow the same metabolic pathways as glucose but will render itself to be detected by imaging. The glucose analogue 18F-fluoro-2-deoxyglucose (FDG) is the most widely used PET-CT radiopharmaceutical

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in clinical routine. Its uptake and trapping in cancer cells can be picked up by a PET-CT scanner as it is unstable. It is an isotope that emits positrons. The positrons are positively charged and readily combined with a freely available negatively charged electron. When the positron and electron collide, they both disappear. This process is called annihilation and it ends in releasing the gamma rays that are detected by a PET-CT scanner.

Availability and Indications for PET-CT

When it comes to high-end imaging studies, particularly PET-CT there are significant global inequities. The availability and cost of PET-CT remain a major issue. The logistics for transport of FDG is another bottleneck as it has a half-life of 110 minutes and needs a cyclotron for its production. Within India most PET-CT scanners are clustered in big cities with hardly any visible availability in tier-2 and tier-3 cities. While an affording patient in a big city has easy and quick access to PET-CT, a needy patient in a remote area may never get one. The referring physicians are over enthusiastic and quick to order a PET-CT regardless of the evidence in a particular situation. Since there are no strict guidelines in India, we often find indiscriminate use or misuse of PET-CT. As most patients pay out of pocket, there is hardly any audit or control by a regulatory body. It is estimated that 20% of PET-CT scans ordered in India are not in line with evidence-based practice.

In the United States, insurance coverage for PET-CT was driven by evidence-based data. The Center for Medicare and Medicaid Services authorized coverage for different cancers over a period of time based on evidence.³ Their strategy has been coverage with evidence development. As of now most cancers are covered for reimbursement. However, it is not covered for screening. Initially the terminology used for initial scan was for “diagnosis and staging.” For subsequent scan, the terminology was for “restaging and monitoring response to treatment.” The current terminology is PET-CT for initial treatment strategy and PET-CT for subsequent treatment strategy. The cancers that are now covered are colorectal, esophagus, head and neck (T3,T3 tumors or bulky nodes), lymphoma, non-small cell lung cancer (NSCLC), ovary, brain, cervix (except for initial treatment strategy), small cell lung cancer (SCLC), soft tissue sarcoma, pancreas, testes, prostate (not for initial treatment strategy), thyroid, breast (for distant metastases), melanoma, myeloma, and other solid tumors in a specific situation. However, there is a limit on the number of PET-CT scans that can be covered for subsequent management after completion of initial anticancer therapy. The total number of PET-CT scans to guide subsequent treatment strategy cannot exceed three.

Preparation before PET-CT Scan

Adequate hydration is recommended as it would ensure reduced FDG concentration in the urine.⁴ This will minimize artifacts. Consumption of 1 L of water prior to FDG injection is helpful. Oral contrast agent is usually not given even for a diagnostic CT scan.

Glucose containing parenteral nutrition and intravenous fluids should be stopped 4 hours before the FDG injection. After the injection of FDG, the patient should remain seated or recumbent and silent. Remaining silent will minimize FDG uptake in laryngeal muscles. The patient should be kept warm to minimize FDG agglomeration in brown fat. Patients must avoid any exercise or physical activity for minimum 24 hours prior to the PET-CT examination. Patients should empty the bladder immediately before the study to minimize urinary bladder activity. The patient should not move during the examination which will take approximately 20 to 40 minutes.

Serum glucose level prior to FDG administration should be checked. For FDG-PET-CT study, plasma glucose level has to be below 11 mmol/L (~200 mg/dL). Levels equal to or higher than 11 mmol/L (~200 mg/dL) requires rescheduling of PET-CT.

Breast Cancer

PET-CT is not recommended for routine staging of early-stage breast cancer. National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology, Spanish Society of Medical Oncology, and the National Institute for Care Excellence, UK, do not recommend PET-CT in females having early-stage (I or II) breast cancer or even in those with operable stage III breast cancer.⁵ However, there are situations where a PET-CT can pick up distant metastases in the bone, soft tissues, or elsewhere thereby changing the initial management strategy, which can happen in locally advanced breast cancer, breast cancer with extensive axillary lymphadenopathy, and triple negative breast cancers. Therefore, it appears reasonable to evaluate such cases with PET-CT which is superior to CT or magnetic resonance imaging (MRI) for detecting distant metastases.

Head and Neck Cancers

The prevalence of head and neck cancers is high in India.

The usual malignancies in the head and neck region are as follows:

1. Head and neck squamous cell carcinoma (HNSCC).
2. Thyroid cancer, mainly papillary cancer.
3. Nasopharyngeal cancer (NPC)
4. Lymphoma (systemic or confined to the neck glands)
5. Minor salivary gland cancers
6. Rhabdomyosarcoma
7. Retinoblastoma

Unless otherwise stated, this part of the article mainly deals with HNSCC.

Imaging for the malignancies in the head and neck is required for:

- a Primary staging
- b Radiotherapy planning
- c Treatment response and post-treatment follow-up

A. Primary staging

Tumor-node-metastasis (TNM) staging guidelines, NCCN, and American Society of Clinical Oncology (ASCO) have all advocated the use of contrast-enhanced CT (CECT) or MRI in the primary staging of HNSCC.⁶ This is in contrast to lymphoma, where a pre-therapy, interim, and post therapy 18F-FDG-PET-CT (PET-CT) is recommended.

Indications of PET-CT in staging of malignancies in the head and neck are limited. NCCN advocates CECT or contrast-enhanced MRI (CEMRI) for the initial staging of both the primary site and for nodal staging. In case of failure of detection of primary on cross-sectional imaging, PET-CT may be used. PET-CT may also be used to guide biopsy and interventions for proper and better sampling especially in the nodes.

For nodal disease too, cross-sectional imagings (CECT, CEMRI) are proposed. When nodal disease reaches midline and a surgical approach is contemplated, PET-CT may be used to assess the contralateral neck.⁷ Again, when there is high nodal burden and chances of distant metastasis is high, PET-CT may be considered.

In HNSCC, if the primary is advanced (T3 or T4 stage) or there is a large neck nodal burden, PET-CT may be considered to exclude distant metastasis.

In NPC, PET-CT may be considered for whole body staging when there are nodes below the level of cricoid cartilage or when the nodes are larger than 6 cm. Again, in thyroid cancers, nodes in the retropharyngeal region mandate exclusion of distant metastasis, which may be performed by PET-CT.

B. Radiotherapy planning

PET-CT guided planning for radiotherapy has been used in head and neck cancer. It has proven superior to CT-based planning in delineating tumor volume, especially in post-surgery neck. There is a high negative predictive value of PET-CT for neck nodes and this helps in planning radiotherapy as well, both in upfront treatment and in post-surgical subjects.

C. Treatment response and post-treatment follow-up

CECT or CEMRI is usually performed for follow-up after local and or systemic therapy. In case of locoregionally advanced disease, PET-CT may be performed for follow-up. PET-CT should be done minimum 3 to 6 months after radiation therapy as there may be high false-positives if done within 3 months.

PET-CT is the initial imaging modality of choice if residual disease is suspected after definitive radiotherapy and where surgery is contemplated.

For lymphoma, as discussed, PET-CT is the best choice in primary staging, interim, follow-up as well as post-therapy imaging.

Pitfalls

Tuberculous nodes are FDG avid and may cause confusion in a patient with known malignancy undergoing a staging scan.

Many patients develop infection after chemotherapy and again false-positive findings on PET-CT cause confusions. PET-CTs performed within 3 to 6 months of surgery or radiotherapy are prone to false-positive findings due to post treatment inflammation.

Recommendation for India

In India, the constraints of widespread use of PET-CT are expense and availability of scanners and cyclotrons for generation of the isotope. The scan being an outpatient procedure is not covered by insurance and is, hence, an out-of-pocket expense. Almost all tier-2 cities are devoid of scanner and it is only of late that all airports are being allowed to carry isotopes. One must also consider the guidelines that clearly have no significant role of use of this scan in first-line staging of all patients as well as for follow-up.

In HNSCC, PET-CT for routine evaluation is justified only if residual/recurrent disease post-radiotherapy is suspected and surgery is being contemplated. Assessment of response at least 12 weeks after chemoradiation may be helpful in avoiding unnecessary neck dissection. Cervical lymph node metastases with unknown primary are another reasonable indication for doing a PET-CT.⁷ It provides value in initial staging of stage III and IV HNSCC. It is not recommended for routine surveillance after 6 months of completion of therapy.

Colorectal Cancer

Colorectal cancer (CRC) ranks third in males and second in females among most common cancers and is responsible for 10% of all tumor types globally. In India, colon and rectal cancers are 9th and 10th most common cancers in males respectively. As far as females in India are concerned, colon cancer ranks 9th, while rectal cancer does not figure in the list of top 10 cancers.⁸ In the last decade, mortality rate of CRC has significantly reduced due to advancement in imaging technology and optimization of surgical, neoadjuvant and palliative therapies. Adenocarcinoma is most common cancer affecting colon or rectum, while other less common cancers of colon include gastrointestinal stromal tumors lymphoma, carcinoid, neuroendocrine, and squamous cell carcinoma.⁹ Certain hereditary syndromes like familial adenomatous polyposis, lynch syndrome, and Peutz-Jeghers syndrome are associated with colonic polyp or cancers and genetic testing has significant role in such patients.

Coloscopy remains the gold standard for primary evaluation of CRCs. It gives a benefit to simultaneous biopsy from the lesion and in same sitting also gives an opportunity for therapeutic polypectomy for small size polyps. Alternative method includes virtual CT colonoscopy and it is recommended as screening tool in an asymptomatic patient by American Cancer Society. Imaging in CRCs has significantly evolved over the time and it has established central role in screening to surveillance of CRC. Various modalities range from barium enema, multi-detector computed tomography (MDCT), MRI to the development of novel tracers, and fusion technologies (PET-CT). PET-CT has evolving role in CRC.

Role of PET-CT in Screening

Many colon cancers develop from preexisting colonic polyps or adenoma and also associated with many hereditary polyposis syndromes. Screening tool should be safe, accurate, easily available, and cost-effective. Normal lymphoid tissue in colon may cause focal or diffuse physiological uptake, and in the same way, inflammatory conditions like ulcerative colitis and diverticulitis can cause focal uptake on FDG-PET-CT; thus, PET becomes least suitable modality for screening of colon cancer or premalignant conditions like polyposis. FDG-PET should not be used as a routine screening or initial staging of CRC patients.

PET-CT in Diagnosis and Primary Staging

Entire tumor removal and regional lymphadenectomy carry the best prognosis for CRC.

PET-CT is suboptimal for T-staging of the primary tumor due to limited spatial resolution and failure to differentiate layers of colon and rectum.

Due to better visualization of anatomic details, transrectal ultrasound and MRI are excellent for T-staging of rectal cancers. MRI is the most reproducible method for T staging of rectal cancers and for tumors of the anal canal. Post-contrast MDCT is standard of imaging investigations for cancers of colon cranial to the peritoneal reflection.

Accurate staging also requires nodal staging and evaluation of distant metastasis accurately.

PET-CT is invaluable for differentiating benign from malignant nodes at a distant location from the primary tumor owing to the metabolic activity. However, small nodes in the proximity to the primary tumor can evade detection owing to FDG uptake of the primary tumor. PET-CT also has limitations in detection of nodal metastasis from mucinous CRC as it does not show significant uptake, small size nodes appear false-negative; while associated inflammatory conditions give false-positive in normal size or in enlarged nodes.¹⁰

FDG-PET has increased sensitivity than CT for identifying liver metastasis and mild peritoneal and omental disease. FDG-PET shows highest accuracy of up to 98% in identification of hepatic metastases. Early detection of hepatic metastasis in colorectal carcinoma provides opportunity of neoadjuvant chemotherapy followed by liver resection. FDG-PET, due to its superiority in identifying extrahepatic metastatic sites, also helps in management decision making as the treatment plan then changes from localized treatment to systemic chemotherapy.

PET-CT in Restaging, Recurrence, and Surveillance in CRC

Colon cancer recurs in a different pattern as compared with the rectal cancer. Rectal cancers recur more locally than colon cancers. For suspected recurrence due to clinical symptoms or rising tumor marker levels, PET has an established role for recurrence detection. FDG-PET is also superior in response evaluation post-radiotherapy, chemoradiation, or local ablative treatment.

On post-treatment scan for response assessment, PET-CT provides useful information on presence of viable tumor, distinguishes disease from fibrosis/scar, and also helps in prognostication. PET-CT also add benefits in rectal cancer patients who develop local recurrence following chemoradiations. PET-CT plays an important role in surgical planning of patients who develop recurrence in the form of operable hepatic or pulmonary metastasis. Although PET-CT is an optimal method for restaging and monitoring treatment response following chemoradiation, many issues like lack of standardization for optimal timing of imaging, universal criteria for response evaluation, and cost-effectiveness offer challenges. In India, MDCT is still most commonly used modality for surveillance and therapeutic monitoring.

PET-CT in Radiation Therapy Planning for CRC

PET-CT guided planning for radiotherapy has been used for CRC patients. Radiation portal field size can be reduced without omitting macroscopic disease in the vicinity of primary tumor by using PET-CT for radiotherapy planning. PET-defined gross tumor volume (GTV) is invaluable for planning the boost volume for adjuvant radiation therapy post-rectal tumor resection.

The development of PET-CT has a considerable impact in decision making and intention to treat from curative to palliative in locally advanced CRCs. However, major limitations of PET-CT include technical, economical, and logistic challenges, as well as lack of robust evidence for standardization and formal guidance for PET-CT protocols in staging, restaging, and surveillance at present. Future implications of development of PET-CT as standard imaging tool for evaluation of CRC will depend upon newer PET-CT machines with radiation dose reduction, better spatial resolution, latest cost-effective isotopes having increased specificity, and more importantly oncologist and cancer imaging specialist jointly working on patient management.

Current Recommendations

- PET-CT scan is not recommended as a standard screening tool for CRCs or for the evaluation of premalignant conditions.¹⁰
- For staging, PET-CT is not routinely used, unless initial CT study suggestive of hepatic metastasis or when there is diagnostic dilemma for hepatic or extrahepatic metastases on CT scan or on MRI. MRI is standard imaging tool for staging of rectal cancers and MDCT for colon cancer.
- PET-CT scan is not routinely indicated for restaging after nonsurgical treatment of metastatic CRC, unless curative resection is considered.
- PET-CT scans are recommended for staging/restaging in surgical resection of hepatic or pulmonary metastasis.

Pitfalls and Challenges of PET-CT Scanning

Lack of standardization across institutions
Mucinous and other non-FDG-avid tumors

Cyclotron and costs
Nonspecific inflammation
Radiation.

PET-CT in Lung Cancer

Role of PET-CT in the management of lung cancer has immensely increased in recent times.^{11–14} Amalgamation of functional and anatomic information has allowed PET-CT to look into various aspects of lung cancer, allowing more precise disease staging and providing helpful data during the characterization of indeterminate pulmonary nodules. Moreover, increased accuracy of PET-CT over conventional modalities in certain situations has made PET-CT an invaluable noninvasive modality for the investigation of lung cancer.

Common indications for PET-CT with regard to pulmonary nodules or masses are as follows;

- For TNM staging of the mediastinum and screening for metastases that might not be detected by CT alone;
- For radiotherapy planning; and
- For restaging lung cancer patients following treatment.

In addition, PET-CT can provide some information on the histopathological type of lung mass. PET-CT is useful for staging and restaging of disease, detecting recurrent or residual disease, assessing response to therapy, and for prognostication. Prior studies evaluating preoperative maximum standardized uptake value have shown that lepidic predominant adenocarcinoma and other well-differentiated tumors have less FDG-avidity than squamous cell carcinomas.¹⁵ Ninety percent of all lung cancer cases are NSCLC on histological analysis.

As per the NCCN imaging appropriateness criteria, FDG-PET-CT covering skull base to knees or whole-body FDG-PET-CT is recommended for stage I to stage IV NSCLC.^{13,16} As per the NCCN guidelines, distant disease detected on PET-CT requires histopathologic or other imaging confirmation, and FDG uptake detected in mediastinal nodes requires histopathologic confirmation. Incidental lung nodule more than 8 mm requires FDG-PET-CT for evaluation as per the NCCN guidelines.

Standardized uptake value more than that of the baseline mediastinal blood pool is considered as a positive PET result. False-negative results of PET can be seen in small nodules, generally less than 8 to 10 mm in diameter (T1a), mucinous adenocarcinomas with a relatively small number of cells, and low-grade malignancies such as carcinoma in situ (Tis) and minimally invasive adenocarcinoma [T1a(mi)]. Occult metastases detected on FDG-PET-CT in locally advanced NSCLC can help to reduce the frequency of futile thoracotomies.

The rates of progression-free survival and overall survival are dismal ($p < 0.001$) in upstaged disease with PET-CT. There is no recommendation to use bone scintigraphy for staging NSCLC. FDG-PET-CT can better differentiate tumor from postobstructive atelectasis than CT, the distinction essential for local tumor staging, deciding biopsy site, planning radiation therapy, and evaluation of treatment response. Studies have shown increased FDG uptake in areas

of atelectasis as compared with normal lung, and reduced FDG uptake as compared with tumor tissue. Gross tumor volume assessed using PET tends to be smaller than CT-measured tumor volume in 13 to 17% of patients. Disadvantage of FDG-PET-CT lies in the evaluation of chest wall invasion owing to blooming artifact.

Conclusion

PET has high accuracy in detecting lymph nodal as well as extrathoracic metastases.¹⁵ As per the NCCN guidelines, FDG-PET-CT covering skull base to knees or whole-body FDG-PET-CT is recommended for stage I to stage IV NSCLC.¹⁴ Imaging specialists should be aware of the advantages and disadvantages of FDG-PET-CT in staging.

Summary and Conclusions

Emergence and availability of PET-CT have transformed the way we stage and manage cancers. It has a proven role for staging of most cancers, assessing response to therapy, and in follow-up. Guidelines for the use of PET-CT in oncology vary across countries and across institutions. In the light of clinical judgement if the possibility of metastatic disease is high and it will entail a change in management, then advising a PET-CT appears reasonable regardless of the guidelines. If use of PET-CT for detection results in change of management, then it is justified. More often the change in management is from a more aggressive treatment strategy to a less aggressive one, thereby saving costs and unnecessary intervention.

Conflict of Interest

None declared.

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