Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Quality assurance of radiotherapy in the ongoing EORTC 1219-DAHANCA-29 trial for HPV/p16 negative squamous cell carcinoma of the head and neck: Results of the benchmark case procedure

Melissa Christiaens [a,b,*], Sandra Collette [a], Jens Overgaard [c], Vincent Gregoire [d], Joanna Kazmierska [e], Pierre Castadot [f], Jordi Giralt [g], Warren Grant [h], Milan Tomsej [f], Raquel Bar-Deroma [i], Angelo F. Monti [j], Coen Wilhelm Hurkmans [k,l], Damien Charles Weber [k,m,n]

[a] EORTC HQ, Brussels; [b] Department of Radiation Oncology, University Hospital Leuven; [c] Department of Radiation Oncology, Aarhus University Hospital; [d] Department of Radiation Oncology, Université Catholique de Louvain, St-Luc University Hospital, Brussels, Belgium; [e] Radiation Oncology, Greater Poland Cancer Centre, Poznan, Poland; [f] Radiation Oncology, CHU Charleroi, Belgium; [g] Radiation Oncology, Hospital General Vall D'Hebron, Barcelona, Spain; [h] Oncology Centre, Cheltenham General Hospital, Gloucestershire Hospitals NHS Foundation Trust, UK; [i] Radiation Oncology, Rambam Health Care Campus, Haifa, Israel; [j] Department of Medical Physics, Ospedale Niguarda Ca' Granda, Milan, Italy; [k] ROG RTQA Strategic Committee, EORTC, Brussels, Belgium; [l] Radiation Oncology, Catharina Hospital, Eindhoven, The Netherlands; [m] Center for Proton Therapy, Paul Scherrer Institute, Villigen; and [n] University of Zürich, Switzerland

ARTICLE INFO

Article history:
Received 10 June 2015
Received in revised form 17 April 2017
Accepted 17 April 2017
Available online xxxx

Keywords:
Quality assurance
Radiotherapy
Head and neck cancer

ABSTRACT

Background and purpose: The phase III EORTC 1219-DAHANCA 29 intergroup trial evaluates the influence of nimorazole in patients with locally advanced head and neck cancer when treated with accelerated radiotherapy (RT) in combination with chemotherapy. This article describes the results of the RT Benchmark Case (BC) performed before patient inclusion.

Materials and methods: The participating centers were asked to perform a 2-step BC, consisting of (1) a delineation and (2) a planning exercise according to the protocol guidelines. Submissions were prospectively centrally reviewed and feedback was given to the submitting centers. Sørensen–Dice similarity index (DSI) and the 95th percentile Hausdorff distance (HD) were retrospectively used to evaluate the agreement between the centers and the expert contours.

Results: Fifty-four submissions (34 delineation and 20 planning exercises) from 19 centers were reviewed. Nine (47%) centers needed to perform the delineation step twice and three (16%) centers 3 times before receiving an approval. An increase in DSI-value and a decrease in HD, in particular for the prophylactic Clinical Target Volume (pCTV), could be found for the resubmitted cases. No unacceptable variations could be found for the planning exercise.

Conclusions: These BC-results highlight the need for effective and prospective RTQA in clinical trials. Even with clearly defined protocol guidelines, delineation and not planning remain the main reason for unacceptable protocol variations. The introduction of more objective quantitative analysis methods, such as the HD and DSI, in future trials might strengthen the evaluation by experts.

Head and neck cancer remains the fifth most common malignancy worldwide, with more than 40% of patients presenting with locally advanced disease [1]. Several modifications of standard radiotherapy (RT) for squamous cell head and neck cancer, such as acceleration and hyperfractionation, addition of a hypoxic modification and/or chemotherapy have markedly improved outcomes in terms of locoregional control, laryngectomy-free, disease specific and overall survival [1–3].

Previous trials performed by the Danish Head and Neck Cancer (DAHANCA) group indicate an improved outcome when combining nimorazole – a 5-nitroimidazole, which was developed in the mid-1980s as a hypoxic radiosensitizer – and RT [4,5]. The combination of accelerated RT, nimorazole and weekly chemotherapy was shown to be feasible and gave superior outcome in comparison with previous reported data in both HPV/p16 negative and positive tumors [6]. This regime has subsequently become standard treatment for Danish head and neck cancer patients. The current European Organisation for Research and Treatment of Cancer (EORTC) 1219 – DAHANCA 29 phase III trial investigates the value of adding nimorazole to chemoradiation treatment and in addition the

* Corresponding author at: Department of Radiation Oncology, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium.
E-mail address: melissa.christiaens@uzleuven.be (M. Christiaens).

http://dx.doi.org/10.1016/j.radonc.2017.04.019
0167-8140/

prognostic and predictive value of hypoxic gene profiling in HPV/p16 negative tumors.

Radiation Therapy Quality Assurance (RTQA) procedures are an essential part of the conduct of clinical trials to ensure that the treatment is delivered in accordance with the protocol [7–11].

In the whole RT process, one of the limiting factors remains delineation accuracy: important interobserver and even intraobserver variability exist in defining RT volumes. The introduction of a Benchmark Case (BC) and Individual Case Reviews within the RTQA process has been shown to lead to more homogeneous contouring among the participating sites [9–12]. In addition, the BC procedure is a crucial step to detect ambiguities and systemic errors in the trial protocol, before inclusion of any patient within the trial [13]. Earlier, a BC-analysis in head and neck cancer was performed for the EORTC 22071–26071 study. This showed overall dismal results in passing the BC step [14]. This current analysis was performed in the hope to see an improvement in passing a BC procedure in head and neck cancer. In this report, the results of the two-step BC procedure of the EORTC 1219-DAHANCA-29 trial are presented.

Materials and methods

The Benchmark case procedure

The participating centers were supplied with the case history, accompanied by a drawing of the clinical and endoscopic examination, diagnostic Magnetic Resonance Imaging (MRI) and planning contrast enhanced Computed Tomography (CT) dataset with 2 mm slice thickness for a test patient, with – according to the Union for International Cancer Control (UICC) – a cT2N2bM0 histologically confirmed grade II p16-negative squamous cell carcinoma of the oropharynx, who would have been eligible for this trial.

In the first step the centers were instructed to define the target and organs at risk (OAR) volumes in accordance with the trial protocol and were supplied with a supplementary delineation atlas [15,16]. After approval of this delineation exercise, expert contours for performing the second step were provided to the centers, which were asked to create a protocol compliant treatment plan.

Submission was performed by the upload of the anonymized digital data (CT, structures, dose and plan data in DICOM-RT format) to the EORTC secured central server. The submissions were assessed by the trial specific RTQA reviewers (3 radiation oncologists and 3 medical physicists) using the VodcaRT software package (Visualization and Organization of Data for Cancer Analysis, version 4.2.3-Medical Software Solutions GmbH; Hagendorm, Switzerland). Submissions were classified as 'per protocol', 'acceptable variations with comments for future cases' or 'unacceptable variations, requiring modification and resubmission' as per the 'Global Harmonisation Group' guidelines [17,18]. Each factor of evaluation was upfront subdivided within this classification by the expert reviewers based on discussion and the requirements mentioned in the protocol. The first 10 BCs were reviewed by all reviewers. As a consensus in evaluation of the BCs was seen between the reviewers, the decision was taken that the subsequent BCs would be reviewed by only one radiation oncologist and one medical physicist. After the comments were collected, centers were provided with individual feedback along with either an approval or a request for resubmission.

Radiotherapy guidelines

Two clinical target volumes (CTV) were defined in this trial: the first CTV, the so-called therapeutic dose CTV (tCTV), includes the primary tumor – Gross Tumor Volume (GTV) – with a security margin of 8 mm and the involved nodes with a margin of 7 mm. The second CTV, the so-called prophylactic dose CTV (pCTV), includes the tCTV and all nodal levels at risk for microscopic infiltration. These nodal levels need to be delineated according to the guidelines defined by a consensus panel for the node-negative and the node-positive neck irrespective of the primary tumor T-stage [15,16].

A CTV to Planning Target Volume (PTV) margin was to be implemented to take into account patient set-up uncertainties. This margin was to be selected by each participating center depending on their equipment, irradiation techniques and experience. Typically, for patients immobilized with a head-neck and shoulder fixation device, a 3–5 mm margin was thought to be adequate. Reduction of the CTV to PTV margin in the direction of the skin was allowed to reduce the skin toxicity.

The spinal cord, brain stem and parotid glands were to be contoured as OAR. The delineation of the larynx and oral cavity was optional but strongly advised. For the spinal cord and the brain stem a planning organ at risk volume (PRV) margin had to be generated, adding a margin that was to be selected based upon the center's equipment, irradiation techniques and experience. A 3–5 mm margin was thought to be appropriate.

A total dose of 70 Gy in 35 fractions 6 times a week was to be delivered to the therapeutic PTV (tPTV) and 54.25 Gy in as many fractions to the prophylactic PTV (pPTV) using simultaneous integrated boost intensity modulated RT (SIB-IMRT) delivered by static or dynamic techniques. Details of the protocol dosimetric requirements related to CTV, PTV and OAR can be found in the electronic appendices.

Contour analysis

The Sørensen–Dice Similarity Index (DSI) and the 95th percentile Hausdorff distance (HD) were calculated retrospectively and used to evaluate the spatial overlap between the participating center's delineations of CTVs and the expert contours. They were not used as factors for evaluation of the submissions. The contours of each center were evaluated as to whether they conformed to the requirements of the protocol, without making comparison of each contouring structure to the expert contours.

The DSI was calculated based upon the following formula: $DSI = 2 * A \cap B/A + B$, with A and B representing the volumes of the contoured region of interest performed by the expert and one of the centers, respectively. The value of DSI ranges from 0, indicating no spatial overlap, to 1, indicating complete overlap between the 2 contoured regions [19–22].

The HD is the greatest of all the distances from a point in one contour surface to the closest point in the other contour surface and was calculated on the Segment Comparison extension for 3DSlicer; details of this software have been published earlier [23,24]. The ideal case with perfect alignment is when the HD is equal to zero. The choice for the 95th percentile Hausdorff distance was made to minimize the impact of large outliers.

Results

Nineteen centers submitted a total of 54 BCs: 34 for the delineation and 20 for the planning exercise.

Delineation

Seven (37%) centers managed to successfully pass this first step in one try. All the other 12 centers (63%) were rejected due to incorrect selection of the prophylactic lymph node regions. Five centers (26%) had additionally used incorrect margins from GTV to CTV and two (10%) had not delineated some of the mandatory OAR. Nine (47%) centers needed to resubmit their case once and

Please cite this article in press as: Christiaens M et al. Quality assurance of radiotherapy in the ongoing EORTC 1219-DAHANCA-29 trial for HPV/p16 negative squamous cell carcinoma of the head and neck: Results of the benchmark case procedure. Radiother Oncol (2017), http://dx.doi.org/10.1016/j.radonc.2017.04.019