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Quality assurance of the EORTC 26981/22981; NCIC CE3 intergroup trial on radiotherapy with or without temozolomide for newly-diagnosed glioblastoma multiforme: the individual case review

Fatma Ataman [a,*], Philip Poortmans [b], Roger Stupp [c], Barbara Fisher [d], René-Olivier Mirimanoff [e]

[a] *EORTC, Data Center, Radiotherapy Group, 83 Avenue Mounier, 1200 Brussels, Belgium*
[b] *Dr. Bernard Verbeeten Instituut, Radiation Oncology, Brugstraat 10, 5042 SB Tilburg, The Netherlands*
[c] *Centre Hospitalier Universitaire Vaudois, Medical Oncology Department, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland*
[d] *London Regional Cancer Center, 790 Commissionner's Road East, London, Ontorio, Canada N6A 4L6*
[e] *Centre Hospitalier Universitaire Vaudois, Radiation Oncology Department, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland*

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Abstract

The phase III randomised European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trail Group (NCIC) Intergroup trial (EORTC 26981/22981; CE3) compares irradiation alone with irradiation plus temozolomide for patients with glioblastoma multiforme (GBM). We evaluated the compliance to radiotherapy (RT) guidelines. All 85 recruiting centres were invited to participate in the individual case review. Fifty-four centres (64%) entering 71% of the patients provided data on one randomly selected patient. All participating centres used individual head immobilisation and computerised tomography (CT)-based treatment planning. Most (74%) performed three-dimensional conformal radiotherapy (3-D-CRT) including dose–volume histograms. Ninety-four percent performed portal imaging at least once. Planning target volume (PTV) and structures at risk were delineated in most of the centres (94%). Although the PTV received <95% of the prescription dose (60 Gy in 2 Gy/fraction/day) in 39% of the centres; all except 2 centres delivered 50–60 Gy to the PTV. The maximum dose to the critical structures exceeded the protocol dose constraints in 39% of the reviewed patients, but in only 9% was this over the acceptable tolerance dose reported in the literature. We found a high rate of compliance with the protocol and general RT guidelines in the centres participating in this individual case review. In multicentre trials with a large of number of investigators from international and national groups, it is essential to confirm the interinstitutional consistency, qualitatively and quantitatively.

Keywords: Randomised clinical trial; Individual case review; Quality assurance; Brain tumour; Glioblastoma multiforme; Radiotherapy; Temozolomide

1. Introduction

Gliomas are a heterogeneous group of neoplasms that comprise the majority of primary brain tumours in adults. Glioblastoma multiforme (GBM) is the most common and the most malignant form of astrocytoma. Radiotherapy (RT) has been the main therapy for the last 30 years [1–3]. Despite RT (±chemotherapy (CT)), recurrence within a 2 cm margin of the primary site will occur in over 90% of patients [4–6]. Whole brain irradiation has been gradually replaced by localised RT to the primary tumour bed with 2–3 cm margins. Conventionally fractionated RT to a total dose of 50–60 Gy in 1.8–2 Gy/fractions is considered as the 'standard of care' for patients in good general condition. Due to the vicinity of

* Corresponding author. Tel.: +32-2-7741664; fax: +32-2-7753545.
E-mail address: fat@eortc.be (F. Ataman).

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organs at risk (OAR), it is critical to ensure a sufficient and homogenous target volume coverage. Deviations from protocol recommendations may result in important variations in dose distribution, under-dosing in some areas of the target volume and over-dosing in normal tissues,which may lead to unpredictable outcomes. The whole process of RT is complex with multiple integrated and interrelated procedures. Especially in multicentre trials, it is therefore of particular importance to conduct quality assurance (QA). The RT Group of the European Organisation for Research and Treatment of Cancer (EORTC) has established trial- and patient-oriented QA procedures [7,8].

New drugs and innovative treatment strategies are explored in clinical trials. Temozolomide, a cytotoxic alkylating agent, has shown some clinical anti-tumour activity against malignant gliomas [9–13]. Furthermore, it may have synergistic effects with radiation by increasing the sensitivity of glioblastoma cell lines to ionising radiation *in vitro* [14]. In a previous phase II study, temozolomide given concomitantly with radiation therapy followed by 6 cycles of adjuvant chemotherapy showed promising results with an acceptable toxicity profile [15]. The EORTC Brain Tumour Group, the EORTC Radiotherapy Group and the National Cancer Institute of Canada Clinical Trial Group (NCIC) embarked on a prospective randomised phase III trial [16]. Patients with newly-diagnosed GBM after surgical resection were randomised between RT alone and RT with concomitant and adjuvant chemotherapy. Herein, we report on the QA survey conducted in the framework of this trial. The presence and level of variations from protocol guidelines as well as the interinstitutional variability between participating centres were investigated.

2. Patients and methods

All participating centres ($n = 85$) were asked to send data concerning a randomly selected patient to the EORTC Data Center. The investigators were given an alternative patient as a second choice, in case the necessary documents were not available for review for the selected patient. The required data consisted of surgical,pathological and radiological reports, diagnostic and simulation films, RT treatment plans,treatment charts and portal films along with a short technology questionnaire. The QA team of this trial reviewed all this clinical and RT data and compared these with the case report forms collected at the EORTC Data Center. The parameters of the RT procedures such as treatment planning, execution and verification procedures were analysed with regard to the trial protocol requirements as well as to the International Commission on Radiation Units (ICRU) recommendations for dose prescription, recording and reporting [17]. The QA evaluation form,adapted for this trial, was used for scoring and computerising. The accompanying short technology questionnaire was used to investigate the basic infrastructure of the participating centres, including all essential procedures for radiation delivery.

A total dose of 60 Gy (2 Gy/fraction/day) should be delivered by conventional fractionation in 6 weeks. The target volume had to be irradiated with a combination of an appropriate number of convergent fields, depending on the tumour size, location and treatment planning technique. All fields were to be treated every day. Patient positioning and immobilisation with an individual head mask and computerised tomography (CT)-based planning were obligatory. The gross tumour volume (GTV) was defined as the enhancing brain tissue at the primary tumour site,as seen on CT or magnetic resonance imaging (MRI). Planning target volume (PTV) was defined as GTV plus a margin of 2–3 cm. No field size reduction after a number of fractions was foreseen, unless necessary to limit the dose to the OAR. Dedicated CT and three-dimensional conformal radiotherapy (3-D-CRT) planning including the use of beams' eye views (BEV) and dose–volume histograms (DVH) were recommended for volumetric dose evaluation. Mega-voltage equipment with photon energies $\geqslant 4$ MV and weekly portal films and evaluation by the radiation oncologist were recommended.

The ICRU reference point was to be located in the central part of the PTV, typically at the intersection of the treatment beams. The minimum requirements included the calculation of dose distributions at the central plane. The minimum and maximum dose to the PTV should be comprised between 95% and 105% of the ICRU reference point dose.

The protocol required contouring OAR, including optic chiasm, brain stem and eyes, whenever it was possible and appropriate. The maximum doses were below 55 Gy for the optic chiasm and the brainstem, and up to 50 Gy for the retina, respectively.

3. Results

Fifty-four centres (64%) entering 71% of all patients participated in this case review (ICR). All forwarded data on the first randomly selected patient except for 3 centres that sent data on the alternative patient. Centres detailed patient data, treatment plan, beam parameters and dose schedule on specifically designed treatment charts and record forms. Fig. 1 shows the compliance of centres to the requested documentation for the ICR. Most centres sent patient reports, simulation films/digitally reconstructed radiographs (DRR) and treatment charts. The copies of the preoperative and postoperative diagnostic films of the selected patient were available for

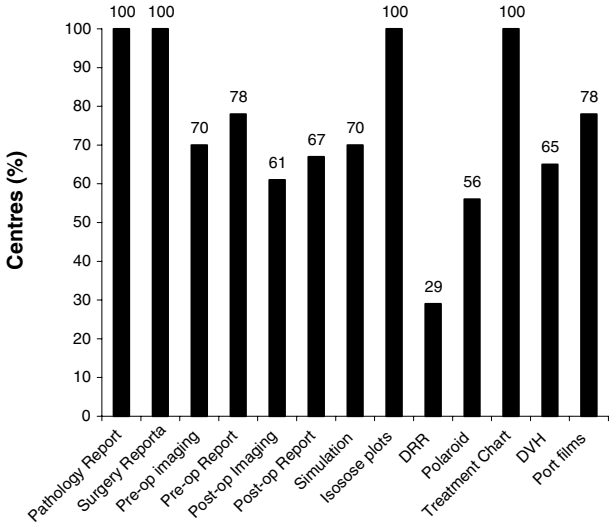

Fig. 1. Compliance to the required documents: pre-op, preoperative; post-op, postoperative; DVH, dose–volume histogram; DRR, digitally reconstructed radiographs.

70% and 61% of the centres, respectively. Fig. 2 summarises the technical capabilities of the essential RT procedures reported on the technology questionnaire, i.e. patient immobilisation, treatment planning, treatment delivery and treatment verification.

3.1. Evaluation of eligibility, imaging, surgery and pathology

All centres performed preoperative imaging, i.e. MRI (66%), CT (28%) or both (6%). Most the centres had postoperative CT (55%) or MRI (19%). The tumour was located in temporal (34%), parietal (29%), frontal (21%), occipital (8%), fronto-parietal (4%) or temporo-parietal (4%) regions. The extent of surgery was appropriately reported in all patients: 45% of the patients had complete resection, 49% partial resection and 6% underwent a diagnostic biopsy only.

3.2. Evaluation of RT procedures and protocol compliance

Individualised head masks were used in all centres for head immobilisation. Most centres (66%) performed a dedicated CT, whereas 34% used only preoperative CT scans for RT planning. Centres used a classical simulator (62%), a simulator with CT-option (12%) or a virtual simulator (26%). Treatment planning computers (TPS) to generate isodose plots in a transverse plane were used in all of the centres. In approximately half of the centres, isodose distributions in the sagittal and/or coronal planes were available as well. DVH for the target volume and for the organs at risk were generated in 3/4 of the centres. Portal imaging of the treatment fields was performed in all centres either weekly (52%) or at least once (42%). Three centres did not provide any information on their treatment verification procedures.

All participating centres complied completely with the required steps of RT procedures for treatment planning, execution and verification. However, some of the protocol specifications (i.e., target volume dose distribution and weekly portal imaging) were not fulfilled fully due to different institutional practices, or could not be evaluated due to missing documentation.

3.3. Treatment volumes and dose schedule

Most of the centres delineated PTV (94%) alone or together with clinical target volume (CTV) and/or GTV. Only 6% of the centres did not draw target volumes for

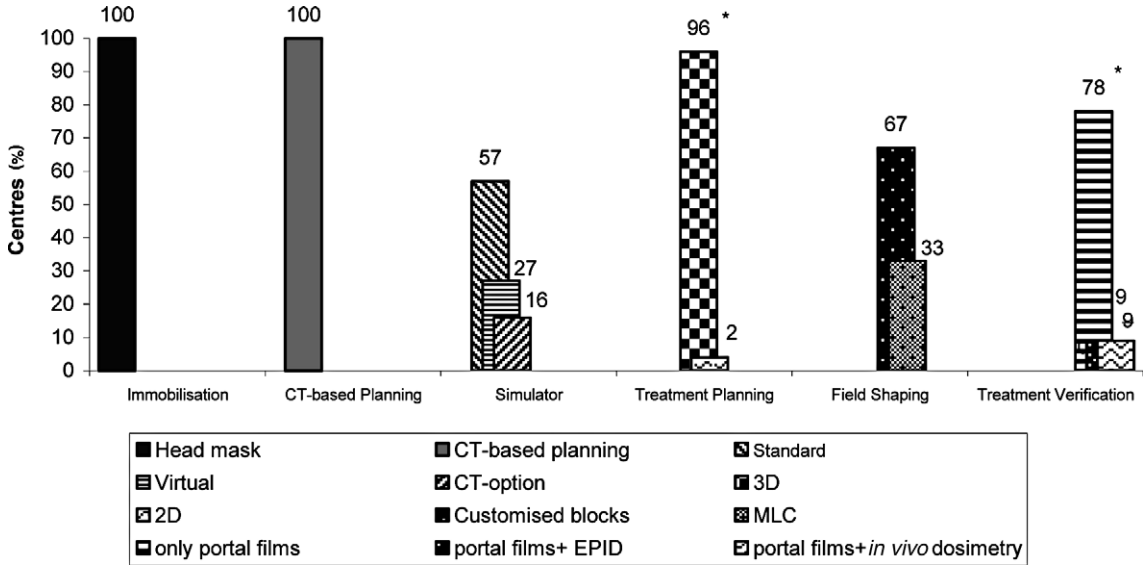

Fig. 2. Evaluation of the technology questionnaire: 2-D, two-dimensional; 3-D, three-dimensional; CT, computerised tomography; EPID, electronic portal imaging device; MLC, multi-leaf collimators; *, some data are missing for some centres.

Table 1
Dose specification for PTV, expressed as absolute doses and ranges[a]

	⩾ 95% PTV coverage (32 patients) (Gy)	90–94% PTV coverage (9 patients) (Gy)	<90% PTV coverage (6 patients) (Gy)	All patients (47 patients) (Gy)
Mean maximal dose in PTV[b]	63 (63–66)	60.8 (58–62)	62.3 (62–64)	62.4 (58–66)
Mean minimal dose in PTV[b]	57.7 (57–62)	55.2 (53–56)	48.8 (42–55)	56 (42–62)
Mean maximal dose in GTV	61.3 (58–64)	61.6 (60–63)	57.8 (57–58)	60.8 (57–64)
Mean minimal dose in GTV	58.9 (57–64)	59.4 (58–60)	60.6 (58–62)	59.1 (57–64)

PTV, planning target volume; GTV, gross tumour value.
[a] ⩾ 95% PTV coverage is recommended by the ICRU 50.
[b] The maximum and minimum doses within PTV were not documented in 3 and 6 patients, respectively.

treatment planning. All centres incorporated contrast-enhanced tumour on MRI/CT plus a 2–3 cm margin for the PTV. All centres except 4 delineated critical structures whenever they were located close to the tumour. Seven centres did not delineate critical structures since they were located distantly from the tumour, whereas 4 centres failed to draw these structures, although the OAR were in the vicinity of the target volume. All centres complied with the protocol dose scheme and delivered 60 Gy in 30 daily fractions except for one patient, who received a total dose of 58 Gy. In all centres, all fields were irradiated for each fraction. Most centres (81%) irradiated only one target volume, without field reduction after part of the dose. For 10 (19%) patients, field sizes were reduced to decrease the dose to adjacent critical structures. Nine patients had a field size reduction after 40–46 Gy, and one patient after 30 Gy. The overall treatment time was $\leqslant 6$ weeks, $>6-\leqslant 7$ weeks, and >7 weeks in 79%, 17% and 4% of the patients, respectively.

3.4. Dosimetry

In all centres, the dose was specified at the intersection of the beam axes according to ICRU-50 recommendations, inside the target volume. Table 1 shows the dose coverage of PTV and GTV. Although a slight under-dosage (<95% of the prescribed dose) was observed in limited areas of the PTV in 39% of the centres, all participating centres except two achieved a dose coverage >50 Gy for the whole PTV. The GTV received between 95% and 100% of the prescribed dose in all patients where this could be evaluated. The homogeneity within the PTV was outside the range recommended in ICRU report 50 for 18 centres, due to under-dosing (15 centres) and/or over-dosing (5 centres). The homogeneity within the GTV was within the range for most of the centres (91%) except for 5 centres, where there was an overdose to a very limited volume. The dose–volume information was available including the DVH for all patients where the OAR were located close to the target

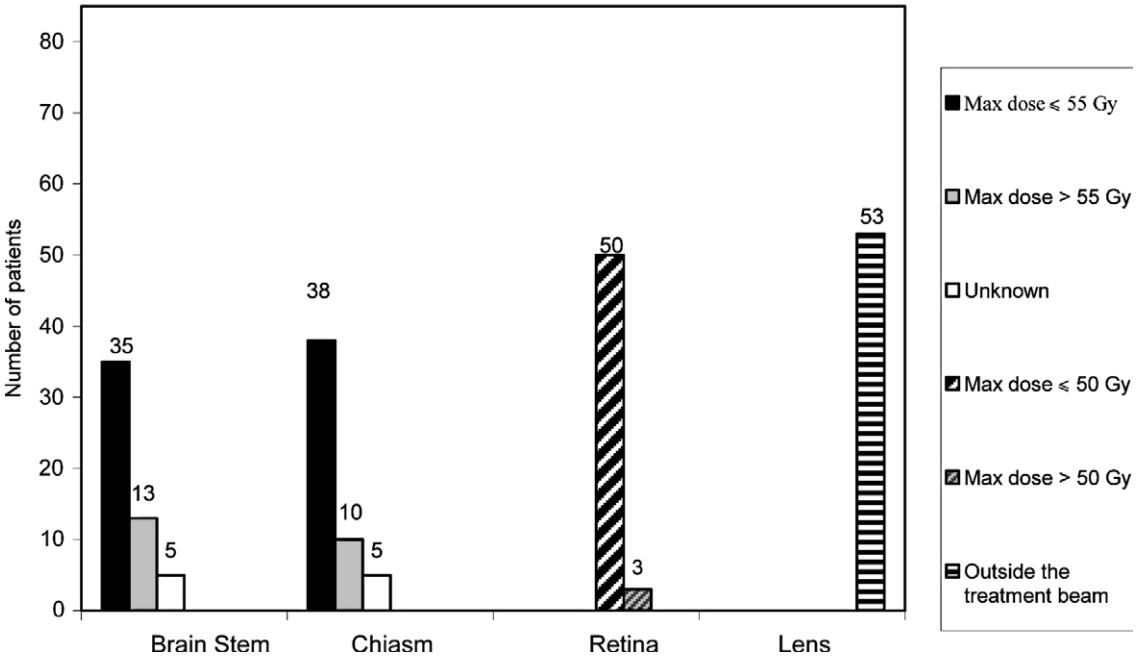

Fig. 3. Dose–volume information for the critical organs ($n = 53$).

volume, except in 4 centres. The maximum dose to the optic chiasm, brain stem and retina was below the protocol maximal dose constraints in over 60% of the reviewed patients (Fig. 3). The patients had either a higher dose to brain stem or chiasm with the exception of 2 patients who received a high dose both to the brain stem, and to the chiasm. The lens was outside the treatment beam in all centres except for one.

3.5. Compliance to the ICRU dose evaluation recommendations

According to the levels for completeness and accuracy of dose evaluation, as defined in ICRU report 50, dose planning and evaluation was done volumetrically, at the highest level (level 3) in most of the centres (75%), whereas in the rest of the centres (25%) it was done two-dimensionally (level 2). The dose at the ICRU reference point and the maximum and minimum dose in the PTV were reported by all but 6 centres.

4. Discussion

The EORTC trial 26981–22981 was set up to investigate the value of temozolomide added to RT with respect to overall survival in adults with newly-diagnosed supratentorial glioblastoma. The accrual of the trial was fast with a high number of investigators from different groups, disciplines and countries. In multi-institutional trials, the compliance to protocol requirements is a key issue to achieve homogeneity in treatment execution between centres. To evaluate this, we performed an ICR focusing on various parameters of patient eligibility and treatment compliance. A good representation of participating centres was obtained with a large amount of information, giving us a thorough insight into the centres ability to cope with the RT requirements. Centres delivered radiation with good compliance to the protocol requirements and ICRU guidelines and with a limited number of deviations concerning the multiple steps in radiation delivery.

The interphysician and intraphysician variations in the delineation of target volumes are known to be wide [18]. There may be several reasons for this, such as physicians' estimations based on their own knowledge and experience, but also due to an insufficient understanding of the ICRU definitions for GTV, CTV and PTV. Although it was not our aim to compare the variations of target volume delineation with this ICR, since each patient had a unique and different target volume, we examined the appropriateness of delineation and reconstruction on planning films. We received preoperative diagnostic data together with the simulation films from half of the centres. The delineation of target volumes was appropriate for all the centres that forwarded this information.

We had enough data on the dose–volume information for most of the centres. Almost all cases received at least 50 Gy to the PTV, and in sixty percent of the patients, the PTV received at least 95% of 60 Gy, thereby complying well with the current standards for GBM irradiation. The documented deviations in PTV coverage could be explained by field size reductions to keep the OAR below the tolerance dose.

ICRU report 50 defines 3 levels of dose evaluation. Level 1 concerns basic techniques, for which only the ICRU reference point and the maximum and minimum doses in the PTV are reported. Level 2 relates to more advanced techniques, including the definition of GTV, CTV and/or PTV in one or more planes. Level 3 includes 3-D dose computation for volumes including the evaluation of DVH. Centres were expected to report at least according to level 2. However, 3-D-CRT was strongly recommended in the protocol, provided the infrastructure was available in the participating centre. In the ICR of this trial, all centres reported at least at level 2 with 75% complying with level 3. With 3-D-CRT, features such as the integration of different imaging modalities, 3-D dose and dose–volume display and evaluation can substantially improve the accuracy of the treatment.

All except three centres performed portal imaging at least once, at the beginning of the radiation course. From the forwarded data, we could not clarify if all continued with weekly checks, as required in the protocol.

Acute effects on normal tissues are rare during conventionally fractionated local field RT to the brain. Potential adverse radiation effects on the optic chiasm and the brain stem develop only after a median latency period of 3 years (range 6 months–10 years). Surgical intervention can increase the risk of long-term toxicity. Dose-response relationship data are scarce and late toxicity to the OAR such as the optic chiasma is reported to be low (<10% in 10 years) after a total dose of 60 Gy in 2 Gy fractions [19]. The maximal recommended dose to OAR was more conservative (55-Gy for the brain stem and optic chiasm) in our protocol, and some centres reported doses slightly over the upper limits. In our review, only one patient received a maximal dose of 61 Gy to the optic chiasm. Brain necrosis in adults is infrequently noted with local doses below 60 Gy delivered with conventional fractionation [20]. According to the available dose–volume information, the dose to the brain stem was below 60 Gy in all but 4 patients, where a slightly higher maximal dose of 61–62 Gy was recorded. In summary, most of the centres complied with the dose constraints for OAR and used cone-down fields whenever necessary. For those exceeding the upper limits recommended in the protocol,

the maximal point doses remained within an acceptable range [21,22].

In general, the compliance of the participating centres to protocol guidelines as well as general RT guidelines and recommendations was very good. We did not find any unacceptable protocol deviations for the RT procedures. Therefore, we conclude from the individual case review of this multi-centre trial that the consistency between centres is high. It is therefore unlikely that interinstitutional variance in treatment techniques will negatively influence the final evaluation of the trial results.

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