Applications in Oncology: An Overview

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Introduction

Treatment of patients with cancer requires appropriate histological diagnosis and, more importantly, staging of the disease using the least invasive and most sensitive and specific procedures. Over the last decades, several studies have demonstrated immense contribution of nuclear medicine to the management of cancer. Positron emission tomography (PET) scanning has added significant clinical value in evaluating cancer patients. PET is an imaging modality that is used to provide a three-dimensional image of functional changes in the body. PET is commonly used to detect and stage different types of cancer. Accurate information about diagnosis and staging of disease is critical for planning the most appropriate treatment strategy (Figs. 6.1 and 6.2). PET has also been used to monitor therapy. The rationale for this is that the early detection of disease that is not responding to treatment could allow for a change to a more effective treatment strategy. PET scanning has, therefore, been used as a tool in diagnosis, staging, restaging, and possibly follow-up of cancer patients. Another potential contribution of PET scan is monitoring delivery of target cancer therapy.

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PET imaging changes the intended patient management strategy in about 40 %. In some studies, it is even more than 50 %. Results were consistent across all cancer types. In as many as 90 % of cases, referring physicians indicated that the scan results allowed them to avoid additional imaging tests or procedures, indicating that PET can significantly reduce the number of testing procedures and result in substantial healthcare savings. PET imaging allowed physicians to avoid costly biopsy surgeries in as many as 70 % of cases.

PET has been found to be a cost-effective modality specially in following situations:

- The differential diagnosis of solitary pulmonary nodules
- The staging of non-small cell lung cancer
- The restaging of colorectal carcinoma after recurrence
- The restaging of Hodgkin's and non-Hodgkin's lymphoma

Cost savings in lung and colorectal cancer primarily result from avoiding costly surgical procedures in cases where no reasonable chance of cure exists.

Role of PET in Lung Cancer

Squamous cell and small cell carcinomas (SCLC) occur predominately in smokers and arise from the proximal bronchial tree. Adenocarcinomas are more often peripherally located in the lung.

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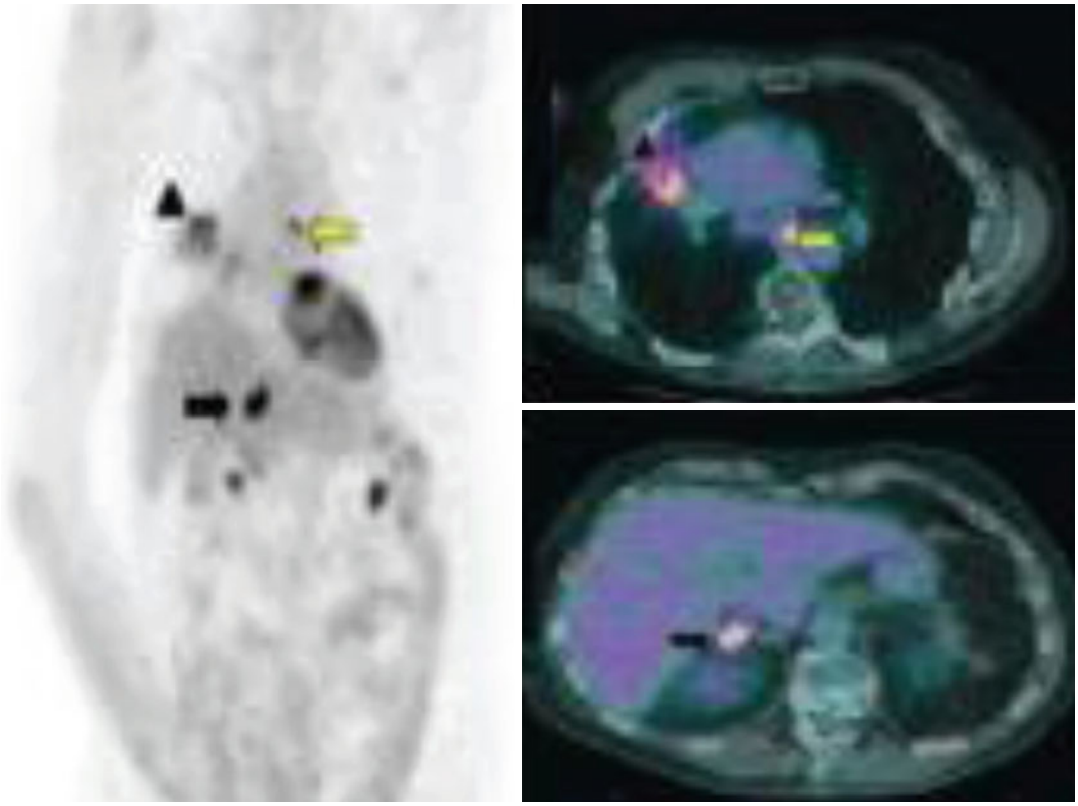

Fig. 6.1 Initial staging of non-small cell lung cancer. MIP image (*left panel*) and fused images (*right panel*) of 18 F-FDG PET-CT showed the primary tumor (*arrowhead*) with mediastinal nodal involvement (*yellow arrow*) and extra-thoracic right adrenal metastasis (*black arrow*)

SCLC is of neuroectodermal origin and has the poorest prognosis, usually having spread systemically at the time of initial diagnosis.

FDG-PET imaging is recommended for the evaluation of indeterminate pulmonary nodules greater in size than the resolution of most imaging systems (5–15 mm). Because of the high negative predictive value of FDG-PET, FDG-negative lesions can be followed at 6-monthly intervals radiographically. FDG-positive lesions need to be biopsied because of the high rate of false-positive active granulomatous processes. FDG-PET should also be performed for staging non-small cell lung cancer (NSCLC), because it can detect metastatic lymph nodes that do not meet CT size criteria for malignancy. Using whole-body imaging, PET can reliably detect unsuspected distant metastases. Unlike CT, FDG-PET imaging can differentiate scar tissue from recurrent tumor and therefore has applications for monitoring therapy and in the evaluation of recurrent disease.

FDG-PET scan complements conventional radiological studies in the evaluation of focal pulmonary nodules, lung cancer staging and tumor recurrence, treatment response, and prognosis. Increased glucose metabolism by malignant cells allows physiologic differentiation of benign and malignant lung lesions. In practice, nodules with low FDG uptake can be followed radiographically, and nodules with increased uptake should be evaluated with biopsy or resection. FDG-PET scanning has also shown tremendous promise in the evaluation of mediastinal node involvement and previously unidentified distant metastasis. However, when pathologic confirmation of lung cancer is required, minimally invasive techniques, such as bronchoscopy, thoracoscopy, and

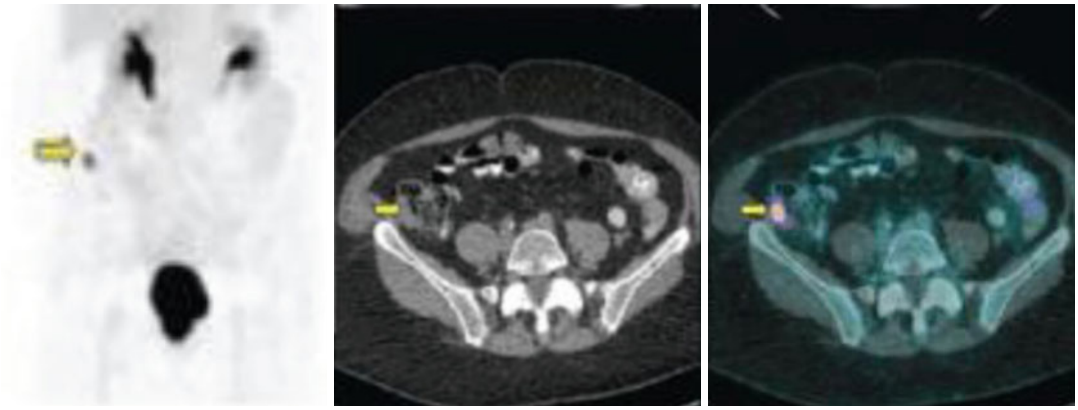

Fig. 6.2 Staging of non-small cell lung cancer. FDG image (*left side*), CT images (*middle*), and fused images (*right image*) in PET-CT show apart from the primary tumor (not shown here) incidental right iliac fossa a small focal uptake (*arrow*) is noted, which cross-correlated to a small soft tissue lesion in the cecum and turned out to be a synchronous primary adenocarcinoma

anterior mediastinoscopy among other methods are valuable and simple ways to obtain tissue.

Anatomic (CT, MRI) and physiologic imaging (PET) techniques should be considered complementary rather than competitive imaging methods. This problem does not exist anymore with the routine use of hybrid machines like PET-CT.

PET is also better than CT for the differentiation of recurrent tumor versus scar in patients who have already been treated. Several studies have shown that FDG-PET can be useful in predicting and assessing the response to radiation therapy as well as chemotherapy.

Role of PET in Colorectal Cancer

The main indications for FDG-PET whole-body imaging in patients with suspected, recurrent, or metastatic colorectal carcinoma are as follows:

(a) When there is a rising serum CEA level in the absence of a known source
(b) To increase the specificity of structural imaging when an equivocal lesion is detected
(c) As a screening method for the entire body in the preoperative staging before curative resection of recurrent disease
(d) To differentiate post-therapy changes versus persistent/recurrent viable tumor
(e) To monitor response to therapy

It may be interesting to know that the US Health Care Financing Administration has approved reimbursement of FDG-PET imaging by Medicare for diagnosing, staging, and restaging colorectal carcinoma since 2001.

Detection and Staging of Recurrent Colorectal Carcinoma

Serial measurements of CEA and CT have been conventionally used in the follow-up and detection of metastases. A large number of patients present with isolated liver metastases as their first recurrence, and 20 % of these die with metastases exclusive to the liver. Hepatic resection may result in a cure in up to 25 % of these patients, but the size and number of hepatic metastases and the presence of extrahepatic metastases all adversely affect prognosis. The presence of extrahepatic metastases is thought to represent a contraindication to hepatic resection. Serial CEA determinations are used to monitor patients for recurrences with a sensitivity of 59 % and specificity of 84 %, and CT has been the conventional imaging modality used to localize recurrence. However, CT fails to demonstrate hepatic metastases in many cases and underestimates the number of lobes involved. Extrahepatic abdominal metastases are commonly missed on CT, and

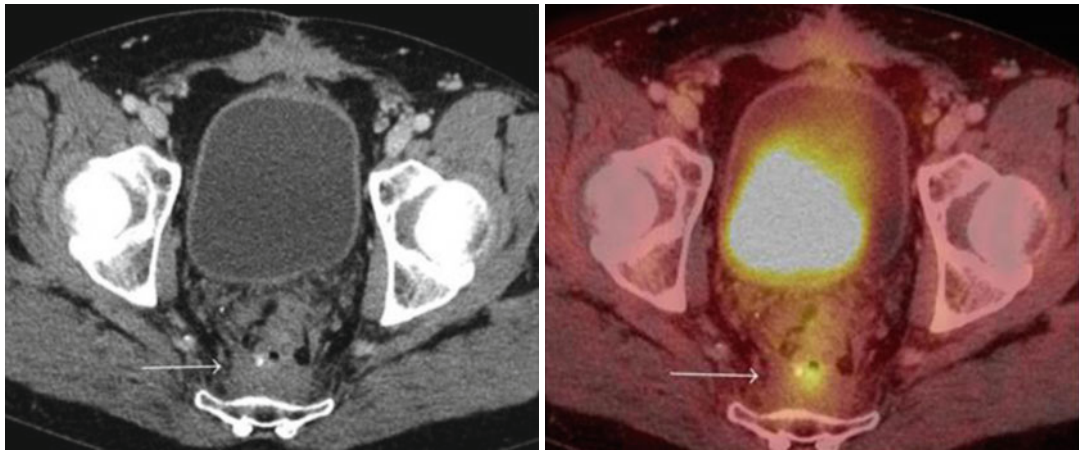

Fig. 6.3 Doubtful recurrence of rectal cancer seen in CT image (*left*) (*arrow*). Confirmation of malignancy in PET-CT image (*right*) (*arrow*)

the differentiation of postsurgical changes from tumor recurrence is problematic. Superior mesenteric arterial CT portography is more sensitive than CT for detection of hepatic metastases but has a high rate of false-positive findings, lowering the positive predictive value.

Functional imaging with SPECT used in the detection and staging of malignancies has well-known limitations. Radioimmunoscintigraphy is limited by difficulties with antigen modulation and variable depiction of tumor and nontumor cells, as well as by physiologic hepatic and bowel activity. Moreover, due to slow blood pool clearance, images are not acquired for several days after injection, a major disadvantage.

Numerous studies have demonstrated a strong role for FDG-PET in identifying recurrences of colorectal carcinoma (Fig. 6.3). For detection of recurrent colon carcinoma, FDG-PET-CT has been found to be more sensitive than CT at all anatomic sites, including the lung. One-third of PET-positive metastases in the extrahepatic abdomen and pelvis are CT negative. Whole-body PET is especially useful for detecting distant metastatic disease, including abdominal nodal disease, pulmonary metastases (indeterminate lung nodules), and differentiating postsurgical scarring from recurrent disease, all of which are problematic for CT. For differentiation of post-therapy scar from local recurrence, PET is clearly more accurate (90–100 %) than CT (48–65 %), and CT is often equivocal. For hepatic metastases, FDG-PET has a higher accuracy (92 %) than CT (78 %) and CT portography (80 %) despite the slightly higher sensitivity of CT portograph. In patients with unexplained CEA elevation and no abnormal findings on conventional evaluation, including CT, the sensitivity of PET for the detection of recurrent disease has been found to be 93–100 %. In multiple studies, including detecting recurrence, FDG-PET imaging led to a change in management in an estimated 32 % of the patients.

Monitoring Therapy of Colorectal Carcinoma

Increased FDG uptake immediately following radiation may be due to inflammatory changes, and is not always associated with residual tumor. Although the time course of postirradiation FDG activity has not been studied systematically, it is generally accepted that FDG activity present 6 months after completion of radiation therapy most likely represents tumor recurrence. There are many reports suggesting that the response to chemotherapy in patients with hepatic metastases can be predicted with PET. Responders may be discriminated from nonresponders after 4–5 weeks of chemotherapy with fluorouracil by measuring FDG uptake before and during therapy.

Regional therapy to the liver by chemoembolization can also be monitored with FDG-PET imaging. FDG uptake decreases in responding lesions. The presence of residual uptake in some lesions can help in guiding further regional therapy.

Role of PET in Lymphoma

Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) belong to those kind of malignancies that are potentially curable. The extent of the disease is the most important factor influencing relapse-free and total survival of patients. Conventional methods for staging like CT and ^{67}Gallium imaging have limitations. Although ^{67}Gallium plays a role in the evaluation of the presence of viable tumor in residual post-therapy masses, it is not superior to CT in initial staging of untreated lymphoma. FDG-PET imaging is recommended for staging lymphoma in addition to CT and other conventional staging modalities, because it can detect additional nodal and extranodal lymphomatous lesions, as well as bone marrow involvement even when bone marrow biopsy is negative.

Both HD and NHL exhibit marked FDG uptake, and FDG imaging is useful both for staging and monitoring therapy. During chemotherapy, FDG-PET imaging can identify the responders early in the course of treatment, allowing alterations in the chemotherapy regimen as indicated. FDG-PET can differentiate scarring from persistent or recurrent tumor in residual masses after the end of treatment and allows improved discrimination of rebound thymic hyperplasia from viable lymphoma. Because of the superior resolution of FDG images compared to ^{67}Gallium scintigraphy, FDG imaging, therefore, is replacing ^{67}Gallium for the evaluation of patients with lymphoma.

Staging Lymphoma

One of the most important factors influencing relapse-free and total survival of lymphoma patients, besides histology, is extent of disease, and accurate initial staging is essential for optimizing patient therapy and determining prognosis. Therapeutic implications for patients with HD and NHL emphasize the importance of initial staging accuracy—patients diagnosed with stage I or II HD and some subgroups of NHL may receive local external radiotherapy alone or in combination with chemotherapy, while those with stage III or IV disease are typically treated with chemotherapy.

Problems of Staging with Conventional Methods

Conventional modalities for staging lymphoma include physical examination; computed tomography (CT) of the chest, abdomen, and pelvis; and bone marrow biopsy. Although CT is the best imaging technique to provide detailed information about the relationship between organs and vascular structures, CT criteria for pathologic adenopathy are based on size alone, which is a major limitation. Benign lymph node enlargement may lead to over-staging, while small malignant lymph nodes may not be recognized, resulting in under-staging. In addition, CT has limited sensitivity for detection of the spleen, liver, and bone marrow involvement. Equivocal CT lesions are common and frequently require additional imaging or biopsy. This prolongs the staging workup and adds to patient expense and morbidity. Patients who are under-staged may receive inadequate therapy for their disease, jeopardizing the opportunity for remission or cure. Conversely, over-staged patients may receive unnecessarily aggressive or investigational therapy and be given an overtly grim prognosis.

Problems with Gallium Scintigraphy

Scintigraphy with ^{67}Gallium is often included in the initial staging of patients with lymphoma. However, it has many limitations. These include suboptimal photon energy leading to noisy images, variable uptake of Gallium by tumor, particularly low-grade NHL, limited detection of abdominal disease secondary to marked

physiologic hepatic and colonic activity, and the potential for false-positive findings related to infectious or inflammatory processes. ^{67}Gallium scintigraphy is also inconvenient for the patient as multiple visits to the imaging facility on consecutive days are typically required. In addition, the value of ^{67}Gallium scintigraphy is not in the initial staging of patients with lymphoma but in the evaluation of the response to treatment and assessment of residual mass after therapy. A pretherapy scan is, however, necessary to confirm that the tumor is ^{67}Gallium avid before trusting follow-up ^{67}Gallium scans as an accurate measure of tumor response.

Staging of lymphomatous involvement of the bone marrow requires invasive bone marrow aspiration; their sensitivity for detecting bone marrow disease is limited by sampling error. Bone scintigraphy is often unreliable for the demonstration of skeletal involvement because of its low sensitivity. Although MRI appears to be the most sensitive imaging technique, whole-body MRI is not applicable as a screening technique and should be reserved for areas that are clinically suspect.

Advantages of PET Scanning in Lymphoma Management

Many of the above limitations of conventional staging modalities for lymphoma can be overcome with the use of FDG-PET. Unlike CT, functional imaging with FDG-PET imaging directly identifies increased metabolic activity in malignant tissue, and does not depend on anatomical distortion or enlargement for the determination of abnormalities. Compared with ^{67}Gallium, FDG is avidly trapped by virtually all lymphomas, although the degree of FDG uptake does seem to correlate with the histological grade of malignancy and proliferation rate. Although physiologic gastrointestinal activity does occur with FDG, the better quality of the images usually allows the differentiation of physiologic activity in the bowel from abdominal and pelvic lesions. With FDG-PET imaging, most of the skeleton is imaged during scanning, enabling noninvasive detection of focal bone marrow disease that may be missed through sampling error with standard iliac crest biopsy.

The degree of FDG uptake seems to be a prognostic factor. The cost-effectiveness of PET compared to conventional staging modalities has also been established.

Role of PET in Breast Cancer

Breast cancer is the most common cancer diagnosed among women in advanced countries and appears to be the same at least in urban India. Once diagnosed, appropriate surgery and adequate therapy can lead to decrease morbidity and improve quality of life. The assessment of axillary lymph nodes for cancer involvement is mandatory for planning and staging breast cancer for the appropriate treatment of patients.

Mammography, magnetic resonance imaging (MRI), ultrasound, computed tomography (CT), and bone scintigraphy play a significant role in breast cancer detection, assessment of treatment response, detection of recurrence, and assessment of complications. In recent times, scintimammography has been playing an important role in detection and follow-up.

Imaging with the positron-emitting isotope 18-F attached to glucose (FDG) and imaging with PET-CT have been a standard imaging procedure in breast cancer. Such PET-CT images are superior to PET or CT alone. The intensity of FDG uptake is related to the biological and histological characteristics with uptake being usually more marked in invasive ductal carcinoma than in invasive lobular carcinoma. Uptake in ductal carcinoma in situ (DCIS) is usually poor or absent, rendering it unsuitable for very early detection. Positive correlation between FDG uptake, tumor grade, and tumor proliferation index has been demonstrated (Fig. 6.4).

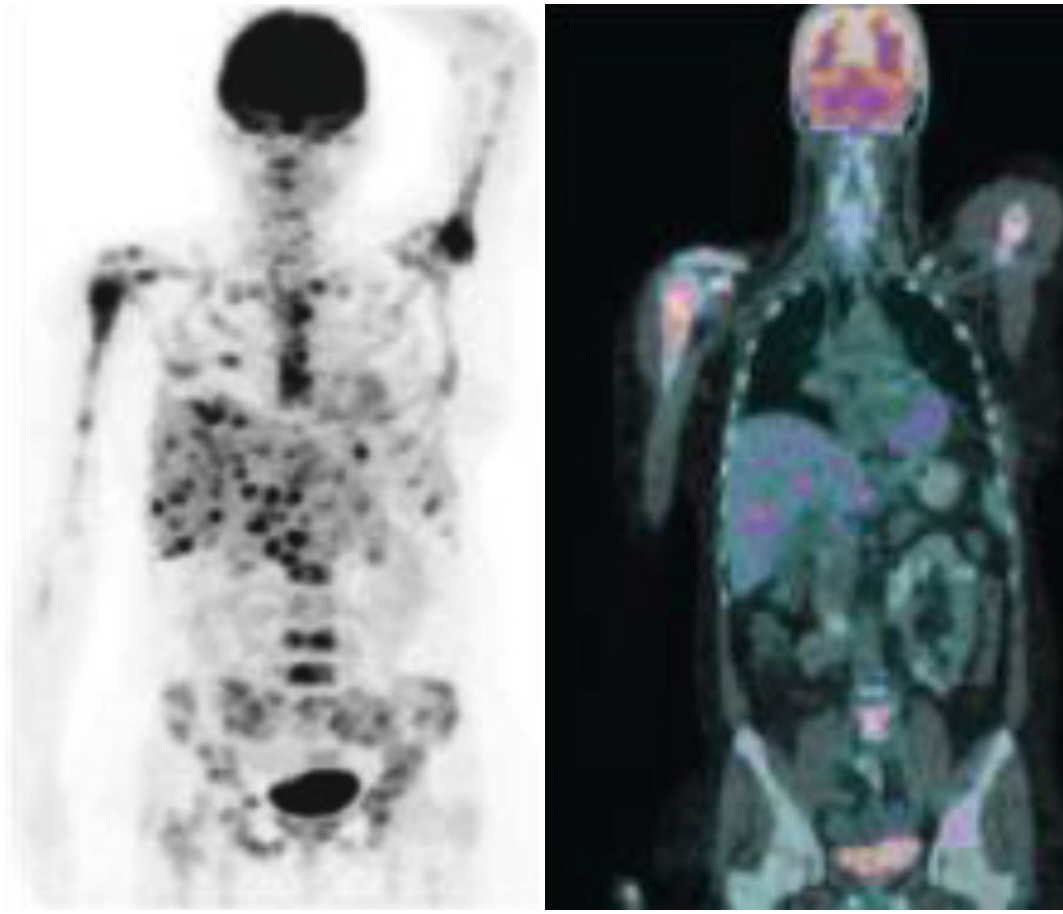

Fig. 6.4 Staging of breast cancer. FDG image (*left side*) and coronal fused images (*right side*) of 18 F-FDG PET-CT showed extensive metastases in the liver and skeleton

Role of PET in Neuroendocrine Tumors

Neuroendocrine tumors develop from cells originating from neural crest and maintain the capacity for amine precursor uptake and decarboxylation, a process essential for the production of monoamine transmitters. They can be located in the thyroid (C-cells), adrenal medulla, lung, skin (melanocytes), nervous system, gastrointestinal tract, and pancreas. These tumors secrete a variety of peptide hormones. Direct assessment of these peptide hormones or their metabolites can be used as tumor markers, both for diagnosis and monitoring treatment response.

The diagnosis of neuroendocrine tumors is mainly biochemical. Localization and therapy of these tumors pose a significant challenge. Conventional morphological imaging modalities such as ultrasound, CT, and MRI are the primary imaging modalities. However, in significant percentage of cases, the localization becomes difficult, and radionuclide images are indicted.

Conventional radiopharmaceuticals used for the diagnosis of neuroendocrine tumors are as follows:

In-111 octreotide (OctreoScan)
I-123 and I-131 metaiodobenzylguanidine (MIBG)
Tc-99 m DMSA (used mainly for medullary carcinoma of the thyroid)

In recent years, FDG-PET and coincidence imaging are gaining considerable importance and popularity in tumor imaging. Comparison of FDG images with OctreoScan in the assessment of neuroendocrine tumors has, however, shown that OctreoScan is more sensitive and specific. But, in case of medullary carcinomas of the thyroid, FDG-PET images have fared better than OctreoScan. The general recommendation is that OctreoScan be a primary imaging in tumors of neuroendocrine origin, and only when OctreoScan fails to localize the tumor or in undifferentiated neuroendocrine tumors, FDG-PET can be recommended.

In the absence of Octreotide Scan or FDG-PET facility, MIBG scans can be recommended. The advantage of MIBG is that it can be used for therapeutic purposes of such tumors.

For Further Reading

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