

Radiotherapy quality assurance of the IAEA-HypoX trial of the accelerated radiotherapy in the treatment of head and neck squamous cell carcinoma with or without the hypoxic radiosensitizer nimorazole

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To the Editor,

Radiotherapy quality assurance (RTQA) programs attempt to validate the assumption that all patients who are treated with radiotherapy (RT) in a clinical trial have received uniform treatment according to the protocol guidelines, and to quantify the extent of any deviations from these guidelines. Thus, RTQA measures are used as a tool to prospectively standardize treatment or to check retrospectively the treatment compliance to guidelines in clinical trials [1]. Such assumption of treatment uniformity requires a precise and clear definition of RT treatment guidelines in the trial protocol [2].

QA programs result in improvement of practice quality, and are considered an important element in any clinical trial, which are required to confirm credibility of trial results and to introduce its outcome into practice. Several trials have showed that implementation of RTQA programs enhances the compliance with RT protocols [3–10]. However, poor RT quality in clinical trials might result in poorer trial outcome [9–11], or hides the potential benefit of an investigated treatment [10].

The IAEA-HypoX trial was a multicenter and multinational clinical trial, conducted in six centers, which randomized patients with head and neck squamous cell carcinoma (HNSCC) to accelerated fractionated RT with or without the hypoxic radiosensitizer, nimorazole [12]. The trial was initiated by International Atomic Energy Agency (IAEA) as part of its activities in promoting the peaceful uses of atomic energy in the field of cancer treatment, under its Program of Action for Cancer Therapy (PACT) initiative [13]. The trial was conducted in collaboration between IAEA and DAHANCA (Danish Head and Neck Cancer) group. The trial opened for recruitment in March 2012 and closed for recruitment prematurely in May 2014 due to insufficient recruitment rate. The final number of evaluable patients was 82 patients, recruited from four different centers.

The purpose of this study was to measure the amount of deviations from protocol guidelines, and to validate the assumption that radiation treatment administered to patients in the IAEA-HypoX trial was adherent to these guidelines.

Material and methods

The IAEA-HypoX study was planned in six centers, situated in four different countries. Two centers were excluded from the final analysis, due to marked insufficiency of data and lack of communication from the local investigators. The RTQA review was conducted in all participating centers, but this report represents only outcome from the four centers that contributed to the final analysis. The trial was

designed according to Helsinki declaration and was approved by ethics committees and health authorities in the participating countries. More details of the trial design, treatment, stratification and randomization procedures are available in the original reporting paper and its supplementary material [12].

In both arms, patients received accelerated fractionated RT in 6 fractions per week, for a total dose of 66–70 Gy/33–35 fractions, 2 Gy/fraction, to the gross tumors. The dose to the elective areas had to be at least 46 Gy, and the maximum allowable dose to the spinal cord was 50 Gy (point dose). The first five weekly fractions were given during weekdays, and the sixth fraction was given on either a weekend day or as a second fraction in one of the weekdays, but always allowing for at least 5.5 hours interval. RT was planned with either a conventional (2D) planning technique on an x-ray simulator, or using computed tomography (CT)-based planning techniques, i.e. three-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT). Doses were prescribed and reported according to the guidelines of the ICRU-50 and ICRU-83 reports.

A retrospective RTQA review of the first five recruited patients from each center was conducted. The centers were asked to send a copy of each of the following: dose prescription sheet, daily treatment record sheet, x-ray simulator films (for 2D planning technique). Moreover, dose-volume histogram (DVH), beam eye views and DICOM files of the planning CT images, volumes delineation and beams arrangement (for 3D-CRT and IMRT techniques).

The treatment plans and documentations were evaluated by a senior radiation oncologist in the Department of Clinical Oncology, Aarhus University Hospital, Denmark. CT-based plans (3D-CRT and IMRT) were visualized by computer-based virtual software, VERT software v. 2.8 (Virtual Limited, UK). VERT software provided a realistic virtual environment of a RT treatment room, and was able to display patient contours, CT planning images, RT beams, and surface dose color wash.

Protocol specified compliance/deviation criteria were evaluated in seven RT components: target volumes definition [planning target volumes (PTVs) and organs at risk (OAR)], RT beams arrangement, planned and received doses (total dose to ICRU point in 2D RT, and mean dose to PTVs in CT-based planning RT), fractionation schedule, dose to critical structures (spinal cord and brain stem), homogeneity in dose distribution (in 3D-CRT and IMRT) measured in term of homogeneity index, and overall treatment time.

Each of the previously mentioned RT components was categorized into one of three documented entries: per protocol, minor deviation, or major

Table I. Number of minor and major deviations in the first five fully-reviewed cases, in each center, per each RTQA component.

	Center A (5)	Center B (5)	Center C (5)	Center D (5)
RT treatment technique	2D (5/5)	2D (5/5)	IMRT (5/5)	IMRT (5/5)
1. Target volumes definition				
Minor	0/5	0/5	0/5	2/5
Major	0/5	0/5	0/5	0/5
2. RT beam arrangement				
Minor	0/5	0/5	0/5	0/5
Major	0/5	0/5	0/5	0/5
3. Dose to target volumes				
Minor	0/5	0/5	2/5	1/5
Major	0/5	0/5	0/5	0/5
4. Fractionation schedule				
Minor	0/5	0/5	0/5	1/5
Major	0/5	0/5	0/5	0/5
5. Dose to critical structures (spinal cord and brain stem)				
Minor	0/5	0/5	0/5	0/5
Major	0/5	0/5	0/5	0/5
6. Homogeneity in dose distribution				
Minor	-	-	0/5	0/5
Major	-	-	0/5	0/5
7. Overall treatment time				
Minor	1/5	0/5	1/5	1/5
Major	2/5	0/5	0/5	1/5
Total deviations				
Minor	1/30	0/30	3/35	5/35
Major	2/30	0/30	0/35	1/35
No. of patients with deviations				
Minor	1/5	0/5	3/5	3/5
Major	2/5	0/5	0/5	1/5

deviation. Minor deviation was defined as a deviation that was unlikely to be of significance for the treatment outcome, whereas a major deviation was defined as a deviation that was likely to be of significant effect for the treatment outcome. For the measurable RT components (i.e. target doses, homogeneity index, and overall treatment time), minor and major deviations were defined as $\geq 3\%$ – $< 5\%$ and $\geq 5\%$ deviation from the protocol specified values, respectively. More details of the RTQA specified criteria are available in the RTQA protocol (Supplementary material, available online at <http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2015.1074721>).

A feedback report was sent to each center following the review of each case. The report included a list of all observed deviations with their categories. In case of minor deviations, centers were asked to send their explanation to the observed deviations; while in case of major deviations in the planning part of radiation treatment, centers were asked to send extra cases for review instead of the cases with major deviations, after correction of the treatment plans.

Results

A total of 21 patients were submitted for RTQA review. One patient treated with an IMRT plan in

one center, was not fully reviewed due to technical difficulty in exporting the DICOM files of the treatment plan, and sending them to the RTQA office for reviewing volumes' definition and dose distribution. The center decided to stop planning further cases with IMRT technique due to frequent machine breakdown, which resulted in prolongation of the overall treatment time of the first IMRT case. Twenty patients were fully reviewed for compliance with RT treatment guidelines, with a total of five patients from each of the four participated centers.

All patients that recruited in the IAEA-HypoX trial from centers A and B were planned with 2D planning technique; while all patients from centers C and D, were planned with IMRT planning technique, except one patient from center D who was planned with 3D-CRT. For each 2D planned patient, six RTQA components were reviewed with a total of 30 entries in the five reviewed patients from each center. While, for each 3D-CRT/IMRT planned patient, seven RTQA components were reviewed with a total of 35 entries in the five reviewed patients from each center. Hence, a total of 130 RTQA entries were documented in the 20 patients submitted from the four centers for the RTQA review (Table I).

Table I shows the number of minor or major deviations for each RTQA component, in each of the

four centers. The first five reviewed patients from centers A and B were all treated with 2D RT; while those from centers C and D were all treated with IMRT technique. As a whole, eight of 130 entries were minor deviations (6.1%) and three of 130 entries were major deviations (2.3%), as defined by the RTQA protocol. Overall, 11 of 130 RTQA entries were either minor or major deviations (8.5%).

In center A, using 2D RT planning, a minor deviation was detected, caused by prolongation of the overall treatment time. The prolonged overall treatment time was explained by occurrence of treatment interruption due to patient non-compliance which remained unexplained. The two major deviations in the same center were due to prolongation in the overall treatment time, due to uncorrected treatment interruptions. The interruption was in the last two days of treatment in one patient, and was due to public holiday in the last week of treatment in the other patient. In center B, all patients were treated with 2D RT and there were no minor or major deviations in the first five reviewed patients.

In center C, three minor deviations were detected in the first five patients. One deviation was prolonged overall treatment time caused by unexplained and uncorrected treatment interruption for one day, while the other two deviations were due to minor increase in the mean dose to the tumor PTV in two different patients.

In center D, one minor deviation was in the overall treatment time due to uncorrected treatment interruption, which was explained by alcohol abuse. Two minor deviations were in the definition of target volumes in two different patients. The other major deviation in another patient was in the overall treatment time. The deviation was explained by the occurrence of influenza and pneumonia during the treatment course, which resulted in marked prolongation of the overall treatment time.

Discussion

The IAEA-HypoX trial was a pragmatic clinical trial [14,15]. It attempted to provide evidence for the effectiveness of nimorazole in daily practice. Hence, the trial protocol allowed the use of different and diverse RT techniques, according to the available institutional facilities. A QA audit conducted by Trans-Tasman Radiation Oncology Group (TROG) demonstrated a reduction in unacceptable protocol deviations due to implementation of the RTQA procedures itself [4]. Thus, the primary aim of the current RTQA program was to avoid poor quality RT. The first step of the RTQA program was aiming to ascertain the clear understanding of protocol guidelines by the local investigators. Accordingly, there were substantial

correspondences between the centers and the clinical trial office in Aarhus, following the submission of the first treatment plans for RTQA review, which resulted in better understanding of the protocol specifications and in preventing any future unacceptable violations.

A dummy run procedure was planned in the RTQA protocol to be conducted in the centers using CT-based planning techniques. However, technical difficulties connected with the procedure hindered its implementation. The dummy run was replaced by virtual evaluation of the treatment plans using VERT software, with the advantage of reviewing the actually recruited patients in the trial. The initial step of the planned RTQA program included 20 patients of the evaluable 82 patients in the IAEA-HypoX trial. This means that about 24% of patients, who contributed to the final analysis of the trial outcome, were reviewed in the RTQA program. The RTQA review showed that 119 of the 130 RTQA entries were classified as protocol compliant (i.e. per protocol). This represents about 92% overall compliance, which is considered sufficient to provide reliable clinical results from the trial.

In IAEA-HypoX study, the goal of the RTQA program was to review at least 10% of patients that recruited from each center. As the first five patients from each center represented 10% of the first 50 recruited patients from that center, no further patients were required for RTQA review due to the premature closure of the study and the low number of patients from each center (i.e. no center with more than 50 recruited patients).

The study revealed only three entries, of the 130 entries, classified as major deviations in three different patients. The three deviations were all in the overall treatment time due to uncorrected treatment interruptions. None of the major deviations were found in the RT planning part of treatment in any of the centers. The previously mentioned distribution of major deviations demonstrates that all centers performed the treatment planning in high compliance with protocol guidelines, and non-compliances were basically due to out-of-control reasons.

In conclusion, the results of the RTQA program showed that centers performed a good quality RT, which was adherent to the protocol guidelines. Overall compliance of about 92% confirms credibility of presented clinical results.

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