

Review Article

Molecular Imaging in Therapeutic Efficacy Assessment of Targeted Therapy for Nonsmall Cell Lung Cancer

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Membrane distillation is a thermally driven membrane process for seawater desalination and purification at moderate temperatures and pressures. A hydrophobic micro-porous membrane is used in this process, which separates hot and cold water, allowing water vapor to pass through; while restricting the movement of liquid water, due to its hydrophobic nature. This paper provides an experimental investigation of heat and mass transfer in tubular membrane module for water desalination. Different operating parameters have been examined to determine the mass transport mechanism of water vapor. Based on the experimental results, the effects of operating parameters on permeate flux and the heat transfer analysis have been presented and discussed in details.

1. Introduction

Lung cancer is one of the most common cancers in the world, as well as the leading cause of cancer death in men and the second leading cause in females globally [1]. Nonsmall cell lung cancer (NSCLC) accounts for more than 85% of all lung cancers [2]. The prevailing treatment options for NSCLC comprise surgery, radiotherapy, and chemotherapy, used either alone or in combination. Although local treatment modalities like surgery and radiotherapy can provide the chance for cure in early stages of NSCLC, about 54% NSCLC patients present with a metastasis disease at diagnosis, with an overall 5-year relative survival 3.8%, as estimated in 17 SEER geographic areas in America during 2001–2007 [3]. However, the option for these patients with advanced NSCLC whose lesions are mostly unresectable is limited to systemic therapy, where chemotherapy plays a predominant role. The use of chemotherapy in the treatment of this frustrating malignancy, which had a median survival measured in weeks or months in early days [4], was once a controversial issue concerning reproducible toxicity and

questionable activity [4–6]. However, with validations of increasing publications of meta-analyses and randomized trials, especially with the advent of novel cytotoxic drugs with less toxicity and more activity, chemotherapy has become the mainstream of the treatment for advanced NSCLC. As an updated meta-analysis of data from 2714 patients of 16 randomized controlled trials revealed, compared with supportive care alone, chemotherapy with supportive care improves 1-year survival rate from 20% to 29% in all patients with advanced NSCLC [7]. Chemotherapy including platinum agents and the third generation drugs produces a cytotoxic effect by blocking cell division or DNA replication. Lots of randomized clinical studies in an effort to improve survival and life quality focused on the efficacy of differing combinations of chemotherapeutic drugs and revealed that variant combinations of chemotherapy agents produce similar response rate and survival [8, 9]. It is generally accepted that the efficacy of chemotherapy for advanced NSCLC has reached a plateau [10], with a response rate of 25–35%, time to progression (TTP, the time from randomization until objective tumor progression) 4–6 months, a 1-year survival

rate of 30–40%, and a median survival of 8–10 months [11]. Overall, the prognosis for advanced NSCLC remains poor.

With increasingly researches on molecular pathways of NSCLC in the last decade, aberrations in signaling pathways and molecules of tumor cells which promote tumor survival, proliferation, metastasis, and neovascularization have come to light. The advent of targeted therapy which acts selectively on the tumor-specific molecular pathways, and biomarkers detection which indicates a likely response to a specific therapy and guides the treatment choice [12], has brought the treatment strategy for NSCLC from empiricism into a new era of personalized therapy. The management of tumor is not “trial and error” modality any longer, but more predictive and efficient, with enhanced sensitivity to therapy and reduced unnecessary toxic effect and costs of likely ineffective treatment [13]. Targeted agents, composing mostly small molecule inhibitors and monoclonal antibodies, block signaling pathways by binding to intracellular domain to inhibit downstream signaling or to extracellular domain of surface receptor and activating immune mechanisms [14]. The target-signaling pathways or molecules such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) have already yielded significant improvements in response rate and progression-free survival (PFS, the time from randomization until objective tumor progression or death) used alone or in combination with chemotherapy compared with standard chemotherapy alone in large randomized clinical studies [15–19], and drugs of these categories such as erlotinib and bevacizumab have obtained FDA approval and have been recommended by National Comprehensive Cancer Center Network (NCCN) guidelines for subgroups of advanced and metastatic NSCLC. Many other targeted drugs acting on various pathways, for instance, heat shock protein (HSP)-90 inhibitors, insulin growth factor-1 receptor (IGF-1R) inhibitor, poly(ADP-ribose) polymerase (PARP) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, histone deacetylase inhibitors and anaplastic lymphoma kinase (ALK) inhibitors, have also shown promising prospect in clinical trials [20]. Recent reviews have been published of development on these targeted therapies for NSCLC [21, 22].

Despite the ever-increasing novel drugs and differing combinations of standard drugs for the improvement of survival of the patients with advanced NSCLC, a significant proportion of patients exhibit or acquire resistance and eventually experience progression [23]. Even in patients with a positive predictive biomarker undergoing a targeted therapy that is likely to be effective, primary resistance is shown in about 30% overall, and disease recurrence occurs uniformly in patients with an initial response [24–27]. Moreover, although EGFR mutations in tumors are believed to be an important predictor of response to EGFR inhibitors, studies demonstrate that patients who benefit from EGFR inhibitors are not limited to those whose tumors have EGFR mutations [28]. Therefore, valid strategy for response prediction to help clinical management is still required.

Furthermore, after disease progression, patients often get to be unsuitable to receive further treatment due to declining

performance status and increased symptom burden [29–32]. Therefore, it is of great importance to identify early whether a patient is likely to respond to the current therapy and whether a resistance has occurs, for it enables an early termination of ineffective therapy and avoidance of unnecessary toxic effect or costs for those nonresponders, as well as more chance to receive a more likely to be effective therapy. In addition, as more novel drugs come into clinical trials with inconclusive efficacy, an early and valid identification of therapeutic efficacy helps to shorten the time for assessment and reduce cost.

While improved survival has been widely accepted as the “gold standard” for establishing clinical benefit in clinical trials, as an ultimate and long-term outcome, survival is not practical for early identification of therapy effect. As a consequence, valid surrogates for shortening the time for therapeutic efficacy assessment have been applied in clinical trials, which can reflect change of tumor and help to make prediction of long-term outcomes. Like tumor markers such as CA-125 in ovarian cancer has been already used as standard markers in the objective response assessment [33], in the context of lung cancer today, imaging that can provide an insight of tumor condition has long been applied in measurement of antitumor effect. The imaging-based endpoints like objective response, PFS, and TTP are commonly used in stage II and III clinical trials. Given the importance of early assessment of therapeutic efficacy in clinical practices and investigational therapies, appropriate imaging modalities as an essential part in response assessment are essential. In this review, we will discuss the current imaging modalities, especially molecular imaging, that applied in efficacy evaluation of targeted therapy for advanced NSCLC.

2. Current Imaging Methods in Efficacy Assessment of Treatment for NSCLC

2.1. Computed Tomography (CT). With the rapid development of cytotoxic drugs since 1960s, there has been an intense need for an acknowledged standard in anti-tumor effect assessment. Since the World Health Organization (WHO) first introduced response criteria of cancer in 1979 [34] in an effort to introduce a common language to report results of investigational antitumor therapies, anatomical imaging has become the standard way to determine oncology response in solid tumors. Because of some limitations of the WHO criteria, an international working group published the Response Evaluation Criteria in Solid Tumors (RECIST) guideline in 2000, and updated it in 2009. These criteria have determined tumor response as complete response, partial response, progression disease, and stable disease, according to the change of target lesions size, and have become the main standards in clinical trials of anti-tumor therapies for NSCLC where the primary endpoints are objective response or progression.

Tumor response is believed to be an indicator of drug effect in traditional anti-tumor trials and was approved by the FDA in 1996 to be used in investigational oncological

treatments, as to accelerate approval of new anti-tumor drugs [35], for a reason that tumor is not likely to shrinkage spontaneously. Lots of trials demonstrated that objective tumor response is associated with longer survival in chemotherapy for solid tumors [36–39], yet whether tumor response can predict therapy efficacy remains an issue open to disputes [40–42]. At the same time, other endpoints such as disease control rate (consisting of CR, PR, and SD), PFS, or TTP [43] are increasingly proved to be more valid measures for therapy efficacy assessment in clinical trials [44–46]. These anatomy-based endpoints, specified by those criteria, are commonly used in investigational trials of advanced NSCLC. CT with its high resolution, moderate costs, and availability has been historically the mainstay in measurement of lung cancer sizes and still the standard method in present. In addition, it is also the recommended method in clinic for surveillance and instructs clinical management.

However, since targeted therapy came into evaluation, there are concerns about whether morphology-based criteria that was established in cytotoxic therapy trials is an appropriate metrics in efficacy assessment of targeted-therapy, where tumor shrinkage is not necessary due to an effect of delaying the tumor growth. It has been observed in diverse tumors types like metastatic renal cell cancer and GIST [47, 48], as well as NSCLC [49–51], that relationship between tumor regression and survival varied widely. Because stability of disease cannot be interpreted as ineffectiveness of a targeted therapy, the response defined in change of dimension as a measure of efficacy in targeted therapy is inappropriate. In this case, endpoints such as PFS or TTP, which focus on progression rather than regression, might be more appropriate and are commonly utilized in clinical studies of targeted therapy. However, these metrics associated with progression need regular evaluation in trials and cannot provide information about treatment efficacy before tumor enlargement occurs and hence cannot be an early predictor of treatment efficacy, which is vital to optimizing a patient's management in clinic or improving efficiency of clinical trials.

2.2. Dynamic Contrast-Enhanced CT (DCE CT). Regarding the limitation of size-based methodology, metrics other than size is also proposed to provide information about tumor response to targeted therapy. DCE CT is also known as functional CT, which can provide information about perfusion. Tumor perfusion versus whole-body perfusion can be measured on images generated following an intravenous injection of a contrast agent. A reduction in tumor perfusion is demonstrated in NSCLC patients responding to chemotherapy [52]. Similar result is also yielded in a study on targeted therapy that has an effect of antiangiogenesis for NSCLC in monitoring response of NSCLC to [53]. In this study, tumor perfusion is measured with DCE CT at week 3 and week 6 after starting treatment, and a reduction of tumor blood flow is observed at week 6. Meanwhile, tumor density used in combination with size has become a new imaging paradigm in assessment of targeted therapy for GIST [54] and metastatic renal cell carcinoma [55]. However,

since there is no such study or criteria in NSCLC, whether combination of tumor density and size is a feasible metrics in evaluation of therapy for NSCLC is still unclear.

2.3. Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE MRI). Although MRI used limitedly in imaging of NSCLC, DCE MRI has been used in evaluation of NSCLC perfusion. With this modality, quantitative parameters reflecting tumor microvessel perfusion, permeability can be obtained [56]. DCE MRI has been verified as a potential role in efficacy assessment of both cytotoxic agents and antiangiogenesis targeted-therapy for NSCLC [57, 58].

2.4. Magnetic Resonance Spectroscopy (MRS). By utilizing the special property of nuclear isotopes in a strong magnetic field, MRS gives information of tissue metabolites [59]. As a molecular imaging modality, MRS has a bright prospect in personalized medicine. It has been reported that the accuracy in discrimination between normal lung and each cancer type with proton MRS (1H MRS) was up to 81.5 to 90.7% [60]. However, there is no utilization of MRS available in response assessment area in NSCLC up to date.

2.5. Positron Emission Tomography (PET). The advent of PET brings about a totally new era of molecular imaging. By detecting the distribution of the radionuclide-labeled tracer that is involved with some specific physiological process within the body, PET makes metabolic change possible to be visualized in vivo, which is fundamentally different from conventional anatomy-based imaging modalities. Because biological features of tumor tissues are usually different from that of normal tissues, this functional imaging technology that makes qualitative, quantitative, and semiquantitative analysis available is especially useful in oncology imaging, playing a role in disease diagnosis, staging and restaging, and therapeutic response evaluation. In addition, since there are various biologic compounds participating different physiological processes, by developing diverse radionuclide-labeled tracers, we can acquire tumor information in an optimal way according to specific tumor or explore different physiologic features of tumor. While depicting an imaging on molecular characteristics of different tissues, PET can sometimes be imprecise in anatomical location. For this reason fusion of PET with traditional modality is developed and comes into application, combining molecular formations with high-resolution anatomical structures. The multimodalities of PET/CT and PET/MRI are currently in practical application with promising prospect.

The positron-emitting isotopes of oxygen, carbon, nitrogen, and fluorine which are the building components of biological substances are the commonly used labels for tracers for PET. A large spectrum of radiopharmaceuticals has been developed associating with various metabolic pathways. 2-[¹⁸F] fluoro-2-deoxy-D-glucose (¹⁸F-FDG) reflecting glucose metabolism is most widely used among all the tracers, with general acceptance in assessment of oncologic therapies. ¹⁸F-FDG is a modified glucose molecular where the hydroxyl group (OH) of glucose is replaced with ¹⁸F, which has

a half-life of 110 minutes. Once being taken up into a cell, it cannot be further metabolized. Therefore, different levels of accumulation of ^{18}F -FDG are reflections of diverse energetic need. It is rational to consider that malignant cells will decrease glucose requirement due to direct or indirect damages. Clinical investigations have validated a reduction in ^{18}F -FDG uptake that occurs in oncological tissues after anticancer treatment in various tumors including NSCLC and is closely correlated with final outcome of therapy [61]. 3- ^{18}F fluoro-3-deoxy-L-thymidine (^{18}F -FLT), a thymidine analogue, as a biomarker of proliferation, is another tracer often investigated in studies on NSCLC.

Radioimmunoimaging has been developed in recent years with increasing knowledge of molecular pathways of cancer cells. Based on a fundamental much alike targeted therapy, by modifying the tracer which target specific molecular of tumor cells, radioimmunoimaging helps provide tumor molecular information and thereby has a predictive value in response to targeted therapy and contributes to individualized medicine [62–64].

Since metabolic change in tumor always takes place earlier than anatomic change, PET has great advantage in early evaluation of treatment efficacy. Regarding to the widespread utilization of PET in assessment of therapy assessment, European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute (NCI) proposed guidelines in 1999 and 2006, respectively, intending to standardize the methodology of data acquisition and analysis of ^{18}F -FDG PET scans [65, 66]. A prospective trial assessed the relationship between PET-evaluated response and clinical outcomes by evaluating on-treatment changes in ^{18}F -FDG and ^{18}F -FLT PET imaging among patients with NSCLC treated with targeted therapy and verified that it is possible to achieve high reproducibility of scan acquisition methodology, as long as strict imaging compliance guidelines are mandated in the study protocol [67]. Furthermore, the relevance for the prediction of clinical benefit of targeted therapy using different quantitative parameters for PET with both ^{18}F -FDG and ^{18}F -FLT in patients with advanced NSCLC, early ^{18}F -FDG PET and ^{18}F -FLT PET can predict PFS regardless of the method used for standardized uptake value (SUV) calculation although several indicators like SUV_{max} measured with ^{18}F -FDG might be more robust to use for early response prediction [68]. All these efforts offer a promising prospect of robust application of this new modality in efficacy evaluation of tumors. With more targeted drugs acting on various mechanisms increasingly coming out, as well as diverse tumor metabolic characteristics, further researches are still required to offer a valid methodology for PET as a biomarker for early evaluation of targeted therapy.

While conventional imaging modalities are fraught with difficulties in early response assessment to cytostatic targeted therapy, ^{18}F -FDG PET meets these challenges both theoretically and practically. Although the reliability and powerfulness of ^{18}F -FDG PET in predicting therapeutic efficacy in NSCLC has been verified in chemotherapy in the last few years [69–72], there are fewer clinical studies on its efficiency in early prediction of outcome in targeted therapy

except for gastrointestinal stromal tumor (GIST) [73–75]. However, preclinical studies have shown evidences that PET may be a promising biomarker for targeted therapies [76–79].

2.6. Single-Photon Emission-Computed Tomography (SPECT). SPECT is also a molecular imaging technique, detecting tracer labeled with radionuclide emitting single gamma rays. The dual modality of SPECT/CT has been used in lung cancer diagnosis [80]. The most investigated trace used in treatment of lung cancer is $^{99\text{m}}\text{Tc}$ -methoxyisobutylisonitrile ($^{99\text{m}}\text{Tc}$ -MIBI), which is reported to play a role in recognition of chemoresistance of tumor cell [81] and thus has been used in prediction of response to chemotherapy for NSCLC. A systematic review of the literature revealed that $^{99\text{m}}\text{Tc}$ -MIBI SPECT can accurately identify patients with lung cancer who will respond to chemotherapy, with an overall sensitivity of 94%, specificity of 90%, and accuracy of 92% [82]. In comparison with PET, SPECT has a lower sensitivity, and the use of SPECT in assessment of treatment of NSCLC is still limited.

2.7. Ultrasound. Ultrasound generates images by detecting changes of sound speed caused by various tissue densities. Since lung is filled with air which hardly echoes, ultrasound, together with a more recent utilization as endoscopic ultrasound (EUS), is not a usual technique used in NSCLC except for mediastinal staging or guiding fine needle aspiration or a metastasis lesion evaluation.

3. Molecular Imaging in Response Evaluation of Targeted Therapy for NSCLC

Molecular imaging modalities are now under evaluation in targeted therapy for advanced NSCLC although limitedly. In various agents targeting diverse pathways of cancer cell, there are only several agents targeting EGFR, and VEGFR pathways have been evaluated by molecular imaging, entirely PET in clinical or preclinical studies.

3.1. EGFR Pathway. EGFR (also known as HER [human EGF receptor] and ErbB1) is member of the human epidermal growth factor receptor family. By triggering the downstream signaling pathways involving phosphatidylinositol-3-OH kinase (PI(3)K)/AKT/mammalian target of rapamycin (mTOR) and RAS/RAF/MEK and signal transducer and activator of transcription (STAT) [83], the activation of EGFR contributes to tumor growth and progression, including proliferation, maturation, angiogenesis, invasion, metastasis, and inhibition of apoptosis [84]. Overexpression or aberrant activation of EGFR is frequent in NSCLC [85, 86], and inhibition of EGFR is a rational anticancer strategy, which have been validated in clinical practice. EGFR is a transmembrane glycoprotein, consisting of an extracellular ligand-binding domain, a transmembrane region, and an intracellular tyrosine kinase domain [87]. Two classes of agents targeting EGFR are used in clinical practice: tyrosine kinase inhibitors (TKIs) and monoclonal antibodies.

3.1.1. EGFR TKIs. TKIs are small molecules that inhibit phosphorylation of EGFR intracellular tyrosine kinase by competing with ATP, leading to cell cycle delay, inhibition of angiogenesis and apoptosis [88, 89]. In all the agents of EGFR TKIs being evaluated in clinical or preclinical studies, erlotinib is the only EGFR-targeting agent approved by FDA for the treatment of NSCLC. Gefitinib is another EGFR TKI that has been extensively investigated.

The value of ^{18}F -FDG PET in predicting efficacy of EGFR antagonist was validated in a preclinical study performed in 2006 [77]. A dramatic decrease in ^{18}F -FDG uptake was observed at as early as 2 hours after treatment in gefitinib-sensitive cell lines, while no measurable changes in ^{18}F -FDG uptake were seen in gefitinib-resistant cells.

A clinical study for early prediction of the efficacy of gefitinib for NSCLC conducted in 2007 monitored tumor response by both CT and ^{18}F -FDG PET [90]. In this study, two of the five NSCLC patients who exhibited stable disease according to RECIST criteria at 4 weeks after initiation of treatment but with long-term PFS (12.9 and 12.5 months) showed a marked decrease in ^{18}F -FDG uptake (measured by SUV_{max}) within 2 days of treatment initiation, while SUV_{max} increase on day 2 had proved progressive disease based on CT evaluation. Although conclusions can be hardly drawn due to the small sample size, it did show the potential of ^{18}F -FDG PET in early response evaluation for targeted therapy.

Another study observed an increase of SUV_{max} as measured with ^{18}F -FDG PET after discontinuation of treatment with erlotinib or gefitinib, due to progressive disease according to RECIST, and reintroduction of erlotinib or gefitinib again resulted in decreases in SUV_{max} [91]. A subsequent introduction of everolimus, the mTOR inhibitor, led to further decrease in SUV_{max} and tumor size after 3 weeks of combination therapy in 5 of the 10 patients, suggesting that some tumor cells remain sensitive to EGFR blockage after PD occurs according to RECIST.

A prospective multicenter trial evaluated response of seventy-four patients with advanced NSCLC to erlotinib treatment with only PET/CT scans [62], further verified early ^{18}F -FDG PET response is associated with improved PFS and OS, even in the absence of subsequent RECIST evaluation with CT.

^{18}F -FLT PET was also applied to early detection of targeted therapy efficacy. A striking and reproducible decrease in ^{18}F -FLT uptake was exhibited in erlotinib-sensitive tumors after two days of treatment and translated into dramatic tumor shrinkage four days later [92]. Another phase II clinical trial assessed the use of ^{18}F -FDG PET and ^{18}F -FLT PET in NSCLC patients following erlotinib therapy [93]. This study enrolled thirty-four previously untreated patients, demonstrated an that early ^{18}F -FDG response (cutoff value: 30% reduction in the peak standardized uptake value) predicted significantly longer PFS, OS, and nonprogression after 6 weeks of therapy with erlotinib, while early ^{18}F -FLT response was only associated with significantly longer PFS. In particular, this study demonstrated early ^{18}F -FDG PET can identify those patients who could be benefited from erlotinib even without the knowledge of EGFR mutation.

3.1.2. Monoclonal Antibodies. EGFR-directed monoclonal antibodies exert an anticancer action by binding to the extracellular domain of the EGFR. Among all EGFR antibodies, cetuximab has been investigated extensively in treatment of NSCLC. A large phase III randomized trial shows that adding cetuximab to chemotherapy (cisplatin/vinorelbine) slightly increases overall survival (11.3 versus 10.1 months, $P = 0.04$) [94]. Other monoclonal antibodies directing EGFR are still in investigation in clinical trials.

A phase II trial evaluating ^{18}F -FDG PET and CT as endpoints for assessing efficacy of cetuximab in combination with chemotherapy for advanced gastric or gastroesophageal junction adenocarcinoma showed that ^{18}F -FDG PET could correctly differentiate responders from nonresponders, with a median TTP 16 months and 11 months, respectively [95]. No clinical studies have been performed regarding molecular imaging in treatment of NSCLC with EGFR-targeted monoclonal antibodies, but the use of ^{18}F -FLT PET has been investigated in a study of human lung cancer xenografts [96] demonstrated that SUV_{max} in tumor tissue significantly decreased versus nontreated control on day 3 after treatment with cetuximab ($P < 0.01$), while no difference in CT image was visualized until day 8.

3.2. VEGFR Pathway. VEGFR pathway plays an important role in angiogenesis, a process of endothelial cell division and migration resulting in formation of new capillaries [97]. Angiogenesis is critical to tumor growth and metastasis, and enhanced VEGF and its receptors expression is found in a variety of tumors [98]; thus, blockage of this pathway is an attractive strategy for anticancer treatment. VEGFR is a transmembrane receptor tyrosine kinase specifically expressed at the surface of endothelial cell [99]. Various antiangiogenic agents have developed in the last few years, and VEGFR-directed monoclonal antibodies and VEGFR TKI are the two classes of VEGFR agents currently used in studies of NSCLC antiangiogenesis treatment. Use of DCE MRI imaging as well as PET has been evaluated in this therapy concerning its effects on tumor vasculature. Despite the limit use of DCE MRI in evaluation of antiangiogenesis in NSCLC, DCE MRI is frequently used in other tumors. As a review exhibited, anti-angiogenic therapies do not always result in reductions of blood flow in the short term, and DCE MRI kinetic response relationships are not universally strong across all tissue sites for all drugs [100]. In treatment for patients with cancer other than NSCLC, ^{18}F -FDG PET exhibited a promising prospect in monitoring antiangiogenesis effect of VEGFR-directed pathway [100]. In VEGFR TKI no study with molecular imaging is available at present.

Bevacizumab is a humanized monoclonal antibody directed at VEGF. It gained FDA approval based on an Eastern Cooperative Oncology Group (ECOG) conducted study [101], in which an increase in survival (12.3 versus 10.3 months) was observed in selected NSCLC patients when added Bevacizumab to standard chemotherapy.

Forty-seven chemo-naïve patients with advanced NSCLC treated with bevacizumab and erlotinib underwent both ^{18}F -FDG PET and DCE MRI scan after 3 weeks of treatment [58], >20% decrease in SUV as measured with ^{18}F -FDG PET is well predicative for longer PFS (9.7 versus 2.8 months; $P = 0.01$), while >40% decrease in K^{trans} (the endothelial transfer constant) as assessed by DCE MRI did not predict for longer PFS though most tumors have a decrease in K^{trans} value after 3 weeks of treatment.

4. Conclusions and Future Directions

This paper reviews the currently available studies of molecular imaging used as early prediction of efficacy of targeted therapy for patients with NSCLC. For patients with advanced NSCLC, although the application of chemotherapy does prolong the OS comparing with supportive care alone [7], the prognosis of NSCLC remains poor, with a median survival of mere 8–10 months [11]. Nevertheless, it is validated that different combinations of chemotherapeutic drugs produce similar response rate and survival [7, 8] and the efficacy of chemotherapy for NSCLC is generally accepted as having reached a plateau. Targeted therapy, developing with the increasing knowledge of tumor molecular pathways, has an approach of blocking specific pathways of tumor cells instead of conventional cytotoxic effect. This new therapy for NSCLC has been investigated in many clinical trials and yielded significant improvement in RR and PFS. As a focus of current studies on therapy for NSCLC, increasing diverse targeted agents is now being investigated in clinical trials or preclinical studies. Meanwhile, the development of targeted agents highlights the need of a robust modality in efficacy assessment because the current prevailing anatomy-based criteria established on the basis of numerous previous studies on chemotherapy can no longer satisfy the requirement for early diagnosis.

Along with molecular metabolic mechanisms of tumor cells that increasingly come to light, rapid development of molecular imaging has taken place in recent years [102]. By directly visualizing and measuring the biological process in vivo [103], molecular imaging enables early assessment of response to anticancer treatment. Although molecular imaging modalities such as PET, SPECT, and MRS are involved in diagnosis of NSCLC, PET with different radiotracers is the primary modality that has been investigated in early prediction of targeted therapy for NSCLC. Despite limited studies are available by now regarding the application of PET in this area, the outcome is encouraging, exhibiting utilization of PET in response evaluation, and outcome prediction is feasible and accurate. Obviously, more investigations are needed. More researches on molecular imaging in early prediction of targeted therapy efficacy should be done considering encouraging outcomes of the available studies and infinite prospect of diverse molecular imaging modalities.

Conflict of Interests

The authors declare that they have no conflict of interests.

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