radiotherapy, e.g. for image guidance and target volume delineation. Compared to rigid registration, deformable image registration (DIR) is much more complex as the number of degrees of freedom in a typical DIR system exceeds the ten-thousands versus 6 for rigid registration. To make DIR tractable, registration systems therefore need to make a compromise between image similarity and smoothness of the deformation, attempting to find the smallest &quot;trick of the trade&quot; solution. Deformation that still optimizes the image similarity. This compromise is achieved by tuning a large amount of parameters, which is the &quot;trick of the trade&quot;. DIR is currently considered the most essential and most complicated component of on- and off-line adaptive radiotherapy, and its validation is therefore essential. Validation programs should look at technical, general, and patient-specific performance. Technical and general QA methods include 4D and anatomically realistic phantoms, natural and implanted fiducials, and manually placed landmarks, potentially using mathematical methods to account for observer variation. Visual verification is an essential patient specific form of QA, but an important caveat of deformable image registration is the inadequacy of visual validation to provide a final verdict on the registration accuracy, as completely different deformable registrations can result in the identical images. This is not a problem for descriptive tasks such as Hounsfield unit correction and autocontouring, where organ boundaries are sought, but is highly detrimental for quantitative tasks such as dose accumulation and treatment adaption around tumour boundaries where anatomical cell to cell &quot;correspondence&quot; is required. Another unsolved issue is that registration performance is poor around sliding tissues and anatomical changes in the patient and specific care should be taken with clinical decisions that depend on dose summation around such regions. I conclude that QA of deformable registration is complex, and that current algorithms lack biological and biomechanical knowledge. I believe that today it is therefore not safe to use them for dose-accumulation and treatment adaptation around shrinking tumours.

Teaching Lecture: VMAT QA: To do and not to do, those are the questions

SP-0573

VMAT QA: To do and not to do, those are the questions

J.B. van de Kamer1, F.W. Wittkamper1
1Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Department of Radiation Oncology, Amsterdam, The Netherlands

Introduction

With the advent of Volumetric Modulated Arc Therapy (VMAT), Quality Assurance (QA) has evolved to a next step regarding complexity. Different parts of the linear accelerator (linac) move synchronously, resulting in a dose delivery that can be highly modulated in both space and time. In this lecture the practical aspects of QA are discussed, in particular focussed on VMAT.

Machine QA

Prior to implementing VMAT treatments in the clinic, the user should be familiar with the dynamic behaviour of the machine. In particular, features such as the lowest maximum leaf speed and the behaviour of the system under both dose rate changes and accelerations/decelerations of the gantry should be determined. Such machine characteristics need to be incorporated in the treatment planning system (TPS) to avoid devising undeliverable plans. To properly measure the dose delivered by the linac, the used measurement systems need to be dosimetrically accurate and have a high degree of spatial and temporal resolution. Usually different QA devices are needed to achieve this.

Patient-specific QA

Before a treatment plan can be delivered clinically, the medical physics expert (MPE) has to be convinced that the correspondence between calculated and measured dose delivery is adequate. This can be achieved by performing patient-specific QA, comparing the measured, integral dose with the computed one in a phantom. For this purpose, a high dosimetric accuracy combined with a high spatial resolution is required. Again, different measurement devices are in general needed to meet these demands. The interpretation of the differences between intended and delivered dose distribution, in terms of a gamma analysis, will be discussed. After gaining experience and confidence with a certain class solution for treatment plans, most MPE resort to using only point dose measurements or computer programs for independent validation. When and how to introduce such alternatives will be discussed in the lecture. The value of continuous patient-specific QA will also be addressed.

Conclusion

After the lecture, the participant should have a clear idea what type of detectors should be used for what purpose and how to optimise patient-specific QA in a busy clinical environment.

Teaching Lecture: Optimising workflow in a radiotherapy department - an introduction to lean thinking

SP-0574

Optimising workflow in a radiotherapy department - an introduction to lean thinking

B. Naddy1
1Health Service Executive, Clinical Strategy and Programmes, Dublin 2, Ireland Republic

Lean Thinking originated from the manufacturing industry in Japan as a method of highly-efficient production. However, Lean Thinking is not confined to manufacturing and as a management strategy focused on improving processes, is applicable to any organisation. It is now well-established in the complex area of healthcare delivery. Lean Thinking has been described as “the dynamic, knowledge driven and customer-focused process through which all people in a defined enterprise work continuously to eliminate waste and to create value” (Rebentisch et al, 2004). For a healthcare organisation, it provides a patient-focused, systematic approach to identifying and eliminating waste (i.e. non-value-added activities) through continuous improvement. The key principle of Lean is distinguishing value-added steps from non-value-added steps, and eliminating waste with the aim that eventually every step will add value to the overall process.

The lean philosophy is not intended to reduce the number of employees working in the hospital. It seeks only to eliminate waste in tasks and processes so that time, materials, resources and procedures can be utilised as efficiently as possible with the aim of dedicating more time and effort to patient care without extra cost to the patient or healthcare organisation. Using case studies and real-life examples, this talk will introduce the lean concepts, principles and tools that contribute to improving efficiency, quality and patient safety in radiotherapy and healthcare.

Symposium: New concepts of tumour radioresistance

SP-0575

Radiotherapy combined with immunotherapy: present status and future perspectives

P. Lambin1,2, N. Rekers1,2, A. Yaromina1,2, L. Dubois1,2
1MAASTRO clinic, Radiation Oncology, Maastricht, The Netherlands
2Maastricht University Medical Centre, GROW - School for Oncology, Maastricht, The Netherlands

Radiotherapy is along with surgery and chemotherapy one of the prime treatment modalities in cancer. It is applied in the primary, neoadjuvant as well as the adjuvant setting. Radiation techniques have rapidly evolved during the past
decade enabling the delivery of high radiation doses, reducing side-effects in tumour-adjacent normal tissues. While increasing local tumour control, current and future efforts ought to deal with microscopic disease at a distance of the primary tumour, ultimately responsible for disease-progression. This talk will explore the possibility of bimodal treatment combining radiotherapy with immunotherapy. L19 targets the extra domain B (ED-B) of fibronectin, a marker for tumour neoangiogenesis, and can be used as an immunocytokine when coupled to IL2. We hypothesize that radiotherapy in combination with L19-IL2 provides an enhanced antitumor effect, which is dependent on ED-B expression.

EXPERIMENTAL DESIGN: Mice were injected with syngeneic C51 colon carcinoma, Lewis lung carcinoma (LLC), or 4T1 mammary carcinoma cells. Tumor growth delay, underlying immunologic parameters, and treatment toxicity were evaluated after single-dose local tumor irradiation and systemic administration of L19-IL2 or equimolar controls.

RESULTS: ED-B expression was high, intermediate, and low for C51, LLC, and 4T1, respectively. The combination therapy showed (i) a long-lasting synergistic effect for the C51 model with 75% of tumors being cured, (ii) an additive effect for the LLC model, and (iii) no effect for the 4T1 model. The combination resulted in a significantly increased cytotoxic (CD8(+)) T-cell population for both C51 and LLC. Depletion of CD8(+) T cells abolished the benefit of the combination therapy.

CONCLUSIONS: These data provide the first evidence for an increased therapeutic potential by combining radiotherapy with L19-IL2 in ED-B-positive tumors. This new opportunity in cancer treatment will be investigated in a phase I clinical study for patients with an oligometastatic solid tumor (NCT02086721). An animation summarizing our results is available at https://www.youtube.com/watch?v=vilHbWQuCTKrC.


SP-0576
The contribution of cancer stem cells to tumour radioresistance

A. Chalmer1

1Inst. of Cancer Sciences-Univ. Glasgow The Beatson West of Scotland Cancer Center, Department of Clinical Oncology, Glasgow, United Kingdom

For a number of tumour types there is increasing acceptance that cancer stem cells play an important role in tumour initiation and recurrence after treatment. In line with this model, increasing evidence indicates that cancer stem cells exhibit resistance to conventional cytotoxic agents. In the case of glioblastoma, an incurable primary brain tumour associated with dismal prognosis and devasting effects on quality of life, a series of influential publications have demonstrated that the radiation resistance of glioblastoma stem-like cells (GSC) is associated with constitutive upregulation of the DNA damage response (DDR). In this presentation I will outline the evidence supporting this model, and present new data that elucidates the relative contributions of DNA repair and cell cycle checkpoints to this phenotype. Subsequently I will investigate the effects of inhibiting various components of the DDR, alone and in combination, and discuss the potential clinical application of a number of promising new small molecule inhibitors.

SP-0577
Novel Insights in radioresistance of head and neck cancer

J. Tinhofer-Keilholz

Charité Campus Virchow Klinikum, Department of Radiooncology and Radiotherapy, Berlin, Germany

Recent technological advances in DNA sequencing with greater speed and resolution at lower costs has provided new insights in cancer genetics. The next-generation sequencing (NGS) technology is tremendously facilitating the in-depth genome-wide search for genetic alterations which might significantly contribute to aggressive and/or treatment-resistant phenotypes of cancers, thereby establishing the basis for improvement of cancer treatment. We hypothesized that NGS should also be useful for dissecting the molecular mechanisms of radioresistance in squamous cell carcinoma of the head and neck (HNSCC).

We therefore applied the technology of targeted NGS to clinical samples from two multicenter studies of definitive and adjuvant cisplatin-based chemoradiation of locally advanced HNSCC. We evaluated whether by molecular profiling using targeted NGS it is possible to prospectively discriminate between patients who clearly benefit from chemoradiation and those with poor locoregional control and reduced overall survival after such treatment. Our studies could confirm previous reports of poor efficacy of radiotherapy in HNSCC tumors harboring TP53 mutations. For the first time, we identified additional mutations in other genes as predictive biomarkers of outcome after chemoradiation.

The talk will summarize the results of NGS studies in HNSCC and other carcinoma models, thereby focusing on studies in which signigicant molecular mechanisms involved in radio-/chemoresistance have been addressed. It will present unpublished results from functional studies in preclinical models in which we are evaluating the mode of interaction of distinct genetic variants with radio-/chemoresistance. Concepts of how to integrate the results from NGS into novel personalized treatment strategies for HNSCC will be discussed.

Symposium with Proffered Papers: Towards Personalised Radiation Oncology (PRO)

SP-0578
New technologies for genomic tumour profiling

W. Weichert1

1Technical University Munich, Institute of Pathology, Munich, Germany

Massive parallel sequencing technologies (also: next generation sequencing) have revolutionized our understanding of the genomic and transcriptional makeup of malignomas. Aided by equally impressive developments in sequencing- and chip-based epigenetic tumor profiling and developments in mass spectrometry which allow for a comprehensive proteomic and metabolomic profiling we are now able to draw fairly comprehensive multi-omics landscapes of individual tumors both from tissue but increasingly also from blood or circulating tumor cells. However, many issues remain still challenging when it comes to a translation of these findings into a potential clinical outreach. This includes matters of tumor heterogeneity specifically with respect to tumor evolution in the metastatic setting as well as under therapeutic pressure. Other widely unresolved issues include the usefulness of identified drivers as novel targets for therapy or as predictive biomarkers and strategies to implement broad high throughput genomic testing into individualized patient care. Specifically the latter issue will decide which of these multi-omics technologies will take the step from tools merely for biological research profiling to advanced and modern routine clinical care.

SP-0579
Gene expression profiles in tumours for PRO

J. Alsner1

1Aarhus University Hospital, Department of Experimental Clinical Oncology, Aarhus C, Denmark

Gene expression profiles hold great promises for PRO (Personalized Radiation Oncology), yet very few - if any - are implemented in routine clinical practice and used as predictive biomarkers for treatment decisions in radiation oncology.