MRI-guided Radiotherapy Identifies Early Pseudoprogression of Glioblastoma

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Abstract

Background The standard glioblastoma treatment paradigm consists of surgery, pre-radiotherapy MRI, six weeks of chemoradiotherapy, followed by post-radiotherapy MRI and continued adjuvant temozolomide. In a significant proportion of patients, post-radiotherapy MRI demonstrates tumor enlargement due to either treatment failure (true progression) or treatment response (pseudoprogression). Recently introduced MRI-guided radiotherapy systems obtain daily MRI of glioblastoma patients, and we hypothesized that progression can be identified early during radiotherapy.

Methods Fourteen glioblastoma patients underwent tri-Cobalt-60 MRI-guided radiotherapy in 30 fractions over 6 weeks delivered with concurrent temozolomide. The tumor target volume was delineated on MRI before each of the 30 fractions. The images obtained by the 0.35 T MRI-guided system is shown to be similar to T2-weighted images obtained by a clinical diagnostic MRI-scanner. Hyperintense volumes were measured over time through radiotherapy.

Results Four of fourteen patients demonstrated increases of at least 25% and 1.5 cc in T2 hyperintense volume through radiation therapy. This volume expansion correlated with both T2/FLAIR and contrast-enhanced volume expansion on post-radiotherapy diagnostic MRIs. In three of four cases, significant volume growth only started at week three of treatment, with the most prominent changes occurring during weeks four and five. While patient numbers are limited, patients with growth during therapy exhibited excellent survival, consistent with the known improved survival of patients with pseudoprogression.

Conclusions Daily MRI acquisition during radiotherapy identifies early pseudoprogression typically starting during week 3 or 4 of treatment. This and other daily MRI techniques during radiotherapy could enable early adaptation of therapy in glioblastoma patients.

Background

Glioblastoma (GBM) is the most aggressive brain tumor in adults (1). Standard clinical treatment for GBM consists of tumor resection followed by six weeks of radiation therapy (RT) with temozolomide, resulting in a median survival of about 15 months (2). Magnetic Resonance Imaging (MRI) following the initial six week treatment period reveals gadolinium-enhanced volume increase in up to 49% of patients (3). Of patients with this volume increase between pre and post radiotherapy scans, about one-third result from progressive tumor growth and two-thirds are due to therapy changes termed pseudoprogression (4–6). True progression is characterized by continuous tumor growth despite treatment with a poor median survival ~ 10 months; while pseudoprogression reflects therapy response with recruitment of blood vessels and/or necrosis and improved median survival ~ 38 months (3, 7). No current clinical modality can reliably separate true and pseudoprogression at early time points. Therefore, patients are typically managed without therapy change for many additional months to determine whether changes are progressive (true progression) or spontaneously improve (pseudoprogression).

Early differentiation of true and pseudoprogression would enable modification of radiotherapy or chemotherapy and prevent unnecessary surgeries (8). Brain biopsies are invasive, and thus there are strong efforts towards using non-invasive methods such as MRI to predict eventual patient survival based on early changes (8, 9). Typically, MRI is obtained approximately two weeks before beginning a six weeks course of chemoradiation and then again four weeks after completion, for a total time interval of three months between scans. Previous studies have assessed different modalities of MRI such as T1-weighted (10), T2-weighted (11), perfusion (12) diffusion weighted imaging (DWI) (13), and radiomics (14) at these several month intervals. However, there is limited data analyzing changes that occur during the radiotherapy treatment time interval because it has not been feasible to perform frequent MRI scans due to the cost and logistics of standalone MRI scans. Therefore, the kinetics of change during radiotherapy has not been fully elucidated.

Recently, the combination of MRI and radiotherapy (MRI-RT) devices has become available, providing the opportunity to acquire daily MRI for radiotherapy patients (15, 16). We observed that GBM patients treated with MRI-RT at our institution had a variable time course of changes during treatment that we hypothesize might provide additional information for predicting treatment outcome and adapting radiotherapy treatment. Here we provide our preliminary experience with 14 GBM patients treated on the MRI-RT device and describe the visualized changes during radiotherapy.

Methods

Patients

Fourteen glioblastoma patients, ten men and four women ages 24–78, underwent RT delivered by tri-Cobalt-60 MRI-RT with concurrent temozolomide (TMZ) at the University of Miami's Miller School of Medicine Sylvester Comprehensive Cancer Center. All patients provided written consent under an institutional umbrella protocol for MRI-RT to analyze imaging findings and outcomes. Seven patients underwent complete resection, one had a partial resection, and six had biopsy alone. Four patients had IDH-1 R132H mutation by immunohistochemistry and six patients had hypermethylation of the MGMT promoter region. Kaplan-Meier survival plots were generated using SPSS (IBM SPSS Statistics version 26).

Radiation therapy planning and delivery

Two to four weeks after surgery patients underwent a pre-treatment diagnostic 1.5 T or 3 T MRI including T1-weighted after gadolinium contrast and T2-weighted scans. Simulation was performed at that time on the tri-cobalt MRIdian system (ViewRay, Mountain View, USA) in position for treatment including MRI compatible thermoplastic mask (Civco, Coralville, USA). Vendor supplied 6-channel surface array posterior torso coil was placed under the masking system and 5-channel surface array anterior head and neck coil was wrapped around the mask anteriorly. Patients received 60 Gy in 30 fractions in a single volume with clinical target volume (CTV) expansion of 2 cm on the cavity and enhancing tumor and

planning target volume expansion of 0.3 cm concurrent with temozolomide 75 mg/mg^2 using MRI-RT with daily MRI [(2)].

Imaging acquisition

The radiation treatment system is equipped with a 0.35 T MRI (Siemens Avanto, version syngo MR B17, IDEA version VB19, Siemens Medical Solutions, Erlangen, Germany). The scanner includes a balanced steady-state free precession (bSSFP) pulse sequence (17). The bSSFP is commonly used in relatively low field MRI acquisition due to its capability of providing an increased signal-to-noise ratio with higher temporal resolution (18, 19). The signal originated by the bSSFP sequence is also known for its mixed composition that is weighted by T1 and T2. However, the use of high flip angles produces high T2-weighting as implemented on this 0.35 T system (17). The bSSFP-derived images were acquired with the following parameters: TE(time to echo)/TR(time to repetition) = 1.92 ms/3.84 ms, flip angle = 60 º, acquisition matrix = 266 × 288 × 266, Voxel size 1.5 mm x 1.5 mm x 1.5 mm (3D-acquisition), coil elements VAP, VAS, VPP, VPS, bandwidth 532 Hz/Px, Gradient mode: fast and acquisition time = 2 minutes and 8 seconds. This choice of acquisition parameters provided whole head images with contrast comparable to the obtained from T2-fast spin-echo images acquired from a diagnostic 1.5 T scanner (Signa HDxt, GE Healthcare, Chicago, USA), as illustrated in Fig. 1.

Image analysis

The volume of hyperintensity on the bSSFP images from each treatment fraction was contoured manually using MIM (version 6.7, Cleveland, USA). Tumors were reported as a significant change if the volume changed at least 25% (similar to Macdonald's criteria for progressive disease (20)) between any two time points (e.g. fraction 1 compared to fraction 30) and that change was greater than 1.5 cc as a threshold to ensure no changes were simply due to contouring variability.

Patients received post-treatment MRI 3–6 weeks after completion of concurrent chemoradiotherapy and continued adjuvant chemotherapy. Patients with observed T2-weighted growth on this study were all noted by post-treatment radiology report to have growth of enhancement and edema on post-treatment MRI.

Results

Four out of fourteen patients (1, 2, 3 and 8) demonstrated an increase of at least 25% and 1.5 cc in hyperintense volume during radiation therapy. All of these patients were confirmed to have possible pseudoprogression or true progression by inspection and radiology report on post-treatment post-gadolinium MRI.

Patient 1 (Fig. 2), a 65 year old man, presented to radiation oncology with multifocal glioblastoma (IDH-1 mutation negative, MGMT nonhypermethylated) in the right temporal lobe after biopsy of a discrete lesion about 1 cm inferior to the axial slice shown in Fig. 2A. A tiny (~ 2 mm) area of equivocal T2 change

was observed as shown, and this area was included in the 60 Gy CTV. Little change was observed in this area until about fraction 18 (late week 4), at which time rapid growth was seen until fraction 26 (week 6) when the size plateaued. No steroids were used at any time during the radiotherapy treatment. The observed findings during treatment were consistent with one-month post treatment diagnostic imaging (Fig. 2A, bottom two panels). Bevacizumab was added to temozolomide after the diagnostic MRI with dramatic improvement in MRI findings. The patient died of multi-focal glioblastoma, mostly out of the initial radiation therapy field, 24 months after biopsy.

Patient 2 (Fig. 3), a 47 year old man, underwent gross total resection of a right temporal glioblastoma (IDH-1 mutation negative, MGMT nonhypermethylated). On treatment planning MRI two weeks later a tiny area of enhancement without surrounding edema was observed in the right frontal lobe suspicious for multifocal disease and added to the 60 Gy CTV. Post-operative dexamethasone taper was stopped at fraction 1 and no further steroids were given during treatment. Similar to the pre-treatment T2 images, no change in the multi-focal area was visualized on the MRI-RT scans initially. Growth was identified on MRI-RT early in week 3 which accelerated through week 4 and 5 and plateaued in week 6. This area continued to progress and underwent resection about 6 months after completion of radiation. Pathology demonstrated only reactive changes and inflammation with no clear tumor. The patient went to hospice 20 months after initial resection due to additional foci of progression outside of the radiation therapy field.

Patient 8 (Fig. 4), a 59 year old man, underwent gross total resection of a right parietal glioblastoma (IDH-1 mutation negative, MGMT nonhypermethylated). Patient was tapered from dexamethasone 4 mg twice daily and maintained at 2 mg twice daily after the start of treatment due to left hand weakness. Significant growth of T2 hyperintensity was identified starting fraction 17 and progressing nearly linearly through fraction 30. Temozolomide chemotherapy was continued through currently 9 months of follow-up.

Among the four patients with 25% or more growth during treatment, we observed non-linear growth kinetics (Fig. 5). Specifically, three of the patients (numbers 1, 2, and 8) demonstrated little change during weeks 1–3 of radiotherapy followed by significant growth starting in week 4. Patient 3 had growth in the first week that plateaued during week 3. Another observation was that three of the patients (numbers 1, 2, and 3) had a plateau in growth during the last week of treatment or earlier, while patient 8 continued to grow through week 6. The bSSFP MRIs from the sixth week of treatment for all fourteen patients demonstrated similar T2-FLAIR abnormalities when compared to the patients' diagnostic T2 MRIs post-treatment completion.

Nine of the fourteen patients are alive after finishing the chemoradiation treatment. Median follow-up was 19.1 months (minimum 6 months) with estimated survival of 23.9 months (Fig. 6). A non-significant difference in estimated survival is seen at 18 months (100% for patients with growth during treatment vs. 67% without, $p = 0.45$), which supports the likely pseudoprogression observed in these patients.

Regarding patients with more minor changes, one patient (patient 7 shown in Fig. 1) had a 23% decrease in bSSFP hyperintense volume beginning at fraction 18 (35.7 cc) trending nearly linearly to fraction 30 (29.0 cc). Patient 5 had a 15% increase in T2 hyperintense volume almost linearly starting at fraction 12 (23.5 cc) and plateauing after fraction 19 (26.8 cc). Patients 11 and 13 underwent gross total resections and the resection cavities were observed to shrink from 1.9 to 0.6 cc and 82.6 to 72 cc, respectively. All of these changes were also reported on diagnostic radiology report post-treatment. The remaining patients had less than 10% or 1.5 cc change of hyperintense volume throughout the treatment period.

Discussion

This is the first analysis of daily MRI changes during radiotherapy of glioblastoma. Four (29%) of fourteen patients were observed with at least 25% and 1.5 cc of growth of the T2-weighted volume during radiotherapy, consistent with known rates of progression on MRI comparing pre-treatment MRI and MRIs obtained in the 1 month post-treatment period (21). Only one patient was observed with reduction in volume. In these patients where changes were present, the majority of patients exhibited the bulk of changes late during the treatment course—starting in week 3–4 and becoming most prominent in weeks 5 and 6. Volume changes correlated with progressive gadolinium enhancement and T2-weighted changes at one month post-treatment. The patients with growth during treatment had a non-significant improvement on the survival curve suggestive of the improved survival observed with pseudoprogression (3).

Prior work has demonstrated that MRI at one or two time points during radiotherapy correlates with overall survival. For example, Galban et al. mapped perfusion changes from baseline at week one and three in 44 patients with GBM and found correlations with overall survival based on these changes (22). Hamstra et al. mapped apparent diffusion coefficient changes from baseline at week one, three, and ten (3–4 weeks post radiotherapy) in 60 patients with GBM and found that changes at week three had the most correlation with survival (23). Nelson et al. obtained magnetic resonance spectroscopic imaging in 25 patients before, during, and one month after radiotherapy and found that decreases in volumes demonstrating elevated choline to N-acetylaspartate ratios mid-treatment correlated with survival (24). This is encouraging that midpoint MRI or spectroscopy may be useful to determine prognosis and potentially adapt treatment. Nevertheless, our results suggest that acquiring MRI early in the treatment course may be sub-optimal for correlations with eventual outcome. For example, Patients 1, 2 and 8 (Fig. 5A, B and D, respectively) only showed T2-weighted volume increase after the fourth week of treatment, indicating that studies analyzing changes during week three or earlier may be premature.

Additionally, there is significant heterogeneity in treatment planning margins used for treatment of glioblastoma (25). While we have planned these cases based on EORTC margins (single 2 cm CTV expansion from resection cavity and enhancement to 60 Gy) (26), the Adult Brian Tumor Consortium (ABTC) uses the typically much smaller margins of 5 mm CTV expansion from edema to 46 Gy and 5 mm CTV expansion on cavity and enhancement to 60 Gy (27). Groups using the ABTC margins have reported no difference in treatment failure rates (28–30), though this is not without controversy (31).

Interestingly, in our study we found that in three of fourteen patients by the end of week 4 (fraction 20) the edema had expanded at least 5 mm from its initial extent (+ 5 mm, + 1 cm, + 1.1 cm). Although the clinical significance of these findings with regards to treatment margin or dose alterations is unclear, it can now be investigated prospectively since such growth during radiotherapy is now identifiable.

Our study is limited by single pulse sequence acquisition during radiotherapy. Studies are underway at multiple institutions to obtain multiparametric MRI longitudinally on the MRI-RT system to address this question (32, 33). In particular, most criteria for growth and progression are at least partly based on gadolinium enhancement (34). We did not give extra gadolinium to patients during radiotherapy in this preliminary study given recent concerns about gadolinium toxicity (35). However, given these findings we do plan to dose gadolinium for 1–2 additional timepoints during RT in future patients for response to therapy and radiotherapy treatment adaptation as well as investigate non-invasive perfusion methods during RT (36, 37). Nevertheless, the association of edema during radiotherapy with post-treatment contrast volume increase suggests that the two are related in this study. Another possible confounding is that both enhancement and edema volume can be sensitive to changes in steroid doses (38). Our default is not to use steroids in patients during radiotherapy unless the patient is symptomatic, and most did not receive steroids after the start of treatment. Thus, we have found no clear correlation between steroids and volume as noted in the case descriptions.

Conclusions

We identified probable pseudoprogression in four of fourteen glioblastomas during MRI-guided primary six week chemoradiotherapy by daily T2-weighted MRI volumes. In three of four cases, significant volume growth was not observed until at least week three of treatment, with the most prominent changes occurring during weeks 4 and 5. Further studies are underway to identify whether the kinetics of volume growth, changes in multiparametric MRI, or radiomics changes of daily MRI during radiotherapy may correlate with overall survival in an increased number of patients towards early adaptation of therapy in glioblastoma patients.

List Of Abbreviations

RT, radiation therapy; MRI, magnetic resonance imaging; DWI, diffusion weighted imaging; GBM, glioblastoma; TMZ, temozolomide; IDH-1, isocitrate dehydrogenase 1; MGMT, O[6]-methylguanine-DNA methyltransferase; CTV, clinical target volume; bSSFP, balanced steady state free precession; ABTC, adult brain tumor consortium; EORTC, European Organisation for Research and Treatment of Cancer

Declarations

Ethical Approval and Consent to participate

The studies herein were approved by the University of Miami Institutional Review Board 20160817. All patients gave informed consent.

Consent for publication

Consent for publication is not applicable. Included data is not identifiable to any individual person.

Availability of supporting data

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EAM conceived, designed, and substantially revised this study.

KJ, SD, and DM analyzed the data and co-wrote the manuscript.

JCF and TD substantially contributed to acquisition of the data.

RS, MG, and TD substantially contributed to data analysis and interpretation

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Figures

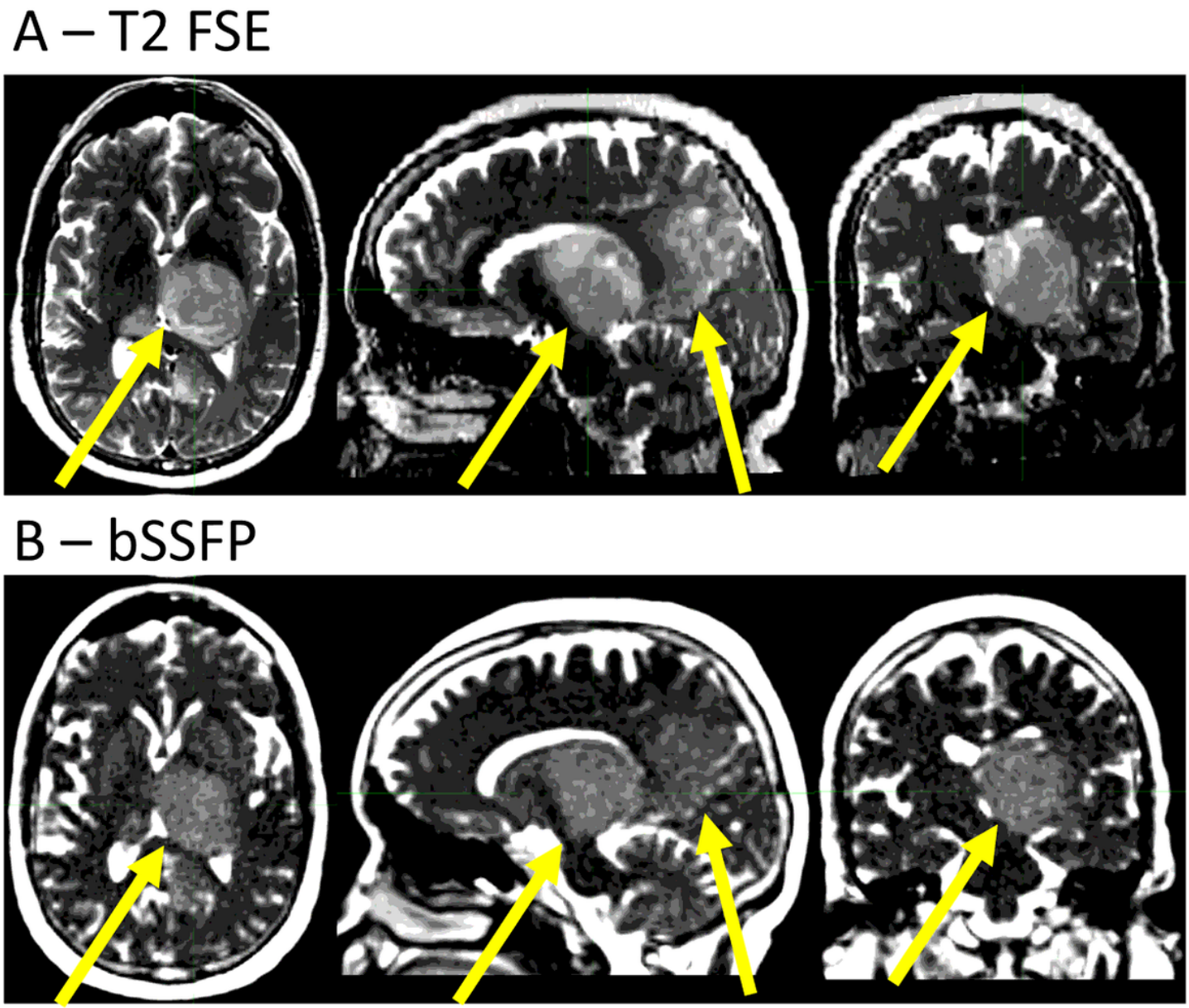

Figure 1

Brain images from patient #7 in this study. A) Pre-treatment T2 FSE from a clinical 1.5T scanner, resolution of 0.94 x 0.94 x 2 mm3, acquisition time of 5 minutes and 43 seconds. B) bSSFP from a 0.35T scanner, resolution of 1.5 x 1.5 x 1.5 mm3 (3D acquisition), acquisition time of 2 minutes and 8 seconds. Contrast and resolution are similar between the two scans. The yellow arrows indicate the MRI finding.

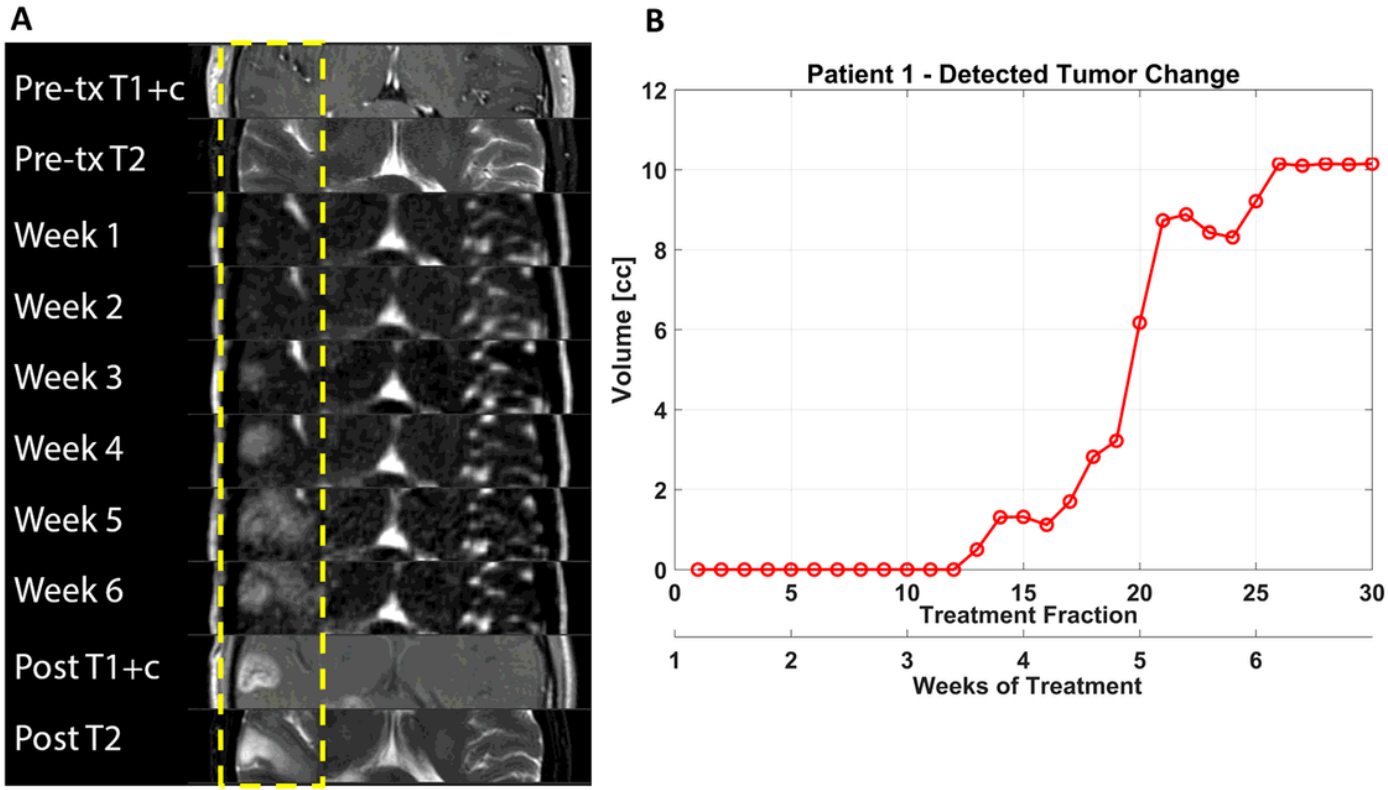

Figure 2

Volume change during treatment for patient 1. A) From top to bottom, the same axial slice of pre, intra-treatment (from first to sixth week) and post MR-images. The pre-treatment (Pre-tx) and post-treatment (Post) MRIs were T1 with gadolinium (T1+c) and T2 weighted. The intra-treatment images result from the mostly T2-weighted bSSFP sequence. The yellow dashed box indicates the MRI finding. B) Volume change of the MRI finding over 30 treatment fractions (six weeks).

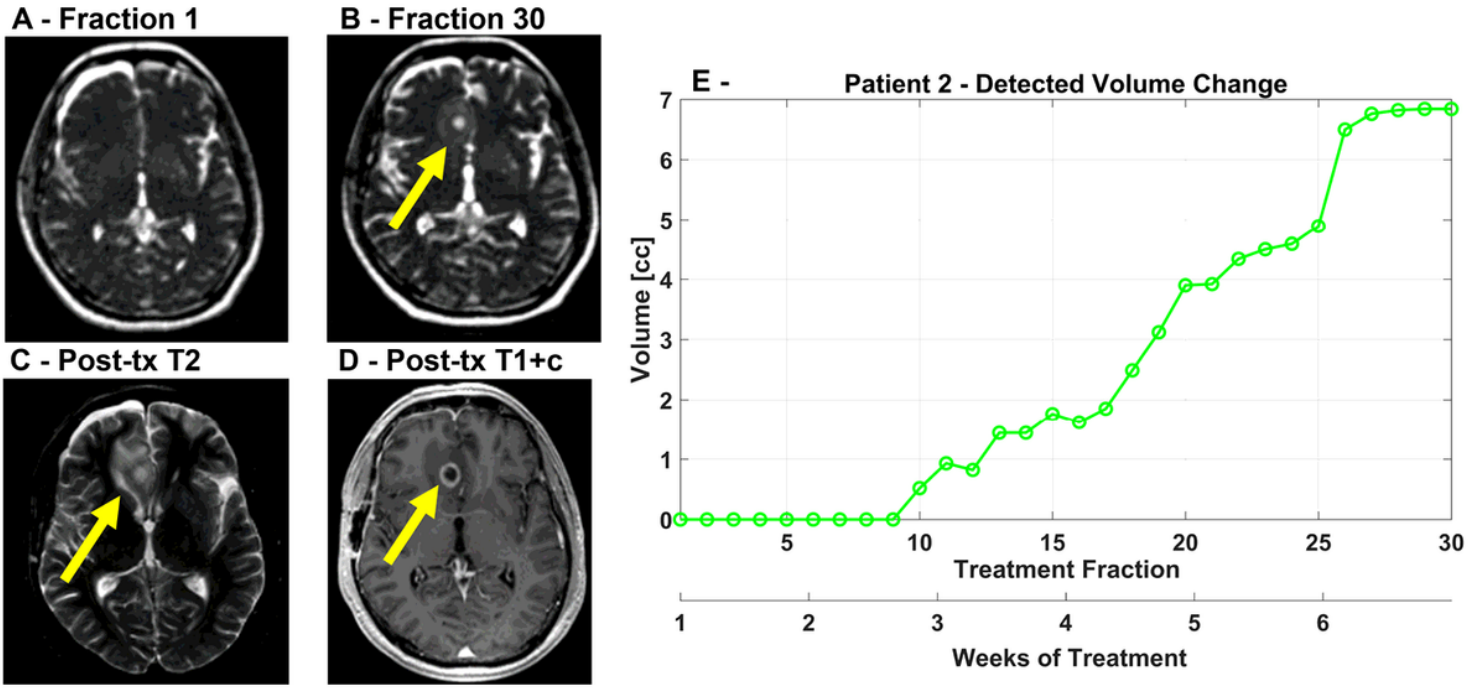

Figure 3

Volume change during treatment for patient 2. Intra-treatment axial slice of bSSFP acquisition from first (A) and thirtieth (B) treatment fractions. Post-treatment T2w (C) and T1 (D) with contrast agent weighted MRIs. The yellow arrows indicate the MRI finding. B) Volume change of the MRI finding over 30 treatment fractions (six weeks).

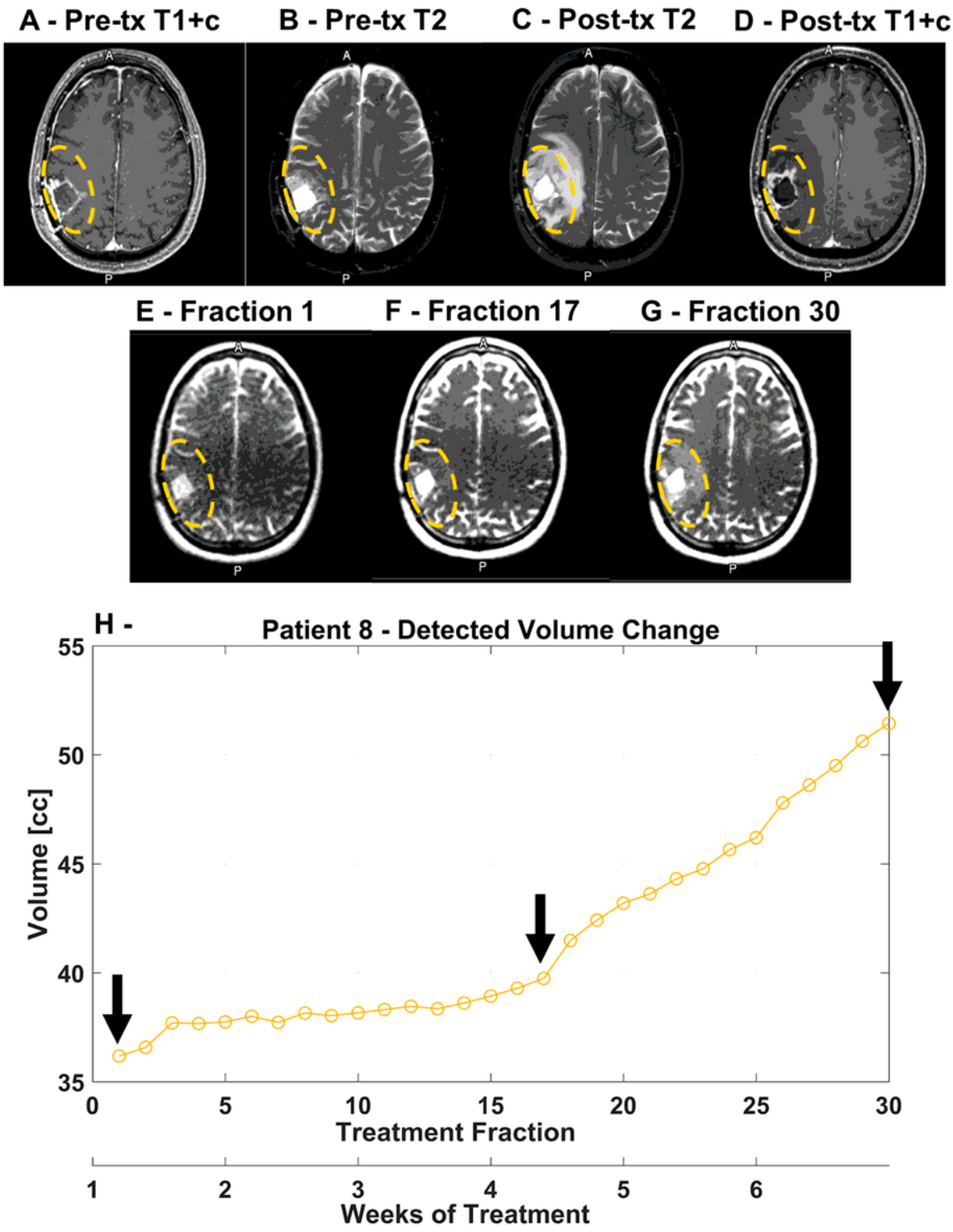

Figure 4

Volume change during treatment for patient 8. (A) Pre-treatment diagnostic T1+c scan shows gross total resection with linear likely post-operative inflammation. Pre-tx (B) and Post-tx (C) images demonstrate significant enlargement of T2-hyperintense volume, and which also correlated with T1+c on post-treatment MRI (D) indicating progression. Little change was observed during treatment from fraction 1 (E) to fraction 17 (F), with growth of hyperintense volume from fraction 17 to 30 (G) as plotted in (H). The

yellow dashed ellipse line shows the maximal extent of hyperintensity at fraction 30, with likely continued progression Post-Tx.

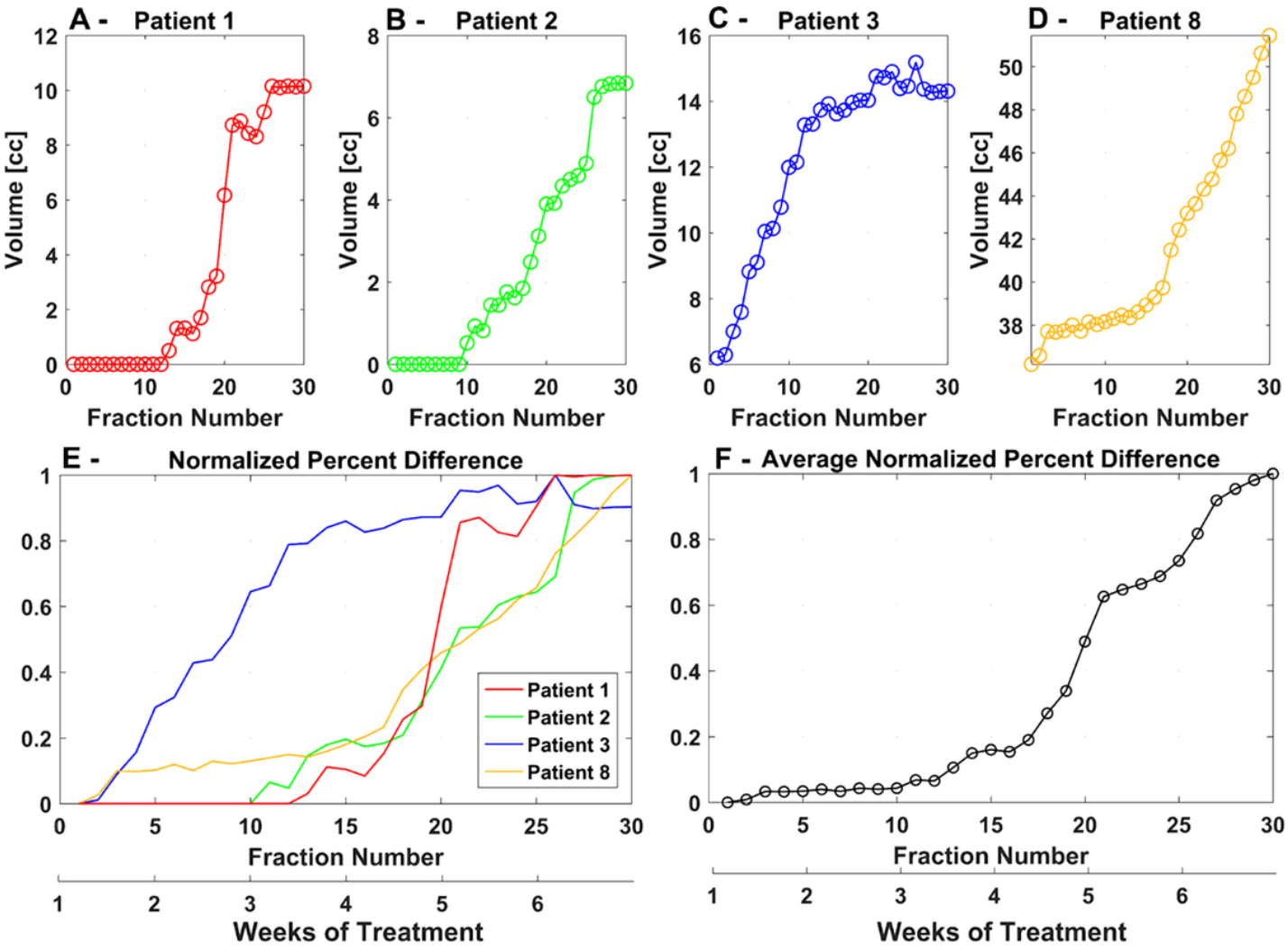

Figure 5

Volume change of the MRI finding over 30 treatment fractions for patients 1 (A), 2 (B), 3 (C) and 8 (D). E) Normalized percent difference for patients 1, 2, 3 and 8 over 30 treatment fractions (six weeks). F) Average normalized percent difference from patients 1, 2, and 8 over 30 treatment fractions (six weeks).

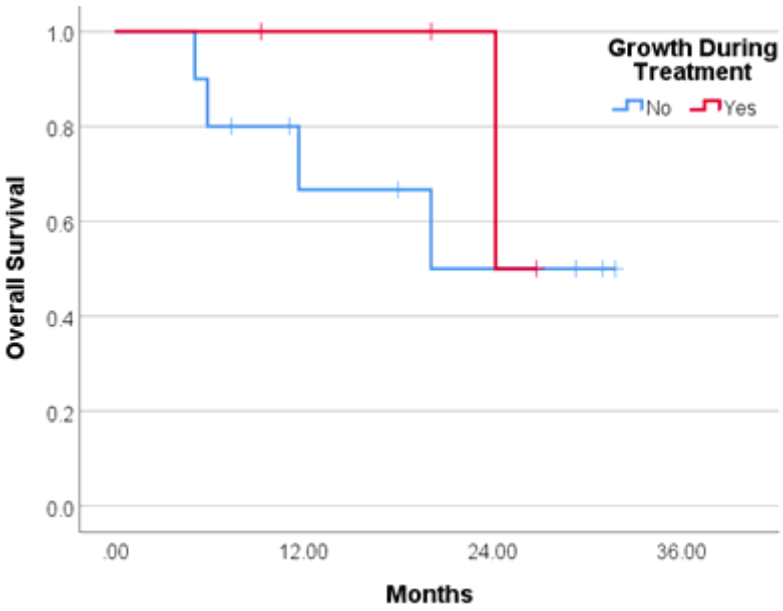

Figure 6

Kaplan-Meier estimated survival of patients with (red line) or without (blue line) 25% or more volume change during primary chemoradiotherapy. This difference was not statistically significant.