Role of PET and PET/CT in Anticancer Drug Therapy Response Evaluation

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Abstract: Anti-cancer drug development is a major area of research. New imaging techniques provide a novel method for anti-cancer drug development and monitoring response to therapy by targeting functional metabolic activity at cellular level. The current assessment of the response to therapy in solid tumors based on measurement of the changes in tumor size have many limitations. Positron emission tomography (PET) has been used to measure changes in drug induced metabolism, cellular proliferation and tissue perfusion. Also, changes induced by immuno-modulating drugs such as apoptosis, telomere activity, growth factor levels and many more can be studied using specific radiolabelled PET tracers. Initially PET was used alone without any computed tomography (CT) or magnetic resonance imaging (MRI) hybridization. Since there are few limitations associated with PET alone, a novel combined PET/CT system has recently been built that improves the ability to correctly localize and interpret radiotracer uptake. Hybrid PET/CT scanners provide both the anatomical and functional aspects of the tissue. PET and PET/CT have been found to be very useful in various cancers. In the present study we have investigated role of PET/CT as a predictor of early response to chemotherapy in locally advanced breast cancer patients, lymphoma, pediatric cancer, lung cancer, etc. We have performed more than 14000 PET/CT at our institute. We have found that fluorine-18 fluoro-deoxy-glucose (^{18}F-FDG) PET/CT plays important role in early assessment of treatment response in various cancer patients. A positive PET/CT scans after the completion of therapy is a strong predictor of residual disease, whereas, a negative study is associated with complete remission in these patients.

Keywords: FDG PET/CT, anticancer drug, treatment response evaluation.

INTRODUCTION

There has been significant development in treating the patients with various cancers either through chemotherapy or radiotherapy. Monitoring the therapy response is important in these cases, keeping in mind the long list of severe adverse effects resulting from this therapy. A novel method for monitoring the response of this therapy has been provided by new imaging techniques, more importantly, the functional imaging techniques like PET and PET/CT. For past many years, ^{18}F-FDG PET/CT has been extensively used in assessment of chemotherapy treatment response in patients with various cancers. A reduction in FDG uptake in tumor within days to weeks after starting the treatment correlates well with the treatment response and also predicts survival in some cases [1]. Several studies have been conducted and the utility of PET/CT in monitoring the therapy response has been proven, but still, the authenticity of these studies is questionable due to their small sample sizes. Large multicentral clinical trials are needed to authenticate these results. Despite being the fact that PET and PET/CT is very useful for assessing the cytoreductive/ cytotoxic treatment response, it is not a standard choice of investigation for most tumor types yet and definitely, more work is required to make it a standard of care.

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Many chemotherapeutic agents like Trastuzumab, Sunitinib, Imatinib, Lapatinib etc., which are used in various cancer conditions, are cytostatic in nature and halt the tumor growth but do not cause tumor cell death [2-6]. Monitoring the response to these agents using conventional imaging modalities such as CT, MRI would not be helpful, as the basis for assessing the therapy response by these modalities is reduction in size of the tumor. Tumor shrinkage and its dissolution is a complex process which takes significant time to occur, usually weeks to months. It causes loss of precious time while evaluating treatment response using conventional imaging. These modalities also can not differentiate the residual disease from post- therapy changes such as fibrosis and scarring. The newer functional imaging such as PET in association with CT or MRI is the best imaging available to date. PET scan provides the functional/metabolic status of the tumor and CT/MRI provides the anatomical localization helping the image interpretation with maximum accuracy. This functional information is very helpful to identify early response to therapy so that therapies which are ineffective can be stopped to reduce the expenses, time wastage and its side effects.

BREAST CANCER

Breast cancer is the most common diagnosed cancer in females and is the second most common cause of cancer deaths after lung and bronchial cancer in this group worldwide. There are multiple options available for the systemic therapy in breast cancer and it is one of the solid

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tumor which is much responsive to the therapy [7]. Treatment options for breast cancer are surgery, chemotherapy and radiotherapy. Various imaging modalities are used for staging, restaging and response evaluation in breast cancer. Conventional techniques available for breast cancer imaging are radiological examinations, such as mammography, Doppler ultrasonography, CT, MRI, magnetic resonance spectroscopy and optical imaging. MRI combined with contrast-enhanced MRI as the functional imaging modality has a diagnostic accuracy of 93% for identifying tumors showing a pathologic complete response [8].

^{18}F FDG-PET has been proven to be an accurate imaging modality for staging, restaging recurrent/metastatic disease and for evaluation of therapy response. As it has ability to detect early changes in tumor glucose use, it has been studied worldwide as a method for assessing tumor response to neoadjuvant chemotherapy and it has shown close correlation of changes in ^{18}F-FDG uptake with the effectiveness of treatment [9, 10]. PET scanning is usually done at different intervals during and after chemotherapy, but there is no general consensus regarding this. FDG-PET done after the first cycle of chemotherapy for evaluating the therapy response has sensitivity and specificity ranging from 39-100% and 74-100%, respectively, shown by several studies [9, 11-13]. Sensitivities and specificities after the second cycle were 69-93% and 75-94%, respectively [12-14]. The above data suggests lower accuracy of PET in treatment monitoring after first cycle of chemotherapy. Applying PET after 3 or more cycles of chemotherapy is too late to make effective changes in chemotherapy regime and by this time patient would have already been exposed to ineffective and toxic chemotherapy. Rousseau *et al.* suggested that treatment response evaluation can be best done after second cycle of chemotherapy [13]. For analysis and assessment of tumor response to therapy, the maximum standard uptake value (SUVmax) method is most widely used. Higher SUV correlates to higher tumor activity and it helps in differentiating responders from non-responders after the chemotherapy. PET is also very useful in evaluating the metastatic disease by scanning whole body in one procedure.

NON SMALL CELL LUNG CANCER

Lung cancer is the second commonest malignancy in both sexes and is a major cause of cancer related deaths. Non small cell lung cancer (NSCLC) is the most common type of lung cancer. As lung cancer is presented at advanced stages, long term survival rate is low. Since the implementation of PET as a functional imaging modality, early detection of NSCLC is possible, which when used along with CT as PET/CT, helps in detecting nodal and distant metastatic disease more accurately [15]. Detection of widespread metastatic disease early by PET is of great help, as it may prevent the major invasive surgery such as thoracotomy and the patient can be simply put on chemoradiation therapy. Treatment response evaluation using conventional imaging might not be accurate because there is high variability in changing of tumor dimensions after therapy as there are usually different proportions of malignant cells, stroma and inflammatory cells in tumor tissue. Also after the cure of NSCLC, fibrotic tissue may remain which may present as false positive in CT or MRI.

PET in combination with CT or MRI assesses the tumor activity with its proper localization. A baseline scan should always be performed before commencement of the chemotherapy. Post-chemotherapy scan is then compared with the baseline scan for proper interpretation of the treatment response. Disease process is assigned complete response, partial response, stable disease and progressive disease according to PET response criteria in solid tumors (PERCIST) [16]. Some studies have evaluated the role of ^{18}F-FDG PET in suspected residual or recurrent NSCLC have shown higher accuracy and ability of providing prognosis than with conventional imaging modalities [17-19]. As described in breast cancer section, SUVmax is taken as basis for determining the tumor metabolic status. Some of the histologic types of NSCLC have an intrinsically low SUVmax which may pose a problem in identifying or correlating the grade of tumor with FDG uptake by the tumor. Goudarzi *et al.* studied 53 patients who had 57 pathologically proven lesions and showed that in 26 lesions having pure bronchioloalveolar carcinoma (BAC) had a median SUVmax of only 1.48 (range, 0.63–4.54) [20]. Out of these BAC lesions, 81% had SUVmax of less than 2.5, which is a cutoff value usually used to differentiate benign from malignant lesions [20]. PET study results also prognosticate the survival. Nahmias *et al.* studied ^{18}F-FDG PET in 16 patients having NSCLC and evaluated serial changes in the SUV during chemotherapy and subsequently demonstrated that patients having reduction in the SUVmax more than or equal to 50% between studies performed after 1 and 3 weeks of chemotherapy survived for more than 6 months, whereas patients with SUVmax reduction less than 50% died within 6 months [21].

GASTROINTESTINAL CANCERS

There are many cancerous conditions involving gastrointestinal (GI) tract. Esophageal and colorectal cancers are important among all GI cancers in view of their higher incidence and associated mortality with them [22]. Squamous cell carcinoma (SCC) occurs in upper two-third part of esophagus and adenocarcinoma occurs in lower one-third part. SCC is more prevalent than adenocarcinoma of esophagus worldwide, whereas, these both types are equally prevalent in USA.

PET/CT is used in esophageal cancer for pre-therapeutic staging, restaging and for assessing response to therapy. Pre-therapeutic staging is important in esophageal cancer to differentiate patients with loco-regional disease from patients having metastatic disease as the treatment regime for each is different than the other. FDG-PET has a sensitivity and specificity of 67% and 97% respectively, in metastatic staging of esophageal cancer [23]. To know about clinical consequences after the chemotherapy is sometimes necessary and so, therapy response monitoring becomes important. FDG PET/CT is best available technique for monitoring the therapy response. Treatment response can be assessed either during the course of chemotherapy or after the completion of the therapy. Many studies have demonstrated the sensitivity and specificity of PET/CT in monitoring the treatment response in esophageal cancer ranging from 62-100% and 55-88%, respectively [24-27].

Recently, because of earlier detection of disease and advancement in chemotherapeutic drugs, the prognosis for

colorectal cancer patients has improved to a large extent. PET/CT has already proved its role in staging of colorectal cancer and now it is also being used for assessing chemotherapy response. As in other solid tumors, therapy response was being done through conventional imaging in earlier times using response evaluation criteria in solid tumors (RECIST) criteria. According to RECIST criteria, therapy response will be considered only if there is decrease in 30% diametric dimension of tumor [28]. It has limited value in differentiating residual fibrotic mass or post-operative changes from recurrent disease. Here, PET or PET/CT has overcome this limitation by providing the functional metabolic status of the tumor. Many authors have provided the data regarding the efficacy of PET or PET/CT in monitoring the therapy response in locoregional and metastatic disease in colorectal cancer. Findlay *et al*. evaluated PET in 18 patients for response evaluation to therapy and found the sensitivity 100% and specificity 75% [29]. Dimitrakopoulou-Strauss *et al*. performed serial 18F-FDG PET scans during the chemotherapy course and found a positive correlation between the PET findings and survival times of the patients [30]. de Geus-Oei *et al*. found increase in mortality rate and disease progression with PET showing worst response after the therapy [31]. Some authors monitored the response after local ablative therapy for treatment of liver metastasis in colorectal cancer and found the positive predictive value and negative predictive value ranging from 80-100% and 96-100%, respectively [32-36].

HEAD AND NECK CANCERS

Head and neck cancer is the sixth most common cancer all over the world. Head and neck squamous cell carcinoma (HNSCC) comprises 90% of these malignancies in western world. Prognosis is worse in non-surgical candidates having advanced disease with less than 10% five year survival [22]. After the chemotherapy, CT, MRI and FDG PET are considered standard investigations for treatment monitoring in HNSCC.

Some studies have evaluated the efficacy of PET or PET/CT in therapy response monitoring in HNSCC [37-40]. Some of them evaluated PET after induction chemotherapy and others evaluated after complete definitive therapy. In these studies, time of performing PET scans after the completion of chemotherapy varied from 4 weeks to 1 year. Some authors have suggested that the PET study should not be done before 2-3 months after the completion of therapy, as by that time inflammatory changes due to chemotherapy did not subside. So, this reduces the false-positive findings. Some of these studies have also depicted that when PET was done within 1-2 months period after chemotherapy completion, a higher false-negative rate was observed. Reason was formulated that by this early time the small-volume residual disease usually did not get detected by PET. All these authors have evaluated the sensitivity, specificity, PPV and NPV of PET in therapy response assessment in HNSCC ranging from 40-87%, 25-91%, 18-70% and 50-97%, respectively. After chemotherapy/radiation therapy, focal and asymmetric FDG uptake is generally considered to be residual disease, whereas, non-focal and diffuse FDG uptake is more suggestive of post-radiation inflammation. There is diffuse increased uptake in laryngeal or oropharyngeal areas after the chemoradiotherapy which remains for longer periods. One has to be careful while interpreting the scans in these cases as focal uptake of higher intensity in between the diffuse uptake may be because of ulceration or persistent disease. Post-therapy PET scan also changes the management plan by showing the presence/absence of nodal disease. Neck dissection is the usual procedure followed for the nodal metastatic disease in neck. Ong *et al*. found that PET/CT findings after therapy reduced the number of planned neck dissections by 75% [37].

LYMPHOMA

There are two major types of lymphomas i.e. Hodgkin's disease (HD) and Non-Hodgkin's lymphoma (NHL). There are many different types of NHL, which can be divided into aggressive [fast-growing] and indolent (slow-growing) types and can be classified as either B-cell or T-cell NHL. HD is marked by the presence of a type of cell called as Reed-Sternberg cell. The two major types of Hodgkin's lymphoma are classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma. ^{18}F-FDG PET/CT has potential value in monitoring the response to treatment in patients with both NHL and HD. PET/CT provides functional and anatomical details in same setting. Treatment response evaluation using PET/CT can be done during treatment and evaluation of treatment response after completion of treatment.

Kumar *et al*. analyzed 19 gastrointestinal lymphoma patients. Of the 19 post-treatment PET scans, 13 showed no pathologic F18-FDG uptake, whereas 6 showed persistent F18-FDG uptake [41]. Among the 13 patients who had negative PET scans, only 1 patient (7.7%) relapsed, whereas all 6 patients (100%) who had persistent abnormal F18-FDG uptake on posttherapy PET scans relapsed. We concluded that ^{18}F-FDG PET has potential value in monitoring the response to treatment in patients with GI tract lymphomas, particularly when pretreatment PET results are positive. In another study, we included 52 patients, of which 19 were of HD and 33 were of NHL. In our study, all patients were of high-grade lymphoma. All patients underwent pre-treatment and post-treatment PET/CT scans on the same dedicated PET/CT scanner. In HD group, SUVmax was 55.5 with a range 4.7-55.5. Post treatment PET/CT scans demonstrated complete resolution of baseline abnormal FDG uptake in 16 of 19 in this group. The sensitivity, specificity, and accuracy of post therapy PET/CT scan in HD group were 67%, 94%, and 90 %, respectively. In NHL group, post treatment PET/CT scans demonstrated complete resolution of baseline abnormal FDG uptake in 27 of 33 NHL group, Fig. (**1**). Six patients showed positive PET/CT. The sensitivity, specificity, and accuracy of post therapy PET/CT scan in NHL group were 71%, 96%, and 91 %, respectively.

Many of the studies showed ^{18}F-FDG-PET is a powerful tool for the imaging of aggressive lymphoma. Their results indicate that FDG-PET has reasonable sensitivity and high specificity for evaluation of post-therapy in HD and in NHL [42-46]. These studies showed a sensitivity ranging 70-100 % and specificity ranging 78-100%. Only few studies were done on PET/CT for evaluation of treatment response in lymphoma. Zhao J *et al*. assessed the value of hybrid PET/CT with ^{18}F-FDG after 3-4 cycles of chemotherapy for

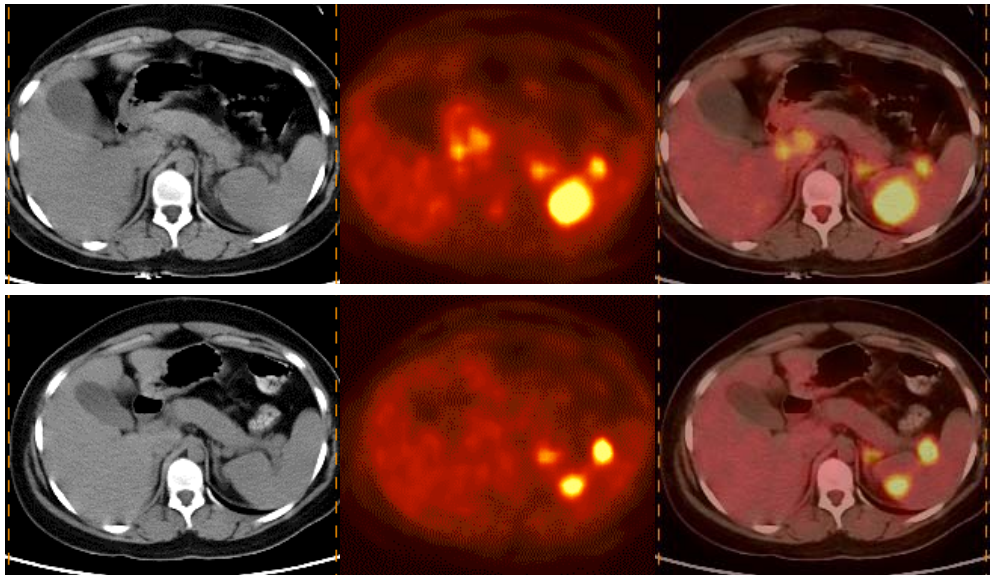

Fig. (1). Pretherapy (upper row) and post therapy (lower row) CT, PET and PET/CT scan showing significant response.

early evaluation of response to therapy and prediction of progression-free survival (PFS) in NHL [47]. Sixty-one consecutive NHL patients were included. After 3-4 cycles of chemotherapy, positive ^{18}F-FDG lesions were found in 28 patients, minimal residual uptake (MRU) in 8 and negative scans in 25 patients. In FDG-positive group, 22 patients showed progress and three died. Nine ^{18}F-FDG-negative patients and 4 patients from the MRU group relapsed. They concluded that early interim FDG imaging is an excellent and independent predictor of PFS in NHL. An early assessment of chemotherapy response with FDG scans may provide useful information for selection of patients for alternative therapeutic strategies.

GYNAECOLOGICAL MALIGNANCIES

Gynecological malignancies are major disease burden in women population worldwide. Cervical, endometrial and ovarian cancers together constitute majority of gynecological malignancies. PET and PET/CT can play an important role in evaluating treatment response in these patients. Since FDG is excreted through the urinary tract and also physiologically accumulated in the bowel, this can interfere with the optimal evaluation of abdomen and pelvis using PET/CT. There were several attempts to avoid urinary bladder activity. In our opinion the best method to deal with this problem to give plenty of fluids with diuretics (furosemide) and empty bladder frequently and the hold the urine till bladder is full with non-radioactive urine [this provide negative contrast].

Invasive cancer of the cervix is the second most common genital malignancy in women, worldwide. Surgery is treatment of choice for early cervical cancer. While, locally advanced cervical cancer is treated with definitive radiation therapy with the concurrent administration of intravenous cisplatin chemotherapy. 18F-FDG PET has been used to assess response after chemoradiation for carcinoma of the cervix. The investigators at Washington University in St. Louis, USA found that post treatment metabolic response is predictive of progression free survival after chemoradiation for cervical cancer [48-51]. In a study by Schwarz *et al.* 92 patients were imaged with 18F-FDG PET after the 3 months of completion of chemoradiation for cervical cancer. The authors demonstrated 3-years PFS rates of 78% in complete response group, 33% in partial response group and 0% in patients who showed progressive disease. A multivariate analysis, only posttherapy metabolic response and pretreatment lymph node status (as defined by 18F-FDG PET) predicted PFS. There are only few studies which evaluate treatment response during the course of radiation therapy for cervical cancer [51,52].

Ovarian cancer is the second most common genital malignancy after uterine cancer in women and has the highest mortality rate among gynecological malignancies in United States and many countries of the world. Avril *et al*. [53] demonstrated a significant correlation between changes in tumor tracer uptake after the first and third cycles of chemotherapy in ovarian cancer. A higher rate of complete tumor resections was achieved in metabolic responders than in nonresponders, Fig. (**2**). In addition, metabolic responders had a longer median overall. In another study, Nishiyama *et al.* [54] concluded that initial SUV derived by FDG PET and percentage change in SUV have the potential to predict response to chemotherapy or chemoradiotherapy in patients with advanced gynecologic cancer. There were 10 responders and 11 nonresponders based on histopathologic analysis. SUV after therapy in responders was significantly lower than that in nonresponders (p, 0.005). When an arbitrary SUV of 3.8 was taken as the cutoff for differentiating between responders and nonresponders after therapy, 18F-FDG PET showed a sensitivity of 90%, a specificity of 63.6%, and an accuracy of 76.2%. Sensitivity of 90%, specificity of 81.8%, and an accuracy of 85.7% was achieved when an arbitrary percentage change of 65% is taken as the cutoff for differentiating between responders and nonresponders.

MULTIPLE MYELOMA

Multiple myeloma constitutes approximately 10% of all hematologic cancers [54]. It is caused by neoplastic proliferation of plasma cells which presents as bone marrow

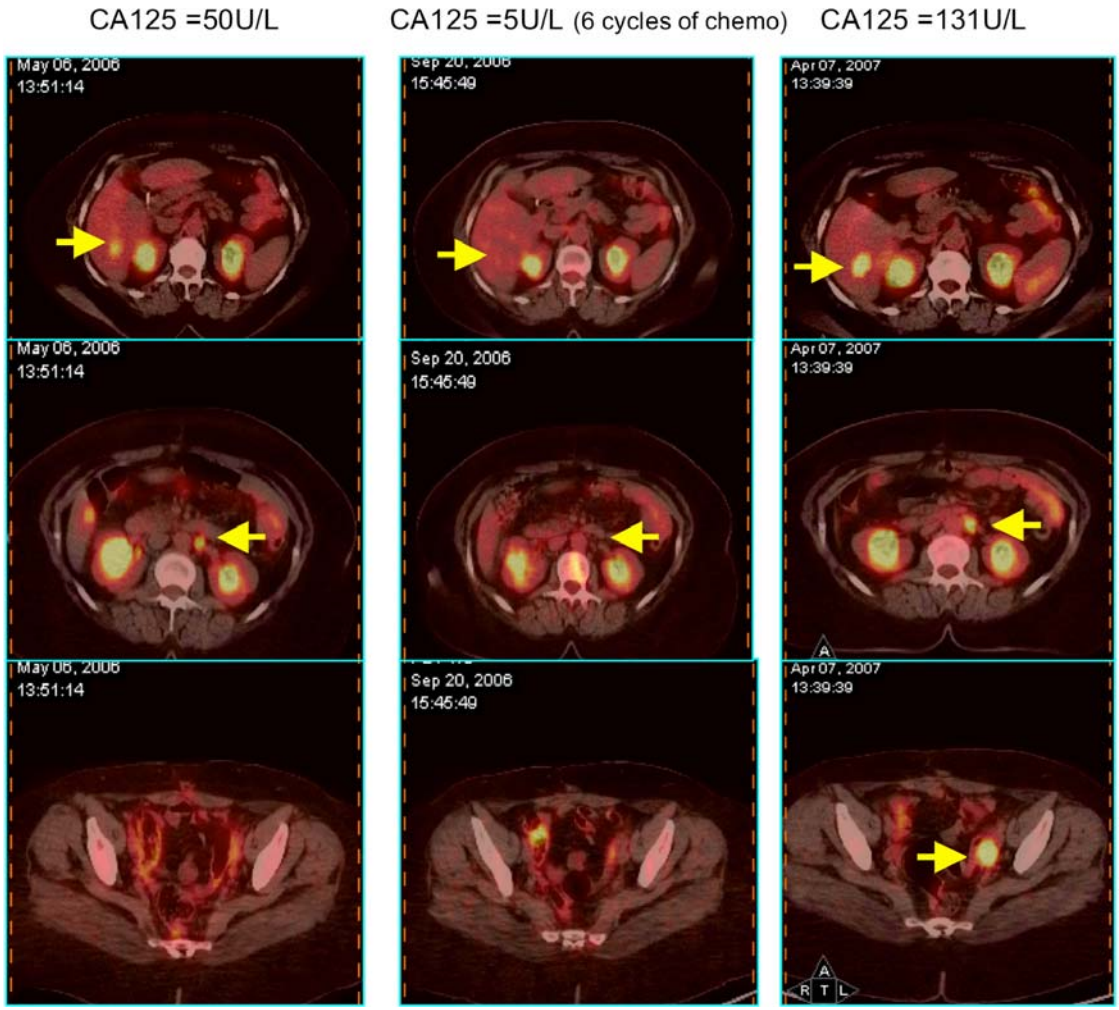

Fig. (2). Serial PET/CT studies (Pre-therapy, post therapy and follow-up) showing significant response after chemotherapy initially and recurrent disease on follow-up scan in patient with ovarian cancer. Note tumor marker correlation with PET/CT findings.

infiltration and uncontrolled formation of light chains of monoclonal immunoglobulins [55]. The diagnosis is made using laboratory parameters such as plasma protein electrophoresis and bone marrow biopsy/aspiration. M-spike on plasma protein electrophoresis is suggestive of multiple myeloma. This disease is characterized by lytic bone lesions which are present in around 80% of multiple myeloma patients [55]. Detection of bone lytic lesions is the most important factor for staging, assessing the treatment response evaluation and prognosis of multiple myeloma patients.

There are conventional and, now a days, functional imaging modalities to evaluate the status of this disease. The conventional imaging modalities have several limitations. The conventional radiography has high false negative rate and, moreover, the lytic lesions are seen on radiography only when more than 30% bone loss has occurred [56]. Whole body multidetector CT (MDCT) is better option than whole body skeletal survey but it exposes the patient to higher radiation dose. Although MRI is better than CT if the radiation safety is considered but, low dose whole body MDCT has an advantage over whole body MRI as it detects residual abnormalities in bone that are not seen by MRI [57]. PET and PET/CT as functional imaging modalities are more helpful in this disease for staging and treatment response evaluation. It has an advantage of scanning the whole body in less time and in a single procedure. It also detects and distinguishes the intramedullary from extramedullary lesions. Bredella *et al.* has reported that PET has resulted in upstaging of disease and more aggressive therapy was instituted to the patients [58]. Being a functional modality, PET accurately shows the presence of active myeloma versus monoclonal gammopathy of undetermined significance.

CONCLUSION

PET and PET/CT play an important role in evaluation treatment response during and after completion of chemotherapy in patients with various solid cancers. PET/CT studies provide both the anatomical and functional aspects of the tissue. As PET and PET/CT detect metabolic changes which happens much before structural changes in tumors, these new techniques are more sensitive in detecting early changes of therapy.

In future, changes induced by immuno-modulating drugs such as apoptosis, telomere activity, growth factor levels and many more will be studied using specific radiolabelled PET tracers using PET/CT.

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