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Is a reduction of radiation dose feasible in patients affected by glioblastoma undergoing radio-chemotherapy according to MGMT promoter methylation status without jeopardizing survival?

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ABSTRACT

Objective: To explore therapeutic results of different radiotherapy (RT) dose schedules combined to Temozolomide (TMZ)-RT treatment in newly diagnosed glioblastoma (GB), according to the O (6)-methylguanine-DNA methyltransferase (MGMT) methylation status.
Patients and methods: Patients with newly diagnosed GB received either standard (60-59.4 Gy) or reduced (54-52 Gy) dose radiation therapy (RT) with concurrent and adjuvant TMZ between June 2010 and October 2016. We retrospectively evaluated the therapeutic effectiveness of the RT ranges schedules in terms of overall survival (OS) with univariate and multivariate analysis, after analyzing the MGMT methylation status.
Results: One hundred and seventeen patients were selected for the present analysis out of 146 total treated patients accrued. Seventy-two out of the selected cases received the standard RT-TMZ course (SDRT-TMZ) whereas the remaining 45 underwent the reduced dose schedule (RDRT-TMZ). The analysis according to the MGMT promoter methylation status showed that, in methylated-MGMT GB patients, SDRT-TMZ and RDRT-TMZ groups did not show different median OS (p = ns) according to the two RT schedules, independently by the extent of surgical resection. Instead, a difference in survival outcomes was confirmed in unmethylated-MGMT GB patients with better survival for patients undergoing to SDRT, particularly in sub-total resection.
Conclusion: In our experience, a reduction of radiation dose schedule does not seem to jeopardize survival in methylated-MGMT patients independently by the extent of resection.

A therapeutic approach to a standard reduction of RT dose for the methylated subset of patients may be feasible and could deserve prospective trials for validation.

1. Introduction

Temozolomide (TMZ) is an oral alkylating agent with a tremendous impact on the treatment of glioblastoma (GB), a brain tumor characterized by a dismal prognosis and a resistance to the therapy, improving survival in patients treated with TMZ plus radiotherapy (RT) in adjuvant setting that nowadays represents the backbone of the management of patients affected by GB [1]. Despite a comprehensive characterization of GB by multiple omics platforms has recently improved our knowledge of the molecular bases underlying GB clinical aggressiveness [2–5], in the clinical setting, the methylation status of the O (6)-methylguanine-DNA methyltransferase (MGMT) promoter, that is, a DNA repair enzyme causing resistance to alkylating agents [6,7], plays a crucial role in prognostic stratification of patients with glioblastoma. MGMT methylated patients show a better outcome in terms of progression and overall survival [8], compared to unmethylated patients. The MGMT promoter methylation positive status has a highly significant predictive role of response to adjuvant TMZ chemotherapy combined with RT treatment [1,7,9,10]. According to guidelines in clinical practice, the gold standard fractionation scheme

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for fit patients is a dose of 60 Gy delivered in 30 fractions of 2 Gy each with concurrent daily oral TMZ [11].

In some cases, to avoid the incidence of the collateral effects due to RT, the optimal standard dose to target volumes could not be delivered because of organs at risk proximity (such as optic chiasm, optic nerves or brainstem) and a reduction of the prescribed dose is performed. Theoretically, this reduction may affect survival outcome [12]; however, any studies had shown whether RT dose reduction might affect survival in the era of TMZ use and MGMT methylation status determination. The present analysis is addressed to retrospectively comparing patients treated in our institution with standard RT (60 Gy) plus TMZ and patients treated with a reduced RT dose (50–54 Gy) plus TMZ taking into account the MGMT methylation status.

2. Patients and methods

2.1. Patient series

We analyzed the medical records from our institutional brain tumor database containing 146 patients affected by GB (Grade IV – WHO Classification [13]), consecutively referred to the Radiation Oncology Unit for postoperative RT-TMZ, after the pathologic diagnosis (CM), from June 2010 to October 2016. The MGMT gene promoter methylation status was assessed using a methylation-specific Polymerase Chain Reaction (PCR), as previously reported [14]. Briefly, genomic DNA was extracted from paraffin-embedded tumor sections and treated with sodium bisulfite using the EZ DNA Methylation-Gold kit (HISS Diagnostics, GmbH, Freiburg, Germany). Primer sequences were used to detect methylated and unmethylated MGMT promoter sequences. PCR products were separated on 2% agarose gel. A glioma cell line with a completely methylated MGMT promoter and peripheral blood mononucleated cells served as positive and negative control samples, respectively. A methylation percentage of 5% was used as a cut-off value: samples with methylation < 5% and > 5% were classified as unmethylated and methylated, respectively.

2.2. Extent of surgical resection

The extent of surgical resection was obtained by the description of surgical procedures and the post-operative CT-MR imaging (72 h and 30 days after surgery) and classified as follows: biopsy (B), subtotal resection (STR) and gross total resection (GTR).

2.3. Selection criteria

Patients with unifocal or extensive GB candidate to a full course RT-TMZ treatment have been considered for the present evaluation. All patients who did not complete TMZ concomitant course, enrolled in clinical trials or undergoing to a whole brain RT were excluded. Clinical and pathological data, including the extent of surgery, Karnofsky Performance status (KPS) before RT start, the baseline magnetic resonance imaging (MRI) (that is, pre-resection or biopsy) study, were available in all cases. The MRI scan was obtained with a standard protocol, as follows: T1-, T2-, Fluid Attenuated Inversion Recovery (FLAIR)- acquisitions, Diffusion-Weighted Imaging (DWI) axial sequences (5 mm slices thickness/5.5 mm separation) and T1-gadolinium enhanced scans, in axial, coronal and sagittal planes. After the repetition of this exam before irradiation, all patients initiated the RT-TMZ adjuvant treatment within 4–8 weeks after surgery, according to the protocol defined by Stupp et al. [1]. The patients received either standard dose treatment (SDRT: 59.4–60 Gy), or dose reduction (RDRT: 54-52 Gy), according to the volume, the region of the lesion and adjacency to critical brain regions (optic pathways and brainstem).

2.4. Radiotherapy treatment planning

SDRT: 59.4–60 Gy: The Clinical Target Volume (CTV) was contoured on CT and post-operative MRI image fusion, and included residual tumor mass (T1 gadolinium-enhanced lesion) and/or post-operative cavity (that is, GTV) plus a 20 mm margin without consideration for peritumoral edema. Volume contouring took into account anatomical barriers, such as ventricular spaces, cranial bones, and the midline except for the region of the corpus callosum. An isotropic margin of 5 mm was added around to obtain the Planning Target Volume (PTV-1). RT was delivered with a Linear Accelerator 6–10 MeV beam and 3D-Conformal or Intensity Modulated techniques up to a planned total dose of at least 59.4 Gy, and with standard fractionation (1.8–2 Gy/day for five days per week). RDRT: 54-52 Gy: A dose reduction was prescribed to respecting OAR constraints in CNS [15] in case of target proximity to OAR. Chemotherapy. All patients also received TMZ, concurrently administered *per os* during RT, according to the Stupp's protocol (daily TMZ 75 mg/m^2 during the RT course), followed by the sequential TMZ schedule (150–200 mg/m^2 for five days every 28 days) until disease progression or complete response after 12 cycles.

2.5. Follow-up

After the completion of RT and concurrent TMZ administration, patients entered a scheduled follow-up program. Brain MRI scans were repeated at four weeks, 12–16 weeks, then every 6 months or in any case showing clinical signs suggesting progressive disease (PD). Taking into account that no patient of this series received anti-angiogenic treatment, PD after RT-TMZ treatment was assessed using the RANO Criteria [16]. A diagnosis of pseudo-progression was made in cases showing an increase in tumor size and/or T1-contrast enhancement within 3–6 months after the end of concomitant RT-TMZ, without worsening of neurological status and with stabilization or resolution in subsequent further MRI studies. Imaging findings suggestive for radionecrosis were recorded.

2.6. Analyzed parameters, survival end-points, and statistical analysis

We categorized all the considered parameters, except for the patient's age at the diagnosis that is treated as a continuous variable [17] as follows: KPS (100-80 and < 70); extent of surgery (GTR: Gross Total Resection; B-STR: Biopsy or Sub-Total Resection), MGMT status (methylated and unmethylated); RT dose (SDRT, 59.4–60 Gy, and RDRT, 50–54 Gy), Radiological Response (CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progression Disease), sequential TMZ duration (> 6 cycles and < 6 cycles). We performed a correlation analysis using Fisher's exact test to determine the probability of non-random relationships between considered variables.

We estimated overall survival (OS) with the Kaplan-Meier method. The univariate survival analysis was used to identify the prognostic parameters. We used the log-rank test to assess the significance of survival differences for the considered parameters (p-values ≤ 0.05 were considered as statistically significant). We also performed a multivariate analysis (Cox regression) to quantify the relationship between survival and potential predictors, to identify a subgroup of independent factors significantly related to survival. All the statistical analyses were performed with the SPSS 15.0 software package for Windows.

2.7. Ethics approval

We obtained ethics approval of the study and signed informed consent by each patient for the anonymous use of clinical and treatment data. All the adopted procedures were in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association.

Table 1
Clinical (Age = age at diagnosis, KPS = Karnofsky Performance Status), treatment (GTR = Macroscopic Gross Total Resection, B/STR = Biopsy or Sub-Total Tumor Resection, Dose RT = total dose for radiotherapy treatment, RDRT = 54-52 Gy, SDRT = 59.4–60 Gy, TMZ = sequential TMZ for > 6 cycles), and biological (MGTM) prognostic factors (Kaplan-Meier method, Survival Analysis).

		N ° pts	OS Median (months)	univariate p-value	multivariate p-value
Age	> 50	100	12	n.s	n.s.
	< 50	17	17		
KPS	100-80	106	14	0.001	0.042
	=70	11	7		
Extent of Surgery	GTR	32	22	0.02	0.001
	B/STR	85	11		
TMZ	**> 6 cycles**	**63**	**20**	**0.001**	**0.015**
	≤ 6 cycles	**54**	**9**		
MGMT status	Methylated	48	25	0.0001	0.0001
	Unmethylated	69	11		
RT DOSE	RDRT	45	10	0.052	n.s.
	SDRT	72	16		

3. Results

Out of the 117 patients selected for this study, 72 (61,5%) patients received a standard radiation treatment (SDRT-TMZ) and 42 (39,5%) a reduced radiotherapy dose (RDRT-TMZ).

The median OS of this whole series was 13 months, OS rate at 6 months and 12 months being respectively 82.6% and 54.4%.

Statistically significant prognostic factors, in the whole series, in the univariate analysis were summarized in Table 1: KPS, the extent of surgical resection, MGMT status, Radiological Response, age, sequential TMZ.

The multivariate analysis (Table 1) confirmed that KPS < 70 (HR: 2,109; 95% CI: 1,029 - 4,324; p = 0.042) and B-STR (HR: 1,783; 95% CI: 1,451 - 4,449; p = 0.001) unmethMGMT status (HR: 3,170; 95% CI: 1,919 - 5,236; p = 0.0001) and no use of sequential TMZ (HR: 2,250; 95% CI: 1,170 – 4,327; p = 0.015) were independently associated with a shorter OS. Out of the whole series, in RDRT-TMZ and SDRT-TMZ groups, a statistically different OS were not shown: median OS of 10 months for the RDRT-TMZ group and 16 months for the SDRT-TMZ group (p = 0.052).

A subgroup survival analysis for MGMT methylation status was performed. In unmethMGMT patients (69 patients), HDRT-TMZ and SDRT-TMZ groups had different median OS (p = 0.01) 8 months for the RDRT-TMZ group and 11 months for SDRT-TMZ group, respectively (Fig. 1). The different OS (p = 0.001) between RDRT-TMZ and SDRT-TMZ schemes, respectively, were also found in patients with macroscopic residual disease, (B/SRT) (Fig. 1). The RT dose was confirmed as an independent prognostic factor at multivariate analysis in unmethMGMT patients un-adjusted (HR: 1,890; CI95%: 1,021 - 3,458) and adjusted for extent of resection (HR 1,907; CI95%: 1,186 - 3,667).

Differently, no difference in survival outcomes was found out of methMGMT patients (48 patients, shown in Table 2B) according to the different RT-TMZ schemes used (p = 0,07), with a median OS in RDRT patients of 32 months and 25 months in SDRT, even when analyzed by the extent of surgical resection (p = 0,13) (Fig. 2). No different distribution of other prognostic factors between the two treatment groups (SDRT vs. RDRT) according to MGMT methylation status (Tables 2A and 2B) was demonstrated, except for the radiological response in the group of unmethylated patients.

4. Discussion

The promoter of MGMT encoding-6O-methylguanine-DNA methyltransferase is a DNA repair enzyme which can effectively protect cells against alkylating agents. Recently, some clinical trials have shown that MGMT methylation corresponds to greater PFS and OS [9] not only in patients who are treated with RT-TMZ. These findings highlight the necessity for different therapeutic approaches in patients with GB depending on their MGMT status in patients undergoing to TMZ use. Alongside with TMZ use, the neuro-oncological community presently accepts an RT dose prescription of 60-59.4 Gy in the treatment of GB, delivered in five weekly fractions of 1.8–2.0 Gy [1–11]. The results of randomized trials [18,19] were pooled in an extensive study of 621 patients showing a dose-response relationship for GB [12] where higher doses (60 Gy - 55 Gy - 50 Gy - 45 Gy) were associated with improved survivals (10.5 months vs. 8 months vs. 7 months vs. 3.4 months, respectively). All these findings derived from studies in the pre-TMZ era and without MGMT methylation status determination. It is unclear whether this relationship is still valid with TMZ use and prognostic stratification based on MGMT methylation status. A recent retrospective analysis [20] of a moderate-dose RT-TMZ escalation protocol-driven [21] schedule suggested that MGMT methylation status could lead a different response to the intensification of RT dose with a dose-survival relationship showed only in unmethylated patients. Herein, we tried to analyze the effect of RT dose reduction, in case of OAR proximity, on GB patients' outcome according to MGMT promoter status. We retrospectively adopted a prognostic stratification according to the MGMT methylation status and, secondary, for surgical extent. A reduction of radiotherapy dose prescription was usually prescribed in patients with a lesion located proximally to organs at risk, and for the same reason, more probably, less resectable. It could be expected, on these grounds, that the RT dose reduction in patients should show a negative influence on local control of the disease and survival. This speculation is confirmed in unmethMGMT patients group where OS was

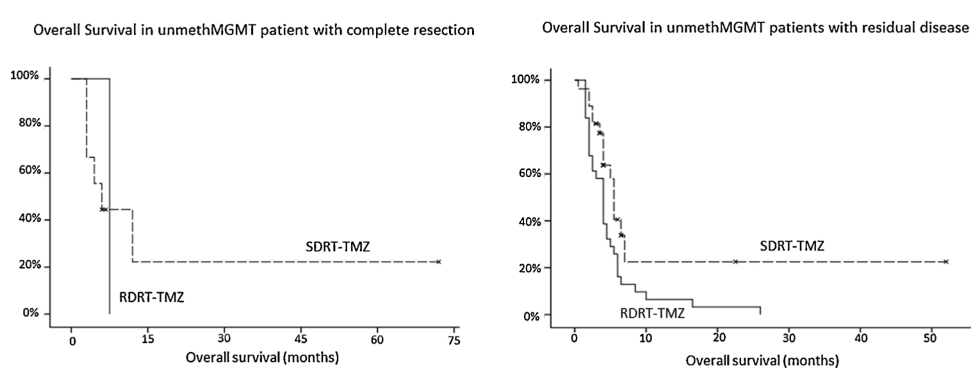

Fig. 1. Overall Survival (Kaplan-Meier method) according to standard (SDRT-TMZ) versus reduced (RDRT-TMZ) RT dose (log-rank test p-value < 0.05) in unmethylated patients with complete resection (left) and unmethylated patients with residual disease (right).

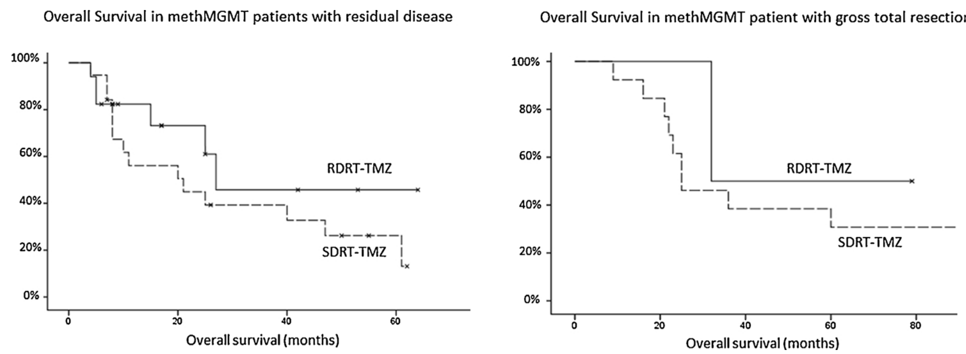

Fig. 2. Overall survival (Kaplan-Meier method) according to standard (SDRT-TMZ) versus reduced (RDRT-TMZ) RT dose (log-rank test p-value < 0.05) in methylated patients with residual disease (left) and methylated patients with gross total resection (right).

Table 2A
Patient's characteristic in the unmethylated group (n = 69) according to different treatment schedules.

		RDRT patients (n = 33)	SDRT patients (n = 36)	Chi-square Significance
KPS	100-80	30	32	p = n.s
	=70	3	4	
Extent of resection	GRT	9	7	p = n.s
	B/SRT	24	29	
Age	> 50ys	29	33	p = n.s
	< 50ys	4	3	
Radiological Response	Complete Response	7	3	p = 0.031
	Partial Response	7	2	
	Stable Disease	7	6	
	Progression Disease	12	25	
Radionecrosis		1	0	p = n.s

Table 2B
Patient's characteristic in the methylated group (n = 48) according to different treatment schedules.

		RDRT patients (n = 12)	SDRT patients (n = 36)	Chi-square Significance
KPS	100-80	12	32	p = n.s
	=70	0	4	
Extent of resection	GRT	6	10	p = n.s
	B/SRT	6	26	
Age	> 50ys	11	27	p = n.s
	< 50ys	1	9	
Radiological Response	Complete Response	6	9	p = n.s
	Partial Response	3	6	
	Stable Disease	1	9	
	Progression Disease	2	12	
Radionecrosis		1	1	p = n.s

significantly affected (p = 0.01) by total RT dose with better survival for patients treated with a standard treatment of 60 Gy respect than ones treated with a reduced RT dose, especially in the presence of macroscopic residual disease (Fig. 1).

Conversely, no difference in median OS between RDRT (35 months) vs. SDRT (25 months) schedules in all methylated patients was demonstrated. In methylated patients, RT dose modification did not influence local control of the disease and survival. Noteworthy, these findings were not influenced by the extent of resection as shown in Fig. 2. The different therapeutic response to different radiotherapy schemes seems to refer only to the MGMT methylation status, as there is no different distribution of other prognostic factors between the two treatment groups (Tables 2A and 2B). We can speculate that methylation of MGMT selects tumors in which the TMZ sensitivity overwhelmed the positive prognostic influence of both extents of surgery [22–24] and RT dose [12]. This data seems to suggest that a "standard" dose reduction could be prescribed in methylated patients, independently by the extent of resection and localization of lesions, without affecting the survival of these patients.

5. Conclusions

The retrospective design and the small number of patients are some pitfalls of the present analysis. However, our results suggest that a reduction of radiation dose schedule seems to do not jeopardize survival in methylated-MGMT patients independently by the extent of resection. To the authors' knowledge, this is the first study reporting a possible isoeffect of a reduction (52–54 Gy) of RT dose compared to the standard dose in methylated patients. Because of the small sample size, retrospective nature of the paper, and non-random application of reduced-dose radiation therapy, no clinical guidance should be inferred from these results. These findings should deserve further investigations, and prospective trials with an up-front reduction of RT dose in Stupp's schedule in methylated patients may be devised on these bases.

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