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Radiotherapy quality assurance for the RTOG 0834/EORTC 26053-22054/ NCIC CTG CEC.1/CATNON intergroup trial "concurrent and adjuvant temozolomide chemotherapy in newly diagnosed non-1p/19q deleted anaplastic glioma": Individual case review analysis

André N. Abrunhosa-Branquinho [a,b,*], Raquel Bar-Deroma [c], Sandra Collette [a], Enrico Clementel [a], Yan Liu [a], Coen W. Hurkmans [d,e], Loïc Feuvret [f], Karen Van Beek [g], Martin van den Bent [h], Brigitta G. Baumert [i,j,1], Damien C. Weber [k,l,1]

[a] EORTC HQ, Brussels, Belgium; [b] Radiotherapy Department, Hospital de Santa Maria - Centro Hospitalar Lisboa Norte, EPE, Portugal; [c] Radiation Oncology, Rambam Health Care Campus, Haifa, Israel; [d] ROG RTQA Strategic Committee, EORTC, Brussels, Belgium; [e] Department of Radiation Oncology, Catharina Hospital, Eindhoven, The Netherlands; [f] Service de Radiothérapie, Hôpital de la Pitié-Salpêtrière, Paris, France; [g] Department of Radiation Oncology, University Hospital Leuven, Belgium; [h] Brain Tumor Center, Erasmus MC Cancer Institute, Rotterdam; [i] Maastricht University Medical Centre and GROW (School for Oncology and Developmental Biology), Maastricht, Netherlands; [j] Dept. of Radiation Oncology, Paracelsus Clinic, Osnabrück & Dept. of Radiation Oncology, University of Müenster, Germany; [k] Center for Proton Therapy, Paul Scherrer Institute, ETH Domain, Villigen; and [l] University Hospital of Zürich, Switzerland

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ABSTRACT

Background: The EORTC phase III 26053-22054/ RTOG 0834/NCIC CTG CEC.1/CATNON intergroup trial was designed to evaluate the impact on concurrent and adjuvant temozolomide chemotherapy in newly diagnosed non-1p/19q deleted anaplastic gliomas. The primary endpoint was overall survival.

We report the results of retrospective individual case reviews (ICRs) for the first patient randomized per institution to detect the compliance with the study protocol.

Material and methods: Sixty-nine institutions were required to submit the radiotherapy plan of their first randomized patient. Full digital datasets uploaded to the EORTC server were assessed by three independent and blinded reviewers through the EORTC radiotherapy quality assurance platform.

Results: Sixty-two (90%) of sixty-nine ICRs were received and assessable. Of the 62 cases, 22 were evaluated as per protocol (35.5%), 11 as acceptable variation (17.7%) and 29 were classified as unacceptable variations (46.8%). Most common unacceptable variations were related to the PTV dose (n = 19, 31%) and delineation (n = 17, 27%) processes.

Conclusions: The ICR analysis showed a significant number of unacceptable variations with potential impact on tumor control and/or toxicity profile. Prospective ICRs are encouraged for future studies to prevent and correct protocol violations before start of treatment.

WHO grade III tumors or anaplastic gliomas correspond to 20–30% of primary brain tumors in adults. Adjuvant radiotherapy (RT) after surgery is standard therapy for patients with malignant gliomas [1–3]. The EORTC study 26951 and RTOG 94-02 showed that the addition of (neo)adjuvant procarbazine lomustine (CCNU) and vincristine (PCV) chemotherapy regimen to 59.4 Gy RT does increase progression free survival (PFS) and overall survival in anaplastic oligodendroglioma and anaplastic oligoastrocytoma in the long-term follow-up analysis [4,5]. Both studies also demonstrated that 1p/19q co-deletion status was a significant prognosticator and predictive for improved survival after PCV [4,5]. Taking into account the significant toxicity from the PCV regimen, temozolomide (TMZ) chemotherapy was proposed for non-1p/19q co-deleted anaplastic glioma as this was found to improve outcome in glioblastoma in a 5-year follow-up analysis [6,7].

The EORTC 26053-22054/RTOG 0834/NCIC CTG CEC.1/CATNON was a phase III intergroup trial assessing the survival impact of concurrent and adjuvant TMZ chemotherapy in newly diagnosed non-1p/19q co-deleted anaplastic glioma. The primary endpoint is overall survival and secondary endpoints are progression free

* Corresponding author at: Radiotherapy Department, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, EPE, Avenida Professor Egas Moniz, 1649-035 Lisbon, Portugal.

E-mail address: andre.branquinho@chln.min-saude.pt (A.N. Abrunhosa-Branquinho).

[1] Equal contribution.

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survival, neurological deterioration free survival, quality of life, toxicity, and development of cognitive deterioration. The interim analysis was recently published [8].

Trial-specific Radiotherapy Quality Assurance (RTQA) programs are developed for radiation therapy delivered within the framework of a prospective trial to identify and reduce uncertainties related to the different steps of treatment planning and delivery that may have an impact on tumor control and/or on the normal tissue toxicity. A *Post-hoc* analysis of 9 studies demonstrated RTQA incompliances affect the primary endpoint in the majority of the studies (62.5%) [9]. The TROG study 0202 also demonstrated the impact of RTQA on overall survival and failure-free survival even when the study objective was to evaluate an experimental drug [10]. Most patient treated with unacceptable RT quality parameters had worse outcomes independently of the study drug. The relation between adherence to RT protocol and survival is also highlighted in other cancer types [11,12].

RTQA programs at EORTC have been established by the Radiation Oncology Group (ROG) since 1982 [13] and includes multiple RTQA levels of different procedures [13,14]. EORTC RTQA levels description have been published [13] and updated according with the uniform global naming convention [15]. The RTQA levels applied for the CATNON trial were the following: level I (Facility Questionnaire and Beam Output Audit), level III (Limited Individual Case Reviews (ICR)) and level V (Complex Dosimetry Check for IMRT credentialing).

The objective of this paper is to report the RTQA limited retrospective ICR (i.e. level III RTQA) results of the 1st patient treated in the EORTC, COGNO and MRC membership institutions who participated in the CATNON trial.

Materials and methods

Radiotherapy and RTQA requirements

The protocol required a planning Computed Tomography (CT) scan with $\leq$3 mm thickness and additional post-operative imaging after resection/debulking was preferred, whenever possible, to determine target delineation.

The Gross Tumor Volume (GTV) was defined as the visible tumor resection margin, the enhanced regions on post-operative CT/MRI imaging and the high signal intensity regions on T2 weighted MRI images or FLAIR sequences (corresponding to the hypodense area on CT images). In case of complete or subtotal surgical resection, the GTV should include abnormalities observed in the planning CT scan and in any post-operative imaging used. The Clinical Target Volume (CTV) was defined by a 1.5–2 cm volumetric expansion of the GTV considering microscopic disease extensions. An alteration of volumetric expansion was allowed in case of invasion of midline structures, presence of anatomical borders (tentorium and meninges) or adjacent sensitive structures. The Planning Target Volume (PTV) was defined as CTV plus an acceptable volumetric margin of 0.5–0.7 cm.

Three-Dimensional Conformal RT (3D-CRT) or Intensity-Modulated RT (IMRT) was allowed and dependent on local principal investigator discretion. Total dose prescription was 59.4 Gy in 33 fractions (1.8 Gy per fraction per day). Dose prescribed to the PTV should satisfy the requirement $V_{95\%} \geq 100\%$ or $V_{95\%} \geq 90\%$ if near to organs-at-risk (OAR) [16,17]. In addition, PTV maximum point dose (D_{max}) should not be more than 107% of the prescribed dose. Eyes, optic chiasm, lenses, optic nerves, brainstem, cochleas and uninvolved brain areas delineations and dose constrains were defined as OARs.

Digital central RTQA platform

The RTQA datasets were collected on an ongoing basis between July 2012 and November 2015. The participating institutions were requested to upload the first randomized patient's digital dataset through the EORTC uploader and provide additional radiation therapy information by filling web-based forms [14]. The complete dataset included: the RTQA webform, the treatment plan in anonymized DICOM-RT format with a planning CT with intravenous (IV) contrast (whenever possible), the MRI used for delineation, volumes (structure contours) and 3D dose distribution files, and all diagnostic imaging exams used to help the planning. RT-related case report forms (CRFs) were also used if the RTQA webform information was not provided.

The digital treatment planning for review was assessed by VODCA-RT software package (Visualization and Organization of Data for Cancer Analysis, version 5, Medical Software Solutions GmbH; Hagendorm, Switzerland).

Central individual case review

Two radiation oncologists (BB, DCW) and one medical physicist (RBD) participated in the central review procedures. The medical physicist reviewed all datasets, and at least one radiation oncologist evaluated each case independently for target and OAR volumes, dose distribution and plan (assessment criteria is described in the Appendix). For each target volumes and OAR, a qualitative evaluation was made by inspection of the dose distributions slice-by-slice and dose histogram volume (DVH) analysis to make sure that the PTV was adequately irradiated and OAR were adequately spared for each patient. A qualitative grading system (per protocol, acceptable variation and unacceptable variation) was implemented for the overall assessment and 5 major subsections determined: planning procedures, volume definition, treatment plan & PTV dose, OAR dose, treatment delivery and verification.

Three consensus meetings during 2015 and 2016 took place involving all three reviewers and EORTC HQ RTQA Office for discrepant reviews, and all reviews were completed by November 7th 2016. The grading attributions were based on a consensus established by 3 reviewers. The additional following rules were applied during the consensus:

- If chiasm, optic nerve or brainstem were missing/anatomically incorrect the "Delineation grading" was classified as unacceptable variation. If other OARs were missing, the overall delineation was classified as acceptable variation.
- The use of integrated boost (SIB) is classified as an unacceptable variation.
- Planning should be performed in one phase of treatment. A second phase is accepted if used to spare adjacent OAR and it should be classified as acceptable variation.
- A 1 Gy tolerance for brainstem, chiasm or optic chiasm D_{max} was considered as an acceptable variation.

Statistical analysis

Consensus review results were collated in a Microsoft® Excel 2010 spreadsheet and summary descriptive analysis was performed using SPSS version 21.0 (IBM Corp., Armonk, NY). Acceptable and unacceptable variables for subsections and RT parameters were summarized. Descriptive analysis was compiled as frequencies for categorical variables.

Results

Sixty-nine institutions from 10 countries participated in the trial with at least one patient randomized and treated (12/2007-10/2015)[8]. Of these, 62/69 sites (90%) uploaded the minimum required dataset for proper RTQA evaluation. The cases were

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