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EORTC Radiotherapy Group: achievements and future projects

V. Budach[a], A. Zurlo[b,*], J.C. Horiot[c]

[a]*Klinik für Strahlentherapie, Universitätsklinikum (Charite)–Humboldt Universität, Schumannstrasse 20-21, 10117 Berlin, Germany*
[b]*EORTC Data Center, Avenue E. Mounier 83, 1200 Brussels, Belgium*
[c]*Department of Radiotherapy, Centre Georges-François-Leclerc, 1, rue du Professeur Marion, BP 77980, Dijon, F-21079 France*

Abstract

The European Organisation for Research and Treatment of Cancer (EORTC) Radiotherapy (RT) Group will celebrate 27 years of activity in 2002. During its long history, the Radiotherapy Group has conducted a large number of studies which have provided valuable information on the radiation treatment of several disease sites. Group efforts have been concentrated on dose–effect studies, optimal fractionation schemes, combinations with other treatment modalities, and new radiotherapy techniques. The EORTC RT Group was the first in Europe to develop and introduce methodologies of Quality Assurance in radiotherapy. The RT Group actively collaborates with other EORTC Groups and international organisations. Currently, several phase III studies are being conducted in collaboration with European, North American and Australian organisations. The collaboration with RTOG led to the setting up of common systems for scoring late normal tissue effects. In the years to come, the Group will keep pioneering pivotal trials in radiotherapy and radio-chemotherapy. It will also explore combinations with novel therapies in phase I trials and implement innovative translational research programmes.

Keywords: Radiation therapy; Randomised trials; Breast cancer; Prostate cancer; Head and neck tumours; Quality assurance

1. Introduction

The European Organisation for the Research and Treatment of Cancer (EORTC) Radiotherapy (RT) Group started its clinical activity in 1975. In fact, radiotherapy studies already took place from the early 1970s within the 'Radio-Chemotherapy Group' who later split into two new Groups, i.e. the 'Hodgkin's and non Hodgkin's Lymphoma Group' and the 'Radiotherapy Group'. It was mostly on a French initiative, led by Maurice Tubiana, Claude Lalanne and Alain Laugier, that these Groups were formed. It soon became a truly European venture under the leadership of Emmanuel van der Schueren and Jean-Claude Horiot. In the early 1990s, the RT Group was already one of the most active Groups within the EORTC, able to complete trials accruing more than 1000 patients. In 1992, for the first time, the Group accrued in its studies more than 1000 patients in 1 year.

By definition, a radiation oncologist needs to have a wide clinical knowledge. Hence, it is not surprising that radiotherapy trials addressed questions relevant to most solid tumours like cervix carcinoma, nearly all head and neck tumour sites, oesophageal, breast cancers, rectal and anal cancers, brain tumours, lung cancers, prostate and bladder cancers, etc.

There were often challenging situations and controversies with the 'organ-oriented Groups', who were lacking radiation therapy expertise but nevertheless reluctant to have another Group activating trials on 'their' tumour location. However, despite this counterproductive situation, it nevertheless gradually led on to joint ventures with other Groups. Some of the most successful trials were conducted in the past 15 years with the Brain Tumour Group, the Breast Group, the Gastro-intestinal Tumour Group, the Genito-Urinary Tract Cancer Group and the Head and Neck Group.

Besides these trials addressing specific tumour sites, the efforts of the RT Group concentrated more on technical and biological topics, such as dose–effect studies, optimal fractionation schemes, investigations of combinations with other treatment modalities and new radiotherapy techniques (stereotactic radiosurgery, conformal radiotherapy). Quality of life and health economic issues have also been investigated in selected trials. The Group scientific activity has also been constantly focused on management and quality assurance

* Corresponding author. Tel.: +32-2-774-1671; fax: +32-2-771-3810.
E-mail address: azu@eortc.be (A. Zurlo).

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(QA) of radiotherapy and international co-operation; more recently, the RT Group Steering Committee recognised the need for more widespread implementation of translational research programmes inside the new protocols of the Group.

The EORTC RT Group was the first European organisation to underline the importance of QA in radiation therapy and, as early as 1982, started a specific Europe-wide programme on QA and dose intercomparison. The RT Group was first to develop methodology of QA in radiotherapy research protocols (with the support of a EU grant for a programme entitled 'Europe against Cancer'). The radiation physics QA programme demonstrated the disappearance of large deviations of photons and electron beams calibrations after two successive audits. This methodology has now become a standard procedure in radiotherapy routine practice in Europe. A survey was conducted in 1994 among 76 centres of the Group aimed at identifying the progress made in terms of treatment planning and therapy equipment. A tentative profile and guidelines for minimum recommendations for European radiotherapy departments involved in clinical research was published in 1996 [1]. Site visits, calibration of radiotherapeutic equipment, simulation of clinical situations and mailed thermoluminescence dosimeters (TLDs) dosimetry have been continuously conducted for several years. This extensive QA activity will be modified in the near future as the EORTC as the EORTC RT Group will join the broader European project that will be launched by the European Society for Therapeutic Radiology and Oncology (ESTRO). Protocol-specific quality control procedures, such as questionnaires, individual case reviews and dummy run procedures will continue to be performed, particularly for trials investigating the most modern technique of radiation therapy delivery.

Besides very productive collaboration with most disease-specific EORTC Groups, the RT Group is also very actively collaborating with other international organisations. Currently several large phase III studies are conducted in co-operation with the most active European, North American and Australian radiation therapy organisations. Furthermore, in 2001, the RT Group Steering Committee changed the format of the biannual Group meetings, implementing disease-oriented working parties, open not only to the members of the EORTC RT Group but also to the active participation of representatives from other Groups, aiming to further facilitate the elaboration of joint clinical studies.

A key achievement was the joint effort of the EORTC RT Group and the Radiation Therapy Oncology Group (RTOG) to set up a common system for reporting and scoring normal tissue late radiation morbidity; this process developed from the original RTOG-EORTC late morbidity scoring scheme to the more recent SOMA-LENT system [2]. This latter system has been validated over the last several years but never reached a high level of clinical acceptance due to its complexity. Therefore, the American National Cancer Institute (NCI) has proposed a review of available late toxicity scoring systems that will start within the next year, and the EORTC RT Group has again been asked for active participation.

Recognising the importance of basic science in modern medicine, a translational research committee composed of a team of young and dedicated scientists has recently been created to support the traditional activities of the Group. It will review all new study proposals with the aim of implementing whenever possible innovative translational research studies in RT trials and also the direct transfer of pertinent basic research knowledge into clinical trial design and implementation.

2. Most recent achievements and future projects

During its long history, the EORTC RT Group has completed a number of pivotal studies that have provided valuable information on the radiation treatment of several disease sites such as head and neck, brain, breast, lung, gastro-intestinal, and genito-urinary cancers. Specific trials investigating fractionation issues, occasionally based on radiobiological concepts and coupled with cell kinetics analysis, have lead to remarkable results. Hereinafter are listed the most recent achievements of the Group and the new projects sorted by disease site.

2.1. Breast cancer

The EORTC RT Group has performed major studies in breast cancer, often in collaboration with the EORTC Breast Group. Among the several studies, we herein summarise the results of the most recently published study.

EORTC trial 10853 investigated in more than 1000 women the value of breast irradiation after local resection of ductal carcinoma *in situ* [3]. After a median follow up of 4.25 years, patients randomised to receive adjuvant radiotherapy had a significant reduction of both invasive and non-invasive ipsilateral recurrence rates.

EORTC trial 22881 investigated the need of a tumour bed boost to improve local tumour control in the conservative treatment of early breast cancer [4]. A treatment arm with homogeneous breast irradiation of 50 Gy plus a 16 Gy boost to the tumour bed for completely resected tumours was compared with homogeneous breast irradiation of 50 Gy without boost. More than 5500 patients were entered in this trial from 31 European centres. After a median follow-up of 5.1 years, 109 loco-regional failures were observed in the boost

Group versus 182 recurrences in the no boost Group, with local control rates at 5 years of 95.7% in boost versus 93.2% in no-boost patient Group ($P=0.0001$). The local failure rates were critically dependent on the age of the patient, as young patients had the largest benefit from the boost. Above the age of 50 years, the boost no longer seems clinically warranted. This study is one of the world's largest pivotal trials and has also succeeded in addressing the cosmetic issues of conservative breast treatment [5]. However, there is still a considerable body of data to be further analysed.

In EORTC trial 22922, patients treated conservatively for early breast cancer are randomised between different volumes of postoperative radiation therapy. The study is accruing well with 42 centres participating and 2555 patients randomised so far (3780 needed). The results will provide an answer to the question of the necessary extension of lymphatic irradiation in early breast cancer.

2.2. Head and neck cancers

From the beginning, the EORTC RT Group has always been very active in investigating new fractionation schemes and/or combined treatments in head and neck cancer patients. Among the trials which changed radiotherapy knowledge and practice, it is worth mentioning briefly the studies that proved the efficacy of hyperfractionation in oropharyngeal tumours and of accelerated fractionation in a broader range of head and neck cancers [6,7]. The final results of a trial of Accelerated Radiotherapy plus Carbogen and Nicotinamide (ARCON), however, did not support this combination of fractionation changes and sensitisers in unselected head and neck tumours [8], because of significant gastrointestinal toxicity observed with the employed dose of 6 g daily of nicotinamide.

Protocol 22931 investigated whether the simultaneous addition of postoperative chemotherapy to radiotherapy improved the loco-regional control and overall survival in patients with resected head and neck cancer; the final results have recently been presented in abstract [9]. The experimental treatment arm consisted of 66 Gy + 100 mg/m^2 CDDP on days 1, 22 and 43 whereas the standard treatment was 66 Gy alone. A total of 334 patients were randomised from 23 European institutions. The patients were well balanced with respect to age, sex, site of the primary and T- and N-stage, histology and tumour margins as well as for the overall treatment time. Grade 3 and 4 functional mucosal reactions were significantly more pronounced with chemo-radiation (44.5% versus 21.3%, $P=0.0004$), which was not true for the objective mucosal reactions. With a median follow-up of 34 months, the DFS rates were 59% for chemo-radiation versus 41% for radiotherapy alone ($P=0.0096$). Overall survival estimates were 65 and 49% ($P=0.0057$). Loco-regional control and progression-free survival were also improved significantly. Chemo-radiation in this pivotal trial might emerge as the new standard treatment for resected high-risk head and neck tumours in the future.

A double-blind placebo-controlled trial investigating the use of weekly subcutaneous Erythropoietin combined with radiation therapy in head and neck tumours was recently opened. This is a large intergroup study with the participation of European and Australian Groups that will also address, in different translational research programmes the open issues related to the complex relation between hypoxia, haemoglobin levels and irradiation outcome.

Together with the EORTC Head and Neck Group, a new trial has been launched investigating the optimal irradiation volumes for metastatic regional nodes from unknown primary tumours. The Group has also recently started collaborating in a RTOG study comparing two fractionation regimens for T2 glottic cancers.

2.3. Prostate cancer

Protocol 22863, carried out with the EORTC Genito-Urinary Group, has definitively demonstrated that for patients with locally advanced disease the association of hormonal treatment with external beam radiotherapy is more efficacious than radiotherapy alone [10]. Another study, protocol 22961, investigating the effect of immediate versus delayed hormone therapy, was closed at the end of September 2001 with more than 1100 patients entered by 40 institutions. This trial will compare the efficacy of prolonged (36 months) versus short-term (6 months) hormone therapy in the same category of patients.

Protocol 22911 is investigating the efficacy of immediate postoperative radiation therapy for patients with pT3 prostate tumours. With nearly 1000 patients entered, this study was likely to be closed to patient entry by the end of 2001. A new study, protocol 22991, has recently been opened, comparing three-dimensional conformal radiotherapy alone to three-dimensional conformal radiotherapy plus short-term hormone therapy in early stage prostate cancer.

A task force on brachytherapy has developed, in co-operation with the European Association of Urology (EAU) and ESTRO, precise guidelines for permanent seed implantation in prostate cancer patients [11].

2.4. Other tumours

The EORTC RT and the EORTC Lung Group have a long history of common studies investigating the feasibility of combined chemo-radiotherapy treatments for lung cancer [12]. A phase III trial comparing sequential

chemo-radiation versus concomitant combined treatment is currently ongoing in patients with inoperable non-small cell lung tumours. An innovative dose-escalation study using modern three-dimensional conformal radiation therapy delivery techniques will be launched in the near future.

The EORTC RT Group has conducted several trials in primary and metastatic brain tumours, often in collaboration with the EORTC Brain Group [13]. Ongoing trials are currently investigating chemo-radiation treatment of grade IV malignant gliomas with the addition of Temozolomide, different schedules of prophylactic cranial irradiation in patients with lung cancer, and optimal management of brain metastases.

The RT Group is also active in the field of gastrointestinal tumours and has a track record of collaboration with the EORTC Gastrointestinal Tract Tumour Group [14]. The Group is currently conducting a large four-arm trial on neo-adjuvant and adjuvant treatment for rectal cancer and has recently joined a French study on oesophageal cancer. New studies on anal and pancreatic cancers are under development and will be activated in the near future.

The RT Group is also currently conducting a phase III study in collaboration with the EORTC Lymphoma Group investigating the optimal extent of irradiation (low-dose total body irradiation versus involved field radiotherapy) in patients with localised low-grade non-Hodgkin's lymphoma and a phase II pilot study of moderate dose radiation therapy in patients with aggressive fibromatosis in collaboration with the EORTC Soft Tissue and Bone Sarcoma Group.

3. Conclusions

The EORTC RT Group is one of the world's most active radiation therapy organisations that has proved able to successfully conduct large-scale clinical trials based on relevant radiobiological questions. Already several years ago, it assumed a leading role in promoting QA in radiation therapy delivery, and it is now recognised as an ideal partner for cancer research by the most important research organisations worldwide. The future challenge of the EORTC RT Group will be an increased transfer of basic science into its protocols through the implementation of relevant translation research programmes. The Group will also embark on phase I clinical studies involving new drugs for concurrent radio-chemotherapy and new radiation technologies like Intensity Modulated Radiation Therapy (IMRT).

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