EORTC Imaging Group

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ABSTRACT

Imaging data have the potential to provide information on disease profiling pertaining to diagnosis, prognosis, selection of therapy, monitoring of response to therapy and pharmacokinetic information of drugs. Selection of the most appropriate imaging modality for a specific task will be vital for diagnosis, stratification, treatment response or treatment efficacy, toxicity assessment, and treatment outcome measures (progression-free survival). The EORTC Imaging Group was formed to establish and maintain the scientific and clinical value of advanced imaging in EORTC clinical trials. The group focuses on the development of specific analytical and review procedures as well as quality control procedures, in the context of clinical trials conducted by the EORTC groups.

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1. Introduction and history

Imaging data have the potential to provide information on disease profiling pertaining to diagnosis, selection of therapy and monitoring of response to therapy as well as providing information on the prognosis of patient and pharmacokinetic information of drugs.

The EORTC Imaging Group (EORTC IG) traces its roots to the EORTC PET (positron emission tomography) Study Group which was created in 1994. In recognition of equivalent needs in functional Magnetic Resonance Imaging (MRI), the EORTC Functional Imaging Group was formed in 2000, and published EORTC guidelines for the use of FDG-PET in assessing response to therapy.

In 2009, the EORTC IG was founded to ensure standardization of image acquisition and quality assurance for EORTC clinical trials for computed tomography (CT), PET, MRI, and newer imaging modalities as they become available. The group aims to increase molecular and functional imaging, i.e. PET/CT and MRI, expertise across the network, and identify and evaluate predictive and prospective imaging biomarkers of interest in multicenter clinical trials. This should enable more robust planning of treatment such as image-guided radiotherapy (IGRT). The goal of the group is also to guarantee that scientifically interesting imaging questions can be implemented in EORTC clinical trials.

The EORTC IG has set up several committees to assist in achieving these objectives in EORTC multicenter clinical trials: (1) The Clinical Trials Advisory Committee (multimodality) ensures optimal use of multimodal imaging technology through interaction with disease-
Variability introduced by biological factors includes
training committee aims to increase imaging expertise
of interest) or VOI (volume of interest) definitions.
use of contrast agents up to 5.9%, 7 and ROI (region
parameters, image reconstruction settings (up to 50%),
methodology-related factors include scan acquisition
ground for normalization, and quality of administration.
inter-observer variability up to 17%, 6 choice of back-
SUVmax, 3 calibration between PET scanner and dose
performance over time has shown 10.7% differences in
clinical trials. 1 Quantification of FDG PET/CT studies is
quality data across different imaging sites in multicenter
standardization of acquisition, reconstruction, interpre-
tation of CT, MRI, and Ultrasound. (4) The Imaging in Radio-
therapy Committee (multimodality) aims to incorporate
advances in imaging technologies into radiotherapy, in-
cluding radiotherapy planning, response assessment and
distinguishing between disease progression and normal
tissue toxicity, and establish bridges with the radiation
oncology community. Finally, (5) The Education and
Training Committee aims to increase imaging expertise
across the network through training, standardization of
central reading, and eLearning.

2. An approach to standardizing imaging readouts
for use in multicenter trials: The EORTC, EANM,
EARL Quantitative PET Imaging accreditation
program

In PET imaging, optimal image quality is essential both
for visual interpretation as well as for quantification.
Standardization of acquisition, reconstruction, interpret-
tation and quantification of the images ensures high-
quality data across different imaging sites in multicenter
clinical trials. 1 Quantification of FDG PET/CT studies is
usually performed by Standardized Uptake Values (SUVs).
SUV is defined as the average activity concentration at
time t (measured in kBecquerels/mL) divided by dose
at time of injection (in MBecquerels) per body mass
(in kg). However, other normalizations, such as lean body
mass and body surface area can be used. Apart from
normalization, a number of factors – both technical and
biological – can affect image quality and quantification,
such as hardware, volume of interest definition and
plasma glucose, so that standardized methods of
obtaining SUV are currently under discussion.

Technical factors that affect SUV are hardware or
methodology related. Inter-scanner variability up to 6%
over scanners of the same model has been observed. 2
In a double baseline study, variation in scanner
performance over time has shown 10.7% differences in
SUVmax, 3 calibration between PET scanner and dose
calibrator up to 10%, 4 residual activity in syringe and
tubing, timing mismatch up to 9.5% for 15 minutes, 5
inter-observer variability up to 17%, 6 choice of back-
ground for normalization, and quality of administration.
Methodology-related factors include scan acquisition
parameters, image reconstruction settings (up to 50%),
use of contrast agents up to 5.9%, 7 and ROI (region
of interest) or VOI (volume of interest) definitions.
Variability introduced by biological factors includes
uptake time which for high-grade tumors can be as
much as 30%, 8 motion from gross patient movement
and respiration, blood glucose levels, change in patient
weight during treatment, and body fat composition. A
minimum standard for acquisition, reconstruction and
interpretation of PET scans in multicenter clinical trials
setting therefore is necessary.

In addition to standardization alone, as FDG PET/CT
quantification depends strongly on spatial resolution of
the reconstructed PET images, multicenter quantitative
PET studies require harmonization of image character-
istics. Harmonization aims at minimizing inter-scanner
and inter-institute differences in image quality and
quantification by means of acquiring data with identical
spatial resolution. The European Association of Nuclear
Medicine (EANM) guideline for quantitative FDG PET/CT
studies therefore provides minimal standards for patient
preparation and scan acquisition, and proposes specific
quality control (QC) measures for harmonizing scanner
performance. The proposed multicenter QC program
aims at verification of PET/CT system calibration, image
quantification, and tracks the scanner performance.
Experiments are based on a uniform cylindrical phantom
(15–30 cm diameter) for scanner calibration verification
and an adjusted NEMA NU 2-2001 image quality (IQ)
phantom to measure (and optimize) SUV recovery
efficiencies as a function of sphere size (reflecting
effective image resolution).

In order to implement the EANM guideline and the
QC procedures, an accreditation program was
set up and run under the direction of EARL (EANM
Research Ltd.) and the EORTC. The accreditation program
is based on QC experiments as described in the EANM
guideline. Manuals, SOPs and online questionnaires were
completed in August 2010 and training of an EARL
coordinator was provided in September 2010. To further
facilitate and standardize the accreditation program,
dedicated software tools for automated analysis of
the QC experiments were developed. These tools
allow automatic VOI (volume of interest) placement,
verification of calibration, and verification of inter- and
intra-plane uniformity. The image quantification QC
software includes automated assessment of volume and
SUV recovery coefficients, cold spot recovery using a
central insert to verify accuracy of scatter correction,
and verification of calibration using several VOIs placed
in the uniform background compartment. Results are
(automatically) compared with reference values to assess
if scanner performance meets the harmonizing quality
standards. All QC experiments are centrally analyzed
at the EARL headquarters and results are stored in
a database. An internet-based submission procedure
has been set up so that imaging sites can upload
QC experiment results to EARL headquarters.

A pilot phase of this accreditation program linked
to the EORTC 22071–24071 trial commenced in October
2010. It included 11 sites and a total of 12 PET/CT systems. All QC experiments were executed over a 3-month period and data were provided to the EARL headquarters. Initial central analysis showed that two out of eleven imaging sites needed to recalibrate their PET/CT systems and adjust image reconstruction settings. Following these corrective actions, all sites met minimal and harmonizing quantitative standards, and received approval. Minor start-up issues such as reading image files, ambiguities with respect to reporting times, phantom availability, and data entry issues were resolved within the three-month time frame.

3. CT imaging

CT is a widely available imaging technique with a high spatial resolution, for which tumor evaluation criteria have been well established. For many solid tumors, CT remains the main imaging method for the assessment of (anatomic) tumor response. Because of the wide and frequent use of CT for morphologic oncologic staging in daily clinical routine, it would appear almost redundant to discuss the need for standardization. However, just because of its wide routine application, it is not implicit that image acquisition and quantification technique are the same and replicable. Delineation of tumor borders is not only determined by factors related to tumor type and tumor growth but also to the CT scanning technique. This makes the need for standardization immediately apparent. Factors determining image quality in CT are image acquisition and reconstruction parameters as well as contrast injection parameters that describe how intravenous contrast agents are administered. These factors determine not only spatial resolution but also tumor-tissue contrast which crucially affects any quantification.

CT performance has advanced rapidly. The scan range that can be covered at minimum section thickness within a fixed scan duration has doubled every two years for more than a decade. For almost ten years now, isotropic resolution is a fact with modern CT scanners. This means that image quality is no longer higher for axial sections than for coronal or sagittal sections. Submillimeter resolution in any imaging plane is nowadays considered standard. While CT is able to provide detailed tumor assessment in three dimensions, most measurement criteria are still based on two-dimensional measurements in the axial plane. This does not reflect the capabilities of modern technology and the general availability of 16-slice CT (or even more) scanners. Volumetric evaluation is possible for lung nodules and becomes an option also for lymph nodes and lesions in other organs. However, accuracy and reproducibility of results strongly depend on the semi-automated software used for analysis and need to be standardized for multicenter trials.

Since the intrinsic tissue contrast in CT is minimal due to X-ray attenuation, the differential increase in attenuation due to the intravenously injected contrast material is crucial for tumor delineation. With modern CT (>16 detector rows), scanning of the chest or the abdomen in less than 10s has become possible and allows for submillimeter isotropic volumetric data acquisition during specific phases of perfusion (arterial, portal venous, equilibrium, etc.) after IV contrast injection. Depending on tumor biology, the phase in which the tumor is best delineated varies. Standardization of the acquisition phase is therefore mandatory for large multicenter trials to ensure comparability of results. CT perfusion imaging is an emerging technology that can be used to derive changes in blood flow, blood volume, mean transit time and permeability. CT perfusion is therefore able to provide functional information about the microvascular environment and reflects angiogenesis and leakiness of the capillary system. Software tools for deriving these functional parameters are frequently vendor-specific and lack comparability. To be used in multicenter clinical trials, standardization is required. This includes the use of identical contrast injection protocols, identical scan sequences, and identical evaluation software to ensure comparability of the quantified results across sites.

4. Standardizing MRI readouts for use in multicenter trials

Unlike CT where tissue contrast is dependent on its X-ray attenuation by virtue of its density, the mechanisms used to generate tissue contrast in MRI are complex and depend on the relaxivity of free water within tissues determined by their molecular interactions. A number of hardware (static magnetic field strength, radiofrequency [rf] signal transmitters, rf signal receivers, magnetic field gradients) as well as software (length, amplitude, duration, spacing of the rf pulses and their sequence) parameters will affect the emitted signal strength, and hence tissue contrast. Primarily, the instrumentation itself determines the received signal and standardization of readouts will need to take account of static field strength, particularly with a variety ranging from 0.5Tesla (T) to 3.0T and now even 7.0T available for human imaging.

Currently the quantified parameters most commonly used in oncology as biomarkers of treatment response are those reporting on lesion water content (T2 [transverse relaxation time] relaxivity), vascularity (derived from dynamic contrast enhanced examinations) and tissue cellular content (derived from diffusion-weighted sequences). The contrast mechanisms generating these parameters are not field-strength dependent. However, their reproducibility, particularly in a multicenter setting, can be extremely variable with quoted values of 15–40% for DCE, and 7–15% for the apparent diffusion.
The greater the SNR from a lesion, the more likely the measurement is to be reproducible. Use of a high static field strength (1.5T or 3T), optimal coil combinations for signal reception and best choice of sequence parameters, repetition time, echo time, flip angle, acquisition matrix, field of view, slice thickness) is required to achieve this. In a multicenter trial these parameters need to be standardized across the portfolio of scanners to be used, and regular QA needs to be done using test objects to ensure that SNR is maintained within acceptable limits without unwanted artifacts. For DCE-MRI the temporal sampling rate will affect accuracy of the derived parameters and hence their reproducibility. An optimal sampling rate is a compromise between spatial and temporal resolution which is affected by the minimum repetition time of the sequence; usually rates of around 3–4 seconds may be achieved for 15–20 slices with a 0.6 × 0.6 × 5 mm spatial resolution. With diffusion-weighted imaging echo-planar readouts are preferred over turbo-spin-echo techniques as they are rapid and effectively “freeze” motion, although distortion from field inhomogeneities and eddy currents can limit their interpretation. Use of a low b-value (a minimum of 100 mm²/s to avoid variable microperfusion effects seen at lower b-values) and a high b-value (~1000 mm²/s) enables calculation of the rate of decay of signal intensity between them which represents the apparent diffusion coefficient. Optimal choice of b-values depends on the ADC of the tissue itself and needs to be established and agreed prior to trial commencement.

4.2. Data analysis

The methodology used for processing the acquired signal introduces a further source of variation. Contrast to noise critically affects lesion conspicuity and determines region of interest delineation. For DCE-MRI data the arterial input function (AIF) may be measured on an individual basis or use of a population-based AIF may be preferred. The latter has the advantage of better repeatability and reduces measurement error. For DW-MRI, multiple b-values in the acquisition enable use of a model that fits the signal decay (bi- or multi-exponential) and potentially yields a more accurate and reproducible result. The number and range of derived apparent diffusion coefficient values in the included pixels critically affects data interpretation because threshold values are commonly used to differentiate tumour from non-tumour tissues. Therefore choice of sequence for lesion delineation, methodology of delineation (manual, automated, semi-automated), model used to fit the data and threshold values to be used need to be clarified and approved at the outset for individual trials.

5. Online central review and quality control during a trial

From the pilot described above, as well as from ongoing multicenter studies that include imaging, we have learned that centralized prospective QC of the (patient’s) scans and prompt feedback to the imaging sites is paramount to ensure successful execution of the imaging guidelines and achieving the trial protocol objectives. There is an increased susceptibility to image quality defects soon after start of a multicenter imaging trial and after the addition of new imaging equipment. The EORTC IG started a QC/QA program and will monitor imaging guidelines compliance across the different imaging modalities on an ongoing basis. For some multicenter clinical trials the EORTC IG has produced standardized or harmonized imaging protocols for acquisition and reconstruction parameters and QC/QA of scans. An additional goal of the EORTC IG is to organize and execute the standardization of DWI-MRI scans across imaging centers, more specifically within the chest and abdomen under the QuIC-ConCePT program. 

Over the past few years, members of the EORTC IG have been involved in several studies, among which were:
- The H10 EORTC/GELA/IIL randomized Intergroup trial on early FDG-PET scan guided treatment adaptation versus standard combined modality treatment in patients with supradiaphragmatic stage I/II Hodgkin’s lymphoma (EORTC 20051).
- A randomized double blind phase III trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or following prior therapy (EORTC 62072).
- Randomized trial assessing the significance of Bevacizumab in recurrent grade II and grade III gliomas – the TAVAREC trial (EORTC 26091).
- Phase III trial on concurrent and adjuvant temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma – the CATNON intergroup trial (EORTC 26053).

6. Web-based analysis for multiple readers: the EORTC Imaging Platform

Although the studies mentioned above have demonstrated the feasibility of performing centralized review of imaging during the execution of a clinical trial there remains a need for improving image data transfer and central image viewing/interpretation. The EORTC Imaging Platform in collaboration with Keosys, an SME
specializing in medical imaging IT applied to clinical research and medical diagnostics, was established to enable the development of a variety of image interpretation and analysis methodologies that suit multimodality image data and image assessment requirements for a variety of trial designs. This platform supports both nuclear medicine and radiology data sets that can be analyzed for staging, evaluation of response, prediction of response, and correlation with pathology. This level of incorporation of imaging technologies into the framework of clinical trials could fully exploit the potential of imaging for optimizing treatment so that the appropriate treatments can be delivered to patients who are most likely to benefit. Use of imaging to aid in decision making during early drug development trials should accelerate patients’ access to more effective therapy. As part of this long-term goal, the validation of functional biomarkers is the key.

7. QuIC-ConCePT − Quantitative Imaging in Cancer: Connecting Cellular Processes with Therapy

The Innovative Medicines Initiative (IMI) was set up to support faster discovery and development of better medicines for patients and to enhance Europe’s competitiveness by ensuring a dynamic European biopharmaceutical sector. The QuIC-ConCePT consortium was assembled to answer the IMI call for Imaging Biomarkers (IBs) for anticancer drug development. A major objective of QuIC-ConCePT is to qualify IBs of tumor cell proliferation, apoptosis, and necrosis that will allow drug developers to reliably demonstrate the modulation of these pathologic processes in patients with malignant tumors in clinical trials. QuIC-ConCePT has the unique opportunity to deliver tools which could markedly improve drug development and benefit cancer patients not only in Europe but worldwide.

It is envisioned that by 2016, drug developers will be able to incorporate IBs quantified and validated by the QuIC-ConCePT program in Phase I trials of investigational therapies and be confident that the IBs are technically valid, that a measured change in the IBs faithfully reflects the desired change in the underlying tumor pathology, and that the IBs can be readily deployed in multiple cancer centers in a robust, consistent, ethical, and cost-effective way acceptable to the patients.

IBs of tumor cell proliferation and necrosis will be developed from 3′-deoxy-3′-[18F]fluorothymidine (FLT) PET and apparent diffusion coefficient (ADC) of water protons measured by MRI, respectively. Recognizing that the science around apoptosis tracers is less secure, studies will initially focus on the novel isatin-5 sulfonamide PET tracer [18F]ICMT-11 (ICMT-11), but the work plan allows additional or alternative apoptosis tracers to be utilized in later years.

A more exploratory objective of QuIC-ConCePT includes a portfolio of highly innovative approaches to devise, evaluate, and introduce IBs of invasion and metastasis.

Overall, QuIC-ConCePT will be delivered using a creative and comprehensive portfolio of animal, human, image analysis, and regulatory work. The project plans to deliver image acquisition and analysis protocols which are technically valid, standardized, and suitable for multicenter use. The plan is to evaluate these IBs, assess their reproducibility, effects of intervention, timing, dose–response, and imaging–histopathology correlation in animals and patients.

Platforms for data acquisition, analysis, and dissemination will be standardized and integrated across the consortium in order to support this project, and an approach based on data collection, transfer, and archiving mechanisms will be adopted.

8. Imaging in radiation oncology

Although the imaging methods used in radiation oncology are the same as used for diagnostic questions, aims and scope of imaging in radiation oncology differ substantially from diagnostic applications in medical oncology. Oncological image data are the treatment tools in the hand of the radiation oncologist guiding indications, target volume selection and delineation, normal tissue identification, response prediction and monitoring, and they provide relevant post-treatment information on local tumor control and normal tissue reactions. In addition, information regarding biological processes such as hypoxia, metabolism, etc. that is available from molecular and functional imaging can potentially be used to customize radiation therapy planning. Imaging in radiation oncology is therefore an additional focus of the EORTC IG. In close collaboration with the Radiation Oncology Group and the disease-oriented Groups, the EORTC IG assists the development of radiotherapy protocols related to imaging. Beyond this, imaging questions in radiotherapy will be addressed in imaging trials which are companion protocols to the EORTC studies including radiotherapy. Furthermore, the infrastructural possibilities are presently being created for research on imaging changes due to tumor response and normal tissue reactions after radiation therapy in relation to dose distributions and clinical data.

9. NCI–EORTC collaboration in clinical imaging

The Division of Cancer Treatment and Diagnosis (DCTD) at the National Cancer Institute (NCI) in the United States has a long and productive history of collaboration with the EORTC on imaging issues in clinical trials. In particular, the Cancer Imaging
Program (http://imaging.cancer.gov) within DCTD has been working closely with the EORTC both on RECIST as well as imaging activities in EORTC trials. Collaborations have included multiple meetings and strategy sessions both in the USA and in Brussels over the past several years, as well as an extended visit to Brussels during the time when the EORTC Imaging Program was conceived and developed. In these ongoing interactions, the Cancer Imaging Program has shared its experiences with developing and managing clinical trials in imaging in the NCI cooperative group system. This NCI–EORTC collaboration aims to enhance the standardization of imaging-related processes in order to increase the utility of data from both NCI and EORTC trials evaluating molecular and functional imaging tools to improve cancer diagnosis, molecular stratification of tumor subtypes, as well as improve response assessment.

Highlights of these ongoing discussions include activities to enhance interaction between the oncologists and imagers during study concept and design and development of successful strategies for either primary or secondary imaging aims in EORTC trials. Issues and processes regarding site qualification (http://www.acrin.org/CORELABS/NCICQIEQUALIFICATIONPROGRAM.aspx), the establishment and operations related to imaging core labs with regard to imaging acquisition SOPs, central review as well as the evaluation process for imaging tools are addressed on an ongoing basis.

10. Summary

The EORTC recognizes the crucial role of imaging in clinical trials. As we advance towards a personalized medicine approach, selection of the most appropriate imaging modality for a specific task will be vital for diagnosis, stratification, treatment response or treatment efficacy, toxicity assessment, and treatment outcome measures (progression-free survival). The EORTC therefore established the EORTC IG to enhance clinical imaging expertise and develop multicenter imaging QA/QC programs and guidelines. To complement this effort, the EORTC is investing in and setting up a web-based system for central image review, analysis, and reporting, and it participates in a European consortium for the implementation of various imaging biomarkers as validated and approved tools in drug development trials.

11. Conflict of interest statement

The authors declare no conflicts of interest.