Chapter 15

Assessment of Biological Target Volume Using Positron Emission Tomography in High-Grade Glioma Patients

Habib Zaidi and Srinivasan Senthamizhchelvan

Abstract High-grade gliomas (HGG) are the most challenging brain tumors to treat. Even though various sophisticated options exist to treat patients with gliomas, the disease invariably leads to death over months or years. The major obstacles encountered in treating gliomas are in determining the exact location, extent, and metabolic activity of the tumor. Molecular imaging of energy metabolism, amino acid transport, cell proliferation and cell death have been found helpful in identifying the biologically active tumor tissues for therapy. It allows a better understanding of pathology at the molecular level. This ability is especially useful in brain tumors where tissue sampling in vivo is associated with significant risks. Positron emission tomography (PET) is one of the most prominent molecular imaging modalities utilized for imaging pathophysiology of tumors at an early stage. In this chapter, the applicability of PET in assessing the biologically active tumor volumes in high-grade glioma patients for radiation therapy treatment planning and therapy monitoring will be reviewed. We will focus on the concept of biological target volume (BTV) and associated methods of image segmentation available for delineating tumor volumes in connection with their applicability in high-grade gliomas.

Keywords High-grade gliomas · PET · Molecular imaging · BTV · Necrosis · Dose painting

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Introduction

The success of cancer treatment depends on multiple factors. One of the most important factors is the accuracy of the information about tumor location, extent and magnitude of disease. Traditionally this information is obtained, through anatomical imaging methods such as x-ray computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). However, it has become clear now, that the acquisition of molecular and physiological information by noninvasive molecular imaging modalities such as positron emission tomography (PET) could vastly enhance our ability to fight cancer at an early stage (Weissleder, 2006). Molecular imaging has the potential to detect physiological alterations that signal the existence of cancer when it is still at a curable stage. Advances in genomics and proteomics technologies have shown the potential to transform the way in which cancer is clinically managed today. Molecular imaging is poised to play a key role in this transformation, since it will allow the integration of molecular and physiological information specific to each individual case with anatomical information obtained through conventional imaging methods. As a noninvasive molecular imaging method PET exploits the unique decay characteristics of positron-emitting isotopes. The isotopes of fluorine, oxygen, carbon, and others have been routinely used in the development of diagnostically useful biological tracers that are available for PET imaging of functional and/ or metabolic assessment of normal tissues or disease state.

Conventional stand-alone PET has now been replaced by PET/CT for improved patient throughput and most importantly for the availability of

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complementary information of molecular PET images and anatomical CT images in one imaging session. There has been a tremendous expansion of clinical applications of PET in oncology for the diagnosis, staging and restaging of cancer patients. More than half of all patients with cancer receive radiation therapy (RT) at some stage during the course of their disease management. Applications of PET in RT have been reported in lung, head and neck, breast, lymphoma, prostate and many other cancers (Zaidi et al., 2009). Studies have also found that PET has advantages over CT in the standardization of tumor volume delineation in the reduction of the risk for geometrical misses, in the minimization of radiation dose to the normal organs, and in the assessment of tumor burden, blood flow, tissue inflammation, and hypoxia. Integration of functional PET data with anatomical CT data has become a standard in RT particularly in treatment planning of various cancers. Imaging plays a key role in the state-of-the-art high-precision RT techniques like three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT), tomotherapy, and stereotactic radiation therapy/surgery (SRT/SRS). These high-precision radiation delivery methods allow better dose distributions within the targeted tumor volume while sparing a larger portion of adjacent normal tissues. Success of these RT techniques requires accurate tumor volume delineation, tumor characterization, and response assessment during and after treatment. Conventionally these tasks are achieved through anatomical imaging (CT, MRI, and US). Of late PET has been increasingly used in high-precision RT for tumor volume delineation and characterization, because PET brings in the crucial functional and molecular information which enable the direct evaluation of tumor metabolism, cell proliferation, apoptosis, hypoxia and angiogenesis. This is a significant advance in cancer imaging with great potential for optimizing RT treatment planning and to the management of cancer patients. The availability of PET and CT in a single imaging system (PET/CT) to obtain a fused anatomical and functional dataset has made the applicability of PET in radiation oncology clinics much easier (Yap et al., 2004). The most recent introduction of PET-MR instrumentation dedicated for concurrent high resolution brain imaging is now revolutionizing the use of multimodality imaging in tumor brain imaging (Boss et al., 2010). Numerous reports are available in the literature in support of the routine use of PET for RT target volume delineation in non-small cell lung cancer (NSCLC), head and neck cancers, lymphoma and in esophageal cancers, with promising preliminary data in many other cancers (Gregoire et al., 2007; Nestle et al., 2009; Zaidi et al., 2009). The focus of this chapter is to update the readers on the potential use of PET imaging in the management of high-grade gliomas (HGG), with particular emphasis being given to the role of PET in the assessment of biological target volumes (BTVs) for RT.

PET-Guided Biological Target Volume (BTV) Delineation

Over the past two decades radiation oncology community has seen a paradigm shift from 2D treatment planning to 3D conformal treatment planning for RT. One of the major advantages of 3D treatment planning and associated treatment delivery techniques is the leverage offered for the dose escalation to tumor volumes while preserving tolerance doses for normal structures. The state-of-the-art 3D-CRT techniques (IMRT, IGRT, tomotherapy, volumetric arc therapy and SRS/SRT etc.) developed to deliver highly conformal radiation beams directed towards targets warrant equally precise imaging modalities for accurate delineation of the tumor extent. Customizing dose delivery to various parts of the treatment volumes ("dose painting" and/or "dose sculpting") based on their dose requirements are possible by 3D-CRT techniques today (Ling et al., 2000). However it is important to know what needs to be "painted", and how much "paint" is required to take complete advantage of these highly conformal radiation delivery techniques (Rickhey et al., 2010).

The principal objective of all form of radiation delivery techniques is to achieve highest possible tumor dose without exceeding the dose level of surrounding normal tissue toxicity. This is achieved in RT today by selective dose escalation also known as "dose painting" with sharp dose gradient along the tumor boundary. The rationale for dose painting is that, treating a selective tumor region to high dose should result in higher tumor control probability and lower normal tissue complication probability. The expected outcome of 3D-CRT is minimal complications and side

effects, while achieving maximum possible dose to tumor tissues. Accurate delineation of the tumor volumes and assessment of the tumor response to the ongoing treatment regimens are necessary for successful implementation of modern RT techniques. In order to achieve the above said goals it is highly desirable to precisely locate and visualize metabolic tumor extensions and delineate boundaries.

Volumetric patient imaging forms the basis for 3D-CRT treatment planning and also helps in the design of radiation fields and dose distributions. Since 3D imaging is used to delineate target volumes and normal structures, the quality of the imaging and information obtained from the images have a direct impact on the patient treatment and potentially on the outcomes and complications. Traditionally, anatomical imaging like CT and MRI are used for radiotherapy treatment planning, monitoring and follow-up evaluation. The major advantage of anatomical imaging is their high resolution, which enables clear visualization of morphological changes. However, the precise delineation of tumor regions with anatomical imaging has some significant limitations. The CT and MRI measure the differential density and magnetic properties of the tissues respectively, both of which may not necessarily be tumor specific characteristics. The morphological changes similar to malignancy can occur due to other confounding factors like infection, treatment (radiotherapy, chemotherapy and surgery etc.) induced inflammation, which makes the distinction between tumor biology from other pathological conditions difficult. Moreover biological changes manifest first and the time frame for the development of detectable morphological changes is too long, during which the disease might have progressed to an advanced stage.

The applicability of anatomical imaging for precise delineation of tumor extension is hampered, when tumor harboring sites have unchanged morphology, density and magnetic properties similar to normal tissue. Successful treatment planning requires information about tumor biological characteristics such as proliferation and hypoxia and the ability to distinguish treatment related scar, edema and necrosis from malignant cells (Sun et al., 2011). Anatomical imaging modalities lack the aforementioned qualities which make them insufficient for the delineation of target volume in most of the clinical presentations and as well treatment response evaluation. Even though PET has lower spatial resolution in comparison to its anatomical imaging counterparts the sensitivity of PET for detecting tumor biology is high with required activity concentration of *nmol* to *pmol* range to detect biological signals (Nestle et al., 2009). A typical example where PET plays an important role in defining biologically active tumor volume over anatomical imaging is shown in Fig. 15.1.

The term "biological imaging" was coined by (Ling et al., 2000) and has become popular in radiation oncology practice. Biological imaging for cancer detection, staging, therapy monitoring and follow up has gained vast interest as the evidence of treatment success with this modality is keep accumulating. The diagnostic utility of PET as the most prominent biological imaging system is evident from the increased interest and utility of PET imaging for cancer imaging and therapy planning for the last few years. The term "biological target volume" (BTV) was also first proposed by (Ling et al., 2000). It is a new method of defining tumor volumes based on metabolism, physiology and molecular biology of tissues. The definition of BTV, apart from the standard definitions of tumor volumes as gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV), is aimed at providing information on the location and extent of tumor margins based on tumor biology. The BTV should also be helpful in assessing the biological response of tumor to therapy. In radiotherapy planning, biological imaging will also guide the radiation oncology community in defining biologically interesting sub-volumes (field in field) of the tumor like a target within the GTV, which could be irradiated with a higher dose through conformal RT (Nestle et al., 2009). Figure 15.2 shows clinical examples comparing biologically defined tumor volumes with anatomically defined tumor volumes. Till date, many PET tracers have been evaluated diagnostically in different cancers. New PET tracers are being developed for staging, RT planning, treatment monitoring and response evaluation during and after completion of RT has gaining more attention in biological imaging.

Techniques for PET-Guided Biological Target Volume (BTV) Delineation

Traditionally CT and MRI have been used as primary imaging modalities for radiation therapy treatment

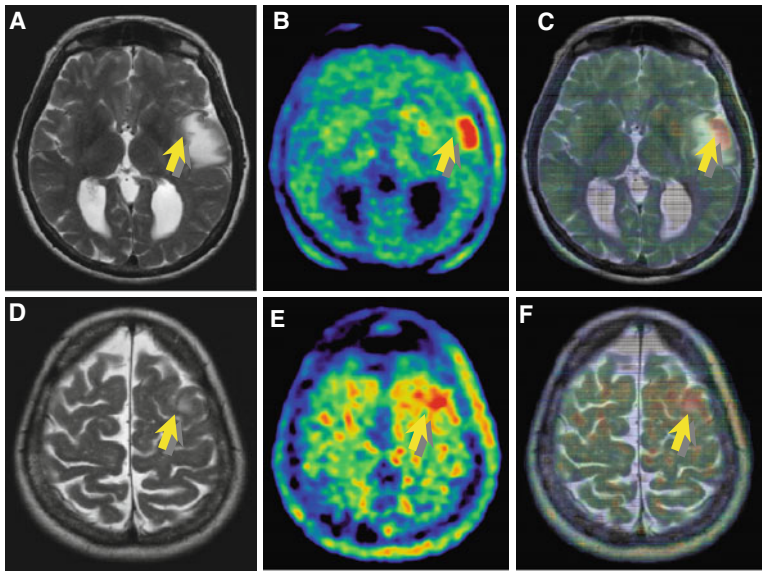

Fig. 15.1 Example of a patient with a glioblastoma (WHO IV) in the left temporal and frontal areas. The images shown on the *top row* (temporal area) correspond to gadolinium enhanced T2-weighted MRI (**A**), coregistered ^{18}F-FET (**B**) and fused PET/MR (**C**) of the first study. The same is shown in the *bottom row* for the same study in the frontal area (**D**, **E** and **F**). The ^{18}F-FET PET study revealed an additional lesion missed on MRI. In addition, the T2-weighted MRI and the ^{18}F-FET PET show substantially different gross tumor volume extension for radiation therapy treatment planning

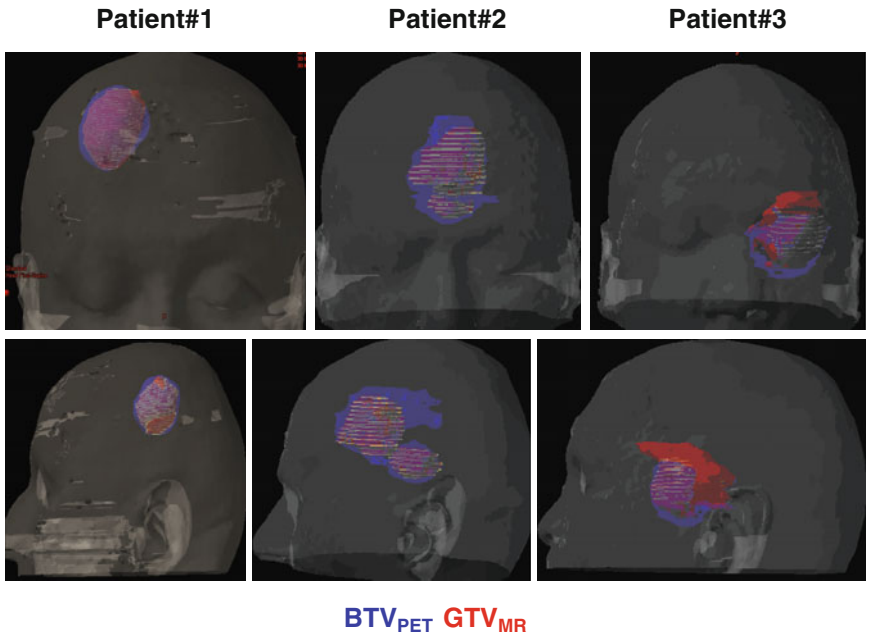

Fig. 15.2 Biological (BTV, *blue*) and morphological gross tumour (GTV, *red*) volume defining the clinical target volume in patients with high-grade glioma. Note the common volume between the tumour volumes (*yellow chicken wire*). Good BTV-GTV matching is shown (*left*) in 1 patient, while substantial BTV-GTV mismatch is also detailed (*center* and *right*) in 2 other patients. Adapted from Weber et al. (2008)

planning. X-ray computed tomography and MRI offer excellent spatial resolution, and soft tissue contrast, but both imaging modalities fail to provide functional properties of the imaged tissues. In cases where the true extent of the disease may extend beyond anatomically defined volumes, despite its inferior resolution compared with CT and MRI, PET has been shown valuable for defining the extent of target volumes. Some of the key contributions of PET in addition to or in combination with other imaging modalities are delineation of tumor volumes, biological characterization of tumor, and assessment of treatment response. With the widespread adoption of hybrid PET/CT scanners, in radiotherapy clinics, PET-based delineation of target volumes appears to be an attractive option in RT treatment planning. One of the most difficult issues facing PET-based RT treatment planning is the accurate delineation of target regions from typical noisy functional images. The major problems encountered in functional volume quantification are image segmentation and imperfect system response function. Image segmentation is defined as the process of classifying the voxels of an image into a set of distinct classes. The difficulty in image segmentation is compounded by the low spatial resolution and high-noise characteristics of PET images. Medical image segmentation has been identified as the key problem of medical image analysis and remains a popular and challenging area of research. Despite the difficulties and known limitations, several image segmentation approaches have been proposed and used in clinical setting including thresholding, region growing, classifiers, clustering, edge detection, Markov random field models, artificial neural networks, deformable models, atlas-guided, and many other approaches (Zaidi and El Naqa, 2010).

Medical image segmentation remains an unsolved problem that has captured the imagination of image analysis scientists over the past three decades. Manual segmentation methods available on most commercial software packages to identify lesion boundaries and to quantify GTVs in terms of standardized uptake value are very laborious and tedious. They discourage physicians from taking advantage of the inherently quantitative data and compel them to use qualitative means in their diagnosis, therapy planning, and assessment of patient response to therapy. Semi- or fully automated segmentation methods enable physicians to easily extract maximum and mean standardized uptake value estimates from a lesion volume. This also allows the physician to track changes in lesion size and uptake after radio/chemotherapy. At present, various methods are used in practice to delineate PET-based target volumes.

Manual delineation of target volumes using different window level settings and look up tables is the most common and widely used technique in the clinic. However, the method is highly operator-dependent and is subject to high variability between operators. Rather large intra-observer variability was reported for many localizations including HGG as shown in Fig. 15.3 (Weber et al., 2008). In this respect, semi- or fully-automated delineation techniques might offer several advantages over manual techniques by reducing operator error/subjectivity, thereby improving reproducibility.

Assessment of PET-Guided Biological Target Volumes in High-Grade Gliomas (HGG)

Accurate determination of the tumor boundary at the microscopic level, assessment of the tumor sensitivity, and/or prognosis to the therapy is essential for successful treatment planning. Glioma cells are one of the most treatment resistant cells and their inherent heterogeneous cell populations, diffuse infiltration into normal brain tissues are the biggest challenge in the tumor localization and precise delineation of tumor extent. Prognosis of cerebral gliomas has continued to remain poor for several decades, albeit significant advances in multimodality diagnostic and therapeutic procedures. Therefore, development of a highly specific and sensitive non-invasive imaging modality is required. The ability to closely correlate diagnosis with pathology, distinguish inflammation and necrosis from tumors, differentiate tumor grades, accurately delineate tumor volume, monitor treatment responses, and identify residual tumor/recurrence are the desirable goals for imaging brain tumors to improve their clinical management.

The specificity of anatomical imaging modalities in distinguishing neoplastic disease from vascular or inflammatory processes can be problematic in high-grade gliomas. Treatment effects including surgical trauma, corticosteroid-induced reduction of edema and contrast enhancement, and radionecrosis cannot

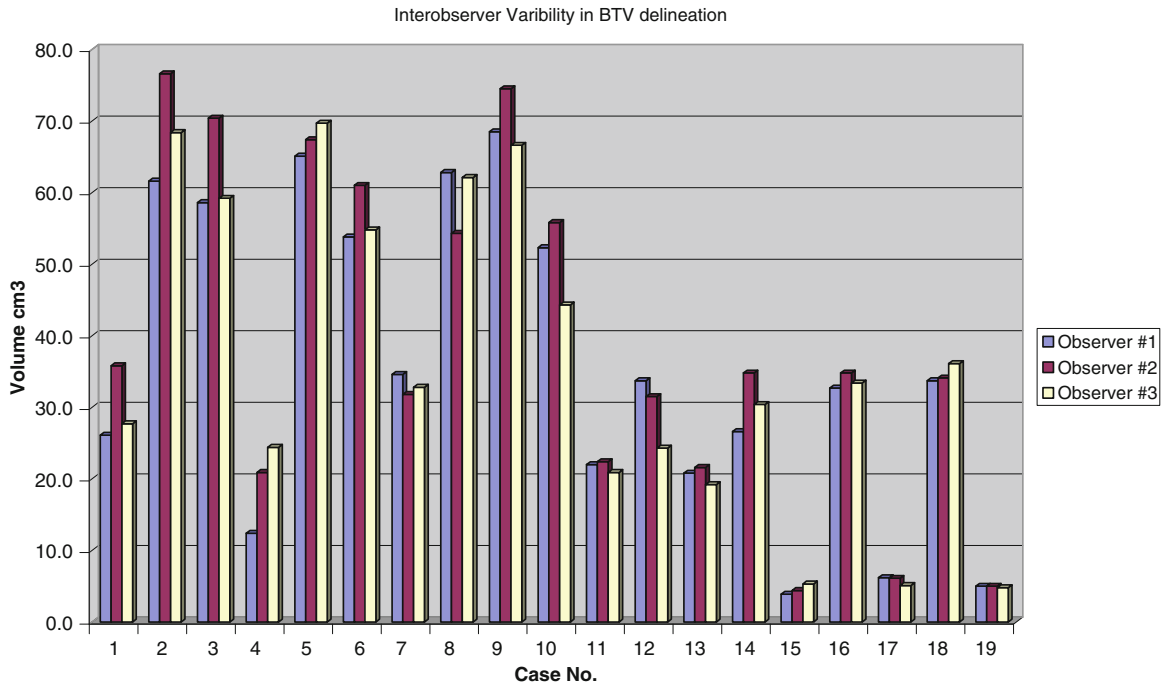

Fig. 15.3 Biological tumor volume measurements by three observers for each high-grade glioma case (1 through 19)

always reliably be distinguished from tumor recurrence or response to therapy. Molecular imaging allows a better understanding of pathology at molecular level. This ability is especially useful in the brain tumors where tissue sampling in vivo is associated with significant risks. Availability of a suitable imaging modality or a multimodality combination to obtain the information of interest noninvasively is also vital for the basic research and development of novel and effective experimental therapeutics required to improve prognosis. Accurate quantitative information on the metabolic state of glioma tumor cells can be achieved through biological imaging using PET. Depending on the radiotracer used, various molecular processes can be visualized through PET imaging, most of them relating to an increased cell proliferation, metabolic rates, and DNA synthesis as well as abnormal microvessel density and thereby define tumor extent better than morphologic imaging in malignant gliomas (Tsien et al., 2009).

PET radiotracers are especially helpful (1) in the localization, grading and finding the extent of glioma cells; (2) in the identification of metabolically active residual tumor after therapy; (3) monitoring of tumor progression; and (4) most importantly in the differentiation between recurrent tumor and radiation necrosis. Various metabolism and biochemical pathways are exploited by PET tracers for glioma imaging. Energy metabolism of cells is imaged by [F-18]-2-fluoro-2-deoxyglucose (FDG). Amino acid transport and incorporation of tumor cells are tracked by L-methyl-[C-11]methionine (MET), L-[C-11]tyrosine, L-[F-18]fluorotyrosine. DNA synthesis is imaged by 2-[C-11]thymidine, methyl-[C-11]thymidine, [F-18]-3′deoxy-3′-fluorothymidine (FLT). Cell membrane/lipid biosynthesis is tracked by 1-[C-11]acetate, [C-11]choline, [F-18]fluorocholine. Hypoxia is an important aspect to consider for assessing the aggressiveness of tumor and predicting the outcome of therapy (Sun et al., 2011). Tumor hypoxia is imaged by [F-18]fluoromisonidazole (FMISO) and many other tracers.

The preferential uptake of malignant glioma cells in comparison to normal cells are exploited by tracers like ^{18}F-FDG, ^{11}C-MET, ^{18}F-FET and ^{18}F-FLT, depending on the tumor grade as a reflection of increased activity of membrane transporters for amino acids (^{11}C-MET and ^{18}F-FET) and nucleosides (^{18}F-FLT) as well as increased expression of cellular hexokinase (^{18}F-FDG) and thymidine kinase (^{18}F-FLT) genes, which phosphorylate ^{18}F-FDG and ^{18}F-FLT, respectively.

Many hypoxia tracers (^{18}F-FMISO, ^{18}F-FAZA, ^{64}Cu-ATSM and ^{18}F-EF5) have already shown their importance in target volume delineation or patient management in RT (Grosu et al., 2005a).

The most commonly available PET tracer ^{18}F-FDG has the potential to detect abnormal metabolic rate, through increased cellular glucose metabolism in brain tumors. However, its use in target definition is complicated by the high level of intrinsic glucose uptake in the brain. FDG imaging is useful in distinguishing low-grade gliomas (LGG) from HGG based on tumor-to-cortex (T/C) uptake ratio and tumor-to-white matter (T/WM) uptake ratio. Selecting the optimum site for tumor biopsy can be done based on the maximum uptake of FDG for sampling of the most malignant areas of tumors. For assessing response by pre- to post-treatment comparisons, FDG appears to be limited in clinical usefulness. The ability of ^{18}F-FDG PET to differentiate recurrent tumor from radiation necrosis is also limited. The false-positive and false-negative FDG-PET could result in unacceptably low sensitivity, specificity, and negative predictive values.

The goal of PET imaging with radio-labeled amino acids is to assess the protein synthetic process of tumor growth. Amino acid uptake in normal brain tissues is low relative to FDG uptake so that the tumor to normal tissue contrast is better with amino acid imaging than with FDG. Radiolabeled amino acids can also penetrate the blood–brain barrier independently of its disturbance. A variety of ^{11}C- and ^{18}F-labeled amino acids such as ^{11}C-methionine (^{11}C-MET) and ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET) have been studied for potential use in oncologic PET. Most brain tumors show an increased uptake of amino acids compared with normal brain tissue. In particular, the uptake of ^{18}F-FET by brain tumors especially by high-grade glioma cells is intense relative to the low uptake in normal cerebral tissue and has shown the potential in the detection of primary and recurrent brain tumors with high sensitivity and specificity. Compared with ^{11}C-MET, ^{18}F-FET PET findings in brain tumors are similar. One of the advantages of ^{18}F-FET over ^{11}C-MET is that the half life, which makes it possible to be used in clinics not having on-site cyclotron.

^{11}C- methionine PET and ^{18}F-fluorothymidine (FLT), provide better differentiation of the tumor from brain background signals than ^{18}F-FDG PET. The ^{11}C-methionine PET scan reflects metabolic activity through increased transport of amino acid carriers at the level of the blood-brain barrier that is highly expressed in malignant tumors compared with low uptake in the normal brain. On the other hand FLT, is a thymidine analog that is incorporated exclusively into DNA. It measures the activity of cellular thymidine kinase, which increases several-fold as cells enter the S-phase and begin DNA synthesis. Increased FLT uptake and therefore thymidine kinase levels provide a direct measure of the cellular proliferation rate.

Tumor hypoxia remains the most challenging condition for treatment. Though oxygen metabolism in gliomas differs from that of normal brain tissue, the lack of oxygen appears to be an important factor in determining glioma aggressiveness and response to therapy. It has been documented in several types of cancers that low levels of oxygen tension are associated with persistent tumor following RT and with the subsequent development of local recurrences. In gliomas, spontaneous necrosis suggests the presence of hypoxic regions that are radioresistant. ^{18}F-FMISO imaging of hypoxic glioma cells shows significant promise, however larger patient population studies are required to ascertain its clinical impact. Identifying the regional distribution of hypoxia may improve planning of resections and allow targeting higher doses of radiotherapy more precisely to the hypoxic areas.

Glioma cell membrane biosynthesis is imaged using ^{11}C-acetate and ^{11}C-choline. The rationale for imaging membrane and lipid biosynthesis is that tumor growth requires both of these processes in parallel with DNA and protein synthesis. These will likely show retention in tumor tissue but not by gray matter, an important advantage over FDG. A very few studies have been done so far on this front to show the potential advantages of this approach.

PET Imaging for Differentiating Recurrent Brain Tumor from Radiation Necrosis

Radiation damage to vascular endothelial cells and oligodendrocytes causes necrosis. Differentiating tumor growth from post-treatment radiation effect (PTRE) remains a common challenge in high-grade glioma tumors. On MRI, appearances of radiation necrosis and of recurrent tumor are quite similar, as both causes' areas of increased signal intensity. Conventional MRI/MRSI are currently used for the

detection of early treatment-bed changes, though accurate diagnosis is challenging because tumor growth, PTRE, and admixed lesions can all have identical MR imaging appearances. Microscopic tissue analysis distinguishes these entities and can document intra-lesion heterogeneity by resolving distinct subregions of tumor from pure PTRE within different locations of the same lesion. Early work on utilizing PET in differentiating radiation induced necrosis from recurrent brain tumor was conducted by Patronas and coworkers using FDG (Patronas et al., 1982). The rationale for using FDG is that radiation necrosis is expected to show decreased uptake in comparison with recurrent tumors. However, in many cases, distinguishing recurrent tumor from radiation necrosis is found to be difficult based on FDG-PET alone (Hustinx et al., 2005). Radiolabeled amino acid analogues like ^{11}C-MET, ^{18}F-FET and proliferation marker ^{18}F-FLT are suggested to perform better in PTRE evaluation, than FDG in detecting residual and recurrent tumors after fractionated irradiation (Hustinx et al., 2005; Reinhardt et al., 1997). Though the exact incidence of true radiation necrosis is largely unknown, differentiating it from recurrent tumor has a larger clinical implication in the clinical management of patients and PET tracers seem to play a major role in it.

Current Practice of Target Volume Delineation in HGG

Conventional target volume definitions in high grade gliomas (HGG) have not incorporated PET. The gross tumor volume (GTV) is mostly defined on post-operative MRI and includes the contrast-enhancing lesion as well as the surgical cavity (Fueger et al., 2010). Clinical target volumes (CTVs) include an MRI defined volume with an addition of uniform margin (about 2 cm) within the brain, which includes areas of microscopic extension and peritumoral edema. When therapy is planned for a second CTV (boost volume) a margin of typically 1.5 cm around the GTV is added to account for areas of microscopic disease. These CTVs are then further expanded by a uniform margin of 0.3–0.5 cm to create a PTV to account for treatment setup uncertainties. Initial imaging for HGG is usually done with CT or MRI, which provides accurate information about lesion anatomy and location. However, follow-up assessment of primary HGG tumors after radiation therapy, chemotherapy and surgery, is often difficult, since the anatomical imaging modalities are usually not able to differentiate recurrent tumor from radiation necrosis, surgical scar or inflammation. Identifying radiation necrosis and differentiating them from tumor recurrence pose a potential diagnostic challenge because the accurate diagnosis has important implications for the patient management.

PET-Guided Biological Target Volumes in HGG

Grosu and co-workers have investigated the use of amino-acid PET and single-photon emission computed tomography (SPECT) in gross tumor volume definition for radiotherapy treatment planning of gliomas (Grosu et al., 2005a, c). They have shown that ^{11}C-MET-PET offers significant additional information about tumor extent in HGG, compared to CT and MRI alone. This study suggested that integration of amino-acid PET in target volume definition might contribute to an improved outcome in HGG patients treatment. It was also showed that abnormal MET PET activity was detected beyond the area of the contrast-enhancing lesion on MRI. In a retrospective study on newly diagnosed glioblastoma multiforme (GBM) who underwent MET PET before radiation, the area of MET uptake was found to be larger than the contrast-enhancing gadolinium volume in 29 (74%) of 39 patients (Grosu et al., 2005c). In the same study it was showed that patients who underwent treatment planning based on ^{11}C-MET PET/SPECT imaging had improved survival compared with treatment planning based on CT/MRI in recurrent gliomas, with a median survival of 9 months versus 5 months, respectively. Other investigators have also suggested that ^{11}C-MET PET has the potential to improve target volume definition in the radiation treatment planning of high-grade gliomas by identifying residual tumor after resection and also in recurrent gliomas. Yamane et al. (2010) have recently showed that ^{11}C-MET PET can provide useful information in initial diagnosis and differentiating tumor recurrence from radiation necrosis. They have also claimed that use of ^{11}C-MET PET has changed the intended clinical management in half of the patients.

Our group (Vees et al., 2009) has studied the contribution of ^{18}F-FET PET in the delineation of GTV in HGG patients compared with MRI alone. In this study PET based tumor volumes were delineated in 18 patients using seven image segmentation techniques. The PET image segmentation techniques included manual delineation of contours ($GTV_{(man)}$), a 2.5 standardized uptake value (SUV) cutoff ($GTV_{(2.5)}$), a fixed threshold of 40 and 50% of the maximum signal intensity ($GTV_{(40\%)}$ and $GTV_{(50\%)}$), signal-to-background ratio (SBR)-based adaptive thresholding ($GTV_{(SBR)}$), gradient find ($GTV_{(GF)}$), and region growing ($GTV_{(RG)}$). Figure 15.4 shows an example of image segmentation using these techniques. Overlap analysis was also conducted to assess geographic mismatch between the GTVs delineated using the different techniques. Contours defined using $GTV_{(2.5)}$ failed to provide successful delineation technically in three patients (18% of cases) as SUV(max) <2.5 and clinically in 14 patients (78% of cases). Overall, the majority of GTVs defined on PET-based techniques were usually found to be smaller than $GTV_{(MRI)}$ (67% of cases). Yet, PET detected frequently tumors that are not visible on MRI and added substantial tumor extension outside the $GTV_{(MRI)}$ in six patients (33% of cases). The study showed that the selection of the most appropriate ^{18}F-FET PET-based segmentation algorithm is crucial, as it impacts both the volume and shape of the resulting GTV. The SBR-based PET technique shown to be useful and suggested that it may add considerably important information on tumor extent to conventional MRI-guided GTV delineation. In a recent study by (Pichler et al., 2010), it has been shown that ^{18}F-FET-PET is highly sensitive for detecting high-grade glioma in patients with neurological symptoms. It was also suggested that, in the evaluation of new brain lesions of unknown significance via ^{18}F-FET-PET a negative image can encourage a wait and see strategy-of course in accordance with the clinical picture and morphological imaging.

There are a few good reviews on the use of functional PET and MRI imaging for tumor volume definition in high-grade gliomas (Benard et al., 2003; Grosu et al., 2005a; Guha et al., 2008; Jacobs et al., 2002; Lecchi et al., 2008; Pirzkall et al., 2001; Tsien

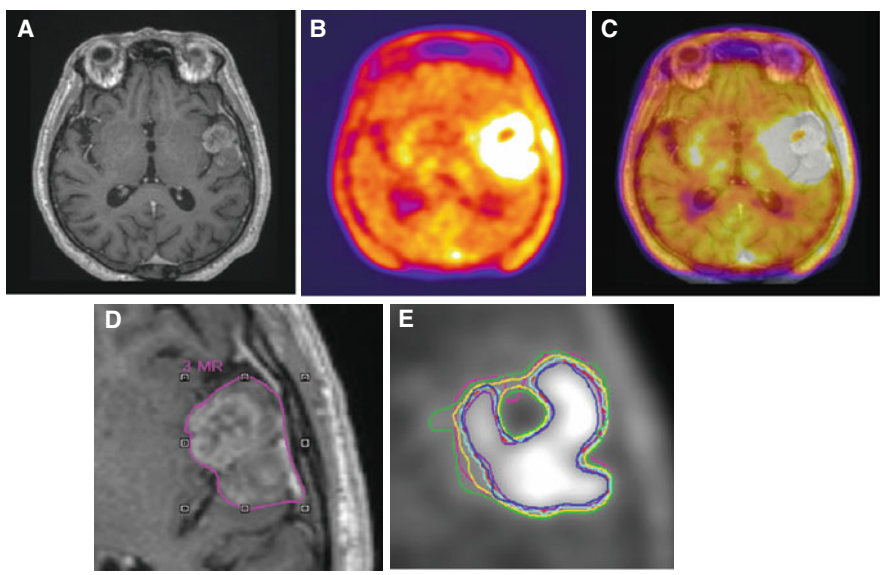

Fig. 15.4 (**A**) Gadolinium enhanced T1-weighted MRI, (**B**) corresponding ^{18}F-FET PET, and fused PET/MR (**C**) transaxial slices of a clinical study with a glioblastoma showing differences in target-volume definition. Indicated are (**D**) the gross tumour volume (GTV) delineated on MRI (GTV_{MRI}), and (**E**) enhanced details of PET-based GTVs obtained by manual delineation of contours (GTV_{man}; *magenta*), an isocontour of a standardized uptake value (SUV) of 2.5 ($GTV_{2.5}$; *purple*), a fixed threshold of 40% ($GTV_{40\%}$; *green*) and 50% ($GTV_{50\%}$; *cyan*) of the maximum signal intensity, signal-to-background ratio (SBR)-based adaptive thresholding (GTV_{SBR}; *yellow*), gradient find (GTV_{GF}; *blue*), and region growing (GTV_{RG}; *red*) segmentation algorithms. Note that GTV_{MRI} overestimates the tumour extension relative to GTV_{man}. Reprinted with permission from Vees et al. (2009)

et al., 2009). The key conclusions are that the PET images could help in detecting metabolic and functional abnormalities beyond the tumor volume seen on conventional MRI, assess early response to treatment, and delineate the regions of high risks for failure in high-grade gliomas.

Concluding Remarks and Future Perspectives

PET imaging provides the opportunity to image noninvasively many biological processes in brain tumors. Regional biological information and pathophysiology of gliomas can be obtained by studying energy metabolism, amino acid transport, hypoxia, proliferation and cell death. None of these has been thoroughly studied and utilized to allow judgment of their potential benefit to the management of gliomas. Future large clinical trials will shed some light on the potential benefits of imaging these specific biological processes. The issue of gross tumor volume delineation using biological imaging modalities for high-grade gliomas is not clearly resolved at present for all clinical situations. A multimodality approach of biological imaging (PET, SPECT, CT, MRI and MRSI) might prove to be an effective way as all the imaging modalities complement each other for better target volume delineation. Despite the limited number of published reports, the use of amino-acid PET, SPECT and MRSI, along with anatomical imaging are shown superior to either CT or MRI alone in visualizing the tumor extent in gliomas. There have been studies comparing SPECT and PET with MRI or MRSI to see the combined effect of anato-molecular approach to identify what volume needs to be treated with high conformity (Grosu et al., 2005b). A number of studies showed the existence of significant differences in the target volumes delineations that result from the use of either PET or MRI/MRSI imaging and it is still too early to recommend the use of biologic imaging as the sole determinant of target volumes. However, the incorporation of biological imaging into a treatment planning process that currently depends entirely on anatomic imaging seems advantages in most of the clinical presentations. In essence PET guided biological target volumes helps treatment planning in radiotherapy, in terms of identifying biological processes. However, the real outcome of biological imaging is yet to be analyzed in a larger clinical setup.

At present limited clinical data is available to prove the superior outcomes in HGG patients with PET defined GTV for RT planning. Retrospective analysis of the outcome of controlled dose-escalation trials that used biological imaging alongside MRI/MRSI for target volume segmentation could provide useful insights for better design of prospective clinical trial for accurate tumor delineation (Grosu et al., 2005a). New studies focusing on the wide applicability of biological imaging in HGG is ongoing, and it remains to be seen how the high precision in gross volume segmentation translates into fruitful results with conformal radiation delivery techniques such as IMRT, IGRT etc, in a large clinical trial settings. In order to take maximum advantages of advances in high precision dose deliver techniques ("dose sculpting" and "dose painting") most accurate available assessment of tumor extent by biological imaging modalities should be used for high-grade gliomas. Future developments of new tracers for biological imaging and robust automated image segmentation techniques will bridge the existing knowledge gap in the high-grade gliomas tumor volume delineation.

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