

The European Organisation for Research and Treatment of Cancer Imaging Programme

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European Organisation for Research and Treatment of Cancer

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Abstract

The European Organisation for Research and Treatment of Cancer (EORTC), an international organisation under Belgian law, develops, conducts, co-ordinates and stimulates translational and clinical research in Europe aimed at improving the management of cancer and related problems by increasing survival and also improving patient quality of life. Imaging is now playing an increasingly important role in the treatment of cancer, and in order to further its mission to improve the standard of cancer treatment through the testing of more effective therapeutic strategies, the EORTC has initiated a cancer imaging programme. The objectives of this programme are to build an image exchange platform for cancer clinical trials, create an EORTC Imaging Group, network with stakeholders in cancer imaging, stimulate the integration of imaging components into EORTC studies, participate in major EU initiatives and link up with US co-operative groups. The EORTC is dedicated to improving the quality and consistency of evaluation of cancer treatment within its clinical trials through the incorporation of imaging technologies used for treatment definition for radiotherapy, staging, prediction and evaluation of response, or pathology.

Keywords

European Organisation for Research and Treatment of Cancer (EORTC), EORTC Imaging Group, cancer, oncology, translational research, clinical research, clinical imaging

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There is currently growing interest in a new generation of anticancer agents – biological response modifiers – that is redefining the manner in which cancer clinical trials are conducted. These novel anticancer agents modulate signal transduction pathways and can affect tumour blood supply, cell growth, cell differentiation or other metastatic processes. These mechanism-based anticancer agents certainly hold promise with respect to fighting cancer, but they also raise new challenges for cancer clinical research.

As anticancer agents, biological response modifiers do not necessarily affect the size of a tumour. The therapeutic end-point for these agents might not be the disappearance of the tumour even though tumour growth itself might have ceased. Instead, subtle changes in the cancer density, the margins of the tumour or other features might signal a useful response status at a very early stage in therapy. It could be that features such as blood flow might provide a significant response measurement. In this context, the ability to measure metabolic changes takes on added significance. There is a need to be able to monitor these specific metabolic changes in order to determine whether these novel anticancer agents are indeed manifesting their intended effect.

For the past decade, a method referred to as Response Evaluation Criteria in Solid Tumours (RECIST) has been used to measure

tumour response utilising imaging modalities such as computed tomography (CT).^{1,2} The European Organisation for Research and Treatment of Cancer (EORTC) was part of the research group that proposed the RECIST criteria along with the National Cancer Institute (NCI) of Canada and the US National Institutes of Health (NIH) NCI. This group reviewed assessment methods for tumours visualised by diagnostic imaging and examined the existing World Health Organization (WHO) method of measurement for evaluating response to treatment in solid tumours. Their work enabled the standardisation of the evaluation of cancer treatment response in clinical trials and became a reference for both scientific publications and regulatory submissions.

RECIST is well suited for monitoring cytotoxic cancer therapies where the expectation is that treatment will lead to a decrease in size or even disappearance of a tumour. However, anticancer agents that modify biological responses require new approaches. There is a need to take into account the improved understanding of cancer biology, the new treatment modalities and the steady progress being made in imaging technologies. There is a need to develop biomarkers with specificity for particular biological processes as well as the means to monitor those biomarkers.

Imaging offers many benefits in cancer therapeutics. Imaging is non-invasive, as opposed to pathology for example, and early

detection of anticancer activity, prediction of efficacy, detection of drug resistance and identification of tumour phenotypes associated with response are all possible. In addition, imaging biomarkers can be used to target specific biological pathways.

Imaging will play an increasingly important role in personalised cancer therapy, and a means to co-ordinate imaging within cancer clinical trials needs to be put in place now. For this reason, the EORTC has initiated a cancer imaging programme in order to further its mission to improve the standard of cancer treatment through the testing of more effective therapeutic strategies.

The EORTC

For nearly 50 years, the EORTC, an international organisation under Belgian law, has been developing, conducting, co-ordinating and stimulating translational and clinical research in Europe aiming to improve the management of cancer and related problems by increasing survival but also patient quality of life. Extensive and comprehensive research in this field is often beyond the means of individual European hospitals and can best be accomplished through the multidisciplinary, multinational efforts of basic scientists and clinicians.

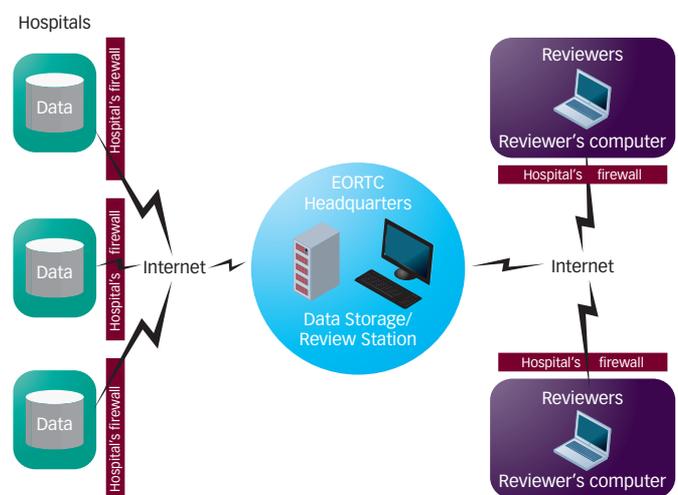
The current EORTC Network comprises over 300 hospitals or cancer centres in over 30 countries. Within this network, some 2,900 collaborators from all disciplines are involved in cancer treatment and research. More than 6,000 patients are entered into EORTC trials each year (database of more than 180,000 patients) and some 50,000 patients are in follow-up. Thirty-six trials are open to patient entry.

The EORTC imaging strategy is multifold. The EORTC plans to participate in major European initiatives that will advance the field of imaging. It is positioning itself as an international reference network for academia and industry, an organisation capable of forming partnerships between academia and industry so as to support the development of quantitative imaging in Belgian, European and trans-Atlantic clinical trials and thereby decrease delays between drug discovery and practice. The EORTC also plans to foster partnerships with other networks, be a key player for imaging training programmes and contribute to the changing clinical research environment for methodology, conduct and analysis, taking into account new imaging end-points in the decision rules.

In this regard, the EORTC has a mission to improve the quality and consistency of evaluation of cancer treatment within its clinical trials through the incorporation of imaging technologies used for treatment definition for radiotherapy, staging, prediction and evaluation of response, or pathology. The objectives of the EORTC imaging initiative were to build an image exchange platform at the EORTC Headquarters and to build the EORTC Imaging Group and a network with stakeholders in cancer imaging, stimulate the integration of imaging components into EORTC studies, participate in major EU initiatives and link up with US co-operative groups.

The EORTC aims to accelerate the access of cancer patients to more effective therapy, and we report here on the EORTC Imaging Platform, a platform that removes many sources of uncertainty in using imaging technologies in the assessment of drug response, and on the EORTC Imaging Group (formed in June 2009 to establish and maintain the scientific and clinical value of advanced imaging).

Figure 1: Firewalls Hinder the Sharing of Imaging Data Collected in Clinical Trials



The EORTC Headquarters Imaging Platform

Before imaging can be successfully integrated into cancer clinical trials, an imaging platform must be built. An imaging platform is necessary because of the many barriers in place that hinder the flow of medical information (see *Figure 1*). Certainly, these barriers are necessary when one considers the confidentiality of medical information, but in order to conduct a cancer clinical trial a means must be found to effectively handle and evaluate the collected imaging data. An imaging platform is a means towards this end.

Prerequisites for an Imaging Platform

Any successful imaging platform should ensure the standardisation of the acquisition of imaging data as well as the quality of those data. The imaging platform should also be able to accommodate data coming from a variety of imaging technologies, such as CT, positron-emission tomography-computed tomography (PET-CT) or magnetic resonance imaging (MRI), among others.

The imaging platform needs to function within the clinical trial setting, and this means that it must be possible for an expert reviewer located at one institution to easily review imaging data that were collected at another. Therefore, the imaging platform needs to be set up so that imaging data can be uploaded from the clinical site and then stored in a central archiving system. The centrally stored data should then be accessible from the reviewer's computer.

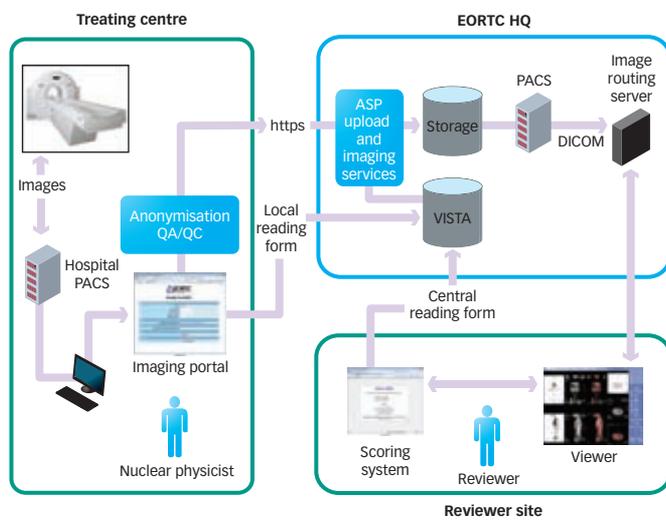
Besides the image itself, imaging data contain many other useful parameters. Parameters such as standard uptake value and quality assurance and quality control quantifiers are all commonly associated with an image, and these must be encoded in the transmitted data set.

Furthermore, the ideal imaging platform should allow for the integration of plug-ins that could automate quality assurance and quality control processes. This is necessary because it should only be possible for a reviewer to upload imaging data that have been validated in terms of quality assurance and quality control. Finally, the processing and analysis of imaging data must support visual analysis.

The EORTC Imaging Platform

The EORTC, in collaboration with Keosys and the EORTC Imaging Group, is building just such an imaging platform for the exchange and

Figure 2: Diagram of the EORTC Imaging Platform Infrastructure



ASP = application service provider; DICOM = digital imaging and communications in medicine; EORTC HQ = European Research and Treatment of Cancer headquarters; PACS = picture archiving and communication system; QA = quality assurance; QC = quality control.

central review of images coming from patients treated in EORTC clinical trials (see Figure 2). The EORTC imaging platform allows clinical centres to upload images and have them reviewed and scored by a panel of expert reviewers.

In order to facilitate the flow of imaging data, the imaging platform incorporates standard protocols that bypass firewall restrictions. It allows clientless installation, an administrator is not needed to manually install a client component on the user's computer, it has a terminal server running as a web application and it supports image viewing and analysis that support the various imaging modalities.

In hospitals, images are usually kept on a picture archiving and communication system (PACS). A nuclear physicist located at the hospital exports these images, anonymises them following in-house guidelines and then connects to the EORTC imaging portal and uploads them using a secure encrypted connection. An automatic procedure built into the imaging platform server then checks the quality and consistency of the uploaded imaging data. Criteria for imaging data can vary from one clinical trial to another, so this analysis step has been designed so that it can be customised according to the particular clinical trial protocol. If the analysis results are acceptable, the image is transferred to the central EORTC Headquarters PACS.

A flow management system at EORTC Headquarters assigns the images to the appropriate reviewer centres and then transparently transmits the imaging data to selected reviewers' workstations in digital imaging and communications in medicine (DICOM) format. Given the large size of these imaging data files, this transfer process could take an impractical amount of time; however, a compression and slicing algorithm that is built into the system reduces the download time to approximately 15 minutes per data set.

Data collected on the transmittal form ensure that the images are automatically linked to the respective patient data in the EORTC clinical database. Upon logging onto the system, reviewers are shown

a list of patients awaiting their review. They select a patient, look at the local reading form data, launch the image viewer and input their reading form. Once the pre-determined quota of reviewers has reviewed the case, a reporter reads all reviews and draws a conclusion. This conclusion is transferred to the patient file in the EORTC database.

The EORTC imaging platform software contains many tools that can assist in the review of an imaging data set. For example, there are algorithms that automatically determine the 3D volume of interest based on whether a tumour region is growing or shrinking, and flexibility is maintained for the user to manually set spatial limits. The platform also contains tools that allow for such tasks as quality control analysis. The report file includes the necessary parameters that define the image, such as the standard uptake value, to help the reviewer analyse the imaging data.

Validation of the EORTC imaging platform is in process, and compliance with the US Food and Drug Administration guidelines on electronic records and electronic signatures (Title 21 CFR Part 11) is also being evaluated.

The EORTC Imaging Group

The EORTC imaging platform is designed to support the use of imaging in EORTC clinical trials, and the EORTC Imaging Group is deeply involved in seeing that imaging technologies are fruitfully and successfully integrated into these trials. The EORTC Imaging Group is a co-operative group within the EORTC Translational Research Division. The Imaging Group operates to establish and maintain the scientific and clinical value of advanced imaging and is involved in the development of specific analytical, review and quality control procedures in the context of clinical trials conducted by the EORTC groups. Ensuring the standardisation of image acquisition and quality assurance for EORTC trials are the main objectives of the Imaging Group, and they aim to increase imaging expertise across the EORTC network. The identification and implementation of predictive and prospective imaging biomarkers are also of particular interest to the Imaging Group.

Integral to the mission of the Imaging Group is to make sure that the EORTC imaging platform is fluid, efficient and capable of handling imaging data collected using various imaging technologies in international cancer clinical trial settings. The Imaging Group is well equipped for this task as it has the expertise to support multidisciplinary studies and applied clinical imaging, as well as research in imaging. Through their work in advancing the use of imaging technologies, they intend to provide input for improving the standard of care for patients with cancer, deliver information needed to make therapeutic go/no-go decisions and explore the biology of disease. The Imaging Group will serve as a forum for creating partnerships for projects in the field of imaging.²

The EORTC Imaging Group is chaired by Professor Sigrid Stroobants of the Universitair Ziekenhuis, Antwerp, Belgium. Professor Stroobants is joined by Vice Chair Professor Jelle Barentsz of Radboud University Nijmegen Medical Center, The Netherlands, Secretary PD Dr Ursula Nestle, University of Freiburg, Germany, and Treasurer Professor Otto Hoekstra, VUMC, Amsterdam, The Netherlands. Notable for the Imaging Group, the Chair and Vice Chair represent different imaging specialities: Professor Stroobants is a specialist in nuclear medicine,

while Professor Barentsz specialises in radiology; thus, the Imaging Group is led by specialists in the two major imaging modalities.

Imaging studies require significant technical support, and a number of Imaging Group Committees have been organised to assist in this endeavour and help the group to achieve its objectives. The Clinical Trials Advisory Committee will ensure optimal use of multimodal imaging technology in EORTC clinical trials through interaction with disease-orientated groups, protocol optimisation, platform development, central review and any other required expertise. The Nuclear Medicine Technologies Committee will ensure optimal use, quality assurance and standardisation of nuclear medicine technologies in clinical trials, and the Radiology Technologies Committee will ensure optimal use, quality assurance and standardisation of CT, MRI and ultrasound in clinical trials. The Imaging in Radiotherapy Committee will incorporate advances in imaging technologies into radiotherapy and establish connections with the radiation oncology community. The New Markers and Technologies Committee will assess, develop and implement appropriate new markers or technologies into cancer clinical trials. The Education and Training Committee will increase imaging expertise across the EORTC Network through training, standardisation of central reading and e-learning. The IG Advisory Committee will liaise with other organisations involved in the field of imaging. Finally, the IT Infrastructure Committee will attend to information technology issues related to the implementation of imaging in clinical trials.

The EORTC has been a pioneer in conducting and co-ordinating collaborative research and large-scale clinical trials in Europe, and many currently available standard cancer treatments are a direct consequence of this continued and systematic effort. By continuing to adapt its structure and functioning, the EORTC intends to conduct clinical and translational research that will meet the challenges of targeted cancer treatment. ■

John Bean is a Medical Science Writer at the European Organisation for Research and Treatment of Cancer (EORTC), where he is active in the EORTC imaging initiative. He received his doctorate in chemistry from Clark University and, supported by a Fulbright Fellowship, pursued post-doctoral studies in receptor–ligand interactions at the Swiss Federal Institute of Technology. Later, at SmithKline Beecham, he used 2D nuclear magnetic resonance (NMR) techniques to investigate bio-active conformations of peptides. Dr Bean has been active in secondary school science education and has designed science laboratories and curricula, and several of his students have had their writing assignments published in science magazines.

Jocelyne Flament works at EORTC Headquarters, where she is responsible for the medical department, including clinical research physicians and pharmacovigilance. She is also in charge of co-ordinating the revival of an EORTC cancer imaging group and the corresponding support infrastructure at EORTC Headquarters. Dr Flament studied medicine in Brussels and then specialised in haematology and pathobiology. After working in an academic hospital in the Brussels area for seven years, she joined Baxter Healthcare's clinical research and development team.

Pascal Ruyskart is Head of the Information Technology Department at EORTC, where he is responsible for the development and implementation of the imaging infrastructure. Following studies in computer science at the Université Libre de Bruxelles, he began his career at the Institut Jules Bordet in Brussels and then joined EORTC 15 years ago, where he was involved in the network and servers architecture. He was responsible for setting up the first online, web-based patient registration and randomisation system for EORTC (ORTA). He led the development of the EORTC Clinical Data Management System (VISTATrials), including the web-based eCRF (RDC) that recently served as a basis for the first imaging project (H10).

Françoise Meunier is Director General of the EORTC, and her mandate is to promote EORTC as a major European organisation in the field of oncology, with a network of 2,500 oncologists in over 300 universities and a Headquarters staff of 160 representing 17 different nationalities. As Director General, she is responsible for the organisation of scientific activities, public relations and medium-term EORTC strategy as defined by the EORTC Board. Before joining EORTC, Dr Meunier was Head of the Infectious Disease Department at the Institut Jules Bordet in Brussels. She completed a research fellowship at the Memorial Sloan-Kettering Cancer Center in New York in 1977–1978 (Fulbright Fellow). In 2009 she received the Pezcoller Foundation–ECCO award in recognition of her unique contribution to oncology and for the dedication of her professional life to the improvement of cancer treatment, care and research. She has published more than 150 peer-reviewed articles and is a member of numerous international scientific societies, including the Belgian Royal Academy of Medicine.

1. Eisenhauer EA, Therasse P, Bogaerts J, et al., New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), *Eur J Cancer*, 2009;45:228.
2. Therasse P, Arbuck SG, Eisenhauer EA, et al., New guidelines to evaluate the response to treatment in solid tumors (RECIST Guidelines), *J Natl Cancer Inst*, 2000;92:205–16.
3. The EORTC Imaging Group will hold its Fall Group Meeting on Friday 17 September 2010 at the VUMC Amsterdam, The Netherlands. For more information visit: www.eortc.be/home/Imaging/meetings.html