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Review

The Quality Assurance programme of the Radiotherapy Group of the European Organization for Research and Treatment of Cancer (EORTC): a critical appraisal of 20 years of continuous efforts

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Abstract

In 1982, the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group established the Quality Assurance (QA) programme. During the past 20 years, QA procedures have become a major part of the activities of the group. The methodology and steps of the QA programme over the past 20 years are briefly described. Problems and conclusions arising from the results of the long-lasting QA programme in the EORTC radiotherapy group are discussed and emphasised. The EORTC radiotherapy group continues to lead QA in the European radiotherapy community. Future challenges and perspectives are proposed.
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1. Introduction

In a period where an overhaul of costly healthcare systems is at the centre of looming budget battles in most industrialised countries, the deleterious consequences of poor quality treatments undoubtedly contribute to the rise of health costs. Moreover, it is now well documented that large national differences in survival rates are found among patients with similar diagnostic backgrounds: variations in care quality not only affect the effectiveness of therapeutic management for a given disease, but also lead to severe complications which significantly reduce the quality of life. In this perspective, the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group developed, throughout the least 20 years, a comprehensive Quality Assurance (QA) programme as a means to develop cost-effective medical practice.

As a rule, this QA programme was implemented in every clinical trial activated by the Radiotherapy Group and has resulted in a specific field of clinical research to develop methodologies that are now gradually transferred from clinical research entities to the entire radiotherapy community.

The objectives of this retrospective analysis are threefold: (1) To revisit the key issues addressed by the cohort of quality control procedures set-up over the last 20 years, by the Radiotherapy Group; (2) To analyse the potential impact of their message(s) on disease outcome following radiotherapy; (3) To show how the experience gained over the last two decades can be used to build a platform of novel approaches in QA.

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2. Quality Assurance in radiotherapy: from strategies to implementation

Since 1982, the year of the activation of its Quality Assurance programme, the Radiotherapy Group progressively extended its original project into pilot studies in an attempt (a) to promote a systematic check of individual patients and (b) to improve the reliability of treatment procedures. Once general requirements needed to warrant a valid cooperation were identified, the group directed its efforts to the clinical ground and, in particular, to the set-up of reliable control procedures to improve the quality of protocols of phase III clinical studies. This general philosophy led to considerable improvements in the writing of protocols, in data management and also in the detection and correction of dosimetric parameters.

The QA programme was actually developed in three main phases articulated around the development of two Quality Systems: the Programme of Physics Audit Quality and the Assurance of Protocol Compliance. In the *first phase*, that roughly lasted 5 years (1982–1987), various centres were visited by a team of radiotherapists and radiation physicists. In 1987, a vast programme of mailed dosimetry was activated to document, through a large number of beam calibrations and measurements, the profile of the dose deviations between the values determined by the team of radio-physicists of the EORTC and those reported by institutions. In 1987, the Radiotherapy Group activated a *second phase* of the QA programme, and set up a series of procedures (dummy-runs) to document systematic errors made in single institutions and control the accuracy of the design and the application of phase III study protocols. Finally, in 1989, a *third phase*, more patient-oriented, was activated to tackle random errors: individual case reviews directed to patient data and treatment parameters were aimed at improving the compliance of the participating centres to study protocols and at detecting obscurities in protocol guidelines.

All this implementation of QA procedures was consolidated during the 1995–1996 period, which was actually characterised by the further development of QA procedures that had been validated during the three phases mentioned above, with a particular emphasis put on the mailed TLD programme for the Programme of Physics Audit Quality, and on dummy-runs and individual case reviews for the Programme for Assurance of Protocol Compliance.

The procedure of QA is defined most generally as all those planned and systematic actions necessary to provide adequate confidence that a product or service will satisfy given requirements for quality. QA in radiotherapy [1] is defined by all those procedures that ensure consistency of the radiotherapy prescription and the safe fulfilment of that prescription, with regard to the dose to the target volume, together with a minimal dose to normal tissues, minimal exposure of personnel and adequate patient monitoring aimed at determining the end result of treatment. Quality Standards are a criterion or set of criteria against which the quality of any form of activity can be assessed. A Quality Audit is a systematic and independent review (examination and evaluation) of the complete treatment delivery, to determine whether the system is implemented effectively and whether the activities and results produce the required end-point complying with the pre-determined quality standards.

The sequence of published actions concerning QA is presented in chronological order and divided into two sections: those related to department-structure and radio-physics and those related to clinical trials.

3. Historical review

3.1. Department structure and physics

The first QA activities in the EORTC Radiotherapy Group were 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 [2] reported the first part of the QA study in terms of assessment of medical staff and equipment. Large variations were observed in the number of patients treated per year, per radiation oncologist, per radiation physicist and per technologist. The number of simulators was sub-optimal in 12/17 centres. In 5/17 centres, major problems were present which made it difficult to comply with all of the requirements of the EORTC protocols. However, the quality of work-up regarding tumour extension was considered to be satisfactory in all centres. The second part was reported by Johansson and colleagues [3] regarding dosimetric intercomparisons. The deviations between the absorbed dose values, for specific points along the beam axis in a water phantom, determined by the QA committee and reported by the hospitals were within an acceptable level of variation ($\pm 3\%$). In some scanning electron beams, large deviations were found. Concerning the flatness and symmetry of the beams, 73% of the X-ray and 60% of the electron beams were within the acceptable levels of variations. The third part was again reported by Johansson and colleagues [4] regarding intercomparison in an anatomical phantom. A tonsillar tumour and a homolateral subdigastric node were marked in an anatomical phantom. The institutions were asked to treat the phantom once as they would treat a normal patient. The phantom

was loaded with dosimeters and irradiated. No major dosimetric problems related to absorbed dose calibration or calculation in the phantom were found.

In 1993, Van Dam and colleagues [5] reported results of mechanical checks of megavoltage units and simulators that were included in the on-site physics programme of the EORTC from 1987. Measurements were obtained in 16 different centres with regard to 23 accelerators, 14 cobalt units and 14 simulators. In general, the deviations observed for accelerators and simulators were smaller than for cobalt units, possibly related to the advanced age (up to 20 years) of some of the latter kind of units. Hansson and colleagues [6] reported the mailed thermo luminance dosimeter (TLD) dosimetry programme for machine output check and clinical application which was started in 1986. The therapy machine output checks have revealed a few large deviations ($>7\%$) between EORTC-measured and institute-stated dose. Special measurements were done for the EORTC trial 22881/10882. It was reported that 80% of the measured doses were within 5% from the doses computed in the institute. Horiot and colleagues [7] in 1993 reported on the minimum requirements for QA in radiotherapy. Several steps of a QA structure were mentioned. First-line radiation physics and radiotherapy parameters were defined such as: beam calibration; mechanical checks of equipment; dose specifications to prescribe and report radiotherapy; treatment planning system and compliance to a programme of measurements and checks in each radiotherapy department. Methodology of QA in radiation physics should include site visits and mailed TLD. Guidelines were also given regarding the QA of the clinical trials (e.g. data management, case report forms, dummy-runs, identification and score of deviations) and the development, testing and promotion of transfer of new methodologies of QA. 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 the photon beams [8]. Inter-comparisons of the results with the EORTC own mailed TLD, have shown an agreement better than 2% for all energies.

In 1996, Bernier and colleagues [9] reported the profile of radiotherapy departments participating in clinical trials of the radiotherapy group of the EORTC and compared it with their earlier report [2]. The general results showed that: large variations in equipment and staff were still observed among participating centres; the number of cancer patients treated per year per radiation oncologist seemed to diminish slightly, especially in those centres experiencing a considerable staff shortage before; the most significant improvement was observed for the number of cases treated per year per member of the radiation physics team; the radiation technologist's workload shows the opposite trend; the situation for equipment is unchanged in comparison with that observed 6 years before. Bentzen and colleagues [10] 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. In 2001, Gomola and colleagues [11] checked 330 electron beam set-ups in the reference centres and some local centres of the EC Network Project and in addition the centres participating in the EORTC trial 22922. The standard deviation of the measured dose to stated dose was 3.2%, while in seven beam set-ups deviations greater than 10% were observed, showing the usefulness of external audits of clinical electron beams.

3.2. Radiotherapy—clinical trials

In the early 1980s, the EORTC Radiotherapy Group observed several major problems related to sub-optimal planning, treatment technique and dose distribution. Subsequently, a consensus meeting in 1987 focusing on QA was held. Several recommendations and guidelines were published for the establishment of a programme of QA in radiotherapy inside the EORTC [12]. It was recommended that this centralised QA programme should include site visits, mailed dosimetric measurements and a review of the radiotherapy treatment records. Criteria for acceptable practices were reported concerning dose delivery, deviation range of prescribed dose and patient immobilisation, as well as verification of (portal) films. Emphasis was given to the mandatory use of the target volume as defined by the International Commission on Radiation Units and Measurements (ICRU) recommendations. In 1990, the EORTC Radiotherapy Group held a consensus meeting in Tübingen, Germany to review the treatment sequence in the 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 [13]. The reports of this meeting considered the most relevant criteria for evaluating pathology, surgery and radiotherapy techniques, not only for selected institutions participating in prospective randomised trials, but also aiming at developing QA procedures for use anywhere for routine standard treatment.

A consensus on a QA programme in the treatment of early breast cancer was reached in a multidisciplinary EORTC and European Society of Mastology (EUSOMA) meeting of surgeons, pathologists, radiation oncologists, physicists and radiation technologists [14]. Specific guidelines were established for treatment preparation, careful location and excision with marking of the primary tumour, target volumes for irradiation of the whole breast and boost area. Radiation dose prescription rules, specification and checking procedures were provided, together with guidelines to achieve a homogeneous dose within the target volume. At a QA meeting of the Radiotherapy

Group in January 1993 [15], three goals 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 [16]. In this publication, special attention was also given to the definitions of acceptable variation, major and minor deviations detected in clinical trials. One of the main aspects of the QA programme is the establishment of clear and representative end-points in terms of radiation-induced morbidity. In 1995, the EORTC Late Effects Working Group, reported together with the US Radiation Therapy Oncology Group (RTOG) the SOMA/LENT scale for the scoring of the late effects of radiation-induced toxicity [17].

The concept of a Master Protocol for phase III studies was realised, in order to make the work of future study co-ordinators easier and to improve the homogeneity in the protocol descriptions of a clinical trial [18]. The Master Protocol defines and explains, in a logical order, the different steps that must be taken in the design of a randomised trial, from the rationale to the references. Particular attention is paid to eligibility criteria, volumes of interest defined according to the recommendations of ICRU Report 50 (gross tumour volume, clinical target volume, planning target volume and organs at risk), simulation procedure, treatment technique, normal tissue-sparing, dose computation, equipment and dose specification. Last, but not least, the different QA procedures are defined (site visits, dummy run procedure, *in vivo* dosimetry, individual case review) to allow working plans to be made in advance.

The first results of a dummy-run procedure for quality checking in the EORTC trial 22881/10882 were published in 1991 by van Tienhoven and colleagues [19]. Three transverse sections of a patient were sent to 16 participating institutions with a request to make a three-plane treatment plan, according to the protocol prescriptions. The evaluation revealed a large variation in the treatment techniques used, especially concerning the use of wedge filters. Two institutions did not apply wedges, whereas wedge angles in the other institutions varied between 6 and 46°. An examination of the dose-distributions showed that the dose was specified at a point according to the protocol guidelines in 11 institutions, to the 90, 95 or 100% isodose curve in four institutions while in one institution the dose was normalised to a point in the chest wall. Twelve institutions applied lung density corrections in their treatment planning, while nine reported problems with their planning system in off-axis dose distribution calculation and/or the simulation of collimator rotation. Recalculation of the dose at the isocentre showed agreement within 2% compared with the stated dose. The dose reported in the tumour excision area varied between 93 and 100%. In 1997, van Tienhoven and colleagues [20] 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. Three types of systematic protocol deviations were detected and defined: deviations due to ambiguities in the protocol prescriptions; deviations not known to the institution, such as mistakes in implementation of treatment planning algorithms resulting in a systematic overdosage or underdosage and inability of an institution to cope with (precise) protocol prescriptions for technical or logistic reasons.

The results of a dummy run involving nine centres participating in a study comparing radiotherapy alone with radiotherapy plus hormone therapy in patients with high metastatic risk prostate cancer (EORTC protocol 22863) were reported in 1995 by Dusserre and colleagues [21]. In all centres but one, patients are treated in the same way. The authors reported also that protocol compliance could be improved by a better assessment of the target volume, by using individualised shields and by using computerised tomography (CT) scan images for treatment planning determining beam position on a large number of slices.

In 1998, Valley and colleagues [22] reported results from a dummy run that was organised to test the compliance of participating centres with the guidelines of EORTC protocol 22931, which compared radiotherapy alone with concomitant radio-chemotherapy in the post-operative setting for patients presenting with locally advanced head and neck carcinomas. The results showed wide intercentre variations in PTV extensions raising the question of the reproducibility when pooling patients in multicentric trials and a large variability in the field arrangements which was left to the discretion of the investigators. Only three out of 10 of the institutions followed the ICRU 50 recommendations for dose reporting and, moreover, protocol requirements were not met for dose distribution homogeneity in any centre. In 1999, an EORTC Scientific Strategy Meeting reported the exceptional and pioneering role of the EORTC in the field of QA in cancer research for radiotherapy, surgery, medical oncology and data management [23].

In 2001, Poortmans and colleagues [24] published a report on the dummy run of the EORTC phase III randomised trial 22922/10925 investigating the role of adjuvant internal mammary and medial supraclavicular (IM-MS) irradiation in stage I-III breast cancer. The evaluation of 32 centres showed a number of more or less important deviations in the treatment set-up and prescription. A deviation of the measured dose in the IM-MS region from the prescribed dose was assessed in a large number of evaluated treatment plans. Due to this sub-optimal dose distribution, a real survival benefit of 5% would be measured as only a 3.8% benefit. Moreover,

Lievens and colleagues [25] by performing an analysis based on the dummy run data of the same trial, showed that if the recommendations of the QA Committee are applied, both standard and alternative IM-MS irradiation techniques produce acceptable dose distributions.

Recently, Julien and colleagues [26] reviewed the medical files of 824 out of 1010 randomised patients (82%) of 10853 EORTC trial investigating the role of radiotherapy in breast-conserving treatment for ductal carcinoma *in situ* of the breast. Large variations occurred, particularly in the surgical procedures and histopathological work-up, emphasising the need for establishing uniform guidelines for diagnostic and therapeutic procedures.

In 2001, within the framework of the Emmanuel Van der Schueren Fellowship, the EORTC Radiotherapy Group will complete QA in three protocols:

- EORTC trial 22961: Long-term adjuvant hormonal treatment with luteinising hormone-releasing hormone (LHRH) analogue versus no further treatment in locally advanced prostate carcinoma treated by external irradiation and a 6-months combined androgen blockade—a phase III study.
- EORTC trial 22921: Four arm phase III clinical trial for T3-T4 resectable rectal cancer comparing preoperative pelvic irradiation with preoperative irradiation combined with 5-fluorouracil and leucovorin with or without postoperative adjuvant chemotherapy.
- EORTC trial 22922/10925: Phase III randomised trial investigating the role of adjuvant IM-MS irradiation in stage I-III breast cancers.

The group continues its efforts in the area of QA with the aim of increasing and consolidating the quality of clinical research and routine daily practice in radiotherapy.

4. Discussion

In order to put into perspective both the orientations that the promoters wanted to give to a project of QA in Radiotherapy and the strategies followed during the development and implementation of the relevant control procedures, it is necessary to revisit the expectations that the EORTC Radiotherapy Group had claimed, when it embarked on this long-term programme. Firstly, it was felt that this QA programme should be a valuable tool to both harmonise treatments and provide clinicians and decision-makers with information on optimal workloads for equipment and human resources. Secondly, this project should have helped EORTC investigators to develop harmonised QA procedures in the therapeutic management of widespread diseases to improve, on a large-scale, local control and survival, and reduce the severity of treatment complications. Thus, one must ask how to interpret the clinical relevance of the achievements mentioned above. The analysis of the clinical impact of a QA Programme has to be stratified according to both radiation physics and clinical parameters.

4.1. Physical parameters

In 1993, Dutreix and colleagues [27] reported on the preliminary results of a QA network for radiotherapy centres in Europe, showing that the large majority of the beams (23/25) with deviations $>3\%$ belonged to centres that did not participate in external audits in the previous 5 years. Moreover, Hansson and colleagues [6], reporting measurements from mailed dosimetry during a period of 6 years (1987/1992), showed an acceptable level of deviation ($\pm 4\%$) between the EORTC measured dose and the institute-stated dose value. However, the most important results coming from this study concerned the positive impact of re-checking using mailed TLDs. The mean ratio subsequently approached unity, and the standard deviation decreased, as the number of consecutive mailings increased. This improvement can be explained by corrections that had been made by the participating institutions after a timely feedback regarding their dosimetric status. Correlating information from the TL measurements and the on-site visits led to further improvements in the beam deviations. This report is an exceptional example of the potential role of mailed TLD and local QA audits. Mailed TLD checks should be an integral part of a continuously ongoing QA activity in radiotherapy. In 1994, the European Society for Therapeutic Radiology and Oncology (ESTRO) published an advisory report to the European Commission within the framework of its 'Europe against Cancer' Programme [28]. The main item of this report was the documentation of guidelines for QA in radiotherapy. Moreover, ESTRO offers to its members the possibility to participate in a programme called EQUAL, an acronym for ESTRO QA in radiotherapy [29]. The aim of this network, is to stimulate more permanent action at the level of the EU member states, typically for those smaller centres which up to now did not have the opportunity to participate in any national or international QA programme. In 2000, Ferreira and colleagues [29] published the first report of measurements regarding the EQUAL project in 102 centres. Approximately 3% of the outputs in reference conditions show deviations outside tolerance level ($>5\%$). The ESTRO-EQUAL report together with a study by Gomola and colleagues emphasised the feasibility and the potential role of external audits with mailed TLDs in detecting deviations in electron or photon beams [11,29]. It seems that nowadays the instruments for measuring the quality of radiotherapy treatment and

performing QA activities are available, easy-to-use and reliable. The final implementation of the QA procedure remains the only problem.

Importantly enough, the EORTC Radiotherapy Group was the first to demonstrate, by means of a Quality Assurance Programme, that small deviations in beam output may lead to clinically important variations in outcome. Bentzen and colleagues [10] by a rigorous evaluation showed that in 10% of the beams with the most pronounced under-dosage, the loss in tumour control probability could be up to 7–8%. Likewise, in the 10% of the beams with the most pronounced over-dosage, the calculated increase in the probability of mild/moderate morbidity would be up to 19–22%. Moreover, for severe morbidity, the same beams raised the estimated probability of severe complications from 5 to 9–10%. The decrease in the probability of an uncomplicated cure was estimated at 1% both for high- and low-energy beams; sequential mailings considerably improved the uniformity of clinical outcome. The clinical impact of beam dose deviations from the stated dose is certain.

The infrastructure of a radiotherapy department can also have an impact on QA outcome, and this should not be underestimated [9]. The organisation of a department should also be subject to a QA system. Leer and colleagues [30], described how the so-called ISO 9001 quality standards can be applied to create a QA system in a hospital department.

4.2. Radiotherapy clinical trials

QA procedures allow a good estimation of patient-to-patient and inter-institutional variations, and early detection of (potential) systematic protocol deviations of 3 types [20]: deviations due to ambiguities in the protocol prescriptions; deviations not known to the institution, such as mistakes in the implementation of treatment planning algorithms resulting in a systematic over-dosage or under-dosage; and the inability of an institution to cope with (precise) protocol prescriptions for technical or logistic reasons. The first two types of deviations may be corrected or avoided by direct discussions with the study co-ordinator, specific recommendations for the dose in the ICRU point and *in vivo* dosimetry. With respect to the third type of deviation, it is up to the trial co-ordinator to accept or refuse a centre's participation, depending upon the relative importance of the particular deviation(s) for the trial endpoints. To be effective, such a QA programme must be implemented as early as possible in the course of a clinical trial [18,20].

This historical review showed, in general, many problems concerning protocol inconsistencies and routine clinical practice. Potential systematic protocol deviations possibly leading to false-negative/-positive results are often detected [10,19,20,22,24,25]. Large or small intercentre variations in planning target volume (PTV) extensions are also recorded. This fact often raises the question of reproducibility when pooling patients in multicentric trials [22]. Unfortunately, not all institutions followed the ICRU 50 recommendations for dose reporting [19,20,22,24,25]. Protocol requirements are often not met for dose homogeneity in participating centres [10,19,20,22,24,25]. Moreover, the possible influence of deviations in treatment delivery on the end-results of studies was calculated and this fact emphasised the immense value of QA in clinical trials [10,24,25].

This retrospective analysis clearly shows that, throughout the last decade, the Cooperative Group for Radiotherapy has been able to extend its basic quality assurance of equipment and dosimetry into prospective investigations consisting of pilot studies for systematic checkings of individual treatment and treatment reliability, resulting in a large body of data on treatment precision level, systematic deviations and individual errors. The tackling of systematic and random errors has been extremely successful since the set-up of QA procedures such as the dummy-runs and individual case reviews enabled the identification of the major sources of ambiguities, as well as all causes of poor compliance to the protocols, resulting in the release of helpful recommendations for all participating centres.

QA programmes are not only well accepted by all participants, but also felt by everyone to be mandatory for the validity of cooperative work between several centres. This project has and continues to provoke lively and very constructive discussions within the group, especially during the last 5 years where individual contacts among investigators and local teams have been promoted. From the experience gained by the Radiotherapy Group, the main axes of research are now centered around the following issues:

- Cost-benefit analysis of the dummy-runs, case report forms and individual case review procedures, in specific randomised trials of the Radiotherapy Group of the EORTC.
- Update of information on required radiotherapy infrastructure in EORTC institutions based on mailed questionnaires, in collaboration with ESTRO and possibly in the frame of a concerted action supported by the European Commission.
- Through the use of telematic services, the EORTC Radiotherapy group will also investigate the feasibility of teleconferencing QA audits by physicists and medical specialists for new radiotherapy techniques such as three-dimensional-conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) planning.
- To identify all prerequisites related to an improved efficacy of 'integrated' QA programmes, which

consider the accuracy of radiotherapy in the framework of multidisciplinary treatments and require a prospective implementation of various Quality System.

5. Conclusions

A QA system should include an interactive feedback procedure in all steps of a clinical protocol and/or of the radiation treatment (prescribed dose, treatment planning, patient-positioning, etc.); corrections should be made immediately after an audit. The main aspect of QA is not only to diagnose an error or inconsistency, but also to give advice, aiming to improve protocol compliance and to ensure that corrections are made as soon as possible. Thus, a QA structure should be friendly, informal and confidential, without aggressive censuring of an investigator/institution, but aiming at improving the quality of their routine clinical practice. Results of a QA procedure should always be published anonymously.

From the experience gained in the EORTC Radiotherapy Group, it is clear that all opportunities to transfer the knowledge of QA have to be identified and enforced on a large-scale between institutions involved in clinical research and lay community hospitals. This should be done by exchanging experience on QA procedures applying to radiation physics parameters, transferring these into daily practice pilot Quality Systems that are able to monitor the effects of measures taken in the context of multidisciplinary treatments and expanding information networks on the generic quality standards developed for new radiotherapy techniques.

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