Results: For all patients, the treatment was tolerated well. In some patients, a lower dose to the PTV was given in order to protect the organs at risk. This was especially the case in patients that received a second salvage treatment. No patients developed a new grade 3 (or more) toxicity. One patient developed an acute urinary retention after primary focal HDR brachytherapy. Other grade 2 toxicity was uncommon in patients that received HDR brachytherapy as a primary treatment. In patients with a salvage treatment, grade 2 toxicity such as urinary infections and incontinence occurred in 3 of 8 patients. The 3 patients that received a second salvage treatment had not developed severe toxicity. However, follow up of these patients is very short (1-6 months).

Conclusion: Focal HDR brachytherapy as focal, salvage and secondary salvage treatment seems clinically feasible and safe. It could be a promising treatment modality to reduce severe side effect in patients with primary prostate cancer. Furthermore, it could postpone hormonal treatment in patients with recurrent or secondary recurrent prostate cancer.

Symposium: Protons or heavy ions?

SP-0041
Physical advantages of particles: protons vs. heavy ions, what is certain what is not?
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In this contribution the physical properties of protons and other ions will be outlined and the differences between different ions will be highlighted. The relevance of these properties with respect to radiotherapy will be discussed. In detail the physical properties to be discussed are the depth dose distribution, lateral scattering and energy loss straggling. These quantities will mainly affect the dose conformational potential of the various ion beams through the distal and lateral penumbra and the dose in the entrance region. The most important difference here arises through the multiple small angle scattering of particles which is strongly depend on the mass of the ions: for heavier ions, the lateral penumbra will be significantly smaller than for protons.

Another very important physical parameter is the stopping power of the particles, as this quantity will influence the radiobiological properties of the different ions. The stopping power describes the energy loss of a particle per pathlength and be accurately calculated using the Bethe formalism. More important for the radiobiological effects is the linear energy transfer (LET), which is often used synonymously to stopping power. LET describes the energy transferred into a narrow region around the primary ion track and can also be calculated using the Bethe formalism. While the LET of a pure beam of ions with a fixed energy is well defined, the LET of a mixed radiation field is more complex. The reason for that is, that in a mixed radiation field, LET has to be averaged over the different ions contributing. This is often done by using the so-called "dose averaged LET", where the LET of each particle is weighted according to the dose it is contributing. Another way of defining an average LET is by averaging over the fluence (or alternatively over the track length). Both average LET definitions are being used for various biological applications and will be presented. When discussing the relative biological effectiveness (RBE) of ion beams, one has to be aware of this difference.

Finally the nuclear fragmentation of ions may lead to strong differences in the spectrum, or mixture of ions of different kind at different points in depth. The relevance of these nuclear fragments becomes clear, when comparing the dose just behind the Bragg peak of a primary carbon ion beam (which is completely due to light fragments) and a proton beam (which is completely due to protons). An overview of the characteristics of the fragmentation spectra of ions will therefore also be given.

SP-0042
Radiobiological benefits of protons and heavy ions - advantages and disadvantages
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Both, carbon ions and protons show an inverted depth dose profile (Bragg-peak) and allow for highly conformal irradiations of tumors in the neighborhood of radiosensitive normal tissues. Heavier ions such as carbon ions additionally show an increased linear energy transfer (LET) towards the distal edge of the Bragg-peak leading to an increased relative biological effectiveness (RBE) with respect to photon irradiations [1]. While the RBE for clinical proton beams is currently fixed to 1.1, the RBE of carbon ion varies significantly within the treatment field and has to be calculated by RBE-models. The RBE-models, however, introduce additional uncertainties, which have to be considered in treatment planning and especially in clinical dose prescription.

As protons and carbon ions exhibit almost comparable geometrical accuracy, the clinical question whether protons or carbon will be more beneficial for the patient mainly addresses the independent role of the high-LET effect in radiotherapy. The answer to this question is related to the following subquestions: (i) How accurate is the applied RBE-model? (ii) Is a fixed proton RBE of 1.1 accurate enough for all field configurations? (iii) Which tumor types are best suited for heavy ions? (iv) Can high-LET irradiations overcome radioresistance of hypoxic tumors?

While questions (i) and (ii) refer to normal tissue reactions, (iii) and (iv) address the impact of tumor-specific resistance factors on the radiation response. An additional benefit of heavy ions will strongly depend on the differential response between tumor and normal tissue. Although the final prove or disprove of advantages has to be provided by prospectively randomized clinical trials, ongoing preclinical experiments can help to study the subquestions (i)-(iv) separately, i.e. to benchmark RBE-models (e.g. LEM I vs IV), to select suitable tumor entities, to setup clinical trials and to generally improve the understanding of normal and tumor tissue response after high- vs. low-LET irradiation.

The presentation will give an introduction on the concepts describing the response to high-LET irradiations and will give an overview on the available in vivo data with focus on the current answers to the above questions.

References

SP-0043
How strong is the current clinical evidence for protons and heavy ions ?
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Particle therapy has been available in hospital setting since 1991. About 100.000 Patients have been treated worldwide with protontherapy and more than 10.000 patients have been treated with carbon ion radiotherapy. After almost 15 years in which this modality was available only in few centres in the last ten years the number of new particle facilities has steeply increased in the US and in Asia and more recently several facilities have been planned in Europe. Protontherapy has traditionally been used because of its strong preclinical rationale based on its favourable biological properties that allow a substantial reduction in integral dose and exposure of non-target tissues. Carbon ion radiotherapy has mainly been used for its radiobiological property that may offer an advantage in the treatment of macroscopic tumours made of
an heterogeneous cell population with a radio-resistant compartment. Evidence to support the use of particle therapy evolved in the past 25 years from level III (preclinical rationale) to level II (prospective non-randomized trials). A hot debate has been on-going in the scientific community about the need of prospective RCT testing head to head particles versus modern X-ray radiotherapy. Those against the need of RCT argued that dose distribution was such a strong surrogate endpoint that RCT were not needed and that dose distribution had always guided the evolution of radiotherapy without the need of RCT. Those in favour argued that the only relevant endpoints were clinical outcome and measurable toxicity and that dose distributions of proton therapy despite its unquestionable advantage in terms of integral dose may be in some case less favourable than advanced x-ray dose distribution because of lateral scattering and shallower dose gradients in the high dose region. Historically only a single RCT of particle versus photons has been conducted, namely the UCSF-LBNL trial comparing helium ions radiotherapy versus iodine-125 plaque brachytherapy for choroidal and ciliary body melanoma. Long term results of the trial showed a clear advantage of charged particles over brachytherapy in terms of local control. However this result did not definitively solve the issue as helium-enriched gas no longer used in local practice and extrapolation of this trial to proton therapy is maybe not straightforward; moreover the trial was criticized because of a supposed suboptimal technique in the brachytherapy arm. With the increased availability of proton facilities the amount of non-randomized evidence is rapidly increasing and several prospective non-randomized trial are being conducted. At present particle therapy has found its way in several guidelines. As an example in the last version of ESMO guidelines for bone sarcoma particle therapy is considered the first option for chordoma both in the post operative setting and for inoperable disease. In this framework also RCT are at present being conducted. A prospective phase II RCT in stage II-IIIB NSCLC patients (NCT00915005) randomized to either photons or protons adaptive IGRT with two levels of photons or protons radiotherapy for head and neck soft tissue sarcoma and adenoid cystic carcinoma (PHRC ETOILE-ULICE) is going to start recruitment in the next year. In conclusion a large effort to produce level I evidence is ongoing worldwide.

Proffered Papers: Radiobiology 1: Radiation effects on normal tissues and the microenvironment

OC-0044
Fingolimod mitigates radiation-induced cognitive deficits by restoring dentate gyrus neurogenesis
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Purpose or Objective: This study evaluates FTY720/Fingolimod as a potential mitigator of radiation-induced neurocognitive dysfunction.

Material and Methods: The effects of radiation and FTY720 on neural progenitor cells (NPCs) and brain tumor stem cells (BTSCs) were tested in vitro. To study radiation-induced neurocognitive deficits, 6 week-old C57/Bl/6J mice received 0 or 7 Gy cranial irradiation and were treated with intraperitoneal FTY720 or vehicle for seven weeks. Fear conditioning and the Morris water maze were then employed to test learning and memory. Immunohistochemical staining for NPCs and mature neurons was used to assess changes in neurogenesis. To test effects on tumor growth, mice harboring BTSC xenografts were treated with intraperitoneal FTY720 or vehicle for six weeks.

Results: In NPCs, FTY720 induced ERK1/2 phosphorylation in the presence of radiation. In glioma cells, ERK1/2 phosphorylation was detected at baseline, and FTY720 did not elicit any further increase. Correspondingly, FTY720 increased the viability of NSCs but not glioma cells after radiation. In irradiated mice, learning deficits were manifested by significantly longer latency times compared to non-irradiated controls (p = 0.012). The deficits were fully restored by FTY720. In irradiated brains, FTY720 maintained a viable NPC pool and restored the cytoarchitecture of the DG granular cell layer. In mice harboring BTSC xenografts FTY720 delayed tumor growth and improved survival (p<0.012).

Conclusion: FTY720 mitigates radiation-induced learning dysfunction by partially restoring DG neurogenesis. Furthermore, FTY720 appears to delay tumor growth and improve survival in a xenograft glioma mouse model.

OC-0045
Dual pathway inhibition attenuates radiation-induced pulmonary inflammation and fibrosis
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Purpose or Objective: Radiation therapy is a mainstay for lung cancer therapy, but the effective dose is commonly limited by the onset of radiation-induced lung damage. Single pathway inhibitors against transforming growth factor B (TGFβ), platelet-derived growth factor (PDGF) and others have been shown in experimental models to attenuate radiation-induced pulmonary injury. However, the effects of multiple pathway inhibition regarding the development of these diseases remain unknown.

Material and Methods: C57BL/6 mice were treated with a single dose of up to 20 Gy photons to their thorax to induce radiation induced lung toxicity. After irradiation, small