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Position Paper

Quality assurance in radiotherapy

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Abstract

In 1999, the European Organisation for Research and Treatment of Cancer (EORTC), being a European pioneer in the field of cancer research as well as in quality assurance (QA), launched an Emmanuel van der Schueren fellowship for QA in radiotherapy. In this paper, the work that has been done during the first E. van der Schueren fellowship is reported, focusing on four phase III EORTC clinical trials: 22921 for rectal cancer, 22961 and 22991 for prostate cancer and 22922 for breast cancer. A historical review of the QA programme of the EORTC Radiotherapy group during the past 20 years is included.

Keywords: EORTC; Quality assurance; Radiotherapy

1. Historical review of the EORTC quality assurance programmes in radiation oncology

1.1. Institution structure and physical parameters

The European Organisation for Research and Treatment of Cancer (EORTC) radiotherapy group was formed in 1975. The main goal of this group was to initiate and conduct clinical research in radiation oncology and its related fields. After a few years, a quality assurance (QA) programme was started to check the consistency of data collected from multiple participating centres. The formal steps of the QA programme were established in 1982. Over the past 20 years, QA procedures have become a major part of the activities of the radiotherapy group. They are routinely used in every clinical trial and have resulted in a specific field of clinical research to develop methodologies that are gradually transferred to the entire radiotherapy community as well inside and outside clinical research.

The first QA programme in the EORTC radiotherapy group was reported in 1986. The evaluation included three steps: a comparison of megavoltage units, technical and staff environment, and data present in clinical and radiotherapy charts for each centre; radiation physics calibration of photon and electron beams; and radiation physics measurements on an anatomical phantom. The study included 17 institutions that were visited by a group of "experts" in radiotherapy and radiation physics from January 1982 to December 1984. Horiot and colleagues [1] reported the first part of the QA study in terms of assessment of medical staff and equipment. The second part was reported by Johansson and colleagues [2] regarding dosimetric intercomparisons. The dosimetric study in an anatomical phantom was reported also by Johansson and colleagues [3].

In 1993, Van Dam and colleagues [4] reported the results of mechanical checks of megavoltage units and simulators that were included in the on-site physics programme of the EORTC from 1987 onwards. Hansson and colleagues [5] reported the mailed thermoluminescence dosimeter (TLD) (*in vivo* measurements) dosimetry programme for machine output check and clinical application that started in 1986. Horiot and colleagues [6] in 1993 reported the detailed steps of the QA structure as well as the minimum requirements for QA in radiotherapy.

In the framework of the experimental implementation of a European QA network for external radiotherapy, a report was published in 1995 on the use of mailed TL dosimeters to check the beam output and the beam quality of photon beams [7]. Inter-comparisons with the EORTC own mailed TL dosimetry have shown an

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agreement better than 2% for all energies. In 1996, Bernier and colleagues [8] reported the profile of radiotherapy departments participating in clinical trials of the radiotherapy group of the EORTC and compared it with the earlier report [1]. Bentzen and colleagues [9] in 2000 reported the possible clinical impact of dosimetry QA programmes assessed by radiobiological modelling of data from the TLD dosimetry study of the EORTC.

1.2. Radiotherapy—clinical trials

In the early 1980s, the EORTC QA Radiotherapy Committee observed several inconsistencies related to non-optimal planning, treatment technique and dose distribution. A consensus meeting of the EORTC Radiotherapy Group, focusing on QA, was organised in 1987 [10]. In 1990, the EORTC held another consensus meeting at Tubingen to review the treatment sequence in conservative management of early breast cancer (EORTC trial 22811/10882: "assessment of the role of the booster dose in breast conserving therapy") from the viewpoint of QA [11]. During the same meeting, a consensus on a QA programme in the treatment of early breast cancer was reached between surgeons, pathologists, radiotherapists, physicists and radiographers [12]. During the EORTC Radiotherapy Group meeting of January 1993, [13] three targets were defined: designation of minimum requirements, evaluation of dose–volume effect in normal tissues and predictive tests for a better characterisation of individual radiosensitivity. The programme of QA of the EORTC radiotherapy group and a historical review was reported in 1993 by Horiot and colleagues [14]. In 1995, the EORTC late effects working group reported together with the Radiation Therapy Oncology Group (RTOG) the SOMA/LENT scale for the scoring of radiation-induced late effects in normal tissues [15]. The concept of a Master Protocol for phase III studies was raised at the Steering Committee of the EORTC Radiotherapy Group, in order to make the work of future study coordinators easier and to improve the homogeneity of future clinical trials [16]. The first results of a dummy-run procedure as QA in the EORTC trial 22881/10882 were published in 1991 by van Tienhoven and colleagues [17]. In 1997, van Tienhoven and colleagues [18] overviewed the QA in the same EORTC trial (22881/10882) with a programme consisting of a dummy run procedure, an individual case review procedure, *in vivo* dosimetry studies and phantom dosimetry studies. The results of a dummy run involving nine centres participating in a study comparing radiotherapy alone with radiotherapy plus hormonal therapy in patients with high metastatic risk prostatic cancer (EORTC protocol 22863) were reported in 1995 by Dusserre *et al.* [19]. In 1998, Valley and colleagues [20] reported results from a dummy run which was organised to test the compliance of participating centres with the guidelines of EORTC protocol 22931, which compares radiotherapy alone with concomitant radio-chemotherapy in the postoperative setting for patients presenting with locally advanced head and neck carcinomas. In 1999, the EORTC scientific strategy meeting reported the exceptional and pioneer role of the EORTC in the field of QA in cancer research for radiotherapy, surgery, medical oncology and data management [21]. In 2001, Poortmans and colleagues [22] published a QA report on the dummy run of EORTC phase III randomised trial 22922/10925 investigating the role of adjuvant internal mammary and medial supraclavicular (IM–MS) irradiation in stages I–III breast cancers.

2. QA in radiotherapy for EORTC clinical trials

2.1. Introduction

Back in 1999, during the first EORTC scientific strategy meeting, a new fellowship was established in memory of Professor Emmanuel van der Schueren who was one of the pioneers in the field of QA in radiotherapy [21] and former President of the EORTC. This fellowship was financially supported by the Vlaamse Kanker Liga. In 2001, Dr Vassilis Kouloulias, the first Emmanuel van der Schueren Fellow, worked on QA in three protocols of the EORTC Radiotherapy Group:

- EORTC trial 22961: long-term adjuvant hormonal treatment with luteinising hormone-releasing hormone (LHRH) analogue versus no further treatment in locally advanced prostatic carcinoma treated by external irradiation and six months complete androgen blockade—a phase III study.
- EORTC trial 22921: four arms phase III clinical trial for T3–T4 resectable rectal cancer comparing pre-operative pelvic irradiation to pre-operative irradiation combined with 5-fluorouacil and leucovorin, with or without post-operative adjuvant chemotherapy.
- EORTC trial 22922/10925: phase III randomised trial investigating the role of adjuvant internal mammary and medial supraclavicular (IM–MS) irradiation in stages I–III breast cancers.

Moreover, the fellow initiated the preparation and the conduct of the dummy-run in the Phase III Randomised EORTC 22991 trial: Three Dimensional Conformal Radiotherapy (3D-CRT) alone vs 3D-CRT plus adjuvant hormonal therapy in localised T1b-c, T2a, N0, M0 prostatic carcinoma. Other work included several smaller tasks, all concerning QA in different protocols of the EORTC Radiotherapy Group.

2.2. 22921 EORTC trial

In the early 1990s, the EORTC Radiotherapy Group published the results of three consecutive phase II studies defining the optimal dose of 5-fluorouracil combined with low dose leucovorin and pelvic irradiation in rectal cancer [23,24]. In 1993, a four-arm phase III clinical trial comparing preoperative radiotherapy with preoperative radio-chemotherapy with or without additional postoperative chemotherapy was initiated [25,26].

In this study, an individual case review procedure was performed to evaluate data consistency and to detect deviations from the trial protocol, the variability of the treated volume and dose homogeneities in a random selection of patients accrued by the most active centres. Twelve radiotherapy departments with more than 10% of evaluable patients recruited in the trial were invited to participate in this individual case review. Full patient records of five randomly selected patients per institution including the chemotherapy charts, surgical and pathology report, radiation treatment chart, treatment planning calculations, Computed Tomography (CT) scans, portal images and follow-up charts were needed for the review. All 12 departments participated. In 21 (35%) of the cases, a three-field technique with two lateral opposed wedge fields and a posterior field was used, while in 39 (65%) of the cases, a four-field pelvic box technique was used. All participants used linear accelerators. Almost all of the patients were eligible, documentation of clinical data was reasonable or good and there were no systematic major protocol deviations. The actual total dose was 44.7 ± 4.6 Gy. Some variation in fractionation size was found. All institutions complied with the protocol in specifying the reference dose at the ICRU point. The clinical target volume (CTV) drawn on the CT scan was very narrow in 7 (12%) cases, but eventually the actually treated volumes in terms of planned target volume (PTV) were correct. In two institutions, although the CTV was drawn correctly, the fields appeared to be narrow especially in cranial-caudal direction.

A considerable variation in treated volumes and total radiation dose was encountered in the individual case review. Quick identification of possible deviations and immediate feedback to the participating centres can reduce treatment variation and improve adherence to the protocol, limiting the unavoidable variations in a multi-institutional setting. To achieve this, emphasis should be given to the development of specific guidelines, based on the findings of the individual case review procedure, resulting in the enhancement of the reliability of the final clinical results.

2.3. 22961 EORTC trial

The EORTC trial 22961, started in 1997, was designed to evaluate the duration of adjuvant hormonal treatment with an LHRH analogue in patients with locally advanced prostate cancer treated with radiation therapy [27]. The present work reports on the dummy-run procedure to evaluate protocol compliance and to detect differences in target volume definition, treatment technique, dose specification and homogeneity as reported by participating centres. In a dummy run, data on a paper patient are sent to participating centres asking them to plan the treatment according to the study protocol guidelines [16,19,21]. The experience gained in previous dummy run procedures in the EORTC radiotherapy group was used in the current work [17–20]. The purpose of the dummy run in general was to check whether the guidelines were clear, to evaluate the technique used by the participants and to evaluate protocol compliance in terms of treatment design, delivery and verification. Thereby, the reliability of the final results of the trial will be enhanced.

CT-data and medical information of an anonymous patient were sent to 19 participating centres, either on a reproduced film, as DICOM files or on a CD-ROM. Participating centres were asked to complete a questionnaire on to their working methods and to plan treatment according to the protocol on the virtual patient. The data were collected from 11 responding institutions and compared to the trial guidelines. Items that were checked include the patient's position, the simulation procedure, the planning data acquisition, the target volume definition and the clinical controls during treatment. All centres use a supine treatment position with alignment of the patients with the use of positioning lasers in the treatment room. During the simulation step, 73 and 45% of the centres performed cystography and rectal opacification, respectively. All centres had 3-D CT-based treatment planning using 3–10 mm CT slice-thicknesses. Among the centres, 45 and 55% use blocks and multileaf collimator (MLC), respectively to treat patients. Sixty-three per cent of the centres treated an extended CTV1 using clinically defined field margins, thereby including the pelvic lymph nodes. The remaining centres treated a conformal small CTV1 with a 10–20 mm margin to PTV1. All centres defined PTV2 according to the protocol guidelines. Doses to the PTVs were correct. It was difficult to assess the treated volumes due to a lack of dose-volume histogram (DVH's) standardisation. Physicians of the participating centres checked patient compliance to the anti-androgens regularly.

In general, guidelines were correctly followed. In EORTC trial 22961, the use of conformally designed portals resulted in an improved treatment homogeneity among the different institutions compared with conventional radiotherapy. The large variation in irradiated volumes was already observed in the former 22863 EORTC trial using a conventional non-conformal radiotherapy technique [19]. This observation favours

the definition of CT-based treatment volumes in accordance with the protocol guidelines.

2.4. 22991 EORTC trial

A modification of the 3D-CRT questionnaire prepared by J. Bernier was used for the evaluation of institutions intending to participate in the 22991 trial on the use of adjuvant hormonal treatment in early stage prostate cancer treated with 3D-CRT [28]. This questionnaire includes several new items concerning the physical parameters of dose delivery and quality of photon-beams. A questionnaire was mailed to 24 institutions. One institution was excluded due to a major deviation concerning the flatness of the photon-beam. All of the 23 institutions participating in the study had the appropriate equipment in terms of LINACS, 3D treatment-planning and DVH computing. The critical limit for the flatness of photon-beam was in all cases ±3% and the frequency of checking was monthly.

A dummy-run with a paper patient eligible for trial participation is now "running". Two sets of images have been sent to the participants. The first one has been acquired with the patient in the supine position and the second one in the prone position. The participants are requested to plan the treatment of this patient (supine or prone or both if possible) according to the guidelines of the EORTC trial 22991 (3D-CRT). The CTV1 is defined as the prostate + seminal vesicles, CTV2 includes prostate + base of seminal vesicles and CTV3 is the prostate alone. The following doses are prescribed: PTV I: 46 Gy, PTV II: 24 Gy and PTV III: 8 Gy. The evaluation of the results of the dummy run will take place during the spring of 2002.

2.5. 22922 EORTC trial

In May 1996, the Radiotherapy and the Breast Cancer Groups of the EORTC initiated a large phase III randomised multi-centre trial. Its objective was to investigate the value of adjuvant irradiation of the IM-MS lymph node chain in patients with localised stage I–III breast cancers with medially or centrally located tumours and/or axillary lymph node invasion [29]. The principal goal of this trial, in which patients were randomised between irradiation of the IM–MS lymph nodes or not, was to solve the controversy about the possible benefit of IM–MS irradiation on survival [30–33].

The results of the dummy run have been published earlier [22]. The individual case review was performed to assess the consistency to the eligibility criteria and to the protocol guidelines for the radiotherapy. Participating institutions were invited to send 6 full patient's records (3 patients with irradiation of IM–MS and 3 without) including the surgical and pathology report, information on diagnosis and adjuvant treatment and the radiation treatment charts including the treatment planning calculations. Nineteen (19) radiotherapy departments have already participated in this part of the QA. Concerning the agreement between the study forms and patient records, inconsistencies were found in three cases (2.7%) of surgery and 16 cases (14.4%) of pathology data. The dose was not prescribed according to ICRU 50 in 11 cases (9.9%), while in two cases (1.8%) no treatment-planning was performed and in three cases (2.7%), the homogeneity was not according to ICRU 50 (±5%). The dose in the IM–MS region deviated significantly from the prescribed dose in 20% of the cases for arm 1, and in 3.6% for arm 2. The IMC irradiation-status could not be found clearly in 14 and 13 cases for arms 1 and 2, respectively.

This individual case review showed a number of more or less important deviations in treatment set-up and prescription. Recommendations were sent to the participating institutions, and this should improve the inter-institutional consistency and promote a high quality irradiation in all of the institutions participating in the trial.

3. Miscellaneous

3.1. Recommendations for tolerance levels and frequency of checking for field flatness and symmetry of photon beams produced by linear accelerators

Flatness and symmetry are the main parameters determining the quality of a photon beam produced by linear accelerators. The quality of the routine clinical delivery of radiotherapy and, consequently, the outcome of the treatment depend definitely on the physical parameters of the treatment machine. Several recommendations from national and international associations are reported [34–41]. By reviewing the current literature including the World Health Organization (WHO) report of QA in radiotherapy [42], a possible suggestion would be that for flatness and symmetry the optimal level of deviation should be within ±3%. Flatness and symmetry should optimally be checked on a monthly basis. Test methods, frequencies and tolerances should always take into account national requirements or recommendations, in terms of minimum requirements. The tolerance levels reported here should not serve as strict recommendations, but, on the contrary, act as a stimulus for further improvement of the QA status in physical parameters possibly influencing the treatment outcome. We do hope that the current large variations in test frequencies and tolerance levels might decrease in the near future, especially inside the European Union (EU) where certain directives are still active and should be considered as a minimum requirements [43].

3.2. A scenario for a web-based radiotherapy treatment planning system

The desire for an easy access to radiotherapy services of high quality, regardless of the patient's location, is one of the main aims of technological applications in clinical radio-oncology. In order to achieve this goal, there are two barriers that have to be raised: patient's mobility, which imposes constraints on the treatment and the follow-up of the patient, and the limited number of experts defining the field of radiation treatment planning (RTP). Both issues can be dealt with with the use of a web-based RTP system, supported by a relevant database distributed among the radiotherapy departments, enabling the on-line collaboration between physicians.

Radiation treatment planning is typically a time-consuming application, requiring the use of dedicated hardware and specialised software, resulting in an acceptable, preferably optimal, radiotherapy treatment plan. In order to achieve this, the physician is supplied from the RTP system with a variety of 2-D and 3-D graphical facilities for real-time interactive visualisation. The strength of such a system relies mainly upon the accuracy of the dose calculation algorithm, but also upon the degree of ease of use of contouring software, the quality and speed of 3-D graphical displays and the availability of evaluation and verification tools. Many RTP systems have been developed [44], often primarily as research projects and later for commercial purposes.

The complexity of the problem of defining an optimal plan reveals the need for a "second opinion" from experts in the field, making the value of tele-consultation apparent. Research projects integrating tele-consultation in a TPS [45] assume that all of the collaborating physicians own a powerful computer, and are able to share the same view of the application, which is installed at every site. As an alternative to such a point-to-point approach, a web-based approach [46] could be set up. Here, the traditional stand-alone RTP is transformed to a client-server application on the Internet. The radiation oncologist, physicist or radiation technologist, who is working on a RTP system, is able to export the plan data to the web-RTP, in order to collaborate on-line with another expert in the field. Likewise, the radiation oncologist is able to collaborate with the physician who has designed previous treatment plan(s) of the patient. All the collaboration sessions take place on the Web using a Web browser regardless of the RTP systems available by the involved parties. The Web-based RTP system provides the physicians with a set of images (CT or magnetic resonance imaging (MRI) scans with beam projections and isodoses, DRR's, dose volume histograms) and resulting parameters (beam configuration, treatment set-up parameters). Collaborating parties are able to perform remote real-time operations such as interactive structure delineation, image processing, beam placement and dose calculation, while a simultaneous video-conferencing session can take place. Permission can be granted to any of the collaborating parties to take control of the workflow, while the results of the actions are simultaneously viewed at both sites. Optimally, during the course and after completion of the treatment, the patient will be able to complete an on-line questionnaire concerning useful information about the treatment outcome. Furthermore, also for the purpose of treatment follow-up, post-treatment patient images could be acquired.

Several benefits might be obtained for the patient with the use of a web-based RTP collaboration system:

- Accessibility of advanced radiotherapy treatment services, minimising patient's transportation. The patient receives high quality treatment close to his/her home and family.
- A framework of security rules and techniques is established, which ensures the accessibility of patient-related information only from authorised users of the system.

The benefits for the physician are the following:

- The co-operating physicians can work on any computer of no specific operating system and of low hardware requirements. Furthermore, the co-operating physicians may use different RTP systems in their clinics, with the web-based application being the connecting ring, enabling the co-operation.
- She/he is using a familiar platform for the user interface (Internet browser), with minimal training required for the average RTP user.
- She/he is making use of high-end security authentication techniques, ensuring the use of the system only by authorised users.
- She/he can get consultation from an expert colleague and a framework of co-operating physicians can be easily established, reducing professional isolation and encouraging networking.
- In the case of tele-consultation, collaboration can be established at the moment the physician needs it, without any delay due to the transmission of CT data.

Potential benefits for organisations and societies involved in multi-centre clinical trials.

- The organisation/society might be the leader in the transition from the traditional RTP system to the web-based RTP systems.
- Quality assurance in terms of dummy runs and/or check of a real-patient treatment planning will be largely facilitated.

- Minimisation of local-audits and the costs that this procedure carries, since the on-site visits for checking the treatment planning would also be available from a centrally located position.
- Evaluation and correlation of treatment outcome (tumour control and acute/late morbidity) with radiotherapy parameters (dose distributions, DVH's) after the completion of the treatment (especially for protocols with a long-term follow-up).

However, a lot of effort still has to be done within the European Radiotherapy Community to reach the standards for a web-based QA structure as described above. Beyond the high-tech requirements of this proposal, the realisation of such a project could be a future challenge for the EORTC Radiotherapy group.

4. Conclusions

A QA system should include an interactive feedback procedure in all steps of a running clinical trial protocol or of radiation treatment carrying-out (prescribed dose, treatment planning, patient-positioning, etc.); corrections should be communicated and implemented immediately after an error is tracked. Frequent local audits are often an essential part of every QA procedure. Individual chart review should always be conducted randomly. A check of eligibility and treatment compliance check should be performed as early as possible. Any inconsistency should be discovered and recorded promptly and designated as a deviation or violation, according to the severity of the discrepancy. *In vivo* dosimetry (conveniently mailed TLDs) as a specific QA procedure can verify the quality of physical treatment delivery. A feedback procedure of tracking deviations and making interactive corrections can improve subsequent treatment delivery.

The rules for the determination and the irradiation of the target volume should be strict and accurate. Any unclarity and abstruseness could lead in misapprehension and, potentially, in a lower quality of treatment delivery and protocol deviations. Determination of violations and variations at the very beginning of a trial is essential. A dummy-run can point out possible weaknesses of the study protocol guidelines. Therefore, it should be performed before the activation of the protocol in order to check the ability of centres to follow specific guidelines and mainly to correct any potential misinterpretations or discrepancies that could lead to protocol deviations or violations and, consequently, to a lower quality of radiation treatment delivery. Control of data consistency by a double data entry procedure in the trial database can minimise random errors. The ICRU 50 recommendations must be a common conscience for all the radiotherapists in the European Society. Guidelines concerning CTV, PTV and dose delivery at the ICRU reference point should be considered always in the routine clinical practice of radiotherapy. Development of a common platform and an interactive connecting ring between the members of the European radiotherapy community can enable the co-operation between several experts and enhance the QA of radiotherapy. The need for specific guidelines might be the future challenge of the European radiotherapy community. QA programmes in multi-centre trials do not only have to assure the individual quality of a treatment delivered and to reduce variations by immediate feedback to participating centres, but should also provide information about the sources of variations of treated volumes, as they will be inevitable to a certain degree in multi-institutional settings. By providing recommendations to the participating institutions, we expect to improve the inter-institutional consistency and to promote a high quality irradiation in all of the institutions participating in the trial.

The former and present experience in QA of radiotherapy is a strong and valid argument to convince the entire oncology community that quality matters: valid and reliable results of clinical trials involving radiotherapy can only be obtained with a good quality of treatment delivery and well-designed, as well as QA-supported, studies.

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