

Dose escalation or intensification by radiation is built on the premise that higher biological doses will lead to better local tumour control. Obviously, the ultimate goal should be to obtain uncomplicated cures. From a theoretical point of view, both the improvement of techniques or the ability to understand the biology of radiation damage to the normal tissues resulting in appropriate patient selection and pharmacological interventions will increase the therapeutic ratio.

Radiotherapy techniques have improved dramatically over the last decade, now enabling to use IMRT and Volumetric Modulated Arc Radiotherapy in daily practice. This results in the possibility to deliver high dose radiation in patients that once were deemed to receive palliative doses. The on-going developments in on-line adaptation will further improve this evolution. Other new developments include dose re-distribution studies in which the whole PTV no longer receives an homogeneous dose, but a higher dose is delivered on the basis of molecular imaging characteristics. In many patients, this allows further dose escalation with equal doses to normal tissues. However, in the PET-boost study, the mediastinal structures were the most frequent dose-limiting (van Elmpt et al; Radiother Oncol 2012). Proton therapy has been shown to allow further dose escalation in many theoretical planning studies.

However, knowledge about the biological characteristics of OARs of individual patients would allow stratification into risk groups for side effects and possibly pharmacological interventions as well. Many studies have been reported on the relation between SNPs and side effects of radiotherapy. Most results were retrospective and could not be replicated in independent prospective validation cohorts (Barnett GC et al. Lancet 2012). With better study design and standardisation as for instance advocated by the Radiogenomics Consortium, and newer techniques such as GWAS, robust genetic features for radiation toxicity may emerge (Talbot CJ et al. Br J Cancer 2012).

In conclusion, dose escalation depends both on optimal techniques and biology, but much research remains to be done in order to build models and workflows with proven clinical value (Lambin et al. Nat Rev Clin Oncol. 2012).

SYMPOSIUM: RIGHT NOW CAN CLINICAL CHOICES BE BASED ON EVIDENCES FROM LARGE DATABASES?

SP-0292

Population based large databases and guidelines in rectal cancer

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Clinical guidelines are recommendations on how healthcare professionals should care for people with specific conditions. The recommendations are based on the best available evidence. Until recently, the highest level of evidence was considered to be derived from randomized clinical trials, or even better, meta-analyses of randomized clinical trials. Undoubtedly, clinical trials are essential but many factors limit their success, such as the costs of long-term follow-up, and participants often not being representative of the general population. In the last decade, realization that population based databases may help in evaluating the generalizability of clinical guidelines has emerged. However, one has to be aware of the pitfalls of population based databases. Even population-based databases can contain a selection bias, and the assumption that the patients in the database are a valid representation of the target group should always be tested. In addition, the accuracy of the data has to be monitored, as well as the setting in which the data have been collected. To make optimal use of population-based databases, comorbidity should be reported as well. For radiotherapy in particular, registration of the treatment details and information on long-term follow-up should be provided to ensure adequate evaluation of the treatment effects. So far, most databases have been initiated by the surgical community or generated by for example National Health Services. The underlying motive has not so much been development of clinical guidelines, but more to implement a clinical auditing system that aims to provide a greater level of insight into the process and outcomes of patients who undergo medical treatment and to continuously improve this. In order to start this improvement cycle (the 'audit cycle'), it is important to identify which quality aspects are important and where improvements are required. The most important objective of clinical auditing is to initiate a cycle for improvement on a national, regional and local level. The feedback that medical specialists are given regarding the care that they provide forms the catalyst for improvement initiatives.

Several European countries have implemented such audit for colorectal cancer, providing much inside in current standards of care. It has already resulted in demonstrable improvements in the

treatment provided to colorectal patients. For example, improvements in adequate pre-operative imaging in colon cancer patients have been observed, as well as increases in the number of patients suffering from rectal carcinoma that were discussed in a multidisciplinary team prior to operation. This has resulted in an increase of administration of (neo-)adjuvant radiotherapy and an improved standard of pathological reporting regarding, for example, number of lymph nodes examined and the reporting of circumferential resection margins (CRM).

In addition, results from the population based databases have identified the problems concerning frail elderly people. Half of patients suffering from bowel cancer are older than 70 years of age. Many of these elderly people have comorbidities and are vulnerable to both the increased occurrence of complications and the consequences thereof. These risks have been definitely confirmed in clinical audits and have resulted in awareness that although clinical guidelines should be suitable for most patients with a specific condition, identification of specific risk groups is warranted.

In conclusion: clinical auditing is absolutely necessary to evaluate and refine clinical guidelines. However, there will always be a need for clinical trials to facilitate practice changing research.

SP-0293

Radiomics: Advanced image analysis for the prediction of outcome. The example of lung cancer

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"Radiomics" refers to the extraction and analysis of advanced quantitative imaging features in high throughput from medical images, including computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) (Lambin et al. EJC 2012; www.radiomics.org). Importantly, these features are designed to be extracted from standard-of-care images, leading to a very large potential subject pool. Radiomic data are in a mineable form that can be used to build descriptive and predictive models. The core hypothesis of radiomics is that these models, which can include biological or medical data, can provide valuable diagnostic, prognostic or predictive information. Also, relating image features to phenotypes or gene-protein signatures is being investigated. The radiomics enterprise can be divided into four processes, each with its own challenges that need to be overcome: (1) image acquisition and reconstruction, (2) image segmentation and rendering, (3) feature extraction and qualification, (4) bioinformatic analyses. Each step, especially involving large datasets, poses unique challenges. The focus of this presentation will be on the predictive value of CT & FDG-PET radiomics features of non-small cell lung cancer and head and neck cancer, complemented by preclinical tumour data. Finally we will describe the current and potential applications of radiomics to other problems in oncology.

SP-0294

Towards image-based tumour dose response relations: Methods to analyse large CBCT data sets

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Over the past decade the progress in individualized medicine has posed major challenges also in radiotherapy of cancer diseases. The development of models for decision making seems crucial for taking advantage of inter- and intra-patient variability to maximize the therapeutic index in RT by increased tumour control and decreased normal tissue complications. Models depend to a high degree on validated predictors such as the tumour dose-response relationship, among many others.

Using modern RT delivery techniques like IMRT and volumetric arc therapy in combination with in-room image-guidance complex dose distributions are administered to cover target and spare organs at risk with high spatial precision. However, the increasing use of volumetric imaging such as cone-beam CT during the fractionated treatment course allow for detection of changes in the patient anatomy and, thus, detect the temporal aspects in the delivered dose distribution which might deviate from the planned one. Utilization of delivered dose-response relationships is expected to increase the accuracy of prediction models.

Several aspects are involved in the analysis of the CBCT image sets. The inferior image quality due to artefacts compared to conventional

CT may hamper contouring and dose calculation accuracy. Although not in widespread routine use, deformable image registration (DIR), preferable unsupervised, is used for auto-segmentation of organs/volumes based on those delineated on a reference planning CT. Using the daily pre-treatment registrations between planning CT and CBCT the delivered dose at each fraction can be recalculated on the CBCT anatomy with proper calibration of the systems. Based on DIR, accumulation of the dose can be performed from day to day, and delivered dose can be compared directly with the planned dose, and dose-volume histograms for OAR can be evaluated. Alternatively, the consecutive DIRs can be combined to represent a mean deformation vector field which can be applied to the planning CT with planned dose distribution to obtain a measure of delivered dose. For dose-response relations, the accumulated delivered dose needs to be combined with validated clinical outcome measures.

LOOK INSIDE: ADAPTIVE RADIOTHERAPY IN PRACTICE

SP-0295

Adaptive RT for head and neck cancer: Methodological approaches and clinical outcome

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Head and neck tumors become on the average 40% and 70% smaller after 2 and 4 weeks of radio(chemo)therapy, respectively. Tumor response, alterations in non-tumor anatomy and treatment-induced toxicity like weight loss or edema, cause a mismatch between pre-treatment planned dose distributions on the one hand and the shapes of tumor and organs-at-risk (OARs) on the other hand. By regularly adapting the treatment to changing anatomy, avoidance of OARs is maintained during the whole treatment. By simultaneously updating dose-painting to changing biology, optimal targeting of radioresistant parts of the tumor is better secured. To investigate this dual hypothesis, dosimetrical effects of adaptive (ART) and non-adaptive (RT) dose-painted radiotherapy were investigated for 10 patients with head-and-neck cancer. Three treatment-phases were preceded by a planning PET/CT scan. In ART, phases II and III were planned using PET/CT2 and PET/CT3, respectively. In RT, the phase-I plan on PET/CT1, was used to calculate dose-distributions on PET/CT2 and PET/CT3. Deformable image co-registration was used to sum dose distributions and to propagate regions-of-interest (ROIs) drawn on PET/CT1 to PET/CT2, PET/CT3 and to a last-treatment-day CT-scan (CT4). Inaccurately deformed ROIs were manually adjusted if necessary. In target ROIs, ART provided higher minimum and lower maximum doses than RT and re-matched dose-painting. For OARs, ART improved critical dose/volume parameters. ART achieved average reduction of 4.6-7.1% in the parotids' median dose ($p < 0.05$) and 3% in the swallowing structures' mean dose ($p = 0.06$). Improvements of dose/volume parameters by ART were more pronounced in individual patients reaching 24.4% minimum-dose increase in elective neck PTV and 29.5% mean-dose decrease in swallowing structures.

Conclusion: Compared to RT, ART readjusts dose-painting, increases minimum and decreases maximum doses in target volumes and improves dose/volume parameters of OARs. Reporting population-average effects in ROIs underestimates the patient-individual benefits of ART.

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SP-0296

Clinical implementation of Plan-of-the-Day strategies for cervical cancer.

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Currently, in external beam radiotherapy of locally advanced cervical cancer, a large safety margin around the tumour is needed to compensate for potentially large day-to-day variations in the target position and shape, as e.g. induced by bladder and rectum volume changes. At Erasmus MC we have developed an individualized adaptive RT approach resulting in significant margin reductions (Bondar et al. IJROBP 2012 Aug 1;83(5):1617-23). In the treatment preparation phase, patients are stratified in two groups with small or large

bladder-volume induced tumour motion. For the first group, a single IMRT plan is created with an individualized small margin. For the second group two IMRT plans are created, adequate for tumour positions and shapes corresponding to smaller and larger bladder volumes. Every treatment day, the best fitting plan is selected based on an in-room acquired Cone Beam CT scan (CBCT), showing internal anatomy and markers implanted around the primary tumour. The first part of this presentation will review the rationale of library-based Plan-of-the-Day strategies for this treatment site. Using data of 14 patients with two series of variable bladder filling CT scans (acquired pretreatment and after 40 Gy), we demonstrated the benefit of 1) individualizing the required margin by using an individualized internal target volume (ITV) and 2) of using two separate ITVs for patient with large cervix-uterus motion.

In the second part of the presentation, we will provide inside in practical issues concerning the implementation of the library-based Plan-of-the-Day strategy. The following issues in the preparatory phase will be discussed: 1) the acquisition of an empty and full bladder filling CT scan, 2) the choice of the number IMRT plans in the plan library, 3) the creation of the ITVs, 4) the implantation of markers around the primary tumour as an aid to quickly verify the position of the cervix at the treatment unit, and 4) the addition of a motion-robust backup plan to the plan library.

Next, inside will be provided in the image-guidance and plan-selection procedure at the linear accelerator. In this procedure daily CBCT scans are acquired for online patient-setup correction and assessment of the position of the uterus and markers (XVI software, Elekta AB). Contours of 10-mm margins around the markers, PTV, and ITV are projected on the bone-matched CBCT scan. The bony anatomy is used because of the nodal CTV to be treated. An intervention decision tree coaches RTTs through the whole plan selection procedure. Plan selection is completed by an online patient setup correction (based on the bony-anatomy match), followed by the manual selection of the plan of the day in the treatment record and verify system. In the final part of this presentation, an evaluation of the clinical protocol will be presented.

SP-0297

Adaptive plan of the minute strategies for prostate cancer: Methods for motion management

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In state of the art image guided, intensity modulated radiotherapy (IGIMRT) of primary prostate cancer, inter- and intra-fractional movements of the organ are still the main reason for safety margins between the clinical target volume (CTV) and the planning target volume (PTV). Margins and side effects in neighbouring structures hinder dose escalations. Even if daily pre-treatment imaging and faster rotational treatment delivery (VMAT) are performed, intra-fractional patient and target motion are limiting factors for a successful radiotherapy.

Different spacer materials (injected gels, balloons) can be used to enlarge the distance between the high dose region (PTV) and an organ at risk (rectum). It was tested, if the bulky volume of spacers can also contribute to a reduction of uncertainties by constraining inter- and intrafractional movements. Preliminary results of our own investigations on >50 spacer patients show that there may be no significant reduction of movements, neither interfractionally nor intrafractionally.