31 CXCR4 Theranostics: A Potential Game Changer in Solid Tumors and Hematological Malignancies

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31.1 Background

A knowledge of receptor expression on the tumor is the key for therapy directed at these receptors and traditionally has been obtained by assay of biopsy material. Advances in molecular cancer biology have demonstrated that many of these tumor targets are receptors and have been reported as earliest targets for cancer diagnosis as well as therapy, with notable success in the effective treatment in few cancers [1]. One such important class of molecules/targets is a class of chemokine receptors, and the human chemokine system includes more than 50 chemokines and 20 chemokine receptors [2]. These receptors play an important role in cancer progression in terms of tumor growth, senescence, angiogenesis, epithelial-mesenchymal transition, metastasis, and evading the host immune system [3]. Among these chemokine receptors, CXCR4 is the most widely expressed receptor on malignant tumors, and its role in tumor biology has been studied extensively [4]. The chemokine CXCL12 is the sole ligand of CXCR4 and the majority of research focusing on the role of CXCR4 in cancer relates to this chemokine/chemokine-receptor pair [5, 6]. Upregulation of CXCR4 has been reported in at least 23 different epithelial, mesenchymal, and hematopoietic cancers [7, 8]. CXCR4 overexpression in tumor tissues has also been correlated with tumor aggressiveness, increased risk of metastasis, and a higher probability of recurrence [9].

It has been reported that an increased CXCR4 receptor density is often associated with metastatic disease which in turn leads to a poor prog-

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nosis [10]. Tumor receptor imaging offers a complementary role not only in providing a noninvasive evidence of tumor receptor expression but also in the evaluation of the entire tumor burden and characterization of the tumor heterogeneity. Therefore, noninvasive imaging using high-throughput PET probes targeting CXCR4 receptors may yield important diagnostic and prognostic information pertinent to the disease process [11]. Plerixafor (AMD-3100), an immunostimulant is a peptide that has been approved by Food and Drug Administration (FDA, USA) as a CXCR4-targeted therapy for hematopoietic stem cell mobilization in AML (Acute Myeloid Leukemia) and non-Hodgkin's Lymphoma (NHL) patients [12]. Several CXCR4-specific PET (^{64}Cu; ^{68}Ga) tracers (AMD-3100; Trade Name—Plerixafor) have been developed but were restricted to preclinical applications [13]. However, the only PET tracer that has undergone the transition to clinical applications is ^{68}Ga-labeled Pentixafor. This PET tracer (developed by a German group) was developed after certain modifications (without changing the physiochemical properties in the motif (Plerixafor—the parent compound)) allowing chemical binding with the metal chelator (DOTA) for achieving effective coupling with ^{68}Ga [14]. These authors in their extensive animal and preliminary human studies have shown that the tracer localizes in the CXCR4-expressing tumors (lymphoma) with high target to nontarget ratios [15]. Further, these authors have shown that ^{68}Ga-Pentixafor offers favorable dosimetry exhibiting whole-body radiation exposure of 2.3 mSv to patients which is almost one-third of that received from a conventional ^{18}F-FDG PET scan [16].

The use of Gallium-68 (half-life $t_{1/2}$ = 68 min; positron emission intensity—87%) is on the rise [17]. Several favorable properties of this radionuclide include superior image quality compared to SPECT radionuclides (e.g., indium-111) and the potential for an on-demand production via generator technologies that provide reliable and high-purity ^{68}Ga in sufficient quantities for routine radiopharmaceutical production without the need for expensive cyclotron operations [18, 19]. Generator technologies for ^{68}Ga production, chemistry of gallium, and emerging applications for ^{68}Ga radiopharmaceuticals have been reviewed in detail [18, 20]. These physicochemical properties provide a strong basis for developing specific ^{68}Ga-labeled probes for molecular imaging in various human cancers including solid tumors and hematological malignancies [15, 21–23].

The central role of CXCR4 in cancer pathogenesis and metastasis is proven beyond doubt; however, no in vivo method suitable for whole-body CXCR4 disease quantification has been described till late. This unmet clinical need or the scientific question has been addressed and 68Ga-Pentixafor having high affinity for CXCR4 receptors have been developed. They synthesized and developed ^{68}Ga-Pentixafor which is a CXCR4 targeting high-affinity nuclear probe and have evaluated the radiotracer in small-cell lung cancer models [22]. Further, proof of concept (POC) studies with ^{68}Ga-Pentixafor in lymphoma-xenografted animal models and in first human hematological malignancies are highly encouraging [23, 24]. And human dosimetry studies demonstrated excellent pharmacokinetics and low radiation burden to patients [16]. In expanding clinical applications of this novel tracer, it has been shown both in preclinical and clinical studies that the tracer provides a high contrast image in comparison to ^{18}F-FDG PET in advanced stage multiple myeloma patients [23]. The other diagnostic applications of ^{68}Ga-Pentixafor in glioma and some other cancers known to have higher degrees of CXCR4 expression are also emerging. We will discuss in this chapter the CXCR4 theranostics in lung cancer, multiple myeloma, and glioma.

31.2 CXCR4-Targeted PET Imaging in Lung Cancer

Lung cancer is one of the most common (after breast cancer) malignancies globally and within India amongst males alone as well as in the combined male and female population [25, 26]. Lung cancer (LC) alone causes higher number of

deaths than that caused by the combination of the other four (breast, colon, pancreas, and prostate) common malignancies [25]. Both epidemiological data and molecular understanding of the disease pathophysiology has shown that LC is associated with cigarette smoking and occupational/environmental factors [26–29]. Approximately, 80% of the LC cases are of the non-small cell lung cancer (NSCLC) and frequently present with advanced disease at initial diagnosis (stages IIIB and IV) where the traditional treatment options like chemotherapy and radiation therapy are aimed at disease and symptom control rather than at achieving a cure [27, 28].

The diagnostic workup of suspected lung cancer depends upon the type, that is, NSCLC or small-cell lung cancer (SCLC), the size and site of the primary lung cancer. This approach involves accurate tissue diagnosis (histopathology and advanced immune-histochemical analysis), staging, and functional evaluation by radiological imaging techniques with high sensitivity and specificity. Amongst, over 150 factors, the tumor stage which guides the therapeutic options (surgery/radiation therapy/chemotherapy) is considered as the most significant prognostic indicator in LC patients [30–33]. Despite significant advances in diagnostic, staging, and surgical techniques as well as availability of newer targeted (both chemo/radio) therapies, the death rate from lung carcinoma has remained high [34, 35].

Hybrid ^{18}F-FDG PET/CT imaging remains the mainstay of the diagnostic workup of patients with lung cancer [36]. This imaging technique scores high over the conventional radiological techniques for example, computed tomography (CT) and magnetic resonance imaging (MRI) in terms of both sensitivity and specificity [37]. Although ^{18}F-FDG/PET imaging has proven its utility in monitoring response to appropriate therapies at early time intervals, yet this technique has fewer limitations. These include its inability to differentiate inflammatory/infectious pathologies from tumor recurrence/relapse, and the high background FDG uptake interferes with the detection of metastatic lesions in the brain [38, 39]. On the other hand, ^{18}F-FLT, a marker of cell proliferation has high specificity for solid tumors. However, this imaging technique has inherent problem of lower uptake thereby poor image contrast, not making it an ideal PET tracer especially for response assessment [40, 41].

Philips et al. reported that distant metastases from NSCLC require a CXCL12 chemotactic gradient [42]. Furthermore, they found CXCL12 levels to be significantly higher in metastatic organs than that in the primary tumors. Likewise, SCLC preferentially metastasizes to the marrow, which has high constitutive CXCL12 expression [43]. The signaling via CXCR4 on SCLC cells induces activation and signaling of tumor-associated integrins that apparently play an important role in tumor progression [44]. A positive correlation between CXCR4 expression and clinical outcome in lung cancer has been reported. In a very interesting study by Spano et al. [45], it was observed that the patients having CXCR4-positive nuclear staining demonstrated confinement of CXCR4 presence in the nucleus and is associated with better patients' survival than those having the receptor expression on the cytoplasmic membrane with absent nuclear staining.

In a recent study, Vag et al. reported their first experience on the use of ^{68}Ga-Pentixafor PET imaging, targeting CXCR4 receptors in solid tumors [21]. These authors concluded that the detectability of solid cancers was found to be lower for ^{68}Ga-Pentixafor than for ^{18}F-FDG PET. However, this study included a small and heterogeneous cohort of 21 patients out of which only two were of NSCLC. The highest SUV_{max} of 10.9 was observed in a NSCLC patient followed by pancreatic cancer (6.2), HCC (5.0), and breast cancer (3.3). On the other hand, highest SUV_{max} of 13.8 was noted in the cervical metastases of the patient with cancer of unknown primary (CUP). In another study, Lapa et al. [22] studied the feasibility of CXCR4-directed ^{68}Ga-Pentixafor PET/CT imaging in ten patients of small-cell lung carcinoma (SCLC) and compared results with ^{18}F-FDG PET/CT or ^{68}Ga-DOTA-TOC PET/CT. These authors concluded that noninvasive imaging of CXCR4 expression in SCLC is feasible and ^{68}Ga-Pentixafor as a novel PET tracer

might serve as a readout for confirming the CXCR expression which might serve as a prerequisite for potential CXCR4-directed radio-chemotherapies.

In a preliminary study [46], we have shown that ^{68}Ga-Pentixafor PET/CT demonstrated higher CXCR4 density in SCLC compared to NSCLC and had superior performance in detection of brain metastases which is a known limitation of ^{18}F-FDG PET imaging. We expanded our initial cohort to image 100 lung cancer patients with ^{68}Ga-Pentixafor PET/CT. We found that the SUV_{max} values on ^{68}Ga-pentixafor PET/CT were 6.14 ± 2.14 and 8.0 ± 1.9 in squamous (n = 60) and adenocarcinoma (n = 20) variants of the NSCLC, respectively. The corresponding values were highest in SCLC (n = 20; SUV_{max} 10.30 ± 5.0). Similarly, the CXCR4 quantitative values expressed as Mean Fluorescence Index (MFI) for in vivo measure of CXCR4 receptor density were 136.0 ± 80; 288 ± 121, and 348 ± 99 in squamous, adenocarcinoma, and SCLC respectively. These findings highlight that the uptake of the tracer increased as a function of the receptor density which in turn supports the specific binding of the tracer to CXCR4 receptors (Fig. 31.1). A representative IHC-stained slide showing CXCR4+ SCLC patient and a control (CXCR4-negative) slide is shown in Fig. 31.2. We have reported that 68Ga-Pentixafor PET/CT targets CXCR4 receptors non-invasively and its uptake varies as a function of CXCR4 receptors' density in different lung cancer subtypes [47]. This imaging

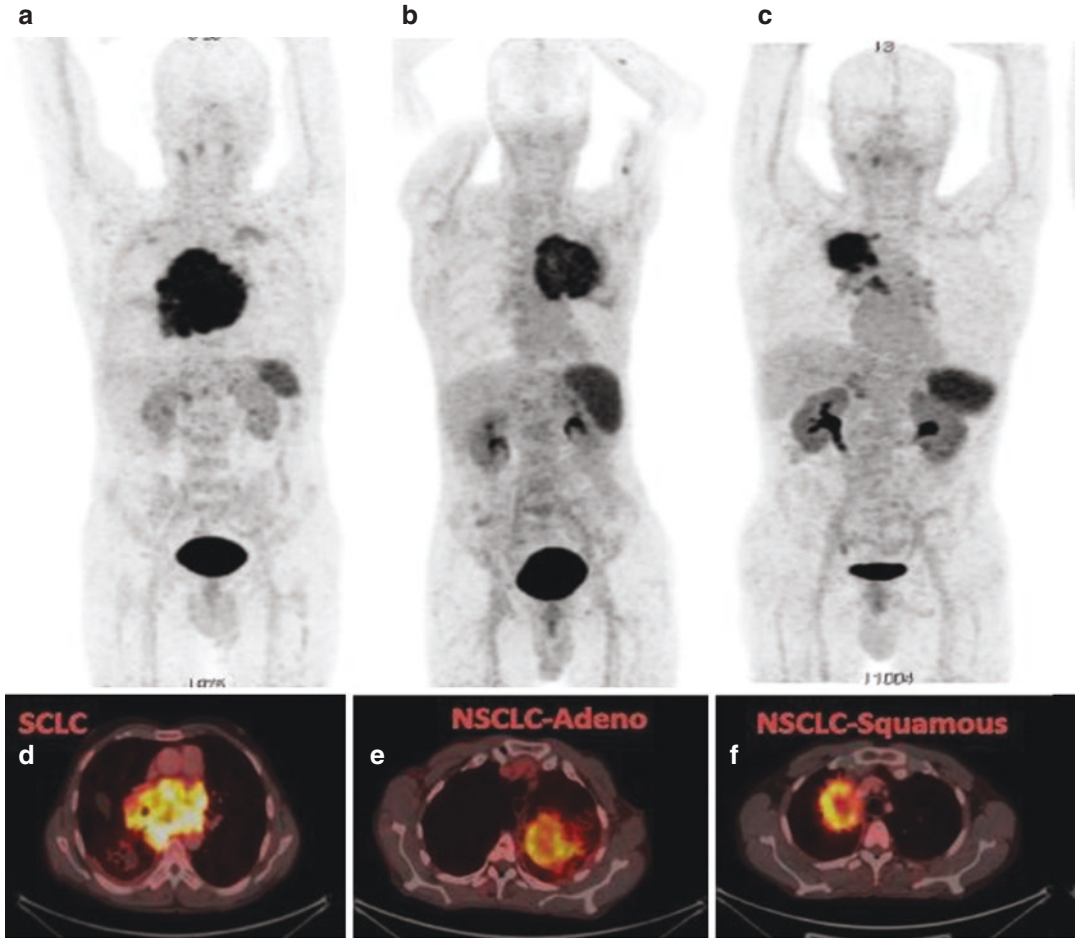

Fig. 31.1 68Ga-Pentixafor PET/CT images in a SCLC patient (**a**, **d**), NSCLC adenocarcinoma (**b**, **e**) and NSCLC-squamous (**c**, **f**) showing SUV_{max} values of 13.2, 10.0, and 7.2 and MFI of 413, 208, and 99.0, respectively

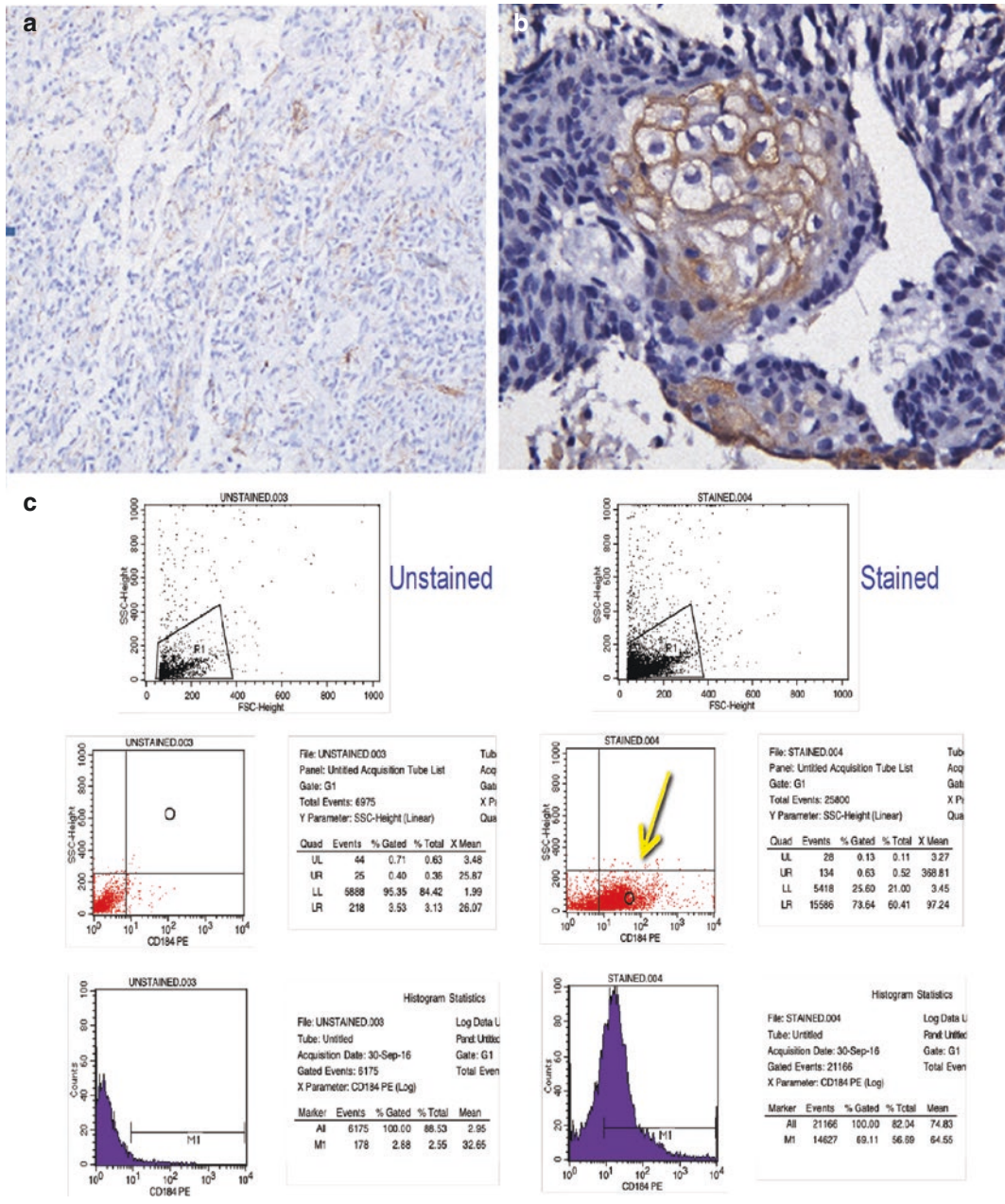

Fig. 31.2 Immuohistochemistry (IHC) analysis showing no stained cells in a control slide (**a**) and slide demonstrating stained CXCR4+ tumor cells (**b**) and quantitative FACS analysis (**c**) showing fractions of unstained and stained cells (CXCR4+ tumor cells) in a SCLC patient

technique can thus be used for lung cancer disease assessment and for patient selection for appropriate CXCR inhibitor therapies and, especially, α/β-targeted radionuclide therapies. Further, this novel PET tracer has the potential of becoming a powerful tool for monitoring therapy response to CXCR4 inhibitors and also for the development of emerging alpha/beta-targeted therapies in advanced stage lung carcinoma.

31.3 CXCR4-Targeted PET Imaging in Multiple Myeloma

Multiple myeloma (MM) is characterized by the clonal proliferation of malignant plasma cells and accounts for 1.0% of all the cancers and 10.0% of all the hematological malignancies [48, 49]. MM patients often present with skeletal and renal involvement and immunodeficiency [50]. Despite significant advances in treatment for MM, most patients will eventually go into relapse or become refractory to the chemotherapeutic interventions [51]. Therefore, the prognosis for MM patients remains poor and the 5-year survival rate is around 45.0% [52]. This underscores the need to properly understand the tumor biology and find new targets for diagnosis and treatment of MM [53]. ^{18}F-FDG PET has a proven role in the diagnosis, staging, response assessment, and management of MM [54, 55]. However, ^{18}F-FDG PET has its own limitations, as a significant decrease in the SUV_{max} value (versus the baseline value) on the post-therapy follow-up has been reported to be not correlating with the progression-free survival [56].

The clinical utility of ^{68}Ga-Pentixafor PET/CT imaging for in vivo imaging of CXCR4 whole-body disease burden has been reported in few recent studies. ^{68}Ga-Pentixafor as a novel PET tracer having high affinity for CXCR4 has been shown to be superior or equal to ^{18}F-FDG for the detection of myeloma lesions [57–59]. Herrmann et al. [23] in their first preliminary clinical experience reported that after disease mapping with ^{68}Ga-Pentixafor PET/CT, CXCR4-targeted radiotherapy with Pentixather appears to be a promising novel treatment option in combination with cytotoxic chemotherapy and autologous stem cell transplantation, especially for patients with advanced multiple myeloma. Therefore, ^{68}Ga-Pentixafor/^{177}Lu/^{90}Y-Pentixather is emerging as a potential theranostics' pair for treatment of CXCR4-targeting therapies when other available treatment options in advanced stage MM patients have failed.

Our experience [59] with ^{68}Ga-Pentixafor PET/CT in MM at PGIMER, Chandigarh, India, showed a higher lesion detection rate with ^{68}Ga-Pentixafor PET compared to ^{18}F-FDG PET (Fig. 31.3). We concluded that the dual tracer imaging may provide additional information on spatial and temporal heterogeneity of MM and may have significance for response evaluation to CXCR4-targeting pharmacologic or endoradiotherapeutic therapies in CXCR4-positive and FDG-negative disease variants of multiple myeloma. In a recent study [60] in 30 MM patients, ^{68}Ga-Pentixafor PET/CT showed a higher positive disease detection rate than ^{18}F-FDG PET/CT (93.3 vs. 53.3%, $p = 0.005$). They further observed that the bone marrow tracer uptake of ^{68}Ga-Pentixafor correlated positively ($p < 0.05$) with the end organ damage, staging, and laboratory markers of tumor disease burden including serum β2-microglobulin, serum-free light chain, and 24 h urine light chain. They concluded that ^{68}Ga-Pentixafor PET/CT is a promising tracer in the assessment of newly diagnosed MM patients. The application of ^{68}Ga-Pentixafor PET/CT in other hematological malignancies is emerging. In a recent study by Luo et al., the application of ^{68}Ga-Pentixafor PET/CT was expanded in patients with Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL) and compared results with ^{18}F-FDG PET/CT [61]. ^{18}F-FDG PET/CT has limitations in the evaluation of WM/LPL which is an indolent B-cell lymphoma and primarily involves the bone marrow. They reported that ^{68}Ga-Pentixafor PET/CT had a higher positive rate for disease detection than ^{18}F-FDG PET/CT (100.0% vs. 58.8%; $p = 0.023$).

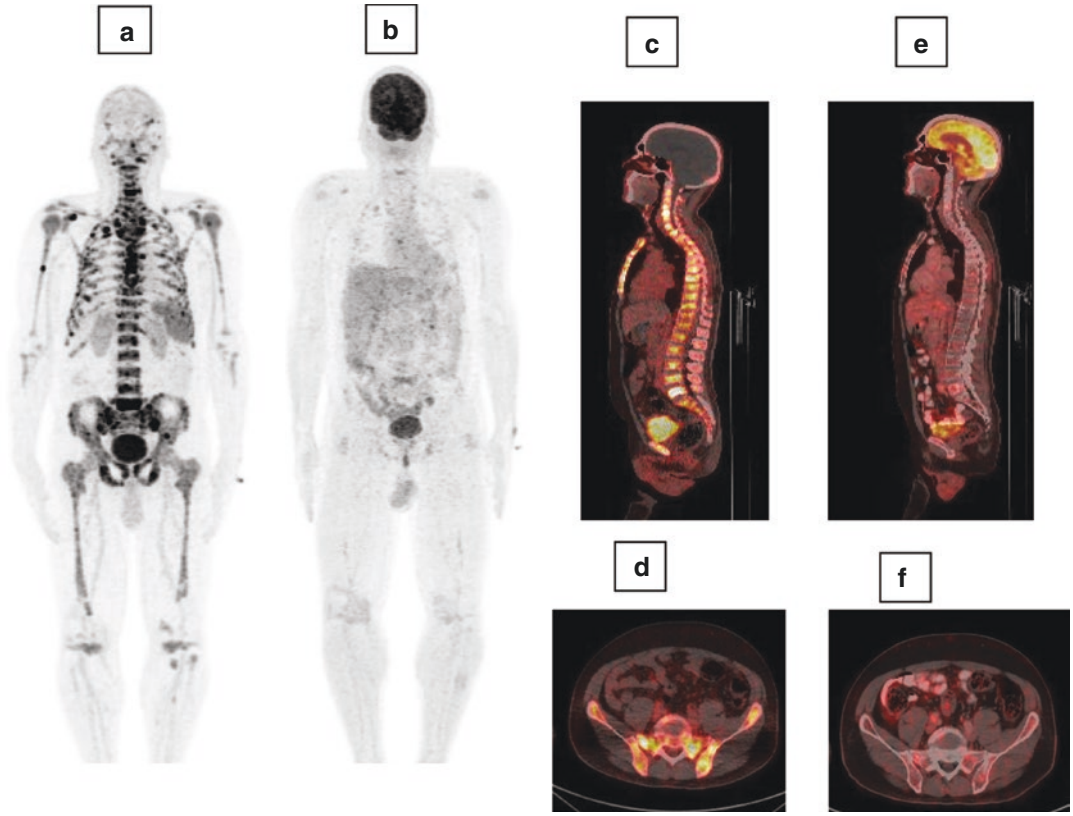

Fig. 31.3 ^{68}Ga-Pentixafor PET/CT in a 60-year-old man with mutiple myeloma and diffuse bony pains. PET/CT images show diffuse and focal tracer uptake in the axial and appendicular skeleton (MIP image **a**), fused PET/CT (trans-axial **c**, sagittal **d**) images show diffuse and focal increased tracer uptake in multiple marrow and lytic skeletal lesions. The corresponding ^{18}F-FDG PET/CT images (**e**, **f**) did not show any abnormal uptake in marrow and anywhere in the skeleton

31.4 CXCR4-Targeted PET Imaging in Glioblastoma Multiforme (GBM)

Gliomas are the most common primary tumors of the central nervous system (CNS) with a reported annual incidence of 20.5/100,000 [62]. Glioblastoma multiforme (GBM) usually have a infiltrative pattern of growth, and surgery is often incomplete, so radiotherapy with or without concurrent chemotherapy has become part of the current treatment regimens to significantly improve the survival in such patients [63]. In the post-surgery/chemoradiation follow-up of glioma, an accurate identification of the disease recurrence and radiation necrosis is important as the treatment strategy for recurrence warrants a change in treatment, whereas radiation necrosis will require continuation of the standard treatment [64]. So, there is a need for noninvasive imaging techniques for the accurate differentiation of tumor necrosis from recurrence and for response assessment to chemoradiation [65, 66].

Over the past few decades, different amino acid-based PET tracers, such as ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET), ^{18}F-fluoro-choline (^{18}F-FCH), and ^{11}C-methionine (^{11}C-MET) have been used in targeting various metabolic and molecular pathways that may add valuable diagnostic information especially in clinically challenging situations to improve diagnosis, detect tumor extent, and to help in therapy planning [67]. Among these trac-

ers, ^{11}C-MET is one of the most extensively investigated PET tracers in the diagnostic workup of glioma. ^{11}C-MET accumulates extensively in proliferating tumors by the mechanism of increased amino acid transport and protein synthesis [68]. Undoubtedly, ^{18}F-FDG PET/CT is not of much use in GBM and all other PET tracers have their own limitations in terms of logistical and cumbersome radiolabeling issues. Therefore, alternative tracers which are easy to synthesize and can be made widely available widely with "ready to label" strategies are needed for the accurate detection and postsurgical/chemoradiation follow-up in GBM.

There has been growing evidence that CXCR4 is overexpressed in GBM and is associated with tumor angiogenesis as well as associated with poor survival outcomes [7–9, 69, 70]. It has also been shown in animal xenograft models that treatment with CXCR4 antagonist significantly inhibits tumorigenicity and tumor growth and proliferation [71]. The latter suggests that CXCR4 may play a crucial role in promoting the growth of gliomas in humans. Therefore, the CXCR4/CXCL12 axis represents a highly relevant molecular target of cancer biology and offers promising new approaches and techniques for targeted cancer therapy [72, 73].

In a recent study [74], ^{68}Ga-Pentixafor PET/CT was used for the detection of primary/recurrent glioma in 15 patients. In this pilot study, the tracer retention was noted in the vast majority of patients, and histological analysis from the tumor areas with high ^{68}Ga-Pentixafor uptake confirmed the CXCR4 expression. On the other hand, regions of the same tumor without apparent tracer uptake showed no or low receptor expression. Further, in this study, head-to-head comparison with ^{18}F-FET PET/CT in 11/15 cases showed similar SUV_{mean} and SUV_{max} values of the two tracers; however, the TBR (target-to-background ratio) for SUV_{mean} and SUV_{max} values were higher for ^{68}Ga-pentixafor by multiples of 37 and 19, thereby resulting in excellent image contrast. It was concluded in this study that ^{68}Ga-Pentixafor PET served as readout for visualization of intracranial CXCR4 expression which might prove as a useful theranostic tool for sensitive noninvasive in vivo quantification of CXCR4 tumor phenotyping. The latter may serve as a useful guide for prognostication and selection of patients who might benefit from CXCR4-directed therapies including β/α radionuclide therapies.

We conducted a pilot study [75] at PGIMER, Chandigarh, India, using ^{68}Ga-Pentixafor PET/CT for quantitative imaging of CXCR4 expression in 28 GBM patients having clinical suspicion of recurrent/residual disease. All the patients received radical radiotherapy (54.0–60.0 Gy) after surgery with or without concurrent temozolomide as indicated and underwent ^{68}Ga-Pentixafor PET/CT and conventional ceMRI of the brain. ^{68}Ga-Pentixafor PET/CT findings with focally increased uptake of the radiotracer were interpreted as positive for recurrent/residual disease in 13/14 patients. The mean SUV_{max} value in these patients (n = 13) was 5.25 ± 2.07 (range: 2.71–9.69). PET/CT findings were concurrent with MRI findings in all the 14 patients. A representative ^{68}Ga-Pentixafor PET image in a patient (58 yrs., female) with recurrent tumor in central primary GBM disease showing intense uptake of the radiotracer (SUV_{max} = 7.9) is presented in Fig. 31.4. The only (1/14) patient who had no focal uptake anywhere in the brain on ^{68}Ga-Pentixafor PET was interpreted as negative

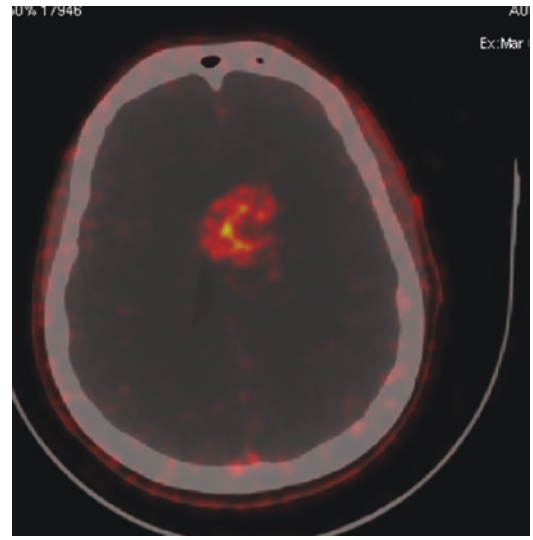

Fig. 31.4 ^{68}Ga-Pentixafor PET/CT in a 58-year-old woman with recurrent centrally located primary GBM (lateral ventricular region) showing intense uptake of the radiotracer (SUV_{max} = 7.9) and an excellent tumor to background contrast

for any residual/recurrent disease. The ceMRI finding in this patient was also negative and was reported as gliosis. The results of this preliminary study demonstrated that ^{68}Ga-Pentixafor PET imaging in GBM (known to have high CXCR4 expression) is viewed to open up new theranostics applications (with beta and alpha radionuclides) for long-term survival benefits. However, the diagnostic utility of this tracer needs to be validated in a large cohort of patients through multicentric trials.

31.5 Conclusion

CXCR4 and its ligand CXCL12 are intricately involved in the growth and proliferation of both solid tumors as well as hematologic malignancies. Noninvasive assessment of CXCR4 expression by PET/CT imaging can provide a useful tool in the management of a variety of oncologic conditions, both in terms of diagnostic and theranostic capabilities. Solid malignancies such as lung, breast, brain, prostate, and colorectal cancer and hematologic malignancies such as multiple myeloma, Waldenstrom macroglobulinemia, acute and chronic leukemia, and non-Hodgkin's lymphoma have shown to overexpress CXCR4. Further large and prospectively planned studies can explore the diagnostic performance of ^{68}Ga-Pentixafor PET/CT versus the conventional imaging techniques.

The need of the hour in aggressive malignancies such as glioblastoma multiforme is the development of novel therapies that can prolong survival, improve quality of life, and potentially offer a cure in these patients. Radionuclide therapies, such as intralesional injection of ^{213}Bi-labled substance-P in GBM has shown some promising results [76]. In this context, the increased expression of CXCR4 in GBM has been utilized to develop novel peptide-based theranostics with beta/alpha emitters [77, 78]. This approach may expand our future PRRT armamentarium in GBM healthcare as an alternative to radio-immunotherapy.

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