

**IS1****EORTC RADIO THERAPY GROUP: CURRENT STUDIES AND PROJECTS**

*Mirimanoff RO*

*EORTC Radiotherapy Group Chair, on behalf of the EORTC Radiotherapy Group*

*Purpose:*

To present the on-going studies and projects of the EORTC Radiotherapy Group (RTG) to the Swiss Radiation Oncology community.

*Background:*

EORTC is one of the largest cancer clinical research organizations worldwide and accrues more than 6000 patients per year. The RTG is the second largest of the 26 EORTC groups and includes more than 1000 patients per year in clinical trials. At present, 12 studies are open and 6 are in preparation. Five pivotal trials have been completed in the last 2 years and are now under evaluation. Swiss centres have been active in some of these.

*On-going studies:*

For brain metastases (1-3), trial 22952 evaluates the need for whole brain irradiation after surgery or radiosurgery. In head and neck (H&N) cancers, trial 24954 compares sequential to alternating RT-CT in hypopharynx-larynx cancer, whereas 22005 randomises patients between extensive and selective RT in cervical node metastases of unknown origin. AMAROS (22023) compares RT to surgery after mapping the axilla in breast cancer. Trial 22993 evaluates the need for prophylactic cranial irradiation (PCI) in extensive disease SCLC, while 22003 randomises patients between high and standard doses of PCI in limited SCLC complete responders. In NSCLC, 22994 evaluates high dose 3D conformal RT with a dose-escalation schedule. Three phase III gastro-intestinal tract cancer studies are open: 22012 looks at the role of post-operative RT/CT in pancreatic head cancer, 22001 evaluates neoadjuvant RT-CT in oesophageal cancer and 22011 compares two RT-CT regimes in anal canal cancer. In localized prostate cancer, 22991 randomized patients between conformal RT (CRT) and CRT plus hormone therapy. Trial 22997 addresses the question of involved field RT with or without low dose TBI in low grade, stage I/II lymphoma. Finally, study 22998 is a phase II study of moderate dose RT in aggressive fibromatoses.

*Recently completed pivotal trials*

Results are awaited from the studies on Temozolomide-RT in glioblastoma, the study on internal mammary chain RT in breast cancer, the study on short versus long term adjuvant hormone therapy in prostate cancer, postoperative RT in prostate cancer, and the neoadjuvant CT/RT rectum cancer trial.

*Studies in preparation*

These concern the following fields: benign and atypical meningioma, low grade glioma, postoperative RT in H&N cancer, DCIS breast cancer and a new postoperative RT in prostate cancer.

*Conclusions:*

A good number of studies concerning common cancers are performed by the EORTC RTG, and Swiss centres are encouraged to participate.

## IS2

### IS THERE A SURVIVAL BENEFIT FROM LOCO-REGIONAL RADIOTHERAPY FOR BREAST CANCER?

Kurtz J

Radiation Oncology, University Hospital, Geneva, Switzerland

*Objective:*

To examine scientific evidence relative to the question posed.

*Material and Methods:*

A review of published meta-analyses of randomised breast cancer radiotherapy (RT) trials was carried out.

*Results:*

RT potentially improves survival not by acting on disseminated micro-metastases (as is the case for systemic therapy), but principally by preventing secondary metastases originating from loco-regional cancer foci left behind after primary surgery. As a consequence the survival benefit in randomised trials is observed only after several years' delay, when it can potentially be obscured by any increase in intercurrent mortality brought about by RT itself. As the survival benefit from RT is small, almost all trials have insufficient statistical power. The EBCTCG Overview of >20,000 patients randomised in RT trials allows the most statistically valid conclusions to be drawn regarding RT effects, despite inclusion of trials using antiquated techniques. On the average, the observed 20% absolute improvement in local control was associated with an absolute 5% reduction in deaths due to breast cancer. In other words, four local recurrences must be prevented to avoid one breast cancer death. Unfortunately, this advantage was at least partly counterbalanced by an increase in non-breast-cancer deaths. Increased intercurrent mortality was clearly seen in trials started before 1974, with a slight (non-significant) increase in later trials. This may reflect both improved RT techniques in later trials, or insufficient follow-up of more recently treated patients. The increased mortality in irradiated patients was accounted for by cardiac and other vascular disease (including strokes), lung cancers, and causes coded as unknown. It seems clear that at least cardiac and other vascular risks can be minimised by improved treatment planning. A meta-analysis (Whelan et al, JCO, 2000) of more recent RT trials, in which all patients received systemic treatment, shows a marked reduction in loco-regional failure (75%, relative) to be associated with a significant reduction in overall mortality (17%, relative, all causes).

*Conclusion:*

It is clear that special attention to minimising irradiation of the heart and great vessels is paramount for optimising survival benefit from loco-regional RT in breast cancer.

## IS3

### THE USE OF AN ASI-BASED EPID FOR ROUTINE ABSOLUTE DOSIMETRIC PRE-TREATMENT VERIFICATION OF DYNAMIC IMRT FIELDS

Van Esch A, Depuyd T, Huyskens DP

University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

*Objective:*

In order to minimise the workload related to the quality assurance of the intensity modulated radiation therapy (IMRT) fields, we have explored the possibility of using a commercially available aSi portal imager (PI) for absolute dosimetric verification of the delivery of dynamic IMRT fields.

*Material and Methods:*

We investigated the basic dosimetric characteristics of an aSi PI (aS500, Varian Medical Systems), using a new acquisition mode especially developed for portal dose integration. Taking the measured characteristics into account, a portal dose prediction algorithm was developed. We have focussed on absolute rather than relative dose distributions, hence eliminating the need for additional measurements. The portal dose image prediction was compared to the corresponding acquisition for several clinical IMRT fields by means of the gamma evaluation method.

*Results:*

Gamma evaluations of the predicted versus measured portal dose distribution were within the predefined acceptance criteria (i.e. 3% local dose difference and 3 mm distance to agreement) for all clinical IMRT fields.

## IS4

### **TOWARDS QUANTIFYING FDG UPTAKE IN PET/CT SCANNING FOR TARGET VOLUME DEFINITION**

*Davis JB*

*Radiation Oncology, University Hospital Zurich, Switzerland*

Variations in target volume definition remains a major challenge in radiation oncology. PET is currently used in clinical oncology for tumour staging, follow-up, tissue differentiation. It may have a predictive potential. In radiation oncology, its role is often limited to tumour volume definition as an increased uptake is indicative of the presence of viable tumour cells. Acceptance is growing despite issues of sensitivity and specificity of tracer uptake. One major problem is the quantification of uptake as this is a complex biological parameter and display can be greatly influenced by trivial external parameters.

To address this issue, phantom measurements are necessary to assess the real physical dimensions of tracer uptake volume in the clinical set-up. This data can be used for generating threshold levels in order to distinguish between tumour specific uptake and background activity. It has been observed for volumes of diameter >12.5mm, that 35% of the peak value minus background activity is a good indication of the real diameter of the uptake. Measured data can then be used in computer algorithms capable of finding peak activity levels, of assessing activity gradients and delineating iso-activity levels in a clinical environment. In other words, the algorithms can produce a computer generated target volume based on tracer uptake.

Assuming that tracer kinetics can be improved, routine use PET/CT in radiation oncology may remove some operator dependence in target volume definition for treatment planning.

## IS6

### **ACCELERATED PARTIAL BREAST IRRADIATION: RATIONAL AND METHODS**

*Gruber G*

*Department of Radiation Oncology, University of Berne, Inselspital, CH-3010 Berne*

Partial breast irradiation (PBI) offers the possibility of shortening the treatment time from 5 to 6 weeks down to one single fraction, which can be given intraoperatively. It is therefore very attractive and is currently the most discussed topic in the field of breast irradiation.

There are several devices in clinical use, either to give the irradiation dose intraoperatively in one single fraction with electrons (ELIOT) or 50kV photons (INTRABEAM®), or peri-/postoperatively in several fractions with interstitial brachytherapy (iBT), a HDR - balloon brachytherapy catheter system (MAMMOSITE®) or with 3D conformal external beam radiotherapy (3D-CRT) including IMRT in the future. Regardless which method is used, adjuvant RT will be usually finished within 1 week.

PBI revives the discussion about target visualization and definition, 'geographic miss' and patient positioning. Its safety esp. in regard to local tumor control is currently investigated in 3 randomized trials using ELIOT (Milan trial), INTRABEAM® (Targit trial) and interstitial brachytherapy (Hungarian trial). A large NSABP trial allowing iBT, MAMMOSITE® and 3D-CRT with a planned accrual of >6000 patients as well as a large European trial using iBT are in preparation.

The field of PBI, its rational and the different methods to achieve the goal of target coverage will be discussed critically in the talk.

## IS7

### THE JANUS FACE OF TUMOR HYPOXIA

Vaupel P

*Institute of Physiol. & Pathophysiol., Univ. of Mainz, Germany*

Cells exposed to hypoxia respond by reducing overall protein synthesis leading to *restrained proliferation* and subsequent *cell death*. Hypoxia can hinder or even completely inhibit tumor cell proliferation *in vitro*. Sustained hypoxia can also change the cell cycle distribution and the relative number of quiescent cells leading to alterations in the response to radiation and many drugs. The degree of inhibition depends on the severity and duration of hypoxia. Under anoxia, most cells undergo immediate arrest in whichever cell cycle phase they are in. Additionally, hypoxia can induce programmed cell death (*apoptosis*) both in normal and in neoplastic cells. p53 accumulates under hypoxic conditions through a HIF-1 $\alpha$ -dependent mechanism and induces apoptosis. However, hypoxia also initiates p53-independent apoptosis pathways including those involving genes of the BCL-2 family. Below a critical energy state, hypoxia may result in *necrotic cell death*. Hypoxia-induced proteome changes leading to cell cycle arrest, differentiation, apoptosis, and necrosis, may explain delayed recurrences, dormant micro-metastases, and growth retardation in large tumors.

In contrast, hypoxia-induced proteome and/or genome changes may *promote tumor progression* via mechanisms enabling cells to overcome nutritive deprivation, to escape from the hostile environment and to favor unrestricted growth. Sustained hypoxia may also lead to cellular changes resulting in a more clinically aggressive phenotype. During the process of hypoxia-driven malignant progression, tumors may develop an increased potential for local invasive growth, perifocal tumor cell spreading, and regional and distant tumor cell metastasis. The intrinsic resistance to radiation and other cancer therapies may also be enhanced, resulting in a poor prognosis.

## IS8

### NOVEL BRACHYTHERAPY (BCT) TECHNIQUES IN PARTIAL BREAST IRRADIATION (PBI): THE RIGHT ROLE FOR THE RIGHT PROCEDURE

J. Bernier

*Department of Radio-Oncology, Oncology Institute of Southern Switzerland, San Giovanni Hospital, CH-6504 Bellinzona*

**Background:** Evidence-based medicine advances most successfully on the basis of prospective clinical trials that compare investigational approaches with standard management approaches. The use of novel BCT techniques should be exemplary in providing evidence of the value of PBI. Although the clinical practice of PBI will considerably improve over the next few years, there is a strong need for reviewing those logistical elements currently considered necessary for optimal treatment performance. **Rationale:** In general careful confirmation in the setting of sophisticated multidisciplinary protocols is required by regulatory and reimbursement agencies before the technique could be adopted into clinical use. **Methodology:** During the investigational phase of a novel, radio-surgical treatment, primary among the methodological elements is the concept of a "team approach" utilizing the expertise of the surgeon, radiation oncologist (authorized user), and medical physicist to ensure the safety of patients and support staff. As a rule, the radiation oncologist is responsible for radiation delivery since he is the one who, in collaboration with the medical physicist, is responsible for the radiation safety of the patient, staff, and public. During the procedure itself, the surgeon will place the balloon and catheter in the tumor bed. The radiation oncologist will confirm the placement patient and check the position of system; moreover he will check regularly the position of the delivery catheter with the medical physicist and deliver the source to the target volume. However, it is important to distinguish the ideal from reality and the interactions among these key individuals will likely be customized to a degree at individual centers. **Conclusions:** We should realize that most documents on team approaches are typically an embodiment of consensus expert opinion, and less a synthesis of evidence. Now that the BCT procedure in PBI has become more routine, there will be pressures to streamline the process described above, perhaps decrease the complexity of the team approach, and even to eliminate the team altogether and place the entire responsibility in the hands of the surgeon as captain of the team. The acuity of this risk will be discussed during the lecture