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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

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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.

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Martin van den Bent has received honoraria from Merck Sharp & Dohme Corp. The author & remaining co-authors have no potential Conflict of Interest.

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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.

Keywords

Radiotherapy; EORTC; RTQA; Anaplastic glioma; Individual Case Review; phase III trial

Introduction

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 in 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 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 incompliance 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 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 constraints 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; Hagendorn, 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) are 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 distributed into the following treatment arms after surgery: RT alone (n=12), RT+concomitant TMZ (n=23), RT+adjuvant TMZ (n=19), RT+concomitant, TMZ+adjuvant TMZ (n=8).

Figure 1 presents the overall grading case and subsections grading. The overall grading for per protocol, acceptable variation and unacceptable variation was, respectively, 22/62 (35.5%), 11/62 (17.7%) and 29/62 (46.8%) of cases (Fig. 1). The most common unacceptable variations were related to the “PTV dose grading” (n=19, 30.6%) and “Volume definition grading” (n=17, 27.4%) subsections. Tables 1-4 present detailed information about RT parameters for each subsection. Illustrative examples of unacceptable cases can be observed in Fig. 2.

All patients were properly immobilized and scanned for planning purposes (Table 1). Fifty-five (88.7%) of 62 cases reported CT slice thickness according to protocol (as stated in the appendix). No IV contrast was used in 47 (75.8%) of 62 patients. MRI was supplied in 49 cases and proper co-registration (acceptable parameter) was performed in only 21 (42.9%) patients.

Most unacceptable variations in the volume definition subsection (n=17) were due to improper GTV (n=9, 14.5%), CTV (n=12, 19.3%), PTV (n=9, 14.5%) and OARs (n=1, 1.6%) contours. In all reviewed cases, acceptable variations for most OAR delineations was observed and it was independent of the overall grading (Table 2, Fig. 1).

In the assessment of the treatment plan and “PTV dose grading” subsection (Table 3), 19 cases were classified as unacceptable due to unacceptable dose distribution for the PTV parameter (n=19). Seven cases had acceptable variations in this subsection which were related to PTV dose distribution (n=7) and RT technique employed (n=1) parameters.

While individual OARs dose constraints were evaluated as per protocol or (un)acceptable variation, a global assessment was also provided for all OARs as a whole, taking into account the presence and quality of outlined OARs, overall reviewers' experience and consensus. Overall dose constraints for OAR were as follow: per protocol (n=15, 24.2%), acceptable variation (n=34, 54.8%) and unacceptable variation (n=13, 21.0%). Most investigators did not delineate uninvolved brain (n=26, 41.9%) or it was not delineated per protocol (n=34, 54.8%).

In the treatment delivery subsection (table 4), dose prescription was per protocol in 55 of 62 (88.7%) cases, 1 (1.6) case was considered unacceptable and 6 (9.7%) cases were acceptable variations. Overall treatment time was per protocol in 55 cases, acceptable variation in 5 cases and unacceptable in 1 case. Imaging verification protocol information was not available in 18 cases (29%) and only 2 cases (3.2%) were considered an unacceptable variation. The overall grading for the treatment delivery subsection was the following: 37

cases were per protocol, 20 cases classified as acceptable variations and 5 cases considered as unacceptable variations.

Discussion

This ICR analysis shows that only a minority of patients accrued into this prospective trial was treated per protocol. This is disquieting, as it has been shown that protocol deviations will have an impact on the study endpoint[10] and outcome of patients accrued into prospective protocols[9]. These observed variations could trigger loss of tumor control and/or an increase in radiation-induced toxicity[9, 10]. As in the TROG 0202 study, it could well be that by coincidental bad luck more deviations would happen on the experimental arm, thus potentially corrupting endpoints of this trial. In the light of the importance of the study hypothesis addressed by the current study, the substantial resources invested in this trial and the potential detrimental effect on patients' outcome, that possibility is troubling.

Most of the unacceptable delineations were related to target volume delineation and a significant amount of acceptable variations were related to inconsistent OAR outlining. These points emphasize once more that delineation is the weakest process in radiotherapy planning/delivery for both clinical trials and routine practice[18]. The amount of delineation variations could be explained through multiple complementary hypotheses (1) there is no widespread international consensus nor atlas for anaplastic glioma delineation or its spread compared to other pathologies (eg.: head and neck) is lower; (2) OARs delineation could have performed without being properly supervised by trained physician and (3) there was no mandatory benchmark case exercise before institution approval for accruing patients and lastly (4) delineation is a difficult process to detail in a RTQA textual section of a protocol. Multiple initiatives are being developed to tackle these issues: proper guidelines (e.g: delineation for glioblastomas)[19], further education for clinical trials and current practice[20]. The EORTC radiation oncology group encourages reporting ICRs in real time, so that actions can be taken to prevent and correct incompliance that may have an impact on tumor control or toxicity. Likewise, the frequency of un-submitted datasets would decrease since fast uploads are demanded for prospective reviews. The results also show that planning and dosimetry variations are less common than delineation variations. Most PTV dose unacceptable variations are radiation under-coverage cases and it was related with (1) OARs protection and/or (2) 3D-CRT limitations to cover PTV irregular contour shape. Prospective ICRs and benchmark cases before institution activation could help to mitigate the occurrence of these variations.

As mentioned, the high incompliance with the 1st patient randomized could be explained by the fact that no benchmark case exercise was conducted before patient accrual[21, 22]. However, the impact of benchmarking and prevention of future protocol non-compliance is questionable and there are conflicting results from other publications who address this issue[23].

No further ICRs beyond the first patient treated were requested or analyzed and we cannot thus evaluate the quality of the treatment for all patients treated within the trial. Additionally, we cannot assess if the number of patients accrued per center was a significant predictive

factor for RT deviations, as other groups have shown[10, 24]. Additionally, our report does not include RTOG and NCIC institutions which perform RTQA with their own national guidelines. The assessment for institutions RT improvement along accrual time cannot be determined. Even in absence of some RT parameters not being assessable due to incomplete data, the cases reviewed still presented multiples inconsistencies related to volume delineation and dose distribution.

The prolonged time to perform the retrospective review for this trial could have impacted the type of assessment between reviewers. Discrepancies between reviewers can be observed depending on the professional background of the reviewer and the length of the RTQA review. This fact is known from inter-variation studies in radiotherapy and radiology independently of the setting. This potential issue was mitigated when a consensus between reviewers was imposed and cases were required to be additionally reviewed again to avoid discrepancies.

Further investigation must be performed to confirm correlation between the RTQA variations and the patient outcome. Analysis of the mature follow-up data is required.

In conclusion, a substantial number of unacceptable variations were observed which may impact tumor control and/or radiation-induced toxicity. The possibility of requesting planning modification before treatment start is of paramount importance. As such, new RT trials should have a prospective ICR component implemented as per EORTC RTQA strategic policy. This might somewhat consequentially increase the trial accrual complexity and costs. However, the continuously improving tools for trial RTQA may substantially reduce the RTQA workload and decrease the overall RTQA costs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Consensus grading for each subsections and overall

Fig. 2.

Examples of unacceptable cases observed during review. *Case A* is an unacceptable volume (target and organ at risk) definition case, in which displays incorrect delineation of the brainstem (brown), PTV (red) is not based on CTV (target volume not found) and GTV (green) does not involve all hypodense areas in the CT scan. *Case B* is an unacceptable case for PTV Dose, in which the PTV (marked in red) is undercovered by the isodose lines 95% (yellow) and 90% (blue), and histogram shows PTV D95=86%. *Case C* is an unacceptable case for dose in OARs, in which displays a Dmax=61.62 Gy for brain stem.

Table 1.

Results from ICR review – Planning Procedure subsection

Parameters	Per protocol	Acceptable variation	Unacceptable variation	Assessment not possible
<i>Patient immobilized</i>	62	0	0	0
<i>Relocation accuracy</i>	54	0	0	8
Planning Procedure: all (n=62)				
<i>CT planned</i>	62	0	0	0
<i>Planning CT slice thickness</i>	55	6	0	1
<i>Use of contrast for planning CT</i>	15	47	0	0
<i>Co-registration of planning CT and MRI</i>	21	4	0	37
<i>Patient immobilized</i>	38	0	0	0
<i>Relocation accuracy</i>	35	0	0	3
Planning Procedure: per protocol (n=38)				
<i>CT planned</i>	38	0	0	0
<i>Planning CT slice thickness</i>	36	1	0	1
<i>Use of contrast for planning CT</i>	12	26	0	0
<i>Co-registration of planning CT and MRI</i>	15	2	0	21
<i>Patient immobilized</i>	24	0	0	0
<i>Relocation accuracy</i>	19	0	0	5
Planning Procedure: acceptable variation (n=24)				
<i>CT planned</i>	24	0	0	0
<i>Planning CT slice thickness</i>	19	5	0	0
<i>Use of contrast for planning CT</i>	3	21	0	0
<i>Co-registration of planning CT and MRI</i>	6	2	0	16

Table 2.

Results from ICR review – Volume definition subsection

	Parameters	Per protocol	Acceptable variation	Unacceptable variation
Volume definition:all (n=62)	<i>GTV</i>	46	7	9
	<i>CTV</i>	41	9	12
	<i>PTV</i>	45	8	9
	<i>All appropriate OARs delineated</i>	6	55	1
Volume definition: per protocol (n=18)	<i>GTV</i>	17	1	0
	<i>CTV</i>	16	2	0
	<i>PTV</i>	18	0	0
	<i>All appropriate OARs delineated</i>	4	14	0
Volume definition: acceptable variation (n=27)	<i>GTV</i>	22	5	0
	<i>CTV</i>	23	4	0
	<i>PTV</i>	21	6	0
	<i>All appropriate OARs delineated</i>	0	27	0
Volume definition: unacceptable variation (n=17)	<i>GTV</i>	7	1	9
	<i>CTV</i>	2	3	12
	<i>PTV</i>	6	2	9
	<i>All appropriate OARs delineated</i>	2	14	1

Table 3.

Results from ICR review – Treatment Plan & PTV Dose subsection

	Parameters	Per protocol	Acceptable variation	Unacceptable variation
Treatment Plan & PTV Dose: all (n=62)	<i>Beam Energy</i>	62	0	0
	<i>Beam arrangement</i>	61	1	0
	<i>Technique</i>	56	1	5
	<i>PTV Dose distribution</i>	32	11	19
Treatment Plan & PTV Dose: per protocol (n=36)	<i>Beam Energy</i>	36	0	0
	<i>Beam arrangement</i>	36	0	0
	<i>Technique</i>	36	0	0
	<i>PTV Dose distribution</i>	32	4	0
Treatment Plan & PTV Dose: acceptable variation (n=7)	<i>Beam Energy</i>	7	0	0
	<i>Beam arrangement</i>	7	0	0
	<i>Technique</i>	6	1	0
	<i>PTV Dose distribution</i>	0	7	0
Treatment Plan & PTV Dose: unacceptable variation (n=19)	<i>Beam Energy</i>	19	0	0
	<i>Beam arrangement</i>	18	1	0
	<i>Technique</i>	14	0	5
	<i>PTV Dose distribution</i>	0	0	19

Table 4.

Results from ICR review – Treatment delivery subsection

	Parameters	Per protocol	Acceptable variation	Unacceptable variation	Not reported for assessment
Treatment delivery: all (n=62)	<i>Total dose delivered</i>	55	6	1	0
	<i>Number of fractions</i>	55	6	1	0
	<i>Fraction size</i>	55	6	1	0
	<i>Overall treatment time</i>	55	5	1	1
	<i>Treatment verification</i>	42	0	2	18
Treatment delivery: per protocol (n=37)	<i>Total dose delivered</i>	36	1	0	0
	<i>Number of fractions</i>	36	1	0	0
	<i>Fraction size</i>	36	1	0	0
	<i>Overall treatment time</i>	34	2	0	1
	<i>Treatment verification</i>	33	0	0	4
Treatment delivery: acceptable variation (n=20)	<i>Total dose delivered</i>	15	5	0	0
	<i>Number of fractions</i>	15	5	0	0
	<i>Fraction size</i>	15	5	0	0
	<i>Overall treatment time</i>	17	3	0	0
	<i>Treatment verification</i>	7	0	0	13
Treatment delivery: unacceptable variation (n=5)	<i>Total dose delivered</i>	4	0	1	0
	<i>Number of fractions</i>	4	0	1	0
	<i>Fraction size</i>	4	0	1	0
	<i>Overall treatment time</i>	4	0	1	0
	<i>Treatment verification</i>	2	0	2	1