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Combined imaging biomarkers for therapy evaluation in glioblastoma multiforme: correlating sodium MRI and F-18 FLT PET on a voxel-wise basis

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Abstract

We evaluate novel magnetic resonance imaging (MRI) and positron emission tomography (PET) quantitative imaging biomarkers and associated multimodality, serial-time-point analysis methodologies, with the ultimate aim of providing clinically feasible, predictive measures for early assessment of response to cancer therapy. A focus of this work is method development and an investigation of the relationship between the information content of the two modalities. Imaging studies were conducted on subjects who were enrolled in glioblastoma multiforme (GBM) therapeutic clinical trials. Data were acquired, analyzed and displayed using methods that could be adapted for clinical use. Subjects underwent dynamic [^{18}F]fluorothymidine (F-18 FLT) PET, sodium (^{23}Na) MRI and 3-T structural MRI scans at baseline (before initiation of therapy), at an early time point after beginning therapy and at a late follow-up time point after therapy. Sodium MRI and F-18 FLT PET images were registered to the structural MRI. F-18 FLT PET tracer distribution volumes and sodium MRI concentrations were calculated on a voxel-wise basis to address the heterogeneity of tumor physiology. Changes in, and differences between, these quantities as a function of scan timing were tracked.

While both modalities independently show a change in tissue status as a function of scan time point, results illustrate that the two modalities may provide complementary information regarding tumor progression and response. Additionally, tumor status changes were found to vary in different regions of tumor. The degree to which these methods are useful for GBM therapy response assessment and particularly for differentiating true progression from pseudoprogression requires additional patient data and correlation of these imaging biomarker changes with clinical outcome.

Keywords

Glioblastoma Multiforme; Therapy Response assessment; Sodium MRI; FLT PET

1. Introduction

Although routinely used for some aspects of cancer care, minimally invasive medical imaging procedures, which can be repeated at regular intervals, have a much greater potential for guiding clinical decision-making than is currently realized. For successful clinical translation, imaging protocols must (a) yield relevant information and (b) be feasible

under the time and resource constraints imposed by clinical operation. These two requirements can be at odds in that information gained typically comes at the expense of protocol and analysis complexity. Multimodality platforms, e.g., positron emission tomography (PET)/computed tomography (CT) and now magnetic resonance imaging (MRI)/PET, help to ameliorate this situation and have substantially increased the opportunity for the use of multimodality data for therapy management. However, optimal use requires the identification and evaluation of effective biomarkers and the development of efficient acquisition and analysis methods. As part of a project to address these issues, this paper examines the joint use of sodium (^{23}Na) MRI and PET using [^{18}F]fluorothymidine (F-18 FLT) to evaluate therapy effect in patients with glioblastoma multiforme (GBM). As described below, F-18 FLT is expected to trace DNA synthesis, and therefore cellular proliferation, but is complicated by blood-brain barrier (BBB) effects [1]. Sodium MRI reveals tissue sodium concentration (TSC), changes in which have also been associated with cellular proliferation in general [2] and in brain tumors specifically [3]. However, its interpretation is complicated [4] since the ^{23}Na signal derives from a combination of intra- and extracellular contributions [3,5]. Thus, the two modalities are expected to have both overlapping and complementary components that could be exploited to improve patient management in GBM.

Glioblastoma multiforme, a grade IV astrocytoma, accounts for 50%–60% of primary brain tumors diagnosed in adults each year in the United States with an incidence in North America of 3.0 per 100,000 population. GBM has an estimated 2-year survival rate of 8.7% in the absence of therapy [6]. Even with treatment, prognosis is poor since the recurrence rate is high; however, there has been modest improvement since 2005 when the standard-of-care treatment for newly diagnosed GBM changed from radiation therapy (RT) alone to radiation therapy plus temozolomide (TMZ) chemotherapy (RT-TMZ) [7]. Patients treated with optimal therapy, including surgical resection, radiation therapy and chemotherapy, have a median survival of approximately 12 months, with fewer than 25% surviving for 2 years and fewer than 10% surviving for 5 years [8]. The increasing array of therapy options (e.g., bevacizumab) and the rapid advances being made in the development of targeted therapeutic approaches coupled with the narrow window for effective GBM management decisions provide a strong impetus to develop noninvasive, molecular, event-specific imaging approaches for early evaluation of therapy. Additionally, such methods can play a key role in expediting clinical therapy trials.

The use of CT and MRI for monitoring of tumor structural properties is well established, and standards have been developed for therapy response characterization based on tumor size measurements, e.g., Response Evaluation Criteria In Solid Tumors (RECIST). Likewise, the use of PET with [^{18}F]fluorodeoxyglucose (F-18 FDG) for measurement of tissue glucose metabolism can be useful for initial tumor staging, restaging and, in some cases, therapy response monitoring. However, monitoring of brain tumors presents special challenges. For example, a transient increase in the bidimensional [9] or unidimensional (RECIST) size of the contrast-enhancing lesion in structural MRI scans, sometimes known as “pseudoprogression” (as opposed to true progression), has been reported in patients undergoing MRI at the standard clinical assessment time of 4 weeks after the completion of radiotherapy (e.g., Ref. [10,11]). For patients on the widely used Stupp regimen [12], it is precisely this time point at which a follow-up MRI scan is performed that serves as the baseline for further adjuvant therapy. Thus, determining whether an apparent radiological worsening is true tumor progression or pseudoprogression is critical to the decision whether or not to continue current chemotherapy or to change to another treatment regimen. The utility of F-18 FDG PET for this purpose is limited due to high normal brain uptake that makes assessment of low metabolic areas of treated but viable tumor or small regions of tumor recurrence difficult. This limitation is exacerbated by reduced uptake in radiation- or

chemotherapy-induced vasogenic edema in the tumor region that can be incorrectly interpreted as a beneficial response [13]. At present, there are no validated imaging criteria for differentiation of pseudoprogression from true progression. Sodium MRI and F-18 FLT PET are potential tools for evaluation of therapy response in GBM.

1.1. MRI measures of intra- and extracellular sodium (^{23}Na) concentration

TSC can be expressed as:

$$\text{TSC} = [\text{Na}^i \times \text{CVF}] + [\text{Na}^e \times (1 - \text{CVF})], \quad (1)$$

where Na^i and Na^e are the concentrations of intracellular and extracellular sodium, respectively, and CVF is the tissue cell volume fraction. For typical values of the above parameters (e.g., $[\text{Na}^i]$ approximately 40 mM, $[\text{Na}^e]$ approximately 140 mM and CVF approximately 70%), a typical tumor TSC is 70 mM, which is in agreement with reported values in the literature.

In neoplastic tissue, sustained depolarization of the cell membrane precedes the high rate of mitotic activity that characterizes abnormal cell growth [14,15] and leads to an increase in Na^i that has been demonstrated in a number of human neoplasms [2,16,17]. Further characterization of Na^i rise in several types of human carcinomas [16,17] and glial cell lines [18,19] has established a positive correlation between proliferative activity and increased intracellular $\text{Na}^+:\text{K}^+$ ratio (mostly due to an increase in Na^i). Once neoplastic changes are set in the tissue, a decrease in CVF is observed due to the different morphology of neoplastic cells. The combined effect of decreasing CVF and increasing intracellular sodium content is a net increase in TSC.

However, other changes in physiology affect measured TSC. Specifically, once a cell's membrane becomes compromised, e.g., in cell death or near cell death, its ability to maintain an intra- to extracellular sodium gradient diminishes or disappears, and an increase in TSC should be observed. A rise in TSC to Na^e levels is an indication of a region of lysed cells.

Thus, it is clear that changes in TSC indicate important oncologic/therapy-related changes in tissue status. However, a precise attribution of physiologic meaning of changing TSC in tumor is not always possible without assumptions, a priori knowledge or additional data. For example, a plausible assumption is that large changes in TSC observed within days of therapy are likely due to therapy-induced cellular membrane compromise. A goal of this work is to develop methods for effective use of ^{23}Na MRI in conjunction with F-18 FLT PET and to demonstrate correlations between combined results of both modalities and patient outcome.

1.2. F-18 FLT PET measures of thymidine kinase-1 activity

F-18 FLT is a pyrimidine analogue that reflects the activity of a thymidine kinase-1 during S phase of DNA synthesis [20]. F-18 FLT was introduced by Shields and colleagues for PET imaging of tumor proliferation in animals and humans [21]. Several studies have investigated the role of F-18 FLT in detecting and staging of different malignancies, such as lung cancer, colorectal cancer, melanoma, soft tissue sarcoma, breast cancer and brain tumors [22–29].

As a marker of proliferation, F-18 FLT is considered a potential tool for monitoring anticancer treatment in solid tumors [30–35]. In the case of brain tumors, significant correlations have been observed between F-18 FLT uptake and Ki-67 proliferation index [13,36–41]. Moreover, a 2007 study performed by Chen et al. [42] demonstrated that F-18 FLT PET scans of GBM patients receiving bevacizumab/ irinotecan treatment showed a

25% reduction in uptake at 6 weeks compared to 2-week early therapy response assessment scans. Furthermore, the same study found that responders, as measured by F-18 FLT, survived three times as long as nonresponders (10.8 vs. 3.4 months) and tended to have a prolonged progression-free survival [42]. Finally, F-18 FLT PET was found to be a more significant predictor of overall survival than contrast-enhanced MRI alone [42].

An important consideration is that F-18 FLT does not readily cross an intact BBB, and it is necessary to account for this in the interpretation of results [1]. Nevertheless, F-18 FLT may be useful in cases where MRI contrast enhancement, typically associated with BBB breakdown, is observed [1]. This is exactly the situation present when the task is to distinguish pseudoprogression from progression. Nevertheless, for such use, it is necessary to verify that the tracer has access to the brain tissue in question. A possible method for achieving this, using scan data acquired during the initial tracer wash-in phase (e.g., within the first 2 min after tracer injection), is examined in this paper.

The purpose of this work is to investigate correlations between ^{23}Na MRI and F-18 FLT PET biomarkers using clinically feasible data analysis and visualization methods necessary for assessing GBM therapeutic response. We evaluate these correlations through voxel-wise comparisons, necessary to account for GBM heterogeneity, both at baseline and in response to therapy.

2. Methods

2.1. Subjects

Studies were performed under a University of Pittsburgh Institutional Review Board-approved protocol. Subjects signed informed consent documents before enrollment. Two patients about to begin treatment for GBM were scanned serially. Histopathology of each tumor was confirmed by fine-needle MRI-guided stereotactic biopsy or craniotomy prior to being scanned. Therapy for each patient included whole field RT to a total dose of 60 Gy, in daily 2-Gy fractions, with concomitant temozolomide on days 1–42. Patient 1 (female; 62 years old; Ki67: 70%) was scanned at day 17 [early therapy assessment (ETA)] and 72 [late therapy assessment (LTA)] from the start of therapy. Subject 2 (male; 40 years old; Ki67: 15%–20%) was scanned at baseline (after biopsy but before the therapy) and had ETA and LTA scans at day 16 and 72, respectively. Although subject 1 did not receive a complete baseline evaluation, this subject's tumor was more aggressive (as measured by Ki 67) and larger than that of subject 2. Thus, subject 1's data were used in development of analysis procedures, and results from both subjects are reported.

2.2. Imaging protocol

Each baseline, ETA, and LTA time point consisted of an MRI acquisition, which included a sodium MRI scan, and a 68-min dynamic F-18 FLT PET acquisition.

2.2.1. MRI acquisition protocol—Images were acquired on a whole-body 3-T TIM Trio using a dual-tuned ($^{23}\text{Na}/^1\text{H}$), dual-quadrature, four-port birdcage radiofrequency (RF) coil (Advanced Imaging Research, Cleveland, OH, USA). All studies included the use of fluid attenuated inversion recovery (FLAIR) MRI, chemical shift imaging (CSI), magnetization-prepared rapid acquisition with gradient echo (MPRAGE) MRI, and both T1-weighted and T2-weighted MRI sequences, in order to provide anatomical referencing and a comparison with conventional imaging schemes. The sodium pulse sequence consisted of a nonselective RF pulse followed by a twisted projection imaging readout, which allows for efficient coverage of k-space leading to a total imaging time of 10 min for each one of the sodium

images acquired during the study. The raw data were reconstructed off-line using in-house image reconstruction software.

2.2.2. Dynamic PET acquisition protocol—PET acquisition commenced simultaneously with intravenous bolus injection of 5 mCi of F-18 FLT. Each PET scan was performed as a 68-min dynamic acquisition using an HR+ ECAT scanner (Siemens). Data were acquired in three-dimensional mode using a frame duration of 6 s/frame for the first 120 s (20 frames), 20 s/frame over the time range 120–180s (3 frames), 30 s/frame from 180 to 300 s (4 frames), 60 s/frame from 300 to 780 s (8 frames) and 300 s/frame from 780 to 4080 s (11 frames). Additionally a 10-min transmission scan, required for attenuation and scatter correction, was performed using the scanner's internal ^{68}Ge rod sources.

PET data were processed using Fourier rebinning followed by reconstruction via the direct Fourier method using the manufacturer's software into a $128 \times 128 \times 63$ (axial) matrix with voxel dimensions of $0.21 \times 0.21 \times 0.24$ cm. Images were smoothed with a 3-mm Hann filter. Reconstruction included corrections for attenuation, scatter, accidental coincidences, dead time and radioactive decay. The final PET images had a resolution of about 5–6 mm, and no partial-volume correction or resolution recovery methods were applied.

2.3. Image analysis

The software PMOD 3.2 (University Hospital Zurich, Zurich, Switzerland) was used for most of the analysis. MRI sodium images were aligned to the corresponding MPRAGE T1 structural MRI images. Each dynamic PET series was examined and, if required, corrected for interframe subject motion using PMOD software. The first 2 min of each PET image series were summed into a single image that primarily shows blood flow. The 2-min PET image was aligned to the corresponding MPRAGE image. The MPRAGE scans at the various time points for a given subject were aligned to the earliest such scan. At each step, transformation parameters were saved and applied to the corresponding F-18 FLT PET and sodium MRI images, resulting in all images from a single subject being aligned. Final images for analysis were resliced to match the PET voxel size.

The dynamic PET image series (46 image frames) from each scan session was analyzed using a voxel-wise Logan analysis [43] in which the time activity curve (TAC) from each voxel was treated separately. The process results in a parametric image of tracer distribution volumes. The method requires an input function which was generated by an analysis of the carotid artery activity in the PET image. The initial 2-min PET image (described above) was filtered using a Gaussian kernel [6 mm full width at half maximum (FWHM) in three dimensions]. A region of interest (ROI) was defined on the internal carotid arteries on four contiguous slices of this image, under the constraint that the ROI contained all voxels that had at least 80% of the maximum voxel activity within the carotid as visualized on the four slices. The ROI was then applied to the original (unfiltered) dynamic image series to obtain a raw blood TAC. A population-based [44,45] average metabolite correction [46] was applied by multiplying the activity at each time point in the raw curve by the correction factor F_m where $F_m(t) = 1 - 0.42[1 - e^{-\lambda t}]$, $\lambda = 0.029 \text{ min}^{-1}$ and t is the mean image-frame time measured from injection. This corrected image-based input function (IBIF) was used in the subsequent data analysis.

The Logan procedure [43] assumes that, after an equilibration time, the relationship between the input and tissue TACs is given by:

$$\frac{\int_0^t C(u)du}{C(t)} = V_d \frac{\int_0^t C_p(u)du}{C(t)} + b,$$

where b is a constant and V_d is the total tissue tracer distribution volume, in this analysis, uncorrected for tissue vascular fraction. The quantity $C(t)$ is the tissue concentration at time t (i.e., C is the tissue TAC), and $C_p(t)$ is the input function at time t , in our case, the

metabolite corrected IBIF. A slope analysis of $\frac{\int_0^t C(u)du}{C(t)}$ versus $\frac{\int_0^t C_p(u)du}{C(t)}$ yields V_d . It is necessary to perform the analysis at sufficiently late times such that a plot of these quantities is linear. Thus, prior to performing the Logan voxel-wise analysis, the above quantities were plotted for a single TAC obtained from the full tumor region from subject number 1. Based on this analysis, the last six time points (i.e., the time domain from 38 to 68 min postinjection) were used in the voxel-wise Logan analysis for all scans.

The rate of F-18 FLT entrance into the system, that is, the degree to which it penetrates the BBB, was parameterized by using the early time frames from the dynamic PET data. Specifically, frames spanning 0 to 2 min postinjection were averaged. The image was normalized by dividing by the mean carotid activity in this image as determined using the IBIF ROI.

Because the sodium MRI and F-18 FLT PET images are in alignment, each voxel has associated F-18 FLT PET V_d and sodium MRI intensity values. Overall change in tumor status as a function of time after therapy initiation was depicted using scatter plot sets. In one set, each voxel within the tumor ROI was represented by a point whose coordinates correspond to the sodium MRI intensity at two scan time points (e.g., ETA vs. baseline, etc.). Spatial localization of changes in sodium intensity between two time points was illustrated by subtraction of the corresponding sodium images. An identical analysis was performed with a set of scatter plots using the F-18 FLT PET V_d values.

In addition to the voxel-wise analysis, mean sodium concentration and F-18 FLT V_d (from the voxel-wise analysis) within the tumor ROI were tabulated for both subjects at the various scan time points.

Changes in the sodium intensity were compared to changes in F-18 FLT V_d . Voxel-wise scatter plots of changes in these biomarkers between the various scan time points were produced. In such a plot, each point falls into one of four quadrants: I, corresponding to increased sodium and F-18 FLT signal; II, corresponding to increased sodium and decreased F-18 FLT; III, corresponding to decreased sodium and F-18 FLT; and IV, corresponding to decreased sodium and Increased F-18 FLT. These differences in biomarker behavior were spatially localized by assigning each voxel within the tumor ROI a particular color corresponding to scatter plot quadrant.

3. Results

3.1. Patient pathology results

Subject 1, a 62-year-old female, was diagnosed with a deep right-sided posterior frontoparietal GBM. On biopsy, pathology showed a Ki-67 score of 70%. Molecular characterization using fluorescence in situ hybridization (FISH) demonstrated amplification of the epidermal growth factor receptor (EGFR) gene. PCR based loss of heterozygosity analysis (LOH) demonstrated loss at the loci of p16 and PTEN (Phosphatase and Tensin

Homologue Deleted from Chromosome 10) genes and deletion of chromosome region 19q. Methyl guanine methyl transferase (MGMT) promoter methylation was identified.

Subject 2, a 40-year-old male, was diagnosed with a right posterior frontal lobe GBM. On biopsy, pathology showed a Ki-67 score of 15%–20%. EGFR was demonstrated to be amplified by FISH. PCR based LOH analysis demonstrated no 1p loss, 33% 19q loss, 100% 9p loss and 100% 10q loss, and MGMT promoter methylation was identified. This patient underwent all three PET and MRI scans sessions: at baseline, ETA and LTA.

3.2. Method development

Fig. 1 shows example ETA data acquired for subject 1. MR images include T1-weighted MPRAGE structural MRI (Fig. 1A), a gadolinium (Gd)-enhanced T1 MRI (Fig. 1B) and FLAIR MRI (Fig. 1C). At the time of the ETA scan, subject 1 showed increased sodium signal at the GBM site compared to the contralateral side (Fig. 1D). The voxel-wise tracer distribution volume (V_d) parameter map (Fig. 1E) demonstrates increased tracer uptake around the lesion in correspondence with the subject's MRI images. Fig. 1F shows the results of summing the first 2 min of subject 1's ETA F-18 FLT PET scan, normalized to average activity in the carotid artery taken from the 2-min image. Significantly, there is a large enhancing region in this image.

Fig. 2A shows the IBIF (blue) and tumor TAC (red), extracted from the ETA scan of subject 1 using methods described previously. The peak IBIF activity is 35.1 kBq/cc, occurring between 30 and 36 s after administration of F-18 FLT. These data served as the input to the Logan analyses (Fig. 2B). This regional analysis was performed to identify a linear region of the curve for fitting. Based on the result shown here, the voxel-wise Logan analysis was performed using the last six points of data for all F-18 FLT PET scans for both subjects.

Fig. 3 illustrates the sodium MRI/F-18 FLT PET analysis procedure outlined above using the data from subject 1. The first column in the figure shows voxel-wise changes in sodium concentration between the ETA and LTA scans. The top figure in the leftmost column is a scatter plot showing changes in all voxel values within the tumor ROI between the two imaging time points. These changes are spatially localized in the image at the bottom of the left column, which was produced by subtracting the ETA sodium image from the LTA image. The middle column is similar, but shows changes in F-18 FLT V_d . The right column shows the correspondence between changes in sodium concentration and changes in F-18 FLT uptake between the two imaging time points. The top part of the right column is a scatter plot of these quantities. The bottom part of the right column is a color-coded map showing the sign of change in the two biomarkers at each voxel. Average tumor sodium concentration and F-18 FLT tracer distribution volume are shown in Table 1 for both the ETA and LTA time points of subject 1.

3.3. Voxel-wise comparison of sodium concentration and F-18 FLT PET V_d

Figs. 4 and 5 illustrate changes in sodium (Fig. 4) and F-18 FLT (Fig. 5) between baseline and ETA (left column), between baseline and LTA (middle column) and between ETA and LTA (right column) of subject 2. Results are presented as scatter plots (top row) in which each point corresponds to a single voxel within the tumor ROI. The bottom row shows sodium (Fig. 4) or F-18 FLT (Fig. 5) subtraction images comparing ETA to baseline, LTA to baseline and LTA to ETA, all overlaid on the same T1 MPRAGE image. Average tumor sodium concentration and F-18 FLT tracer distribution volume are shown in Table 2 for all three assessment time points of subject 2.

Correspondences and differences between sodium and F-18 FLT biomarker changes on a voxel-wise basis are plotted in Fig. 6. The top row shows scatter plots of F-18 FLT change

vs. sodium change between baseline and ETA, baseline and LTA, and ETA and LTA. To identify specific regions of change on the tumor ROI, voxel maps are shown (bottom row) overlaid on subject 2's baseline MPRAGE MRI. The color of each voxel corresponds to joint direction of biomarker change between time points.

Part A of Fig. 7 shows T1-weighted Gd-enhanced MRI for spatial reference. Parts B–D show F-18 FLT PET data averaged over the first 2 min of acquisition and normalized to carotid artery activity from subject number 2's baseline (B), ETA (C) and LTA (D) scans. Compared with subject number 1 (Fig. 1E), subject number 2 exhibits relatively low early uptake in the region of tumor.

4. Discussion

Therapy responses of brain tumors are conventionally assessed by size and contrast enhancement characteristics on CT or MRI [47]. This approach is limited for several biological reasons. First, because of the heterogeneous tissue and growth patterns of brain tumors, a region of contrast enhancement is generally a mixture of necrotic tissue, vascularity, normal brain cells and tumor cells, all changing in population density over time and each subject to different biological processes and effects. Thus, the interpretation of a changing contrast enhancement pattern can be ambiguous, e.g., true progression versus pseudoprogression. Second, to determine if a response to therapy is effective, the size of an enhancing region does not accurately reflect the viability status of tumor cells related to growth or death potential since contrast enhancement cannot determine tumor cell mitotic activity or the metabolic state of tumor cells. Third, the micrometastatic state of the surrounding tumor environment is not reflected by the primary tumor size of contrast enhancement, especially in GBM, in which intracerebral spread is common. Clearly, to accurately assess brain tumor cell response to therapy, more sophisticated imaging methods are required. As in the current case, such methods are likely to involve multiple modalities resulting in complex data sets requiring effective and efficient analysis methods.

The PET tracer F-18 FLT is a fluorinated version of thymidine and traces steps of the thymidine salvage pathway. Its uptake is expected to correlate with cellular proliferative activity. A possible advantage to the use of F-18 FLT in brain tumor studies is that its uptake and retention in normal brain tissue are minimal. This is in sharp distinction to F-18 FDG, which is readily taken up by normal brain tissue, producing high background signal that can confound analysis. Additional information from a PET F-18 FLT scan is obtainable by performing dynamic PET followed by kinetic modeling providing information about F-18 FLT transport across the BBB and F-18 FLT phosphorylation flux.

Sodium MRI has a tremendous potential for the study of brain neoplasms because the cell membrane depolarization that precedes the large degree of cell division in the neoplastic tissue leads to an increase in the intracellular sodium concentration (ISC) and a concomitant rise in the total TSC. This increase in TSC is readily measurable using ultrashort echo time (UTE) sodium MRI but is difficult to correlate directly with the rise in ISC because of the high sodium concentration in the edema and necrotic compartments often found in brain tumors. Unlike F-18 FLT uptake, changes in sodium concentration occur without limitations from the state of the BBB.

A major part of this work focused on investigating multimodality, multi-time-point, voxel-wise methodologies and image processing and display techniques. Fig. 3 summarizes some promising approaches, in which, for example, voxel-wise changes in sodium MRI concentration and F-18 FLT distribution volume across the entire tumor volume are represented by color-coding schemes. In our case, the resolution of the two modalities

differs. As reconstructed, the PET images have a spatial resolution function that is typically modeled as Gaussian with an FWHM of about 5–6 mm. The sodium MRI images have a resolution of 0.3 cm×0.3 cm×0.3 cm. As part of the voxel-wise data processing, the sodium MRI images were resliced into PET-sized voxels (0.21 cm×0.21 cm×0.24 cm).

Fig. 4 shows voxel-wise comparisons of sodium changes between the baseline, ETA and LTA imaging time points for GBM subject 2. The figure illustrates the potential of sodium MRI for following therapy response. While there is signal heterogeneity within the tumor bed, there is clearly a change in the distribution in voxels with a signal intensity in the range of 60–80 mM (i.e., the tumor bed) (center graph and image). The use of a larger pool of subjects is required to fully address the significance of these observations for evaluating GBM therapy response. However, the ability of sodium MRI to provide the aforementioned information in a complete three-dimensional fashion with a short imaging time offers a distinct advantage over more technically challenging MR studies. The relatively small region of T1 MRI contrast enhancement seen in subject 2 (Fig. 7A) is echoed in the 2-min PET images (Fig. 7B – D) which may indicate a low rate of tracer delivery to the tumor due to a relatively intact BBB. As discussed earlier, this complicates F-18 FLT analysis. Fig. 5 shows voxel-wise comparisons of F-18 FLT changes between baseline, ETA and LTA imaging time points for GBM subject 2. The patient has not progressed and is currently receiving adjuvant, standard-dose temozolomide. While both modalities independently show a (voxel-wise) change in tissue status, which may be related to therapy, it is also clear that the information provided by each modality is not redundant. This is apparent from the combined modality plots of Fig. 6. The degree of complementarity and overlap of the two modalities is suggested by the scatter plots in the top row of the figure, in which all quadrants are populated; spatial localization is provided by the images in the bottom row. The significance of each quadrant remains to be determined, but important information could potentially be communicated rapidly by this type of relatively straightforward analysis and presentation. For example, one possibility is that regions showing increases in both sodium MRI and F-18 FLT tracer distribution volume (yellow) indicate that BBB breakdown may have occurred or increased during therapy, causing increased transport.

Others, e.g., Muzi et al. [1], have pointed out the importance of accounting for the issue of BBB integrity in the interpretation of F-18 FLT data in brain tumor studies, suggesting that F-18 FLT is useful only in the case of sufficiently high initial transport, which is generally the case in MRI contrast-enhancing regions. In the work of Muzi et al. [1], initial transport (reflected by the kinetic rate parameter K_1) was determined using a full kinetic modeling analysis. In the current work, we used the 0–2-min early uptake images to serve this purpose. The utility of this method is a subject of continuing study; however, we observe that notable differences can be seen in the degree and extent of early uptake in the 0–2-min images of subjects 1 and 2. This is, at least qualitatively, similar to differences in the MRI contrast enhancement observed in these subjects.

5. Conclusion

Multimodality, serial-time-point imaging data were acquired, analyzed and displayed using methods that could be adapted for clinical use. The work presented shows that sodium MRI and F-18 FLT PET imaging biomarkers demonstrate correspondences and differences in assessing GBM therapy response, suggesting that the two biomarkers may provide complementary information on tumor status. Deducing the degree to which these methods are useful for GBM therapy response assessment and particularly for differentiating true progression from pseudoprogression requires additional data and follow-up, and is the subject of continued research.

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Fig. 1.

Example of acquired data from subject 1, a patient who had a deep right-sided posterior frontoparietal GBM. Images include (A) MPRAGE structural MRI; (B) contrast-enhanced T1 MRI; (C) FLAIR; (D) sodium MRI; (E) F-18 FLT PET tracer distribution volume derived from a 68-min dynamic PET series and (F) an F-18 FLT PET image acquired over the period from 0 to 2 min post tracer injection (normalized to average activity in the carotid artery) showing early tracer wash-in.

Fig. 2. Dynamic F-18 FLT PET analysis of the full tumor in subject 1. Left side shows TACs from the IBIF and the mean activity within the tumor ROI. Right is a Logan plot with a linear regression fit to the final six points (solid line).

Fig. 3.

Example of comparison of sodium MRI and F-18 FLT data from subject 1 at two different scan times on a voxel-wise basis. The first column shows the sodium comparison between time points. The top diagram is a scatter plot, in which each point represents an image voxel within the tumor ROI. The y-axis is the LTA sodium concentration (mmol/L), and the x-axis represents sodium concentration at ETA. Spatial localization of changing voxel values is provided by the bottom figure, which was formed by subtracting the ETA sodium image from the LTA image and masking by the tumor ROI. The subtraction image is shown by the color scale, and the magnitude of positive and negative changes throughout the tumor volume can be seen. The subtraction image is overlaid on an MPRAGE structural MR image. The second column is similar to the first but for F-18 FLT tracer distribution volume. The third column summarizes the first two. The top diagram is a scatter plot of change in sodium concentration between the two time points vs. change in F-18 FLT tracer distribution volume. These results are spatially localized by the bottom image that color codes the sign of the change in the sodium and F-18 FLT biomarkers between the two scans.

Fig. 4.

Voxel-wise comparison of sodium changes between the three imaging time points for subject 2. The top row shows scatter plots in which the coordinates of each point are the sodium concentration (mmol/L) of an image voxel within the tumor ROI at two scan time points (left: ETA vs. baseline, center: LTA vs. baseline, right: LTA vs. ETA). The bottom row shows sodium intensity subtraction images (color scale) overlaid on the baseline MPRAGE MRI.

Fig. 5.

Voxel-wise comparison of F-18 FLT changes between the three imaging time points for subject 2. The top row shows scatter plots in which the coordinates of each point are F-18 FLT tracer distribution volumes of an image voxel within the tumor ROI at two scan time points (left: ETA vs. baseline, center: LTA vs. baseline, right: LTA vs. ETA). The bottom row shows F-18 FLT tracer distribution volume subtraction images (color scale) overlaid on the baseline MPRAGE MRI.

Fig. 6.

Comparison of sodium MRI concentration (mmol/L) changes to F-18 FLT PET tracer distribution volume changes between the various scan time points for subject 2. The top row shows voxel-wise change in each biomarker between time points (left: change from baseline to ETA, center: baseline to LTA, right: ETA to LTA). Images in the bottom row correspond to the scatter plot directly above and map out the direction of change jointly in the two biomarkers.

Fig. 7. Baseline contrast-enhanced T1 MRI (A) and F-18 FLT 2-min averaged images (normalized to average activity in the carotid artery) are from subject 2, showing blood flow and tracer delivery. F-18 FLT PET images were acquired at baseline (B), ETA (C) and LTA (D).

Table 1

Whole-tumor imaging quantities — subject 1

	ETA	LTA
Sodium concentration (mmol/L)	74.	96.
F-18 FLT V_d	0.80	0.99

Table 2

Whole-tumor imaging quantities — subject 2

	Baseline	ETA	LTA
Sodium concentration (mmol/L)	58.	59.	57.
F-18 FLT V_d	0.63	0.74	0.65