European Journal of Cancer (2012) **48**, 1048–1054

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Position Paper

Development of clinical trial protocols involving advanced radiation therapy techniques: The European Organisation for Research and Treatment of Cancer Radiation Oncology Group approach

A. Fairchild [a], R. Bar-Deroma [b], L. Collette [a], K. Haustermans [c], C. Hurkmans [d], D. Lacombe [a], P. Maingon [e], P. Poortmans [f], M. Tomsej [g], D.C. Weber [h], V. Gregoire [i,*]

[a] *EORTC Headquarters, Brussels, Belgium*
[b] *Oncology Department, Rambam Medical Centre, Haifa, Israel*
[c] *Dept. of Radiation Oncology, UZ Gasthuisberg, Leuven, Belgium*
[d] *Dept. of Radiation Oncology, Catharina Hospital, Eindhoven, The Netherlands*
[e] *Dept. of Radiotherapy, Centre Georges-Francois-Leclerc, Dijon, France*
[f] *Dept. of Radiation Oncololgy, Institute Verbeeten, Tilburg, The Netherlands*
[g] *Dept. of Radiotherapy, CHU Charleroi, Charleroi, Belgium*
[h] *Dept. of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland*
[i] *Radiation Oncology Dept., Université catholique de Louvain, Cliniques universitaires St-Luc, Brussels, Belgium*

Available online 1 March 2012

KEYWORDS
Radiation therapy
Phase III
Clinical trial
Protocol
Intensity-modulated radiation therapy (IMRT)
Quality assurance

Abstract The European Organisation for Research and Treatment of Cancer (EORTC) Master Protocol for phase III radiation therapy (RT) studies was published in 1995 to define in a consistent sequence the parameters which must be addressed when designing a phase III trial 'from the rationale to the references'. This was originally implemented to assist study investigators and writing committees, and to increase homogeneity within Radiation Oncology Group (ROG) study protocols. However, RT planning, delivery, treatment verification and quality assurance (QA) have evolved significantly over the last 15 years and clinical trial protocols must reflect these developments. The goal of this update is to describe the incorporation of these developments into the EORTC-ROG protocol template. Implementation of QA procedures for advanced RT trials is also briefly described as these essential elements must also be clearly articulated. This guide may assist both investigators participating in current ROG trials and others involved in writing an advanced RT trial protocol.

* *Corresponding author:* Address: Cliniques universitaires St-Luc, Service de Radiothérapie oncologique, 10 Ave Hippocrate, 1200 Brussels, Belgium. Tel.: +32 2 764 9443; fax: +32 2 764 9425.
E-mail address: vincent.gregoire@uclouvain.be (V. Gregoire).

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doi:10.1016/j.ejca.2012.02.008

1. Introduction

Properly conducted trials in radiation oncology are required to establish new treatment approaches in terms of improved tumour control and/or lower complication rates. Interest in the quality of radiation therapy (RT) delivered within a clinical trial setting has increased in parallel with the growing complexity of diagnostic and therapeutic procedures, cost of studies and numbers of patients accrued.[1] The amount of new knowledge generated from each trial must be maximised to optimise shrinking resources.[2] Uncertainties in terms of volume delineation, target and normal tissue doses and machine output may not only decrease the effectiveness of therapeutic management, but increase complication rates and reduce patient quality of life.[3] The worst case scenario is that non-compliant RT in a comparative phase III trial may contribute to a negative statistical conclusion regarding the primary end-point, reflecting the value of treatment of low quality, and thus failing to assess the benefit of the planned RT.[4,5] Such instances also call into question the feasibility of the study treatment.

RT protocols should define all critical procedures in order to minimise variation between investigators.[1] Modern trials are often multidisciplinary, multi-centric and international, further focusing attention on the critically important issue of a clear, well-written protocol, especially if participants' first language is not English. Although a protocol is usually written by experts in a certain disease site, institution investigators may not be familiar with the subject to the same extent. RT protocols must serve the informational needs of many disciplines, such as radiation oncologists, medical physicists, radiotherapy technologists, study nurses and clinical research associates. Therefore, protocol writing should be supported by an infrastructure of experts in areas including data management, bioinformatics, pharmacovigilance and regulatory affairs. Although it can be difficult to write a simple, straightforward but thorough RT protocol on a complex treatment technique, the aim should be to create this document in a manner that addresses potential areas of ambiguity in all steps of treatment preparation, delivery and reporting.

The European Organisation for the Research and Treatment of Cancer (EORTC) is a pan-European structure charged with improving cancer treatment through the testing of new therapeutic strategies in phase III randomised trials. The EORTC also conducts early phase combined modality trials investigating optimal integration of new molecular agents with radiotherapy, and protocols exploring new RT delivery methods. The concept of a Master Protocol for phase III studies was originally considered by the EORTC Radiation Oncology Group (ROG) in the 1990's in order to help facilitate writing and increase consistency of study protocols.[6] The Master Protocol was also instituted to help address disappointing quality assurance (QA) in RT results of past EORTC ROG studies, which has been explained by misinterpretation of protocol instructions.[7–11] In some cases, this inter-centre variation was significant enough to have triggered protocol amendments.[9–11]

The aim of this consensus document is to describe the current EORTC ROG approach to protocol writing of RT trials, focusing on the requirements of advanced external beam delivery techniques in multicentre clinical trials. In addition to the CONSORT guidelines for interpretation and reporting of clinical data,[12] ROG protocols should be clearly aligned with the recommendations of the International Committee on Radiation Units & Measurements (ICRU) Report 83 on prescribing and reporting of intensity-modulated radiation therapy (IMRT).[13] The following parameters must be included in all EORTC ROG clinical protocols unless their omission is clearly justified (Table 1).

2. Radiation therapy

A key component of an effective process improvement and workflow management infrastructure is consistent RT structure and terminology. As such, the use of international recommendations on terminology and prescription practices is mandatory, together with inclusion of uniform naming conventions in a common language.[13]

2.1. Facility and equipment

Describe minimum technical requirements and procedures with which institutions must comply. Allowed equipment and treatment techniques should be described and under which circumstances each may be used. Give information about beam quality, the minimum (and/or maximum) beam energies allowed and required technical capabilities (e.g. intensity-modulated radiation therapy [RT], cone beam CT). Consideration should be given to the foreseen development of new treatment techniques within the lifetime of the trial and a provision for their future use should be included whenever possible.

2.2. Patient positioning and simulation

Explicit patient preparation guidelines should be given, such as bowel and bladder filling instructions. Requirements for the treatment planning CT that should be included are: recommendations on patient positioning and immobilisation; anatomic references for the minimum scan volume; use of contrast or other visualisation aids; range of acceptable slice thickness and maximum inter-slice gap. All potential beam entrance and exit areas should be included in the planning CT range in order to