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Hypercellularity Components of Glioblastoma Identified by High b-value Diffusion-Weighted Imaging

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Abstract

Purpose—Using conventional MRI for target definition, glioblastomas may receive inadequate radiation dose coverage of the nonenhanced hypercellular subvolume. This study aimed to develop a technique to identify the hypercellular components of GB by using high b-value DWI and to investigate its relationships with the prescribed 95%- isodose volume (PDV) and progression-free survival (PFS).

Methods—Twenty-one patients with glioblastoma underwent chemoradiotherapy post-resection/ biopsy. RT treatment planning was based upon conventional MRI. Pre-RT DWIs were acquired in 3 orthogonal directions with b-values of 0, 1000, and 3000 s/mm². Hypercellularity volume (HCV) was defined on the high b-value (3000 s/mm²) DWI by a threshold method.

“Nonenhanced” signifies regions not covered by the Gd-enhanced gross tumor volume (GTV-Gd) on T1-weighted images. The PDV was used to evaluate spatial coverage of the HCV by the dose plan. Association between HCV and PFS or other clinical covariates were assessed using univariate proportional hazards regression models.

Results—HCVs and nonenhanced HCVs varied 0.58-67 cc (median: 9.8cc) and 0.15-60 cc (median: 2.5cc), respectively. Fourteen patients had incomplete dose coverage of the HCV, of which 6 patients had 1+ cc HCV missed by the 95%-PDV (range: 1.01–25.4cc). Of the 15 patients who progressed, 5 progressed earlier, within 6 months post-RT, and 10 patients after. Pre-RT HCVs within recurrent GTVs-Gd were 78% (range: 65–89%) for the 5 earliest progressions but lower, 53% (range: 0–85%), for the later progressions. HCV and nonenhanced HCV were significant negative prognostic indicators for PFS ($p < 0.002$ and $p < 0.01$, respectively). The hypercellularity subvolume not covered by the 95%-PDV was a significant negative predictor for PFS ($p < 0.05$).

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Conclusions—High b-value DWI identifies the hypercellular components of GB and could aid in RT target volume definition. Future studies will allow us to investigate the role of high b-value DWI in identifying radiation boost volumes and diagnosing progression.

INTRODUCTION

The standard-of-care for glioblastoma is resection followed by concurrent temozolomide chemoradiotherapy (RT+TMZ) with adjuvant TMZ chemotherapy. Conventional Gadolinium (Gd) contrast-enhanced T1-weighted (T1W) and T2W or fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) used for radiation treatment planning may inadequately represent the extent of this heterogeneous disease.[1] Differentiating hypercellularity components of glioblastoma from high-vascular components, edema, and normal tissue is a challenge using FLAIR and conventional (b 1000 s/mm²) diffusion-weighted imaging (DWI).[2] The hypercellularity components may appear nonenhanced on Gd-enhanced T1W-MRI and indistinguishable from edema and normal tissue on FLAIR-MRI thus may receive inadequate treatment.

Metabolic and molecular imaging may have higher sensitivity to tumor than conventional MRI. ¹¹C-Methionine positron emission tomography (MET-PET) is an imaging modality that measures metabolic activity by cellular uptake of MET via L-type amino acid transport across the blood-brain-barrier. An intense accumulation of MET in glioblastoma is indicative of actively proliferating tumor, increased microvessel density, elevated Ki-67 protein expression, and may represent high-risk regions of recurrence.[3–6] Previous studies have shown that MET-PET-based treatment planning might improve overall survival.[5] However, MET-PET GTVs may not adequately encompass the low proliferating tumor components. The short half-life time of ¹¹C-MET, approximately 20 minutes, limits its availability to centers without an onsite cyclotron.

Proton MR Spectroscopy imaging (MRSI) is a technique to measure the spatial distribution of proton metabolites such as choline, creatine, N-acetyl-aspartate (NAA), lactate and lipid. In high-grade gliomas, an increase in choline, reflecting increased cell proliferation from cell membrane phospholipid turnover and/or increased cell density, and decrease in NAA has been shown to be characteristic of tumor compared to normal tissue or edema.[7–10] Elevated choline signals have been found beyond the Gd-enhanced gross tumor volume (GTV-Gd) or T2/FLAIR hyperintensity abnormality volume (FLAIR-abnormality).[11–14] Adequate dose coverage of high choline signals by the radiosurgery target volume in patients with recurrent gliomas seems to have a trend for greater survival benefit.[15, 16] However, low spatial resolution and long acquisition time make MRSI a challenging technique to use in a clinical setting.

Diffusion-weighted MRI, as another modality, measures the mobility of water within tissues and is sensitive to tissue microenvironment and cell density. Many studies have shown that high cellularity tumor is correlated with low diffusion coefficients in animal tumor models and human cancers.[17–20] However, in the FLAIR abnormality region of glioblastoma, the mixture of high cellular tumor, normal tissue and edema, for which diffusion coefficients vary from low to high, results in inconsistent and often elevated apparent diffusion

coefficients (ADCs) when using conventional b-value (1000 s/mm² or lower) for diffusion measurement. Diffusion-weighted signals from tissues attenuate exponentially with b-values and ADCs, indicating signals from tissues with higher ADCs decay more than those with lower ADCs at a given b-value. At conventional b-values, signals from edema and normal tissue cannot be attenuated sufficiently. Therefore, increasing b-values in the diffusion sequence beyond the conventional b-values can suppress signals from edema and even normal tissue to distinctly reveal high cellular tumor with highly restricted diffusion characteristics.

Another alternative form of diffusion-weighted imaging is to measure tissue diffusion anisotropy and to create anisotropy indices. Again, at conventional b-values, some anisotropy indices show high sensitivity for detection of tumor but is poor at distinguishing tumor from edema.[21] Intravoxel diffusion kurtosis imaging shows its capability to differentiate low-grade from high-grade gliomas but not to separate normal tissue from solid tumor.[22–25]

In this study, we aimed to develop a high b-value diffusion imaging technique to differentiate hypercellularity components of glioblastoma by suppressing signals from fluid, edema, and even normal tissue. We evaluated spatial relationships of the hypercellularity volume (HCV) detected by this technique with the GTV-Gd and FLAIR-abnormality. Furthermore, we investigated the radiation dose coverage of the HCV by conventional treatment planning. Finally, we evaluated the predictive value of HCV for progression-free survival.

METHODS

Patient

This was an institutional review board approved retrospective study of twenty-one patients (age 23–76 years, 9 women and 12 men) with pathologically diagnosed WHO grade IV glioblastoma (Table 1). All patients had MRI scans for radiation therapy (RT) treatment planning and simulation after surgical resection/biopsy. All patients except one had newly diagnosed glioblastoma and were treated with concomitant RT and TMZ. The median radiation dose was 60 Gy (range: 41 to 72 Gy in 1.8 to 3 Gy fractions). All received adjuvant TMZ treatment except two patients who had early recurrence or died soon after RT. One patient had recurrent glioblastoma and was treated with RT and TMZ and also with the anti-angiogenic drug, bevacizumab, pre- and post- RT. Clinical evaluations and clinical MRI followups were conducted every 1 to 3 months post-RT to determine disease progression.

MRI

The radiation treatment planning MRI scans were performed on a 3.0 Tesla (T) scanner (Skyra, Siemens). In addition to conventional clinical post-Gd T1WI and FLAIR-MRI, DW-MRI in 3 orthogonal directions with b=0, 1000, and 3000 was acquired in all patients. DW-MRI was acquired by a spin-echo echo-planar pulse sequence with GRAPPA=4 (parallel imaging factor), phase-encoding direction=anterior to posterior, receiver bandwidth=1040

Hz/pixel, mean TE/TR=99.3/8222 ms (range: 98-105/7400-9200 ms), and mean spatial resolution=1.3x1.3x5.2 (range: (1.2–1.4)x(1.2–1.4)x5.2 mm). Clinical follow-up scans included conventional DWI, post-Gd T1W and FLAIR images.

Image registration

All images were registered using our in-house functional imaging analysis tool (FIAT). The post-Gd T1W images pre-RT of each patient were used as the target for registration of DW images as well as clinical images at recurrence. The treatment planning computed tomography (CT) scans were also registered to post-Gd T1W images pre-RT, through which radiation dose distributions were transformed onto the post-Gd T1W images. Rigid-body transformations were used for all image registrations. DWI geometric distortion was measured and shown to be minimal.

Tumor Volumes

GTV-Gd and FLAIR-abnormality were determined on post-operative post-Gd T1W and FLAIR images, respectively, including surgical cavity. The GTV-Gd and FLAIR-abnormality were contoured by physicians blinded to the DWI scans for RT planning. HCV was determined on the b=3000 s/mm² DW images within the FLAIR-abnormality first by using a threshold (the mean intensity plus 2 standard deviations) calculated from a volume of interest in the normal-appearing tissue most contralateral to the tumor. The extent of HCV both within the FLAIR-abnormality and contiguously beyond the FLAIR-abnormality was evaluated in each patient. Similarly, the subsection of HCV overlapping with GTV-Gd was designated as enhanced HCV, while the non-overlapping subsection was designated as nonenhanced HCV. The 95% prescribed isodose volume (95PDV) that was planned based upon the conventional MR images was used to demarcate the planned high radiation dose region and evaluate the spatial coverage of the HCV by the plan. The tumor volume on the post-Gd T1W images at recurrence was contoured and compared with the HCV. All volumes of interest were converted to the pre-RT post-Gd T1WI space using the appropriate transformation parameters in FIAT.

Definition of Progression

In this retrospective study, disease progression was determined by recording from the patients' charts whether, in the opinion of the treating team of radiation oncologists, neuro-oncologists, neurosurgeons and neuro-radiologists, progression had occurred based on clinical and radiographic findings that prompted a change in clinical management. Patients were typically evaluated for progression 1 month post-RT and, thereafter, at least every 2 months for 6 months, and then every 2–4 months with a clinical exam and brain MRI. With the exception of the first 3 months after RT when worsening could represent pseudoprogression, enlargement of the enhancing mass or new enhancement on MRI would prompt a change in therapy, especially if accompanied by clinical worsening. Bulky FLAIR abnormality and findings on MRS were also considered in some patients. In addition, for the purposes of this study, an independent review of all brain MR images by a neuro-radiologist was performed to evaluate and confirm progression. Pathological specimens obtained from post-RT surgery were available for confirmation in 6 patients.

Statistical analysis

Associations between HCV and time to progression (TTP) or progression-free survival (PFS) or other clinical covariates were assessed with univariate proportional hazards regression models. TTP was measured from start of RT to date of the MR scan evidencing progression. PFS was measured from start of RT to date of scan showing progression, or date of death. Clinical covariates, including age, sex, HCV, GTV-Gd, and dose coverage, were analyzed. Spearman's rank correlation coefficient was computed to study the relationship between the clinical covariates and time to progression. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics and Progression

A total of 21 consecutive patients undergoing RT for glioblastoma between April 2012 and January 2014 were included in this study. As of September 2014, 15 patients had disease progression post-RT, of whom 6 died and 9 were alive (Table 1). Post-RT surgical specimen pathology confirmed residual/recurrent glioblastoma in 6 patients. In addition, one patient died before progression could be established. The remaining 5 patients remained alive and progression-free with a median follow-up of 14 months (range: 9–21 months).

Hypercellularity volumes: enhanced and nonenhanced

The HCVs detected by high b-value diffusion-weighted imaging obtained post-operatively, prior to RT varied widely in size, ranging from 0.58 to 67 cc (Median: 9.8cc) (Fig 1a). The HCVs contained both Gd-enhanced and non-enhanced components. The nonenhanced HCVs, indicating minimal to no blood-brain-barrier opening, ranged from 0.15 to 60 cc (Median: 2.5cc) (Fig 1c), representing the percentage of the total HCVs from 2.2 to 97% (Median: 38%). 76% of the patients had 20% or greater percentage of HCV non-enhanced. In seven patients, HCVs extended beyond the FLAIR abnormality volumes an average 13 mm (range: 5–27 mm). However, overall, the HCVs were only 12% of the FLAIR-abnormalities (a median value of 69.7cc and range: 23.3-180cc) (Fig 1b), indicating the potential risk of radiation toxicity if the FLAIR-abnormality is used for high-dose treatment.

Radiation Dose Coverage

The smaller HCVs tended to present as a nodular-type located around the rim of the surgical cavity and/or the Gd-enhanced tumor, while larger HCVs extended beyond the GTV-Gd (Fig 2). Seven patients had complete coverage of the HCVs by the 95%- PDV, and 14 had incomplete coverage, of which 6 had 1cc or greater HCV missed by the 95%-PDV (range: 1.01-25.4cc), indicating insufficient radiation dose coverage of the HCVs, particularly for the extended non-enhanced components (Figs 1d and 3).

Prediction for Progression-free Survival

Of the 15 recurrent patients, TTP was significantly, negatively correlated both total HCV (cc) ($r_s = -0.67$, $p < 0.005$) and nonenhanced HCV (cc) ($r_s = -0.52$, $p < 0.05$). Using univariate Cox regression, we found that the total HCV (cc) and the non-enhanced HCV (cc)

were significant negative prognostic indicators for PFS ($n=21$, 95% Confidence Interval [CI]: 1.01-1.08, $p < 0.002$; and 95% CI: 1.00-1.07, $p < 0.01$, respectively), indicating the biologically aggressive nature of the HCV. The volume of the HCV that was not covered by the 95%-PDV was also a significant negative predictor for PFS (95% CI: 1.00-1.19, $p < 0.05$), implicating the importance of high dose coverage for the HCV. However, post-Gd GTV (cc) was not a significant prognostic indicator ($p=0.28$).

Relationship between Recurrent Tumor and HCV Pre-RT

The patients who recurred more rapidly had, on average, a greater percentage of recurrent GTV-Gd spatially overlapping with the pre-RT HCV than those who recurred later. For the 5 patients who progressed within 6 months post-RT and the 10 patients who progressed after 6 months post-RT, median percentage of pre-RT HCV within the recurrent GTVs-Gd was 78% (range: 65–89%) and 53% (range: 0–85%), respectively. There were two exceptional cases with very little spatial overlapping between the pre-RT HCVs and GTV-Gd at recurrence. One who had two progression sites 16 months post-RT had recurrent GTVs-Gd outside of the pre-RT GTV-Gd, FLAIR-abnormality and HCV. The second patient (#7) had Gd-enhanced recurrence within the 95%-PDV 8 months post-RT and located in the anteroinferior temporal pole and adjacent to the surgical cavity. Examples of recurrence are shown in Figure 2. Patients #20 had Gd-enhanced recurrent tumor growing posterior to the GTV-Gd pre-RT and within the pre-RT HCV. Patient #15 had Gd-enhanced recurrent tumor growing posterior to the pre-RT GTV-Gd and across the midline and within the pre-RT HCV. Patient #4 had recurrent tumor at the bed of surgical cavity and in the region with the HCV nodules pre-RT.

DISCUSSION

In this study, we investigated high b-value diffusion-weighted imaging to delineate the potential hypercellular tumor volume of glioblastoma before radiation therapy. Suppressing MR signals from fluid, edema and normal tissue by increasing b-value diffusion gradients is able to reveal hypercellular components of the tumor, particularly nonenhanced ones that are unable to be differentiated within the FLAIR abnormality. We found that the patients who had large HCVs had shorter time-to-progression, suggesting a biologically aggressive nature of tumor in the HCV (Fig 4). Furthermore, we found that patients who had large volumetric extents of the hypercellularity components that were not covered by the prescribed dose volumes had shorter time-to-progression, indicating the importance of adequately treating these regions with high-dose radiation and the current limitation of conventional MRI for radiation target definition. High b-value DWI that provides complementary information to vascular-based imaging techniques could aid in radiation target definition, as well as the differentiation of progression from pseudoprogression and pseudoresponse of glioblastoma.

Post-Gd T1-weighted and FLAIR MRI are the two standard images for defining the respective GTV and clinical target volume (CTV) for treatment planning. However, the tumor areas at high-risk of recurrence may extend beyond the Gd-enhancing lesions, which has been shown previously by elevated MET uptake using PET and abnormal choline signals using MR spectroscopy.[3–6, 11, 13, 14] Apparent diffusion coefficients have been

long demonstrated to be inversely corrected with the hypercellular tumors in animal models [17–20, 26, 27]. However, as described in the introduction, in human glioblastoma, the ADC in a single image voxel can have contributions from hypercellular components of tumor, edema, high-perfusion component and normal tissue, which resultantly yields unpredictable ADC values that do not clearly correlate with actual tumor cellularity. Systematically suppressing MR signals from fluid, high-perfusion, edema or even normal tissue by increasing the b-value in diffusion imaging appears to enable the isolation of the hypercellular components of the tumor.

The hypercellular components of glioblastoma may present as a nodule located around the rim of Gd-enhancement or surgical cavity, or they may extend into or beyond the FLAIR abnormality. Our study shows that inadequate radiation dose coverage of the HCV is associated with shorter time-to-progression. The HCV identified by high b-value DWI differs from the FLAIR-defined CTV in its spatial extent, and may possibly differ in the risk-level of recurrence. The large size difference between the FLAIR-abnormality and HCVs, as the FLAIR-abnormality was nine times greater than the HCV, indicates that using a FLAIR abnormality-defined volume for high-dose radiation may prohibitively increase the risk of radiation toxicity. High b-value DWI has the potential to identify the hypercellular tumor volume that may potentially be boosted to a higher radiation dose. Moreover, the nodule-like hypercellular component, although likely covered by 95% of the prescribed dose volume based upon conventional MRI, could be used to define the boost target beyond a conventional dose. The non-enhanced hypercellular components can be spatially extensive in some cases and likely undertreated by either radiation or TMZ due to less blood-brain-barrier opening.[28, 29] Intensifying the treatment for the hypercellular components could prolong time-to-progression or even survival—a hypothesis that could be tested in future clinical trials.

Glioblastoma is a highly heterogeneous disease. ^{11}C -MET-PET and choline metabolism by proton MR spectroscopy are able to detect disease components beyond the Gd-enhanced lesions. Furthermore, studies suggest that the disease components detected by these two imaging techniques are associated with a high risk of recurrence. It is unknown whether the disease components detected by ^{11}C -MET-PET, choline MR spectroscopy, and high b-value DWI are the same, different, or partially overlapped, given that each technique is based on different tumor biology and processes. These imaging techniques could capture different aspects of the same disease process or identify different image phenotypes; they may even provide complementary information. Compared to ^{11}C MET PET and proton MR spectroscopy, high b-value DWI is easily implemented as part of routine MR simulation and clinical MR follow-ups. It only takes a few minutes for acquisition. Prospective pathological validation and/or clinical trials could further answer these questions.

DWI acquired by the echo-planar pulse sequence is susceptible to B_0 -field inhomogeneity-generated geometric distortion, which can be reduced by increasing the parallel imaging factor. In brain DWI, we used a parallel imaging factor of four, which reduced geometric errors to an average 1.1 mm (maximum: 5 mm) around the tumors. The geometric distortions that were 3+ mm occurred only anteriorly or inferiorly in 5 patients. The geometric errors can be corrected to an extent using available post-processing techniques, or

using the pulse sequence less sensitive to B_0 -field inhomogeneity, e.g., RESOLVE.[30] In the region with large B_0 -field inhomogeneity, signal-to-noise in DW images is lower. Also, this study used rigid-body transformations for image registration. At recurrence, the tumor volumes could have changed, and surgical cavities may have shrunk or shifted, which could lead to inaccurate spatial definition of recurrent tumor volumes. This may be targeted as an area for future improvement.

This study has limitations typical of retrospective studies. The patient population may not be as homogeneous, and the treatment and assessments as uniform, as would be expected in a prospective clinical trial. Progression was determined clinically. It is a challenge to diagnose progression of glioblastoma after chemo-radiation therapy from pseudoprogression or pseudoresponse particularly treated with anti-angiogenesis drugs. High b-value DWI that is independent of Gd-enhancement could provide complementary information to improve the accuracy of a diagnosis of progression. Finally, our study raises an exciting hypothesis: boosting the hypercellular volume delineated by high b-value DWI could delay time-to-progression, which is an area for future study.

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SUMMARY

It is a clinical challenge to differentiate nonenhanced solid tumor from edema in glioblastoma using conventional magnetic resonance images, which could lead to inadequate radiation dose coverage. This study provides evidence to show that high b-value diffusion weighted imaging, which is a widely available technique, has the potential to identify this nonenhanced hypercellularity component and aid in for radiation target or boost target definition.

Figure 1.

Distributions of hypercellular volume of glioblastoma (HCV) (1a), FLAIR abnormality volume (1b), nonenhanced HCV (1c), and the HCV that was not covered by the 95%-prescribed isodose volume (PDV) (cc) (1d). Fourteen patients had complete 95%-PDV coverage of the HCV pre-RT. N=21 patients.

Figure 2. Pre-RT post-contrast T1-weighted (column 1), FLAIR (column 2), conventional ADC (column 3) and $b=3000 \text{ s/mm}^2$ diffusion-weighted images (columns 4 and 5), and post-contrast T1-weighted images at recurrence (column 6) from three patients (#20, #15, and #4). Red, green, yellow and cyan contours represent post-Gd GTV pre-RT, FLAIR abnormality volume pre-RT, HCV pre-RT, and post-contrast GTV at recurrence.

Figure 3. Post-contrast T1-weighted (left), FLAIR (middle), and diffusion-weighted images with $b=3000 \text{ s/mm}^2$ pre-RT of two patients (#20 and #15). Red, dark pink and yellow contours represent post-Gd GTV pre-RT, 95%-prescribed isodose volume, and HCV pre-RT.

Figure 4. Kaplan-Meier progression-free survival curves for patients with small hypercellular volume of glioblastoma (HCV)(n=11) versus large HCV (n=10) using median HCV=9.8cc as threshold.

Table 1

Patient Information

Subject #	Age (years)	Sex (M/F)	Total/Fx Dose (Gy)	Concomitant chemotherapy	Pre-RT post-Gd GTV (cc)	Pre-RT HCV (cc)	% HCV nonenhanced on pre-RT	% HCV covered by 95%-PDV	Time to Progression (months)	Time to follow-up (months)
1	54	M	60/2	TMZ	46.0	14.3*	17.3%	100%	9	9
2	56	F	72/2.4	TMZ	7.55	2.20	9.82%	100%	14	14
3	50	F	60/2	TMZ	9.75	2.49	16.7%	100%	12	12
4	55	F	72/2.4	TMZ	34.5	6.54*	65.1%	93.9%	13	13
5	54	F	60/2	TMZ	24.7	6.69	2.24%	100%	recurrence not confirmed	9
6	56	M	60/2	TMZ	25.2	6.10	58.9%	96.7%	11	11
7	63	F	56/2	TMZ	23.7	2.26*	89.5%	85.0%	8	8
8	76	M	66/2.2	TMZ	52.0	10.3	41.1%	99.8%	16	16
9	23	M	42/3	none	6.19	16.4*	97.0%	23.4%	7	7
10	66	F	72/2.4	TMZ	29.8	22.0*	64.9%	67.0%	9	9
11	32	M	56/2.1.8	TMZ	38.5	2.86	39.9%	64.8%	recurrence not confirmed	21
12	54	M	60/2	TMZ	22.5	7.90	22.6%	100%	recurrence not confirmed	21
13	53	M	60/2	TMZ	20.2	12.2*	61.6%	100%	6	6
14	47	M	60/2	TMZ	30.0	6.05	31.4%	100%	recurrence not confirmed	14
15	49	M	72/2.4	TMZ	65.0	67.1	89.2%	62.2%	5	5
16	58	M	60/2	TMZ	47.1	11.8	21.5%	99.1%	6	6
17	63	F	60/2	TMZ	41.4	9.79	15.4%	99.8%	recurrence not confirmed	14
18	44	F	60/2	TMZ	14.5	0.579*	91.7%	93.3%	12	12
19	73	M	41/2.3	partial TMZ [†]	39.6	24.4	20.1%	97.6%	recurrence not confirmed	3
20	53	F	66/2.2	TMZ	93.8	58.4	37.7%	97.8%	2	2
21	43	M	69/2.3	TMZ	23.6	11.3	27.7%	90.6%	5	5

Patients #1, 4, 7, 9, 10, 13, and 18 had HCVs extending beyond their FLAIR abnormality (*). Patient #19 started treatment with concomitant RT+TMZ, however due to several episodes of pneumonia, treatment was changed to hypofractionated RT and chemotherapy was discontinued (†).