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# Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide

Giuseppe Minniti [a,b,*], Dante Amelio [c], Maurizio Amichetti [c], Maurizio Salvati [b], Roberta Muni [a], Alessandro Bozzao [d], Gaetano Lanzetta [b], Stefania Scarpino [e], Antonella Arcella [b], Riccardo Maurizi Enrici [a]

[a] Department of Radiation Oncology, Sant' Andrea Hospital, University "La Sapienza", Rome, Italy; [b] Department of Neurosurgical Sciences, Neuromed Institute, Pozzilli (IS), Italy; [c] ATreP – Provincial Agency for Proton Therapy, Trento, Italy; [d] Department of Radiology; and [e] Department of Pathology, Sant' Andrea Hospital, University "La Sapienza", Rome, Italy

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ABSTRACT

*Purpose:* To analyze the recurrence patterns in patients with newly diagnosed glioblastoma (GBM) treated with conformal radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ), and to compare the patterns of failure according to different target volume delineations.

*Methods and materials:* One hundred and five patients with GBM which recurred after three-dimensional (3D) conformal RT plus TMZ were evaluated. The clinical target volume (CTV) used for our treatment planning (S'Andrea plans) consisted of residual tumor and resection cavity plus 2-cm margins according to recent randomized trials of the European Organisation for Research and Treatment of Cancer (EORTC). MRI scans showing tumor recurrences were fused with the planning computed tomography (CT), and the patterns of failure were analyzed dosimetrically using dose–volume histograms. For each patient a theoretical plan based on the addition of postoperative edema plus 2-cm margins according to current guidelines of Radiation Therapy Oncology Group (RTOG) was created and patterns of failure were evaluated.

*Results:* The median overall survival and progression-free survival were 14.2 months and 7.5 months, respectively. Recurrences were central in 79 patients, in-field in 6 patients, marginal in 6 patients, and distant in 14 patients. Analysis of $O^6$-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status showed different recurrence patterns of GBMs in patients with MGMT methylated compared with patients with MGMT unmethylated status. Recurrences occurred central/in-field and outside in 64% and 31% of methylated patients, and in 91% and 5.4% of unmethylated patients, respectively ($P = 0.01$). Patterns of failure were similar between the different treatment plans, however the median volume percent of brain irradiated to high doses was significantly smaller for our plans than for RTOG plans ($P = 0.0001$). Conclusion: Most of patients treated with RT plus concomitant and adjuvant RT have central recurrences, however distant new lesions may occur in more than 10% of patients. The use of target delineation using postoperative residual tumor and cavity plus 2-cm margins is associated with smaller volumes of normal brain irradiated to high doses as compared with plans including expanded edema, without a significant increase of the risk of marginal recurrences. Future clinical randomized studies need to compare the different planning methods in terms of efficacy and risk of late radiation-induced toxicity.



The current standard of care for newly diagnosed glioblastoma (GBM) is maximal surgical debulking, followed by adjuvant radiation therapy (RT) and temozolomide (TMZ) chemotherapy. Radiation treatment planning has improved the precision of defining the tumor extension with the use of computed tomography (CT) and magnetic resonance imaging (MRI), however the optimal treatment volume for GBM is still a controversial issue, and different imaging modalities are used in the delineation of target volume. According to the method of target delineation practised at Sant'Andrea hospital the clinical target volume (CTV) is defined by the residual tumor and resection cavity plus 2 cm without the intentional inclusion of peritumoral edema and the planning target volume (PTV) as CTV plus 0.3 cm, as previously reported [1] and being similar to that used in some recent trials of the European Organisation for Research and Treatment of Cancer (EORTC) [2,3]. In contrast, according to the Radiation Therapy Oncology Group (RTOG) current guidelines, the initial CTV typically includes postoperative peritumoral edema plus 2 cm, followed by a boost field

* Corresponding author at: Sant' Andrea Hospital, Department of Radiotherapy Oncology, Via di Grottarossa 1035, 00189 Rome, Italy.
*E-mail address:* Giuseppe.Minniti@ospedalesantandrea.it (G. Minniti).

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defined as a residual tumor plus 2 cm and prescribed to 60 Gy (as for RTOG 0525 and RTOG 8525 trials).

The main reason for this lack of uniform guidelines is related to the aim of treating all possible microscopic areas of infiltrating tumor. The rationale for including peritumoral edema is that histologically identified tumor has been found in such areas in few studies [4–6]. However, large brain volumes irradiated to high doses especially in case of significant edema may increase the potential toxicity of radiation treatment. In contrast, some published series found that the majority of recurrences occurred within 2 cm of tumor margins, suggesting that the proximity to the tumor rather than the zone of peritumoral edema is correlated with tumor recurrence [7–13]. So far, there is still no agreement in the definition of GBM target volumes.

We have evaluated the recurrence pattern in 105 patients with newly diagnosed GBM treated with RT and concomitant and adjuvant TMZ. An important objective of the study was to compare the patterns of failure of our plans with the RTOG plans that include the expansion of peritumoral edema.

## Patients and methods

### *Patient characteristics*

Between February 2004 and July 2009 one hundred and 32 patients with GBM were treated with three-dimensional (3D) conformal RT at University Hospital Sant'Andrea. To date, 105 patients recurred as determined by the follow-up MRI. Characteristics of patients are listed in Table 1. All patients received RT plus concomitant daily TMZ, followed by adjuvant TMZ. RT started within 4 weeks of surgery and consisted of fractionated focal irradiation, at the dose of 60 Gy delivered in 30 fractions of 2 Gy over a period of 6 weeks, using 4–8 orthogonal beams. Dose was delivered by the dual high energy (6–15 MV) Varian DHX-S linear accelerator using a multileaf collimator (MLC). Concomitant chemotherapy consisted of TMZ at the dose of 75 mg/m$^2$, given 7 days per week from the first day of RT. Adjuvant TMZ was started 4 weeks after the end of RT and delivered for 5 days every 28 days up to 12 cycles. The dose was 150 mg/m$^2$ for the first cycle and was increased to 200 mg/m$^2$ from the second cycle. The dose was reduced or suspended in patients with disease progression or RTOG Grade 3–4 toxicity. The methylation status of the $O^6$-methylguanine-DNA-methyltransferase (MGMT) promoter was assessed according to methods described by Esteller et al. [14]. DNA was isolated from paraffin-embedded sections and methylation in CpG islands of the MGMT promoter determined by methylation-specific polymerase chain reaction (PCR) after sodium bisulfite DNA modification. For each PCR reaction both methylated and unmethylated DNA were used, as well as normal blood DNA without bisulfite modification as negative control. The PCR products (10 μl) were directly loaded onto non denaturing 6% polyacrylamide gels, stained with ethidium bromide, and visualized under UV illumination.

**Table 1**
Characteristics of 105 patients with glioblastoma.

| Characteristics | No of patients (%) |
|---|---|
| Age (years) | 61 |
| Median (range) | (34–74) |
| *Sex* | |
| Male | 61 |
| Female | 44 |
| *Karnofsky performance status* | |
| Median | 80 (60–90) |
| Range | 70–100 |
| *Extension of resection* | |
| Total | 21 |
| Subtotal | 46 |
| Partial/biopsy | 38 |
| *Chemotherapy cycles* | |
| Median (range) | 7 (2–12) |
| *Whole brain volume (cm$^3$)* | |
| Median | 1352 |
| Range | 1177–1609 |
| *Gross tumor volume (cm$^3$)* | |
| Median | 31.2 |
| Range | 10.2–96.3 |
| *Edema volume (cm$^3$)* | |
| Median | 68.5 |
| Range | 16.2–154 |
| *Recurrence volume (cm$^3$)* | |
| Median | 18.7 |
| Range | 5.2–73.8 |

MRI was repeated before RT, before the first cycle of adjuvant TMZ, and thereafter every 8 weeks or as appropriate according to neurological status. Neuroradiographic response criteria as defined by Macdonald et al. [15] were used. Tumor progression was defined by an increase in tumor size more than 25% or by the presence of a new lesion on imaging. Radiological progression had to be confirmed at two different MRI evaluations (at least 2 months apart). In patients with tumor progression the recurrence was recorded at the time of the first MRI showing tumor progression.

### *Treatment planning and treatment parameters*

Radiation treatment planning was performed with the Varian Eclipse Treatment Planning System. CT (General Electric Medical System) scanning was done in spiral mode using slices in thickness and spacing of 2.5 mm acquired throughout the entire cranium. Postoperative MRI scans were fused with the planning CT images in each patient. The gross tumor volume (GTV) encompassed the resection cavity and any residual tumor as seen on a contrast-enhancing T1 postoperative MRI. Delineation of clinical target volume ($CTV_1$), considered to contain the microscopic disease, was carried out by adding 2-cm margins to the GTV. For CTV more than 250 cm$^3$ the prescribed dose was 50 Gy in 25 fractions to the CTV, and a boost to the GTV plus 1-cm margin ($CTV_2$) of 10 Gy in 5 fractions. The CTV margins were reduced to 0.5 cm around natural barriers to tumor growth (the skull, ventricles, falx, etc.), and also to allow sparing of the optic nerve/chiasm, if necessary. The CTVs were expanded by 0.3 cm to create the planning target volumes ($PTV_1$ and $PTV_2$) to compensate for variability in treatment setup and patient motion.

The prescribed dose was normalized to 100% at the isocenter and 95% isodose surface covered the PTV as the minimum dose (ICRU Report 50). Treatment was given using 3D conformal vertex and noncoplanar fields to produce the optimal conformal plan according tothe volume definition and shaped to exclude excessive irradiation of the normal brain and other critical structures as possible. Normal tissue was contoured to include cerebral hemispheres, brainstem, optic nerves and chiasm, eyes and cerebellum. Maximum dose was 55 Gy to the eyes, optic nerve or chiasm, and 54 Gy to the brainstem.

### *Plan comparison and dosimetric analysis of recurrences*

Planning CT, postoperative T1-weighted postcontrast and FLAIR (for edema delineation) MRI images, and postradiation T1-weighted postcontrast MRI images showing recurrent GBM constituted the imaging data set. All MRI datasets were registered with the planning CT.

In all relapsed tumors, a theoretical plan that included edema was created according to RTOG target delineation guidelines. The