Quality assurance of radiation therapy for head and neck cancer patients treated in DAHANCA 10 randomized trial

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To the Editor,

Previous studies have shown that poorly executed radiotherapy in clinical trials may potentiality obscure the benefits of a new treatment technique or drug [1] or significantly change the clinical outcome as reviewed by Ohri et al. [2]. For this reason, numerous quality assurance (QA) programs have been setup to ensure that the basic radiation treatment technique is of high and homogeneous quality [3–11]. Also, several meta-analyses, reviews, and editorials have stressed the importance of pre-trial QA and even online independent case reviews to secure and document quality [12–18].

Since 1990, the Danish Head and Neck Cancer Group (DAHANCA) has produced national guidelines for radiotherapy of head and neck cancer. The DAHANCA QA group sought to evaluate whether the quality of radiation treatment in different centers lived up to these recommendations by monitoring the performance of radiotherapy in a prospective clinical trial.

DAHANCA 10 was a multicenter, double-blind, randomized, placebo-controlled phase III trial on darbepoetin-α concurrently with radiotherapy for squamous cell carcinoma of the head and neck (HNSCC) carried out by DAHANCA. Patients were recruited from 2002 to 2006, but the trial was stopped after a planned interim analysis in 2006 because of a superior three-year loco-regional control rate in favor of the control group [19].

The purpose of this study was to audit whether the dose prescriptions and technical components were in adherence to the DAHANCA radiation treatment guidelines as delivered by the five Danish centers involved in head and neck cancer radiotherapy for patients enrolled in DAHANCA 10.

Material and methods

An expert panel consisting of one senior radiation oncologist and one experienced medical physicist from each of the five Danish centers in DAHANCA formed a retrospective quality assurance scheme (QAS) in which the quality of the radiotherapy was assessed in accordance with the DAHANCA radiation treatment guidelines of January 2002 and September 2004, including guidelines for intensity-modulated radiotherapy (IMRT). The guidelines are available at www.DAHANCA.oncology.dk. The expert panel had three site visits, where patients were audited including patients from the host center. Not all members of the panel were present at all the visits. Four of the centers used Varian/Eclipse and one center Elekta/Pinnacle.

In the QAS, 29 clinical and technical components, derived from the DAHANCA radiotherapy guidelines, were reviewed within the following areas: Delineation of gross tumor extension and lymph node levels, delineation of organs at risk (OARs), definition of planning risk volumes (PRVs), appropriate margin expansion, target dose coverage [planning tumor volume (PTV)-tumor/PTV-elective], dose per fraction, fractions per week, overall treatment time and fixation devices. All components are listed in Table I, including per protocol, minor and major deviation criteria.

Each of the components was documented by patient record notes and individual radiation treat-

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ment plans. Subsequently, a central consensus audit was performed by the review board who evaluated the 29 different components, including all three-dimensional (3D) dose plans, and compared them to the recommendations of the DAHANCA guidelines.

All clinical and technical components and each treatment plan were classified within four categories:

1. Full compliance to protocol guidelines;
2. Minor deviations;
3. Major deviations;
4. Not relevant (e.g. OAR not close to the treated area).

Minor deviations were defined as deviations unlikely to be of significance for the treatment outcome, whereas major deviations were defined as deviations increasing the risk of treatment failure significantly.

From 522 patients in DAHANCA 10, a subgroup of 53 patients were randomly selected by the DAHANCA secretariat, i.e., 10–11 patients were

Table I. Quality assurance scheme formed by the DAHANCA QA expert panel.

Audit object	Per protocol	Minor deviation	Major deviation
General components			
Fixation	Yes		No
CTV-T prescription	68 or 66 Gy		Anything else
CTV-E prescription	50, 48 or 46 Gy		Anything else
Dose per fraction	2.0–1.5 Gy per fraction	2.2–1.3 Gy per fraction	$>$2.2 Gy per fraction or $<$1.3 Gy per fraction
Treatment length	$<$42 Calendar days	42–49 days	$>$49 days
Contouring components			
GTV	Visible tumor	Inaccurate contouring, e.g. including air	Missing clearly visible tumor
CTV-T	0–10 mm expansion of GTV excluding modifications	Inaccurate contouring, e.g. including air	Not including GTV
CTV-E 60 Gy	Including of CTV-T and not outside of patient	Outside of patient	Not including GTV and CTV-T
CTV-E 50 Gy	Recommended node levels	Outside of patient	Not including proper level
PTV-T	Proper expansion	Incorrect expansion	Expansion including incorrect organs
PTV-E	Proper expansion	Incorrect expansion	Expansion including incorrect organs
Brain stem	Visible OAR	Not contoured, but dose well below dose constraints	Not contoured, but dose close or over dose constraints
Spinal cord	Visible OAR	Spinal canal	Not contoured
Chiasm	Visible OAR	Not contoured, but dose well below dose constraint	Not contoured, but dose close or over dose constraint
Optical nerves	Visible OAR	Not contoured, but dose well below dose constraint	Not contoured, but dose close or over dose constraint
PRV Brain stem	Proper expansion	Incorrect expansion	Expansion including incorrect organs
PRV Spinal cord	Proper expansion	Incorrect expansion	Expansion including incorrect organs
PRV Chiasm	Proper expansion	Incorrect expansion	Expansion including incorrect organs
PRV Optical nerves	Proper expansion	Incorrect expansion	Expansion including incorrect organs
Dose constraints components			
Brain stem	$<$54 Gy	54–59 Gy	$>$59 Gy
Spinal cord	$<$50 Gy (2D and 3D) $<$45 Gy (IMRT)	50–55 Gy (2D and 3D) 45–50 Gy (IMRT)	$>$55 Gy (2D and 3D) $>$50 Gy (IMRT)
Chiasm	$<$54 Gy	54–59 Gy	$>$59 Gy
Optical nerves	$<$54 Gy	54–59 Gy	$>$59 Gy
PRV Brain stem	$<$60 Gy	60–65 Gy	$>$65 Gy
PRV Spinal cord	$<$50 Gy	50–55 Gy	$>$55 Gy
PRV Chiasm	$<$60 Gy	60–65 Gy	$>$65 Gy
PRV Optical nerves	$<$60 Gy	60–65 Gy	$>$65 Gy
PTV-T (Skin excluded)	95% of prescription dose to 98% of PTV-T, and 90% of dose to the remaining 2% of PTV-T	95% of prescription dose to 95% of PTV-T, and 90% of dose to the remaining 5% of PTV-T	$<$95% of prescription dose to $\geq$5% of PTV-T
PTV-E (Skin excluded)	95% of prescription dose to 98% of PTV-E, and 90% of dose to the remaining 2% of PTV-E	95% of prescription dose to 95% of PTV-E, and 90% of dose to the remaining 5% of PTV-E	$<$95% of prescription dose to $\geq$5% of PTV-E

extracted from each of the five Danish centers performing radiotherapy of HNSCC. The patients were equally distributed across the five centers, randomizations arms, and time of inclusion. Two patients were excluded, one with adjacent esophageal involvement, and one treated in collaboration between two hospitals where full information was unattainable, leaving 51 patients for detailed audit review. All reviews were undertaken without knowledge of the randomization arm of the patient.

The treatment techniques used were 2D radiotherapy (2D-RT) for seven patients, 3D conformal radiotherapy (3D-CRT) for 39 patients, and IMRT for five patients.

Results

A total of 1479 components in 51 patients were reviewed. Not all components were relevant for each patient which excluded 677 components, leaving 802 criteria for analysis.

The audit demonstrated full compliance to the guidelines in 95.5% (766/802) of the evaluated factors. Deviations were mainly associated with target dose coverage and a minor target dose coverage deviation was observed in 12 of 99 components concerning target coverage. In contouring, 95.6% (327/342) of the evaluated components demonstrated full compliance to the definitions. Correct fraction prescription was demonstrated in 50 patients. In five of the patients (9.8%), the total treatment duration surpassed 42 days which was scored as a minor deviation. The mean treatment length for these five patients was 42.8, ranging from 42 to 45 days.

Full compliance to guidelines was found in 29 of the patients (57%). Eighteen patients (35%) had minor deviations of which four had two minor deviations and four had three minor deviations. Two patients (4%) were found to have major deviations and two patients (4%) had both a major and a minor deviation.

Major deviations

Four observations in four different patients (7.8%) were regarded as major deviations: One patient was treated with 5 fractions per week despite being prescribed to 6 fractions per week. One patient with tonsillar carcinoma received 60 Gy after tonsillectomy where the guidelines recommended 66 Gy to the clinical target volume (CTV) of the tonsillar fossa. Two patients had T2 carcinoma of the vocal cord with tumor extension beyond the vocal cord. Both patients were treated without including elective nodal areas as prescribed in the guidelines.

At the time of the QA audit, all four patients were alive without evidence of recurrent disease.

Minor deviations

A total of 32 minor deviations were recorded out of 802 evaluated components (12%). Five of these were related to contouring of the brainstem. With boost fields in the region of the brainstem, the brainstem should have been contoured to verify that the dose was below 54 Gy. However, none of the five patients actually received 54 Gy or more when the brainstem was subsequently contoured during the audit.

In one patient receiving IMRT, the spinal cord and the associated PRV were not contoured as recommended. Here, the spinal canal was used as a proxy for the spinal cord and its associated PRV. Thus, a minor deviation was scored for both structures.

Six of the minor deviations were observed in the CTV and PTV contours. For two patients, the elective CTV contours were not delineated as recommended. In four patients, PTV expansions were not performed correctly in all directions.

Two minor deviations were related to prescription of dose to elective CTVs. One was associated with the major deviation described above of a patient receiving only 60 Gy to the tumor bed. The other patient was treated with IMRT with integrated boost, but only to 48 Gy in 33 fractions with 1.45 Gy per fraction, compared to the recommended minimum of 1.5 Gy per fraction.

Twelve of the treatment plans had minor dose coverage deviations. Four of these belonged to the high-dose PTV and eight to the elective PTV. There were no failures in dose coverage of the corresponding CTVs.

Five minor deviations were related to the overall treatment time exceeding the recommended maximum of 42 days.

The relative risk of minor deviations increased with increasing treatment complexity with 14%, 29% and 60% for 2D-RT, 3D-CRT, and IMRT, respectively.

Discussion

QA studies of radiotherapy trials in HNSCC have demonstrated improved tumor control and overall survival rates from good quality radiation performance in centers with a high throughput of patients [1,2]. Thus, high quality RT in the clinical and technical management of head and neck cancer treatment is important.

To support the clinical findings from the randomized DAHANCA 10 trial of darbepoetin and radia-

tion in HNSCC, the QA group of DAHANCA reviewed a subgroup of 10% of the study population to evaluate the quality of the radiation treatment. The patients were retrieved blindly from the DAHANCA secretariat and represented both treatment arms equally. All five Danish centers contributed to the study with a high proportion of patients, exceeding the number of enrolled patients in the best performing centers of the TROG trial [1]. Here, a predicted major adverse impact of treatment deviations on local tumor control of 5.4% (contribution of >20 patients) compared to 29.8% (contribution of <5 patients) was reported.

In our study, four observations in four patients (7.8%) were scored as major deviations from the radiotherapy guidelines by the QA panel. This is in line with the overall findings from the TROG trial (11%). In the meta-analysis of Ohri et al., radiotherapy deviations ranged from 8% to 71% reflecting a large variability in the definition of a minor or a major deviation between different studies which may be related to less strict deviation criteria and fewer factors being investigated.

The fraction of patients with minor deviations is closely related to the large number of factors investigated and the restricted tolerance levels for acceptance within each factor. From the DAHANCA 10 audit, it was evident that 2D-RT was subject to a less strict audit since the data available for auditing were limited. With only radiographic simulator images at hand, it was not possible to audit on contouring of targets and organs at risk. Therefore, target dose coverage in defined volumes was also not available and, consequently, not subject to investigation.

For some patients treated with 3D-CRT, the contours were created on computed tomography (CT) images, however, treatment plans were made from 2D digital reconstructed radiographs (DRR's) again limiting the available components for audit.

With the introduction of the DAHANCA IMRT guidelines in 2004, the number of QA components available for audit increased due to the more complex novel treatment technique. This introduced several new elements for audit including PRVs and it resulted in a relative high rate of minor deviations related to PRVs of the brain stem as well as to the spinal cord. This was also the case in the RTOG 0022 trial on IMRT for early stage oropharyngal cancer, where Eisbruch et al. [3] reported deviations in all patients evaluable (six major and 47 minor of 53). In the TROG trial [1], 47% of the patients were treated with 2D-RT and 53% with 3D-CRT while IMRT was not allowed in the trial.

The present study of curative radiotherapy for HNSCC demonstrated only few deviations (four major) from the recommended treatment guidelines and a low risk of predicted impact on tumor control or clinical outcome in organs at risk. All four major deviations were characterized by clinical decisions not strictly following the DAHANCA guidelines. None of the affected patients with major deviations in this study experienced recurrent disease. Two patients with T2 glottic carcinoma were treated without including elective nodal areas as recommended, however, it may be argued that the indication for elective treatment in this situation is weak due to a low propensity for neck recurrence. In contrast, it was decided to record treatment protraction exceeding 42 days as a minor deviation, though overall treatment time significantly reduced local tumor control. This touches on the dilemma of defining major and minor deviations in relation to treatment guidelines and whether protocol deviations may actually affect clinical outcome. The QA panel consisted of experienced physicians and radiation physicists who met at meetings and workshops to evaluate clinical and technical issues in all aspects of the head and neck radiation treatment which initiated a review of the DAHANCA guidelines that were published in 2013.

Irrespectively of how deviations are defined, the above mentioned QA trials seem to underscore the benefit of QA reviews which is supported by the large Swedish head and neck study, ARTSCAN [6]. This study clearly demonstrated improved results over time with a continuous QA scheme during the trial period.

In conclusion, the QA of 802 radiotherapy related factors in 51 patients belonging to the DAHANCA 10 trial revealed four major and 32 minor deviations in 22 patients. It was perceived by the QA panel during the QA process that minor deviations from treatment guidelines had no clinical impact on treatment outcome. Only four major deviations were recorded, none affecting tumor control.

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