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CLINICAL STUDY

Tumor recurrence or treatment-related changes following chemoradiation in patients with glioblastoma: does pathology predict outcomes?

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Abstract

Background Despite surgical resection and chemoradiation, all patients with GBM invariably recur. Radiological imaging is limited in differentiating tumor recurrence (TR) from treatment-related changes (TRC); therefore, re-resection is often needed. Few studies have assessed the relationship between re-resection histopathology and overall survival (OS). We performed a large retrospective study to analyze the clinical significance of histopathology following re-resection and its influence on genomic sequencing results.

Methods Clinical, radiographic, and histological information was compiled from 675 patients with GBM (2005–2017). 137-patients met the inclusion criteria. IDH1 p.R132H immunohistochemistry was performed in all patients. Next-generation sequencing interrogating 205 tumor-related genes was performed in 68-patients. Molecular alterations from initial and subsequent resections were compared in a subset of cases.

Results There were no differences in OS (17.3-months TRC vs. 21-months TR, $p = 0.881$) and survival from progression (9.0 vs. 11.7-months, $p = 0.778$) between patients with TR and TRC on re-resection. TR patients were more likely to receive salvage radiotherapy (26% vs. 0%) and tumor-treating fields (25% vs. 5%,) after the 2nd surgery than the TRC group ($p = <$ 0.045). There was no correlation between mutations and TRC. IDH status was not predictive of TRC. Fifteen-patients had sequencing results from multiple surgeries without evident differences in genomic alterations.

Conclusions Histopathologic findings following chemoradiation do not correlate with clinical outcomes. Such findings should be considered during patient management and clinical trial enrollment. Standardization of tissue sampling and interpretation following reoperation is urgently needed. Future work is required to understand the relationship between the mutation profile following TRC and outcomes.

Keywords Glioblastoma · Tumor recurrence · Radiation necrosis · Radiotherapy · Treatment-related changes · Reoperation

Introduction

Glioblastoma (GBM) is the most common and aggressive primary brain tumor with a poor prognosis despite aggressive therapies [1]. The current standard of care includes maximal safe surgical resection followed by radiotherapy with concurrent temozolomide (RT/TMZ) [2]. Unfortunately, due to the infiltrative nature of the tumor, all patients invariably develop worsening radiological findings with subsequent progression [3]. These radiographic changes represent either tumor recurrence (TR) or treatment-related changes (TRC). Diagnosis of TR versus TRC is a challenging task as clinical symptoms are similar. Furthermore, conventional imaging techniques are limited in differentiating these two conditions [4] and no defined histologic criteria is consistently utilized in clinical practice.

In approximately 30% of cases, the increased contrast-enhancement and peritumoral edema is a result of treatment effect, which falsely mimics TR and can cause delays in therapeutic decisions that can impact patient outcomes [5].

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The treatment effect, termed pseudoprogression, typically appears within 3 months of chemoradiation and is due to the pathological process of radiation-induced injury. Despite advances in neuroimaging, none of the current techniques can distinguish between these conditions with high certainty, leaving histopathological evaluation following a second surgery to characterize post-treatment lesions and management strategy. Those who are postoperatively confirmed to have TRC will have arguably undergone unnecessary surgery and treatment interruption, particularly in the case of recurrence without mass related symptoms. The role of TRC, associated factors and its impact on clinical outcomes has not been thoroughly evaluated. The wide range of reported TRC following reoperation suggests a lack of standardized histologic features and heavily subjective individual interpretation [6, 7]. In addition, there are varying reports on the relationship between histologic evaluation, TR vs. TRC, and clinical outcomes. The majority of prior studies include a small sample size and has not included comprehensive genomic characterization of tumors [8, 9]. In this study, we performed a retrospective review of histology and genomic alterations in a cohort of re-operated GBM patients ($n = 137$) and determined the prognostic significance of TR vs. TRC at reoperation. To the best of our knowledge, this is the first study to evaluate TRC in the context of genomic alterations and its prognostic significance.

Materials and methods

Patient selection and clinical characteristics

From 675 patients diagnosed with glioblastoma, clinical information for all GBM patients who underwent second surgery based on radiologic disease progression in the Memorial Hermann Health Care System between 2005 and 2017 was collected. All cases with histologic evaluation for both, first and second surgery, and accessible clinical and follow-up information, were selected for the study. Exclusion criteria included: oligodendroglial tumors, histologic diagnosis of grade II or III, and incomplete demographic, clinical, or histologic information.

Study data were collected from Memorial Hermann Hospital electronic medical record and managed using REDCap electronic data capture tools hosted at the University of Texas Health Science Center at Houston (UTHealth) [10, 11]. These included age, gender, Karnofsky performance status (KPS), histologic diagnosis, tumor location, radiographic extent of resection, treatment strategy, recurrence, and survival. Tumors were classified by a board-certified neuropathologist following the 2016 WHO Classification of Tumors of the Central Nervous System [12]. This study was approved by the institutional review board of the UTHealth and Memorial Hermann Hospital, Houston, TX.

Histologic evaluation

All cases were classified as TRC or TR according to the pathology report. Cases in which any evidence of tumor was identified in addition to TRC were assigned to the TR category for analysis. Pathology reports in which recurrent/residual glioma was the diagnosis were classified as TR. Recurrent glioma was diagnosed as robust tumor regrowth with dense cellularity and evidence of proliferative activity (e.g., mitoses, vascular proliferation). Residual glioma was diagnosed as tissue with treatment-related effects such as marked nuclear atypia with low cellularity and without signs of proliferation (e.g., low cellularity, no mitoses, no vascular proliferation). TRC were defined as histological evidence of vascular hyalinization and/or necrosis and no evidence of mitotically active tumor.

Targeted sequencing and IDH1 p.R132H immunohistochemistry

Tumor samples were analyzed (n = 68) for genomic alterations by a targeted next-generation sequencing (NGS) interrogating 205 tumor-related genes, Online Resource 1, as previously described [13–15]. IDH1 p.R132H was evaluated through immunohistochemistry (IHC) for patients (n = 64), in which NGS was not performed. A detailed methodology is available in the Online Resource 2.

Statistical analysis

Descriptive statistics were used to depict and compare patients' demographics, medical comorbidities, presenting symptoms, and tumor locations between TRC and TR using Fisher exact test and Mann–Whitney *U* test for categorical and continuous variables, respectively. Kaplan–Meier methods were used to estimate the progression-free survival (PFS) and overall survival (OS), the difference between survival functions was tested by two-sided log-rank test. OS was calculated from the first surgery to death or last available follow-up. Also, survival from the second surgery to death or last available follow-up was calculated. Univariable and multivariable analyses were applied by Cox proportional hazards model. The models were conducted to estimate HRs and 95% confidence interval (95% CI) by adjusting potential confounders. To evaluate the association between genetic alterations and TRC status, Fisher's exact test was performed with genes mutated in > 5% of tested samples. Statistical analyses were performed with Stata IC 15.0 (StataCorp, College Station, TX), SAS (Version 9.3, SAS Institute, Cary, NC), EZR v.1.4 [16], and GraphPad Prism v.8.4.3

(GraphPad, La Jolla, California, USA). *P*-values were two-sided and considered statistically significant at $p \leq 0.05$. To account for multiple testing, we adjusted the *p*-value using the false discovery rate (FDR) with the Benjamini–Hochberg method (FDR < 0.25) [17].

Results

A total of 137 patients met the inclusion criteria; demographics, comorbidities, presenting symptoms, and tumor location are presented in Online Resource 3. The median age at diagnosis was 58. Gross total resection was obtained in 47% of patients undergoing primary resection. A majority of patients underwent concurrent chemoradiation (91% overall, 22 TRC and 102 TR) following primary resection. A total of 11 (8%) patients underwent additional therapy with bevacizumab, while 24 (17.5%) received gamma knife radiosurgery prior to the re-resection. Details of postoperative findings and treatment are presented in Table 1.

Disease progression

Progression of disease, defined according to the RANO criteria, was diagnosed by contrast enhancement on radiological findings compared to prior imaging during discussion in a multidisciplinary tumor board conference [18]. PFS (TRC 6.5 vs. TR 5.9-months, $p = 0.847$, Fig. 1a) and time between first and second surgery (TRC 7.0 vs. TR 7.4-months, $p = 0.970$, Fig. 1b) did not vary between the two groups.

Effect on survival and adjuvant therapies

Histological findings of TR were found in 115 patients (83.9%), while 22 (16.1%) patients were identified as TRC. Both groups had a similar number of high KPS patients (80–100) prior to re-resection ($p = 0.469$). The TR group was more likely to receive salvage radiotherapy (26% vs. 0%, $p = 0.004$) and tumor-treating fields (TTF) (25% vs. 5%, $p = 0.045$) after the 2nd surgery than the TRC group. Although there were no statistically significant differences, the tumor recurrent group was more commonly treated with salvage therapies including temozolomide (TR 45% vs. TRC 27%), bevacizumab (TR 56% vs. TRC 32%), and other salvage strategies (irinotecan, lomustine, targeted therapy, and clinical trials regimens). Postoperative, radiological findings and treatment following second surgery are presented in Table 1. The median OS was 17.3-months in those with TRC and 21-months in TR, $p = 0.881$, Fig. 1c. Median survival from secondary resection was 9.0-months in the TRC group and 11.7-months with TR, $p = 0.778$, Fig. 1d.

Mutational analyses

Out of 137 patients, 68 had NGS from their primary resection, 12 of which would later be classified as TRC upon reoperation. Mutation data for each patient is presented in Fig. 2. No mutational profile was found to predispose to a specific histologic finding on recurrence after multiple testing adjustments. However, patients that would develop TRC harbored a non-statistical higher frequency of *TERTp* (100% vs. 66%) and *PTEN* (63% vs. 37%) mutations than TR. Table 2 shows the mutated genes in > 5% of our subanalysis. IDH1 p.R132H testing was performed in an additional 64 patients who did not have NGS, 5 of which were found to be IDH1 p.R132H mutant. IDH mutational status was not found to be predictive of TRC, ($p = 0.16$).

Additionally, 15 patients had NGS analysis from both 1st and 2nd surgical tissue samples. TR was determined in all of these patients with multiple NGS. No driver mutation differences were observed between primary and secondary resections Online Resource 4.

Discussion

The current study evaluates the relationship between histopathological findings and outcomes following reoperation in a large GBM cohort. Despite our large sample size and genomic characterization, our study showed no significant difference in OS between patients determined to have TRC or TR following re-operation. These results are consistent with previous smaller reports, which found no survival difference based on histological findings at disease recurrence, Online Resource 5. Only Kim et al. reported a survival benefit although it was not related to patients with TRC. They concluded that the extent of TR was more important and correlated with worse OS. Furthermore, regardless of the percentage of TRC noted on histology, there was no association with PFS or OS [19].

There is currently a lack of consensus or guidelines to interpret histopathological samples from GBM recurrence. This lack of consensus represents a major challenge in the neurooncology community and there is an urgent need to address this problem [20]. Recent recommendations from RANO, an international multi-institutional collaboration study to optimize histopathological criteria, suggest that pathologist should make every attempt to avoid "recurrent/residual glioma" instead of employing residual glioma only when tumor cells show unequivocal treatment-related effects without signs of proliferation and recurrent glioma when tissue displays solid growth, dense cellularity and active proliferation [20]. When both recurrent and residual tumor is identified the tissue should be classified as recurrence, as this is most clinically relevant, and may report a percentage

Table 1 Extent of resection, post-operative findings, and adjuvant therapies between treatment-related changes and tumor recurrence after the first and second surgery

Variables	TRC n = 22	Tumor recurrence n = 115	*p*-value
Extent of resection, n (%)			0.560
Biopsy	1 (5)	5 (4)	
GTR	8 (36)	57 (50)	
NTR	4 (18)	20 (17)	
STR	9 (41)	32 (29)	
Post-operative findings, n (%)			
Surgical complications	3 (14)	8 (7)	0.387
Length of stay (≥ 4 days)	8 (36)	37 (32)	0.805
Post-operative treatments, n (%)			
Temozolomide	19 (86)	107 (93)	0.383
Bevacizumab	3 (14)	8 (7)	0.383
Gamma knife post-progression, pre-second surgery	6 (27)	18 (16)	0.368
KPS pre-second surgery (80–100), n (%)	16 (73)	72 (63)	0.469
Extent of resection of second surgery, n (%)			0.368
Biopsy	1 (5)	2 (2)	
GTR	12 (55)	51 (44)	
NTR	6 (27)	37 (32)	
STR	2 (9)	22 (19)	
Post-operative findings, n (%)			
Surgical complications	4 (18)	12 (10)	0.273
Length of stay (≥ 4 days)	12 (55)	31 (27)	**0.022**
Treatment after the second surgery, n (%)*			
Gamma knife	3 (14)	30 (26)	0.281
Radiation therapy	0 (0)	30 (26)	**0.004**
Temozolomide	6 (27)	52 (45)	0.158
Bevacizumab	7 (32)	64 (56)	0.061
Irinotecan	3 (14)	34 (30)	0.189
Tumor-treating field	1 (5)	29 (25)	**0.045**
BCNU wafers	4 (18)	15 (13)	0.509
Lomustine	0 (0)	9 (8)	0.354
IT chemotherapy	1 (5)	4 (4)	0.589
Other treatment[a]	1 (5)	21 (18)	0.200

A p-value of less than 0.05 was considered significant

The Fisher exact test was performed to compare the difference of categorical variables between TRC and tumor recurrence

TRC treatment-related changes, *GTR* gross-total resection, *NTR* near-total resection, *STR* subtotal resection, *KPS* Karnofsky Performance Score

[a]Other treatment included: osimertinib, plerixafor, everolimus, metformin, niacinamide, afatinib, isotretinoin, and clinical trials

of recurrent tumor present. Regardless of TR or TRC, biopsy samples should be tracked to their respective radiological location and correlated with enhancing or non-enhancing regions. Additionally, utilizing a number of histopathological variables allows for stratification and can be effectively applied to the interpretation of recurrent glioma. Utilizing RNA-seq to identify transcriptional signatures that correlate with recurrence patterns shows early promise. Lastly, a standard for surgical sampling and pathological processing are being developed including submission of the entire resected specimen is recommended.

Two prior studies [8, 9] and ours, stratified patients into TRC when there was no evidence of any active tumor, while others have classified samples according to quantitative amounts of necrosis/active tumor [21–23]. It is important to note that Kim et al. report a survival benefit when the biopsy sample contained less than 20% of recurrent tumors compared to 20–80% or greater than 80% [19]. Our current work lacked a quantifiable assessment of the

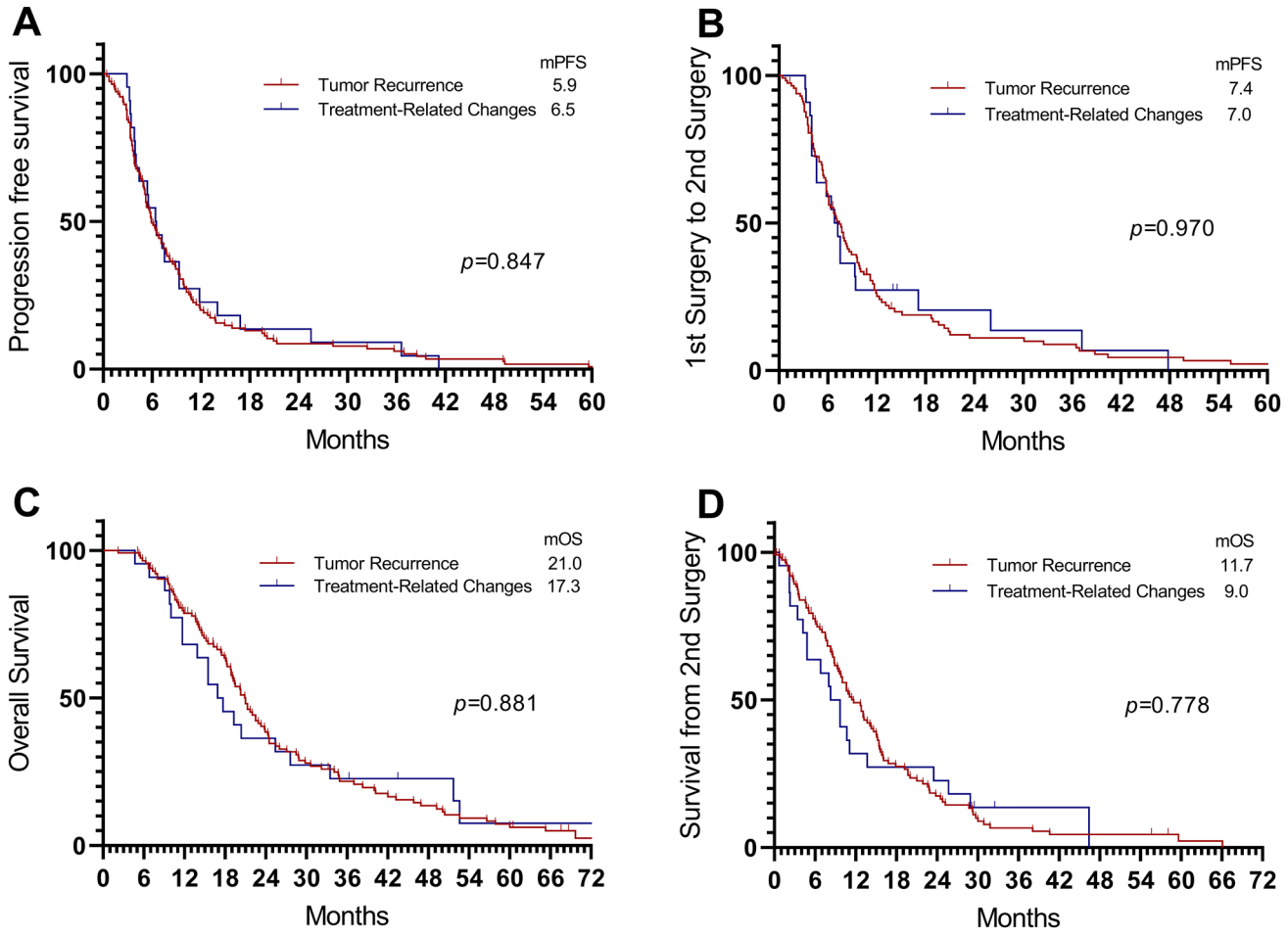

Fig 1. Outcomes of glioblastoma patients by 2nd surgery histopathology. **a** Progression-free survival of patients diagnosed as treatment-related changes (n = 22) and tumor recurrence (n = 115), in which no significant difference is observed (TRC 6.5 vs. TR 5.9-months, $p = 0.847$). **b** Time between 1st and 2nd surgery of patients diagnosed as treatment-related changes and tumor recurrence, in which no significant difference is observed (TRC 7.0 vs. TR 7.4-months, $p = 0.970$). **c** Overall survival of patients diagnosed as treatment-related and tumor recurrence, in which no significant difference is observed (TRC 17.3 vs. TR 21.0-months, $p = 0.881$). **d** Survival from 2nd surgery of patients diagnosed as treatment-related changes and tumor recurrence, in which no significant difference is observed (TRC 9.0 vs. TR 11.7-months, $p = 0.778$)

biopsy sample itself, as well as compared to the volume of the total resected mass. Careful analysis of specimen sampling and its corresponding radiographic correlates to further understand variability within a lesion will be vital moving forward.

Despite varying methods in defining TRC none of the prior studies, including ours, report differences in OS. These data collectively suggest that the histologic distinction between TRC and TR at the time of reoperation may not be associated with OS. Strict criteria as discussed by Haider et al. [20] must be uniformly adopted in diagnosing residual, recurrent tumor, and treatment-related changes while also determining successful management of the latter [24]. We acknowledge that sampling bias of the "resected mass" is an inherited limitation of our study and all prior studies. We must consider that all patients may have some proportion of recurrent disease that fails to be assessed by histology, as not all tissue that is resected is sent to pathology for examination. This sampling bias may lead to ill-informed decisions, which may impact further management strategies, providing a false sense of disease control.

In our cohort, several patients in the TRC (32%) received no further adjuvant chemotherapy following reoperation and we also noticed a significant decrease in adjuvant radiotherapy (0% TRC vs. 26% TR, $p = 0.004$) and TTF (5% TRC vs. 25% TR, $p = 0.045$) following second resection. Additionally, 18% of patients with TR underwent targeted therapies or clinical trial enrollment compared to 5% of TRC. It begs the question of whether patients deemed to have TRC should continue aggressive regimens, which may potentially result in improved outcomes. Further studies are

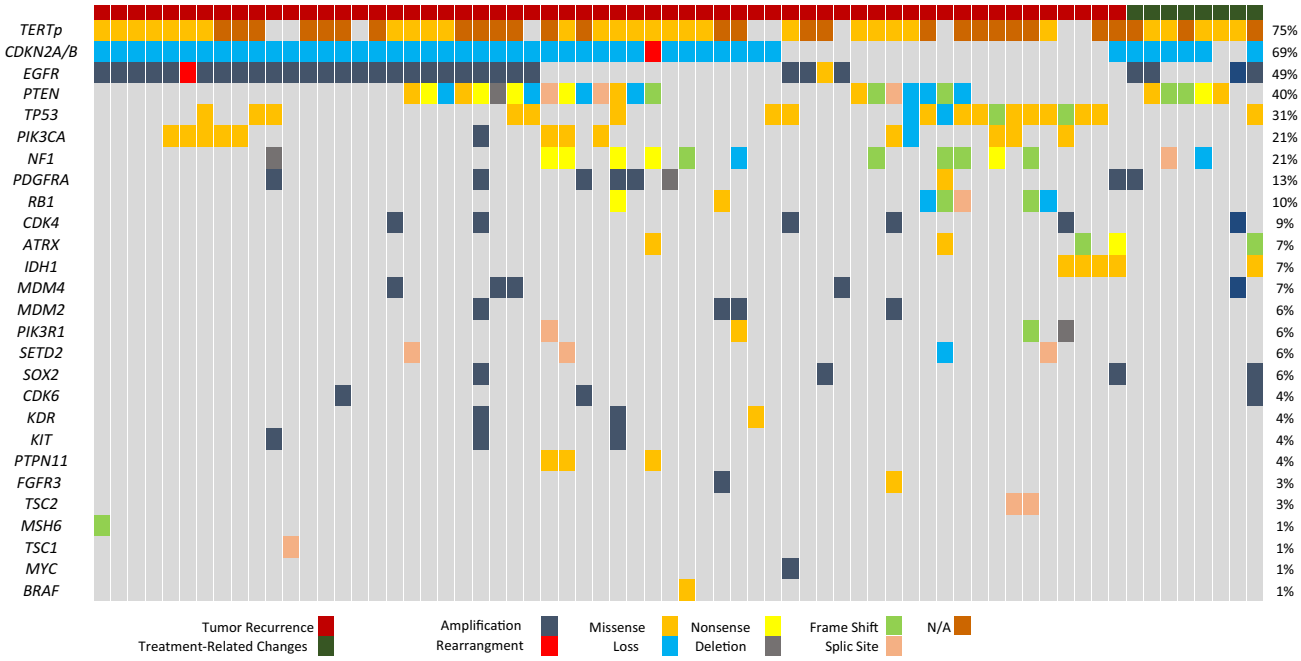

Fig. 2 Oncoplot of patients with next-generation sequencing by histology at primary resection

Table 2 Most common genetic alterations relationship with treatment-related changes and tumor recurrence

Genetic alteration, n (%)	TRC n = 8	Tumor recurrence n = 60	*p*-value
TERTp[a]	5 (100)	23 (66)	0.298
CDKN2A/B	6 (75)	41 (68)	1.000
EGFR	4 (50)	30 (50)	1.000
PTEN	5 (63)	22 (37)	0.250
TP53	0 (0)	20 (33)	0.094
PIK3CA	0 (0)	13 (22)	0.337
NF1	2 (25)	12 (20)	0.665
PDGFRA	1 (13)	8 (13)	1.000
RB1	0 (0)	7 (12)	0.587
CDK4	1 (13)	5 (8)	0.543
ATRX	1 (13)	4 (7)	0.476
IDH1	1 (13)	4 (7)	0.476
MDM4	1 (13)	4 (7)	0.476
MDM2	0 (0)	4 (7)	1.000
PIK3R1	0 (0)	4 (7)	1.000
SETD2	0 (0)	4 (7)	1.000
SOX2	1 (13)	3 (5)	0.401

Fischer's exact test

TRC treatment-related changes

[a]*TERTp* information was not available for 28 patients (3 TRC and 25 tumor recurrence)

required to determine to what extent histologic evaluation should inform treatment-related decisions at reoperation and preclude patients from enrolling in clinical trials.

Unfortunately, radiographic techniques have previously failed to prospectively differentiate between TRC and tumor progression due to a lack of specific imaging metrics. Recently, the combination of ferumoxytol and gadolinium contrast-enhanced MRI proved diagnostic for TRC versus TR. For the past decade perfusion imaging has been an additional tool in distinguishing TR from TRC, by taking advantage of the increased vascularity of malignant tumors [25]. Dynamic susceptibility contrast (DSC) MRI has shown promise in the ability to differentiate the two conditions (specificity 77.8% and sensitivity 80%) [26] as well as being easily repeated to track progression. However, due to the artifact created by leakage of required gadolinium, DSC has limitations. Recently, 3D arterial spin labeling has been shown to be an alternative to DSC, with fewer susceptibility artifacts, in differentiating TR from TRC [27]. Further advances in imaging techniques could potentially be utilized pre-operatively to guide treatment decisions and avoid unnecessary invasive procedures [28–30]. Additionally, liquid biopsies to measure cell-free DNA, RNA, proteins, and circulating tumor cells, is a rapidly evolving non-invasive method for detecting and monitoring tumors, and may potentially be useful to distinguish TR from TRC [31, 32]. Continuing improvements in radiographic techniques and the development of tissue-specific biomarkers may aid in distinguishing TRC and TR [4].

Sixty-eight patients in this cohort, 8 of whom were found to have TRC on second surgery, had tissue from their primary resection analyzed by NGS. We found no association between tumor mutations and a predisposition to TRC or TR after adjustment for multiple comparisons. Even though, our results did not show a significant difference in the mutations present in cases of TRC and TR, patients with TRC had a non-significant increase in *TERTp* and *PTEN* mutations. Interestingly, *PTEN* loss of function mutations have been described to sensitize GBM cells to radiotherapy; conversely, pY240-*PTEN,* which causes gain-of-function of the gene, is a key mechanism of radiation resistance and its inhibition improves radiotherapy efficacy [33]. However, the relationship between *PTEN* mutations and the development of TRC is unknown. The *TERT* gene encodes a reverse transcriptase, which adds repeats to the end of chromosomes preserving telomeres [34]. Mutations in the *TERT* promoter (*TERTp*) allow tumor cells to avoid cellular senescence [35, 36]. Gao et al. showed that patients with relative long telomere length due to *TERTp* mutations have poor survival and resistance to radiation therapy [37]. Further studies with larger cohorts should explore the possible relationship between these genes and the development of TRC. An additional sixty-four patients had IDH1 p.R132H analysis performed on tissue from the primary resection. It is well established that mutations in *IDH1* are associated with reduced malignant progression and significantly favorable PFS [38, 39]. We found no association with IDH status and histopathological parameters. Dalle et al. analyzed the *IDH1* status of 70 patients and found no association with TRC. Furthermore, the MGMT promoter methylation status was available for 38 of their patients, and no association with TRC was established [23]. We were unable to assess this parameter in our study, as MGMT promoter methylation status was not routinely tested. Importantly, IDH-mutant tumors are typically associated with MGMT promoter methylation [40].

O6-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein, is hypothesized to be resistant to DNA alkylating agents such as Temozolomide [41]. A recent meta-analysis found that patients with MGMT methylation showed improved OS compared to those with un-methylated status [42]. Interestingly, Bandes et al. found the MGMT promoter methylation was associated with pseudoprogression as well as increased time to disease progression and OS [28]. MGMT promoter methylation is believed to improve the efficacy of temozolomide, enhancing its anti-tumor effect. There is evidence that continuous therapy with temozolomide considerably depletes MGMT. Interestingly, we observed a de-escalation in therapy in patients with TRC, suggesting that continued therapy may provide benefit to those individuals who present with MGMT promoter methylation and TRC. Further studies are needed to address this.

Our study was performed on tumor tissue obtained during primary resection. However, fifteen patients had NGS analysis performed in tissue obtained at the time of reoperation, all of who presented with tumor recurrence. Future studies including TRC tissue sequencing might help to identify the prognostic significance of the presence/absence of oncogenic drivers in the second resection of these patients. Additionally, we observed that in the 15 patients that had NGS in both surgeries, the mutational profile of the second surgery resembles the initial mutational profile. This is in concordance with the recent findings by the GLASS consortium in which standard of care therapies did not frequently coerce GBM to predictable mutational pathways [43]. Instead, GBM appears to evolve stochastically from early driver events that are consistent at initial surgery and the second surgery as observed in Online Resource 4.

Individual predisposition to radiosensitivity must also be considered when attempting to distinguish between TR and TRC, as previously reported in various conditions [44, 45]. Recently, a single nucleotide polymorphism in *CEP128* was found to be associated with an increased risk of temporal lobe necrosis in patients undergoing RT for nasopharyngeal carcinoma, providing evidence of individual susceptibility to RT [46].

Conclusions

Our results show no difference in survival between histologically diagnosed TRC or RT patients. This begs the question of not only whether patients deemed to have TRC should continue aggressive regimens but also their eligibility for clinical trials and escalation of therapies. Moreover, a consensus of the histopathological definition of TRC is urgently needed to standardize diagnosis across institutions. Even though our study did not identify particular mutations that could predict TRC, future studies should aim to identify predisposing molecular factors and the prognostic significance of the presence/absence of oncogenic drivers in TRC patients.

Author contributions Study design: AP, LYB, and YE. Data Recollection: AP and AD. Data analysis: AD and PZ. Manuscript writing: AP, AD, and YE. Manuscript revision and editing: AP, AD, NT, LYB, and YE. Study Supervision: LYB and YE. Approved final manuscript: all authors.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.Code availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This retrospective study was approved by the institutional review board of The University of Texas Health Science Center at Houston and Memorial Hermann Hospital, Houston, TX following the 1964 Helsinki Declaration and its later amendments.

Consent to participate Not applicable.

Consent for publication Not applicable.

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