decelerated protons, or with carbon ions mimicking the tumor treatment situation. RBE values were determined relative to x-rays.
For protons a sharp increase in RBE was found only for the stopping particles at the very distal (decreasing) end of the dose deposition profile. For low energy carbon ions, the RBE is increased over a broader range of energies corresponding to the peak of dose deposition. Therefore, after therapy like irradiation, for carbon ions in contrast to protons a considerable fraction of the dose deposited will correspond to ions with a high RBE.
At the molecular level, the enhanced effectiveness is believed to be based on the production of complex DNA double-strand breaks (DSBs) that are difficult to repair. To study the induction and repair of DSBs under conditions mimicking therapeutical ion irradiation, stacks of cells grown on glass plates were exposed to high energy carbon ions in a water phantom. Immunostaining of phosphorylated histone H2AX was used for DSB detection. After post irradiation incubation, despite efficient repair even of ion-induced DSBs, the level of residual DSBs was slightly but consistently increased after exposure to ions in the tumor region compared to the entrance channel.
In summary, based on their physical properties both protons and heavier ions are advantageous to treat deep seated tumors. For carbon ions an increase of the RBE towards the end of the particle range, together with the concomitant increase in dose potentiates the inactivation effect in the tumor region. The molecular basis is the localized production of complex damage and the impaired repair.

80 INVITED

Particle therapy: Physical potential amid clinical realities

T. Bortfeld. *Mass. General Hospital / Harvard Medical School, Department of Radiation Oncology, Boston, USA*

Background: Proton radiation therapy has moved mainstream. Many new proton centers have recently been completed, or are under construction or at planning stage. The main physical advantage of both proton and heavier charged particle therapy is the finite range of the beam in the patient, which may be utilized to reduce the overall integral dose to healthy tissues and to improve local dose conformality. However, the range of a particle beam in a patient on a given day is often not exactly known. The range is therefore not used for tight dose conformation. Instead, dose shaping with the lateral dose fall-off is preferred, just as in the case of conventional photon therapy.
Materials and Methods: We will review the state of the art in proton therapy and focus on sources of range uncertainties, such as motion, imaging artifacts, and dose calculation errors. We will discuss how the impact of range uncertainties is limited in current clinical practice using methods such as field patching and feathering. We will also discuss methods for in-vivo dose measurements, either directly or indirectly through PET/CT imaging of the positron emitters activated by the particle beam. We will then review the potential of intensity modulated proton therapy (IMPT) to improve dose conformality and the robustness of the treatment plan.
Results: In some cases, especially in lung cancer treatments, the range of a particle beam can vary by several centimeters during the treatment course. Even in cases where motion and anatomic variations are not an issue, the range can be off by 5mm, for example due to metal artifacts. In-vivo dosimetry and PET imaging are two methods to substantially reduce range uncertainties. Unavoidable residual uncertainties can be taken into account by carefully designing IMPT treatments using robust optimization techniques.
Conclusions: Particle beams can produce highly conformal dose distributions, but, primarily due to range uncertainties, the dose in the patient may differ substantially from the treatment plan. Image guided radiation therapy and motion management are therefore more critically important in particle therapy than in photon therapy. Without them, the physical advantage of particle beams cannot be fully utilized for the benefit of the patient.

81 INVITED

Critical review of the clinical evidence

D. De Ruysscher[1], M. Pijls-Johannesma[2], P. Lambin[3]. *[1]University Hospital Maastricht, Radiotherapy/GROW/MAASTRO Clinic, Maastricht, The Netherlands; [2]MAASTRO clinic, MAASTRO clinic, Maastricht, The Netherlands; [3]University Hospital Maastricht, Radiotherapy/GROW/MAASTRO clinic, Maastricht, The Netherlands*

Background: Protons and light ions (mainly Carbon), generate much excitement, for they exhibit a superior dose-distribution than the currently used photons. Light ions are on top of this biologically more active than photons and protons. We performed a systematic literature review of the clinical evidence.
Materials and Methods: Twelve databases were searched. No limit was applied to publication year, language or study design. Only studies with at least 20 patients and with a follow-up period of at least two years were included.
Results: *Prostate cancer*: Two phase III trials in locally advanced prostate cancer were identified (n=492). However, one used inadequate photon doses and techniques and the other used protons in both arms. From pro-and retrospective series, local tumor control, 5 year overall survival and late GI and GU toxicity were for protons 74%/89%/15%/7% and for C-ions 100%/89%/6%/<5%. The results with high dose photon therapy were similar
Ocular tumors: In the only phase III study, Helium ions were compared to brachytherapy. Tumor recurrences were more observed in the brachytherapy than in the He arm (13.3% vs. 0%, $p < 0.001$), with more side effects in the He group. From 9522 patients treated with protons, local tumor control and 5 year overall/cause specific survival were 97% and 85%/85% respectively. Eye retention was 90%, whereas neovascular glaucoma occurred in 12% of patients. Similar results were obtained with C-ions and in selected photon series. The latter were much smaller and with in general only short follow-up times.
Central nervous system: For common glioma's, no gain with protons or C-ions was observed. However, for chordomas of the skull base, the weighted local tumor control rate and 5 year overall survival treated with protons was 63% and 81% respectively and for C-ions 72% and 83%. With conventional photon therapy, local tumor control rates and 5 year survival were 25% and 44% respectively.
Head and neck cancer: For squamous cell carcinomas, the results of photon therapy were similar to protons or C-ions. However, for adenoid cystic carcinomas, local tumor control rates of over 75% as achieved with C-ions are much higher than reported with photons (approximately 25% local control).
Esophageal, hepatocellular, pancreatic, non-small cell lung, sarcomas, cervix and bladder cancer: no clear superiority of protons or C-ions was established, but all series were small.
Conclusions: Although most studies with protons and C-ions were performed in non-clinical research settings, the clinical results were superior to photons for tumors that are relatively radio-resistant (adenoid cystic carcinomas) or where normal tissues are critical (ocular tumors, base of skull chordoma's). For common malignancies, however, their superiority has not been established. The advent of multiple clinical facilities will enable to improve these new radiation qualities.

Special session (Tue, 25 Sep, 13:30−14:30)
Tumour responses – the contribute of targeting host cells versus tumour cells

82 INVITED

Radiation and endothelial cell damage

Z. Fuks. *USA*

Abstract not received.

83 INVITED

Pericytes and tumour cell metastases

H. Semb. *Lund University, Stem Cell CenterBMC B10, Lund, Sweden*

Tumour cells use two major routes to spread during metastasis, e.g. lymph vessels and blood vessels within or surrounding the primary tumour. The growth rate of the primary tumour often correlates with the quantity of new blood vessels that form within the tumour. However, recent studies directed our attention to the quality of tumour blood vessels, illustrating that the deficiency of the tumour environment to support or instruct a regular patterning and stabilization of blood vessels has profound effects on both perfusion of the primary tumour and escape of tumour cells into the circulation. Our recent evidence for a novel role of the supporting mural cells in limiting blood borne metastasis will be discussed.

84 INVITED

Gastrin – a pro-angiogenic factor and down stream target of HIF1a in gastro-intestinal malignancy

S. Watson, P.A. Clarke, R. Kumari, A.J. Tobias, E.L. Royal, A.M. Grabowska. *University of Nottingham, Academic Unit of Cancer StudiesD Floor West BlockQueen's Medical Centre, Nottingham, United Kingdom*

Background: The gut hormone gastrin is a transcriptional activator of a number of malignancy-associated genes including those involved in angiogenesis. The ability of gastrin to modulate endothelial cell activity via heparin-binding epidermal growth factor (HB-EGF) expression and shedding was assessed.