

High-dose Radiotherapy in Newly Diagnosed Low-grade Gliomas with Nonmethylated O6-methylguanine-DNA Methyltransferase

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Research

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Abstract

Background: Patients with low-grade gliomas (LGGs) harboring *O*⁶-methylguanine-DNA methyltransferase promoter nonmethylation (*MGMT*-non-pM) have a particularly short survival and are greatly resistance to chemotherapy. The objective of this study was to assess the efficacy of high-dose radiotherapy (RT) for LGGs with *MGMT*-non-pM.

Methods: 269 patients with newly diagnosed adult supratentorial LGGs from the multicenter Chinese Glioma Cooperative Group (CGCG) received postoperative RT during 2005-2018. *MGMT* promoter methylation analysis was conducted by pyrosequencing in all patients. Univariate and multivariable analyses were performed using the cox regression to determine the prognostic factors for overall survival (OS) and progression-free survival (PFS). RT dose-response on *MGMT* status defined subtypes was analyzed.

Results: On univariate analysis, the following were statistically significant favorable factors for both PFS and OS: oligodendrogliomas [HR = 0.002 and $p = 0.005$], high-dose RT (> 54 Gy) [HR = 0.017 and $p = 0.023$] and 1p/19q codeletion [HR < 0.001 and $p = 0.001$]. On multivariable analyses, RT dose (> 54 Gy vs. ≤ 54 Gy) and *IDH* mutation were independently prognostic markers for OS (HR, 0.44; 95%CI, 0.21-0.92; $p = 0.029$; and HR, 0.43; 95%CI, 0.20-0.90; $p = 0.025$, respectively) and PFS (HR, 0.48; 95%CI, 0.27-0.90; $p = 0.021$; and HR, 0.52; 95%CI, 0.27-0.98; $p = 0.044$, respectively). High-dose RT was associated with longer OS (HR, 0.55; 95%CI, 0.32-0.93; $p = 0.026$) and PFS (HR, 0.57; 95%CI, 0.35-0.93; $p = 0.026$) than low-dose RT in *MGMT*-non-pM subtype. In contrast, no significant difference in either OS ($p = 0.240$) or PFS ($p = 0.395$) was observed with high-dose RT in the *MGMT*-pM subtype.

Conclusions: High-dose RT (> 54 Gy) is an independently protective factor for LGGs and associated with improved survival in patients with *MGMT*-non-pM.

Background

Low-grade gliomas (LGGs) mainly refers grade II by the WHO grading system and are relatively uncommon, constituting approximately 10% of all primary brain tumors in adults [1–2]. Although often considered as “benign”, over half of these patients will develop tumor progression within 5 years and the rate of progression-free survival (PFS) at 10 years was 21–51% [3–4]. Therefore, postoperative radiotherapy (RT) is frequently utilized after surgical resection. Recently, molecular alterations, especially *isocitrate dehydrogenase 1/2* mutation (*IDH* mutation) and chromosome arm 1p/19q codeletion (1p/19q codeletion), provide important diagnostic and prognostic information that can greatly improve diagnostic accuracy and management decision-making in patients with LGGs [5]. *IDH* mutation and 1p/19q codeletion are required for LGGs classification within the revised 2016 WHO guidelines. However, *O*⁶-methylguanine-DNA methyltransferase promoter methylation (*MGMT*-pM) was rarely reported in patients with LGGs, even though it accounts for about 79–92% in these patients [6–7]. Only one study RTOG (Radiation Therapy Oncology Group) 0424 has so far reported the association of *MGMT* status with survival of patients with LGGs [8]. In this study, *MGMT* status was an independent prognostic biomarker of high-risk, LGGs treated with radiotherapy combined with concomitant and adjuvant temozolomide (TMZ) chemotherapy. A survival benefit was observed in LGGs contained a methylated *MGMT*; Similar with glioblastoma [9], *MGMT*-non-pM confers a shorter OS (3 years vs. not reached) and PFS (2 years vs. not reached) compared with *MGMT*-pM in high-risk LGGs. Unfortunately, most of clinical trials tended to test new drugs as alternatives to TMZ for patients with *MGMT*-non-pM have failed. Bevacizumab plus irinotecan, paclitaxel poliglumex with RT, Cilengitide combined with TMZ, temsirolimus and procarbazine et al. have been proved to be not satisfactory in nonmethylated GBM [10–13]. Thus, new therapies for these patients are urgently needed.

Because of the requirements for long-term follow-up for patients with LGGs, most of studies on RT dose were conducted early, before the year 1990, and have many limitations in both diagnostic (computed tomography, CT) and treatment modalities (2D planning). However, modern technology (intensity-modulated radiation therapy, IMRT and magnetic resonance imaging, MRI) can greatly improve dose distribution of targeted field and reduce dose of adjacent structure. Therefore, we hypothesize that RT dose escalation might be effective in LGGs with *MGMT*-non-pM based on modern technology. In this study, we analyzed retrospectively the potential survival benefits of high-dose RT (> 54Gy) in 269 patients with LGGs containing the information of *MGMT* promoter methylation. These data provide evidence for making treatment decisions and designing clinical trials for LGGs based on *MGMT* status.

Materials And Methods

Patient Population

269 patients with newly diagnosed adult supratentorial LGGs (WHO II) were obtained from the multicenter Chinese Glioma Cooperative Group (CGCG) and the Chinese Glioma Genome Atlas (CGGA) in China during 2005–2018 (www.cgga.org.cn). Tumor histology was confirmed independently by two neuropathologists based on the 2007 WHO classification and the 2016 updated edition. The study protocol was approved by the Ethics Review Board of Tiantan Hospital in Beijing, China. Written informed consent was obtained from all participants. The patients had to be in good general condition as indicated by performance score after surgery: Karnofsky Performance Scores ≥ 60 . Patient characteristics (stratified by the *MGMT* status) are summarized in Table 1.

Table 1
Clinical features of patients with LGGs stratified by *MGMT* status

characteristics	<i>n</i> (%)	<i>MGMT</i> -pM <i>n</i> (%)	<i>MGMT</i> -non-pM <i>n</i> (%)
Total	269	115 (42.8)	154 (57.2)
Sex	269 (100)		
Male	153 (56.9)	62 (53.9)	91 (59.1)
Female	116 (43.1)	53 (46.1)	63 (40.9)
Age (years)	269 (100)		
≤ 40	154 (57.2)	55 (47.8)	99 (64.3)
> 40	115 (42.8)	60 (52.2)	55 (35.7)
Histopathology	269 (100)		
A*	221 (82.2)	83 (72.2)	138 (89.6)
O	48 (17.8)	32 (27.8)	16 (10.4)
Seizure	205 (72.6)		
Yes	122 (59.5)	33 (56.9)	89 (60.5)
No	83 (40.5)	25 (43.1)	58 (39.5)
Resection	249 (92.6)		
Total	116 (46.6)	57 (54.3)	59 (41.0)
Subtotal	133 (53.4)	48 (45.7)	85 (59.0)
RT dose	269 (100)		
High	155 (57.6)	64 (55.7)	91 (59.1)
Low	114 (42.4)	51 (44.3)	63 (40.9)
Chemotherapy	261 (97.0)		
Yes	88 (33.7)	42 (38.9)	46 (30.1)
No	173 (66.3)	66 (61.1)	107 (69.9)
IDH mutation	251 (93.3)		
Yes	206 (82.1)	93 (92.1)	113 (75.3)
No	45 (17.9)	8 (7.9)	37 (24.7)
1p/19q codeletion	162 (60.2)		
Yes	63 (38.9)	43 (50.0)	20 (26.3)
No	99 (71.1)	43 (50.0)	56 (73.7)
*A: including astrocytoma and oligoastrocytoma which was eliminated from the 2016 WHO classification.			

Treatments

All patients underwent surgical excision and postoperative three-dimensional conformal radiotherapy (3DCRT) or IMRT. The radiation fields were based on the postoperative T2 or FLAIR MRI-defined residual tumor and/or surgical cavity plus a 2 cm margin. The median dose was 55.8 Gy (range, 40–66 Gy) (1.8–2.0 Gy daily, 5 days per week). The distribution of doses in LGG patients was shown in Supplementary Fig. 1. All patients received RT at 4–8 weeks after surgery. The extent of resection was evaluated using preoperative and postoperative MRI. A total of 33.7% (88/261) of patients received RT followed by chemotherapy using carmustine, nimustine, or TMZ. In the first 2 years, follow-up and MRI were performed after RT every 6 months, and every 9–12 months thereafter until tumor progression.

Pyrosequencing of MGMT promoter

DNA was extracted in formalin-fixed paraffin-embedded samples with a QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). Then 100 ng DNA was bisulfite converted with an Epitect Bisulfite kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. The bisulfite-treated DNA was amplified and then sequenced by pyrosequencing. The amplification forward primer 5'-GTTTYGGATATGTTGGG ATAGTT-3' and the biotinylated reverse primer 5'-biotin-ACRACCCAAACACTCA CCAA-3'. The methylation levels of CpG sites 75–78 were obtained with the sequencing primers 5'-GATATGTTGGGATAGT – 3' or 5'-GTTTTTAGAAYGTTTT G-3'. The methylation levels of CpG sites 76–79 were detected with a commercial *MGMT* pyrosequencing kit (Qiagen, Hilden, Germany) with a PyroMark Q24 System (Qiagen, Hilden, Germany). Standardized positive and negative controls were included in all routine pyrosequencing testing, and every test was performed by 2 experienced molecular neuropathologists together (Supplementary Fig. 2).

Statistical Analyses

The clinical features of the different groups were compared using the χ^2 test with SPSS v22.0 (IBM, Armonk, NY, USA). OS and PFS curves were estimated by the Kaplan–Meier method and compared with use of the two-sided log-rank test. OS was calculated from the day of surgery to the date of the first event. The date of progression was defined as the date of the CT or MRI examination that confirmed progression or related neurologic symptoms. Cox proportional hazards regression was used to identify independent risk factors for OS and PFS. $P < 0.05$ (two-sided) was considered to indicate statistical significance.

Results

Patient Characteristics

Among all patients enrolled in this study, the median age was 38 years (range, 11–69 years), and the male-to-female ratio was 1.32:1 (153:116). Median follow-up time was 9.12 (7.93–10.30) years. There have been 79 deaths (29.4%) and 101 recurrences (37.5%) to date. Of the 269 samples, 221 (82.2%) were astrocytoma or oligoastrocytoma (oligoastrocytoma was essentially eliminated based on the molecular pathology on the updated WHO classification in 2016) and 48 (17.8%) were oligodendrogliomas. The 5-year OS and PFS rates were 80.6% and 73.3% in all patients. Median PFS was 11.4 years, and median OS was not yet reached. The baseline characteristics of patients, stratified by MGMT status, are reported in Table 1.

Analyses with the Cox Proportional-Hazards Models

A dose of 54 Gy was extensively used in clinical decisions and trials of LGGs [1, 3, 8, 14]. Depending on the dose of 54 Gy, we divided patients into 2 groups: high dose (> 54 Gy) and low dose (≤ 54 Gy). On univariate analysis, the following were statistically significantly favorable factors for both PFS and OS: oligodendrogliomas ($p = 0.002$ and $p = 0.005$), high-dose RT [$p = 0.017$ and $p = 0.023$] and 1p/19q codeletion [$p < 0.001$ and $p = 0.001$]. *IDH* mutation [$p = 0.076$] and seizure symptom [$p = 0.074$] indicate a favorable prognosis, although the difference was not significant in analysis of OS and PFS, respectively. Multivariate analysis showed that high-dose RT (HR, 0.44; 95% CI, 0.21–0.92; $p = 0.029$; HR, 0.48; 95% CI, 0.27–0.90; $p = 0.021$, respectively) and *IDH* mutation (HR, 0.43; 95% CI, 0.20–0.90; $p = 0.025$; HR, 0.52; 95% CI, 0.27–0.98; $p = 0.044$, respectively) were significantly prognostic factors of both OS and PFS. 1p/19q codeletion [$p = 0.072$] indicates a favorable prognosis, although the difference was not significant in analysis of OS (Table 2).

Table 2
Univariate and multivariate analyses for PFS and OS based on clinical and molecular variables

Variables	n	Univariate analyses			Multivariate analyses								
		PFS			OS			PFS			OS		
		HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age ≤ 40 vs. ≥40	269 115/154	1.08	0.72–1.61	0.73	1.03	0.65–1.62	0.907	1.09	0.60–1.97	0.78	1.32	0.68–2.57	0.417
Sex Male vs. female	269 153/116	1.19	0.80–1.78	0.395	1.03	0.66–1.60	0.907	1.83	1.00–3.35	0.050	1.26	0.64–2.48	0.498
Histopathology A* vs. O	269 221/48	3.20	1.55–6.59	0.002	3.32	1.44–7.64	0.005	2.20	0.78–6.18	0.135	1.88	0.58–6.05	0.290
Seizure Yes vs. no	205 122/83	0.69	0.46–1.04	0.074	0.63	0.40–0.99	0.045	0.86	0.47–1.58	0.625	0.86	0.43–1.70	0.657
Resection Total vs. subtotal	249 116/133	0.61	0.40–0.94	0.024	0.77	0.48–1.24	0.280	0.83	0.45–1.53	0.826	0.94	0.47–1.87	0.849
Chemotherapy Yes vs. no	261 88/173	1.56	1.04–2.34	0.030	1.00	0.62–1.61	0.991	1.46	0.81–2.63	0.204	1.00	0.49–1.99	0.972
Dose > 54 Gy vs. ≤54 Gy	269 155/114	0.62	0.42–0.92	0.017	0.60	0.38–0.93	0.023	0.48	0.27–0.90	0.021	0.44	0.21–0.92	0.029
IDH mutation Yes vs. no	251 206/45	0.59	0.36–0.96	0.033	0.61	0.36–1.05	.076	0.52	0.27–0.98	0.044	0.43	0.20–0.90	0.025
1p/19q co-deletion Yes vs. no	162 63/99	0.31	0.16–0.58	0.000	0.27	0.12–0.57	.001	0.43	0.19–0.97	0.042	0.41	0.15–1.08	0.072
MGMT pM Yes vs. no	269 115/154	0.82	0.53–1.28	0.389	0.65	0.38–1.12	0.119	0.79	0.43–1.44	0.436	0.63	0.30–1.31	0.217
* A including astrocytoma and oligoastrocytoma which was eliminated in the 2016 WHO classification													
PFS: progression-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval													

Dose-Response in patients with MGMT-non-pM

MGMT promoter methylation was profiled in all patients. A significant protective effect on PFS and OS with a RT dose ≥ 54 Gy was observed in patients with *MGMT*-non-pM (HR, 0.57; 95% CI, 0.35–0.93; *p* = 0.026; and HR, 0.55; 95% CI, 0.32–0.93; *p* = 0.026, respectively) (Fig. 1A and B), but this was not the case in patients with *MGMT*-pM (*p* = 0.40 in PFS and *p* = 0.240 in OS) (Fig. 1C and D). Most clinical characteristics were comparable between groups (Supplementary Table 1). Among 261 patients, 88 received RT followed by chemotherapy (carmustine, nimustine, or TMZ). But patients with *MGMT*-pM did not receive benefit from the addition of chemotherapy (*p* = 0.058 in PFS and *p* = 0.195 in OS) (Supplementary Fig. 3A and B). Chemotherapy did also not improved the OS (*p* = 0.826) and PFS (*p* = 0.109) in patients with *MGMT*-non-pM (Supplementary Fig. 3C and D).

Discussion

Gliomas with *MGMT*-non-pM are striking resistance to chemotherapy or targeted therapy. In our study, high-dose RT (> 54 Gy) was an independently protective factor of patients with LGGs. More importantly, patients with *MGMT*-non-pM can benefit from high-dose RT, but no benefit was observed with high-dose RT in patients with *MGMT*-pM. The results showed that replacement of TMZ chemotherapy by high-dose RT might be feasible for these patients with *MGMT*-non-pM. To the best of our knowledge, this is the first report on the relationship between RT dose and *MGMT* status. *MGMT* status could serve as the primary predictor of response to RT in LGGs.

MGMT is a DNA repair protein and a marker of resistance to the first line chemotherapeutic drug (TMZ). Methylated *MGMT* resulted in reduced protein and is a strong prognostic and predictive biomarker for benefit from TMZ chemotherapy in patients with GBM, especially in elderly patients [15–16]. Even in patients with treatment by only radiotherapy, *MGMT*-pM also confers a survival advantage [9, 17]. However, patients with *MGMT*-non-pM derive less benefit from TMZ or other alkylating agents and have a shorter median survival compared to those whose tumors are methylated (15.3 months vs. 21.7 months). Though many trials have tried to test new drugs as alternatives to TMZ, none of these was effective against unmethylated GBM. LGGs have relatively higher rates (75–92.5%) of *MGMT*-pM than GBM, but the association of *MGMT* status with survival of LGGs rarely reported. In RTOG 0424, *MGMT*-pM was found in 76% (57/75) of high-risk LGGs and was an independent prognostic biomarker based on RT and adjuvant TMZ chemotherapy. *MGMT*-non-pM was significantly associated with worse OS and PFS than *MGMT*-pM in high-risk LGGs [8]. However, the implication of *MGMT* status with respect to radio-chemotherapy sensitivity in patients with LGGs is not further studied.

Learning from the failed clinical trials in GBM with *MGMT*-non-pM, we hypothesize that RT dose escalation might be effective in these refractory tumors. Earlier retrospective studies have observed a dose-response relationship in LGGs. Although these studies were retrospective and had limited sample sizes (< 150 patients), they found that high-dose RT (> 52 Gy, > 53 Gy, or even > 55 Gy) confers a survival advantage compared with those who received low-dose RT (< 52 Gy, < 53 Gy, or even < 55 Gy) [18–20]. However, two randomized trials (the European Organisation for Research and Treatment of Cancer 22844 and the North Central Cancer Treatment Group 86-72-51) did not show an OS or PFS benefit to high-dose RT (59.4 Gy and 64.8 Gy) over low-dose RT (45 Gy and 50.4 Gy) [21–22]. The point to emphasize here is that these studies were activated in 1985 and 1986, respectively, and have many limitations in diagnostic and treatment modalities. Patients were treated in an era with older surgical, diagnostic instrument (CT scan) and radiation techniques (2D planning). Currently, IMRT and MRI are routinely used in clinical practice that has been a significant improvement in dose distribution of targeted field and dose limitation of adjacent structure [23]. More importantly, molecular pathology provides additional diagnostic and prognostic information that can greatly improve diagnostic accuracy and management decision-making. Therefore, it is needed to be reconsidered based on modern technology whether high-dose RT can obtained improved survival in some molecular subtypes. In our study, 269 patients with newly diagnosed LGGs received postoperative 3DCRT or IMRT. The results that RT dose is an independent prognostic factor for both OS and PFS indicated that the survival of patients with LGGs might be further improved by increasing RT dose in modern technology. High-dose RT was associated with longer PFS and OS in *MGMT*-non-pM subtype. In contrast, no significant difference in survival was observed with high-dose RT in the *MGMT*-pM subtype. The data showed that high-dose RT as alternatives to TMZ or other drugs might be effective in LGGs with *MGMT*-non-pM. The associations of *MGMT* status with RT dose were first reported in present study, our data is helpful in choice of therapeutic strategy for these refractory molecular subtypes. Although confirmation by prospective trials is needed, this study is also helpful in designing clinical trials for LGG based on *MGMT* status.

Conclusion

High-dose RT (> 54 Gy) was an independently protective factor for patients with LGGs. Patients with *MGMT*-non-pM may have improved survival upon administration of high-dose RT. Our findings will help to define the standard of care and assist decision-making as well as the design of prospective clinical trials for LGGs. However, the limitations of our retrospective study should be acknowledged. No information on quality of life was available. The adverse effects of high-dose RT must be assessed in further studies.

Declarations

Ethics approval

This study was reviewed and approved by the Institutional Review Board of Beijing Tiantan Hospital (Grant number: KY2013-017-01). Informed written consent from patients was waived by the Institutional Review Board of Beijing Tiantan Hospital due to the retrospective study design.

Consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and material:

All data were presented in the manuscript and supplementary materials.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study concept and design: Xiaoguang Qiu and Yanwei Liu; Data acquisition and analysis: Yanong Li, Peng Wang, Li Chen and Jin Feng; Statistics analysis: Yanwei Liu; Writing the first draft: Yanwei Liu, Yanong Li; Supervision study: Xiaoguang Qiu; Read and approved final version: All authors.

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Figures

Fig.1

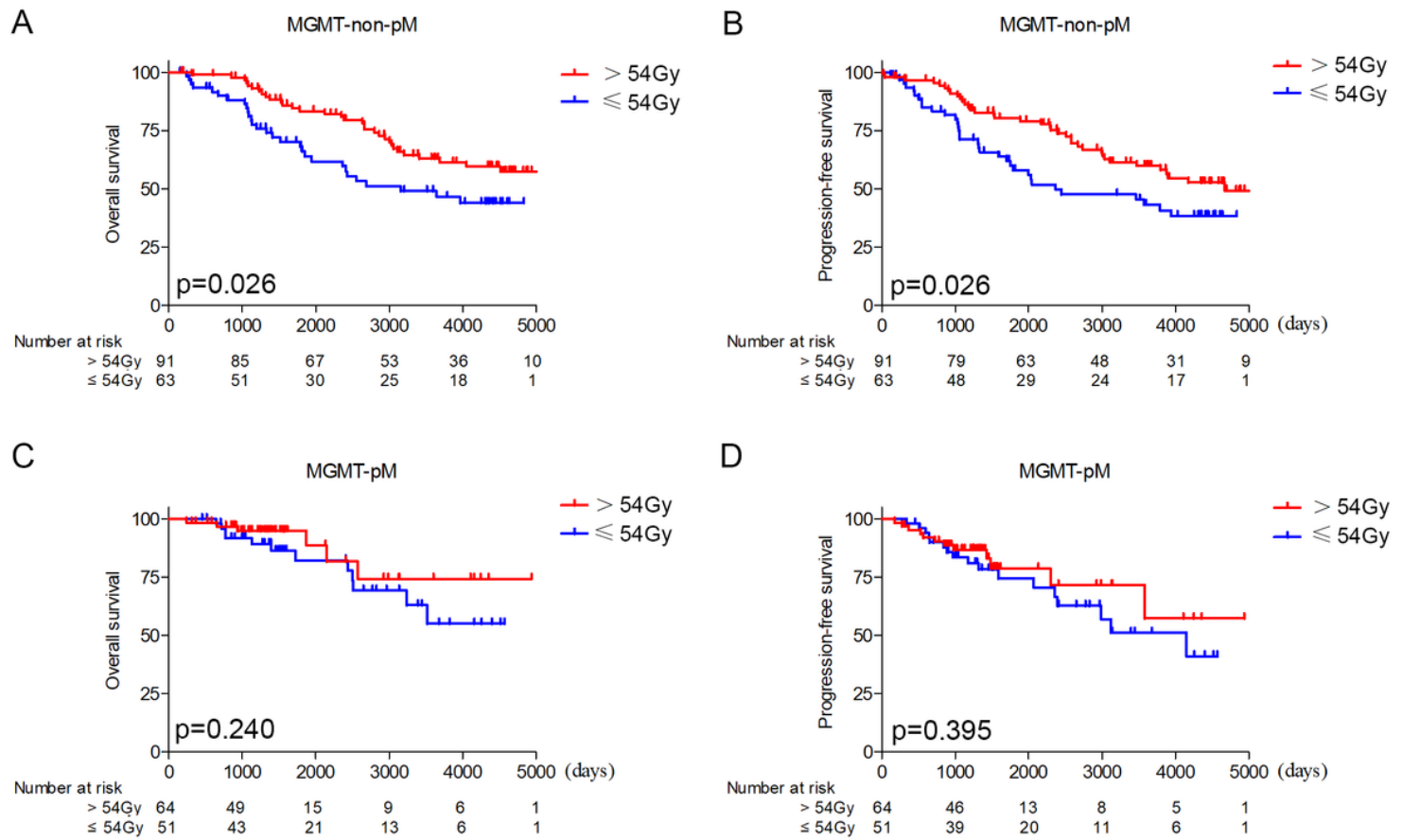


Figure 1

RT dose effects on MGMT status defined subtypes. Patients with MGMT-non-pM (A and B) could benefit from high-dose radiotherapy (> 54 Gy); Patients with MGMT-pM did not benefit from high-dose RT (C and D).

Supplementary Files

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