12 INVITED

New imaging in cancer clinical trials

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There is increasing use of novel imaging methods in oncology trials. Aims include the development of early indicators of clinical response, proof of principle or pharmacodynamics studies. Methodology involves contrast enhanced or radio isotope techniques such as DCE-MRI or FDG PET where the physiological properties of the probe determine information available, and modality sensitive studies such as diffusion weighted or spectroscopy MRI.
In order to carry out these studies the investigator must have expert help to address important considerations. Imaging tests must be practical, affordable, ethical and relevant. Analysis of the results of tests requires quality control and knowledge of inter and intra patient reproducibility. Data must be analyzed and handled according to the same constraints as all clinical trials data. These issues are particularly difficult when setting up multi-centre trials.
This talk reviews the various imaging approaches available, potential problems and possible strategies.

13 INVITED

A clinical development paradigm for cancer immunotherapies: novel endpoints

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The effect of cancer immunotherapies is on the immune system and not directly on the tumor. The kinetics of immunotherapy is characterized by a cellular immune response followed by potential changes in tumor burden or patient survival. To adequately investigate immunotherapies in clinical trials, a new development paradigm including reconsideration of established endpoints addressing this biology is needed. Between 2004 and 2009 several initiatives across the cancer immunotherapy community were facilitated by the Cancer Vaccine Consortium of the Cancer Research Institute (CVC-CRI). They systematically evolved an immunotherapy-focused clinical development paradigm and proposed to re-define trial endpoints. On that basis, analysis of several large data sets generated throughout the immunotherapy community support three novel endpoint proposals: (1) Results from T-cell immune response assays are highly variable and often non-reproducible. Harmonization of assays can minimize this variability and support to establish cellular immune response as a biomarker and test it for clinical surrogacy. (2) Immunotherapy induces novel patterns of anti-tumor response not captured by WHO or RECIST criteria. New immune-related Response Criteria (irRC) were defined which more comprehensively capture all response patterns. (3) Survival curves in randomized immunotherapy trials can show a delayed separation, which can impact study results. Altered statistical models are needed to describe the hazard ratios as a function of time, and differentiate them before and after separation of curves to improve planning of Phase 3 trials. Taken together, these recommendations may improve our tools for cancer immunotherapy investigations.

Advocacy session (Mon, 21 Sep, 11:00−13:00)
Advocacy in practice

14 INVITED

Patient groups − meeting the challenge of sustainable funding

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Advocating for a cause has been part of peoples behaviour for centuries. This is what is entailed in moving away from the personal experience to advocating for a cause that is much broader and in using this experience to effect change.
Where patient rights are concerned individulas have organised themselves into groups in order to raise their voices, to have dignity and equality in key issues, and to finally take part in the decision making process.
Patient groups have had to become more and more organised and structured, voices have to be well informed and well educated, in order to maintain the strength in collective action.Patient groups have in many cases moved away from being seen as threatening to professional and scientific organisations to being equal partners.Health care professionals have been under pressure to recognise and follow these changes, while patient groups have had to rise to a different set of challenges.
The changing voice of patient advocacy has led to the voices leading to political change. It has led to legislations that have safeguarded patient rights, that have led to the aims and goals placed by cancer advocacy movements to be translated into governmental policies and decisions, it has led to lobbying at national and other levels, thus placing the foundations for all that has been achieved in the revolution of cancer diagnosis, prevention and treatments.
Patient rights have been cemented by Charters and even acquired legal status so that they are not left up to individuals.
As science has progressed, issues have become more complicated, and patient groups have had to become more diverse and work together not only with professionals, but also with media, politicians and industry. This has in its turn created new realities for the processes needed by patient groups and placed demands on their needs for funding.
Issues related to the source of funding, the necessary transparency and the diversity have been in the forefront of many discussions over the last few years.
The issue of sustainable funding and the relationship of patient groups to industry has been a source of debate and often of controversy.
Patient advocacy is never static, it is a changing journey that aims at impacting positively on all those affected by a disease. The credibility of this voice will determine its effectiveness and strength- and this is what is required when any patient group is brought before the issues related to funding.

Society session (Mon, 21 Sep, 11:00−13:00)
The European Society for Therapeutic Radiology and Oncology (ESTRO)

15 Klaas Breur Award

From patients to Voxels: Individualized oncology and "Voxel control/complication probability"

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*Inter*patient heterogeneity: the need of a "Decision Support System" to facilitate tailored oncology.
Over the past decades we have witnessed an unprecedented increase in our basic understanding of cancer at molecular level, experienced a huge improvement in medical technology and have access to an ever increasing amount of data on cancer. As a consequence, modern medical diagnostic systems confront doctors with a flood of digital and molecular data.as well as a greater than ever amount of therapeutic options. "One size fits all" and "more for all" are no longer an option. Doctors are notorious for being bad at predicting the outcome of various treatments. Therefore doctors need a "*Decision Support System"* (DSS) which not only integrates all diagnostic information and therapeutic options but also, in the future, will take into account the wishes of the patient. Such programmes will make it possible for medical professionals to propose tailored made treatment plans to patients. We anticipate that DSS will become compulsory as Treatment Planning Systems are presently for complex Radiation. An example of first generation DSS, namely validated nomograms or gene signatures in solid cancer will be presented (Valdagni *et al.* IJROBP 08; Dehing *et al.* IJROBP 08−09; Starmans *et al.* BJC 08; van Stiphout *et al.).* The development of DSS has already made an impact on the way we carry out clinical research.
*Intra*patient heterogeneity: the need of "Voxel Maps & "Uncertainty Based Planning"
It is now clear that both tumours and many dose-limiting organs are not homogeneous structures with respect to their biology, environment and radiation sensitivity. Importantly, new imaging modalities are enabling the possibility of both assessing this heterogeneity and incorporating it into therapeutic decisions.
We hypothesise that future processes of radiation oncology will be based no longer on margins, but on at least *two probability maps* and verification of the delivered dose. (1) *Imaging-based Voxel Control Probability (VCP)* or *Parametric Response Map* which consists of fused images before and during treatment that will lead to information on the probability of relapse per voxel (Laprie *et al.* IJROBP 2008; Galban *et al.* Nature Med 09; Aerts *et al.;* Petit *et al*. R&O 2009). This allows optimization of the tumour dose distribution to minimize the probability on residual disease. (2) *Voxel dose probability,* describes the chance that a voxel has of actually receiving a certain dose given a planned dose distribution. This is needed to make the multi-dose level treatment plan more robust when not using margins. (3) Verification of the actual cumulative dose delivered using *3D in vivo dosimetry* (van Elmpt *et al.* IJROBP 09). Further refinements of this approach are possible by taking into account the effect of *systemic treatments* and other *clinical, biological and genetic factors* present in the above mentioned DSS.

Conclusions: Individualized oncology will *revolutionize* health care providers: it will increase the complexity of health care but not necessarily increase the costs and it will improve the therapeutic ratio of our treatments through a better use of the existing knowledge. We anticipate that Decision Support Systems will.be the cornerstone of this revolution. Voxel Control/Complication Probability will give new opportunities to modern high precision radiation oncology. It will allow sculpting radiation dose alone or combined with drugs by taking advantage of tumour and normal tissue heterogeneity. In short, *both intra and interpatient heterogeneity give* new opportunities to improve our treatments

16 INVITED

Educating RTTS – a European adventure

M. Coffey. *St. James' Hospital Trinity Centre for Health Science, Division of Radiation Therapy, School of Medicine, Dublin, Ireland*

Background: The word education comes from the Latin *e-ducere* to lead out. Socrates saw education as drawing out what was already within the student. Education is a collaborative enabling process between the teacher and the student to stimulate a continuously enquiring mind. Essentially we fail if our students do not ultimately know or are not able to do and achieve more than we have.
Education should be an equaliser bringing professional freedom and autonomy. The education level of RTTs impacts on professional practice, multidisciplinary relationships and ultimately the preparation and delivery of optimum treatment to our patients. The theme of this presentation is on the efforts that have been made to improve education in order to enable RTTs to achieve autonomy and greater professionalism.
Education programmes for RTTs vary very significantly across the world, ranging from no specific education to an honours degree. This variation is also reflected in the lack of a unified title with as many as 50 different titles for this professional group. The variation in title has many implications for education and practice and results in a lack of recognition of the RTT internationally.
Over a twenty year period, I have developed the radiation therapy honours BSc programme in Trinity College Dublin and been involved in education initiatives such as the European Core Curriculum for RTTs, organising biannual conferences in conjunction with the main ESTRO Conference and the Physics meeting, developing and facilitating short courses and the final, and most exciting to date, the Train the Trainers project.
Train the Trainers: Twenty three participants, representing eight countries, were accepted onto the Train the Trainers project. The participants spent one week in Vienna in August 2008 where they were assisted by the teaching faculty to prepare an outline of a short course on a subject of their choice to deliver to a local audience of RTTs in their own country. Issues relating to the practical organisation of the short course were also considered. Each group committed to delivering three short courses over a two year period and to consider how the topic chosen could then be integrated into their national education programme.
Seven of the participating countries succeeded in preparing and delivering a short course. The topics covered a wide range of areas relevant to the local situation. Several of the countries attended each others courses and are making plans to share further short courses in the future. A feedback session is scheduled for August 2009 when each group will share their experience and discuss how they will now proceed.
During this presentation I will describe my experiences both nationally and internationally in raising the education level and professional profile of RTTs and how this work might be continued in the future.

17 Emmanuel van der Schueren Award

PET-CT imaging in radiation oncology

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Positron emission tomography (PET) with fluorodeoxyglucose (FDG) is a useful imaging tool in the management of cancer patients. The potential gains of integrated PETCT imaging are progressively being recognized. FDG-PET is able to measure and visualize metabolic changes in cancer cells. This feature results in the ability to distinguish viable tumor from scar tissue, in the detection of tumor foci at an earlier stage than possible by conventional anatomic imaging and in the measurement of alterations in tumor metabolism, indicative of tumor response to therapy. PET provides biological tumor information complementary to anatomical imaging by CT or MRI. Integrated PET-CT has found its way into clinical practice and FDG-PET is being introduced for staging, detection of recurrences, radiation treatment planning and therapy response monitoring and prediction. In addition to FDG, other PET tracers are available for imaging specific biological tumor characteristics involved in radiation resistance, such as hypoxia and proliferation.
Notwithstanding the potential of PET-CT, a critical appraisal of the current clinical state-of-the-art and the experimental application of this novel modality is necessary to allow timely implementation of clinical trials in daily patient care, but also to avoid overutilization.

18 INVITED

Combining EGFR inhibitors with radiation

P. Harari[1]. [1]*University of Wisconsin, Dept of Human Oncology, Madison, USA*

The incorporation of molecular targeted therapies into modern cancer treatment regimens is relatively recent, reflecting several decades of molecular biology coming to fruition in the form of new anti-cancer drugs. The EGFR inhibitors are one class of highly promising agents in this arena. Thousands of cancer patients are currently receiving EGFR inhibitors and a broad series of clinical trials that incorporate these agents are in progress. Combining EGFR inhibitors with radiation has shown particular promise for patients with cancers of the H&N. Indeed, the first Phase III clinical trial to identify a survival advantage when combining a molecular targeting agent (anti-EGFR) with radiation emerged fairly recently in H&N cancer (NEJM 354:567−78, 2006).
Accompanying the promising clinical development of EGFR inhibitors in cancer therapy are several challenges. For example, molecular strategies of EGFR inhibition demonstrate major tumor regression in approximately 10−20% of cancer patients. However, many tumors do not show response to EGFR inhibition and some responders eventually manifest resistance to treatment. The underlying mechanisms of intrinsic and acquired resistance to EGFR inhibitors remain largely unexplored. Although the toxicity profiles for EGFR inhibitors do appear milder than that of conventional cytotoxic chemotherapy agents, the unique toxicities of EGFR agents are nonetheless important to recognize and treat appropriately. Finally, many of the new molecular targeted therapies (including EGFR inhibitors) are remarkably expensive. This high cost reflects the manner in which new drugs are discovered, developed and promoted in the current era, and this feature carries implications regarding the broad availability of these new cancer drugs in the future.
The logical integration of basic science with clinical research will further define the spectrum of benefits and toxicities associated with each new cancer therapy. This is certainly true for the combination of EGFR inhibitors with radiation (or chemoradiation); an area that is advancing, but still at a relatively early stage of overall development. As with all treatment advances, it is valuable for oncologists to remain actively engaged in evaluating the rational and judicious application of each new treatment approach.

19 INVITED

Identification of gene variants and gene expression profiles predicting long term adverse side effects of radiation treatment in breast cancer patients

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In breast cancer (BC) patients with regional lymph node metastases loco-regional radiotherapy (RT) is an established adjuvant treatment. Improved detection and early diagnosis are likely to increase the importance of loco-regional control and hence the success of RT. Radiation oncologists have for a long time known that individuals respond differently to radiation. In addition to the variation in tumour response, some patients show severe side effects when exposed to small doses of radiation, while others tolerate larger doses without much complication. To be able to protect radiation sensitive (RS) patients against the adverse side effects of RT, identification of such patients before initiating therapy is needed. RT kills cells unselectively and irradiation of normal tissue may cause severe side effects that appear at different time points. Acute side effects may emerge during or shortly after a course of RT and these early reactions condition for many BC survivors, leading to a reduction in quality of life. To explore the underlying cause of radiation sensitivity we have taken several approaches. Germline variation in genes like *ATM, CHK2*, *BRCA1/2* and *GSTs* are studied in several series like the WECARE (Women's Environment Cancer and Radiation Exposure) involving 700 cases with contra lateral BC and 1400 matched unilateral BC with detailed information about radiation treatment, and in a series of 245 receiving a high dose of radiation compared to a control series receiving standard dose, both extensively evaluated for radiation damage 10 – 15 years after treatment. These studies are ongoing and updated results will be reported.
Gene expression profiling of fibroblasts exposed to radiation form BC patients previously treated with IR and evaluated for response and morbidity identified a set of genes involved in extracellular matrix to predict fibrosis.