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attention to the radiotherapy planning and delivery elements, and careful systematic and prospective documentation of tumor and normal tissue outcomes. Even if randomised trials are deemed unsuited to the setting, protocol based approaches in registered phase I/II trials are appropriate to enhance standards and should probably include audit and quality assurance processes, as well as realistic stopping rules to address unexpected or aberrant outcomes.

Symposium: Selection of patients for proton therapy

SP-0009
Patient selection for proton therapy: a clinicians view

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Proton therapy is a radiation modality that has become increasingly available world wide over the past decade. It is an attractive radiotherapy intervention because of the charged particles dose deposition profile of characterized by the Bragg peak. By using proton therapy strategically, there is the possibility to deliver effective radiation dose to the target while reducing radiation to the surrounding non-target structures. The goals of any radiotherapy approach is to improve tumor control and/or reduce side effects and proton therapy offers an opportunity to achieve either one or both of these goals.Despite the promise of proton therapy, one must consider its associated risks and benefits, and as with any other radiation approach, to maximize the benefit to the patient. In general concepts that are useful in selecting and predicting a the benefit of proton therapy in individual patients include the following:
1) Proton therapy has the same risk of injury within the target area and high dose as other radiation therapies. For infiltrative tumors that require irradiation of a margin of normal tissue (example rhabdomyosarcoma) or those that have normal cells embedded within the tumor (example low grade glioma), the tissues receiving the high dose of radiotherapy will have similar risks of injury as non-proton approaches; therefore, one would not expect a lower risk of injury in the high dose area.
2) Since proton therapy is typically associated with a lower risk of late effectsPatient who has a very low chance of surviving a long time due to the natural history of the disease, may not benefit from proton therapy, example widely metastatic cancer.
3) Patients, for example children, who can derive benefit from normal tissue radiation dose reduction are usually good candidates
4) Patients who require high doses of radiation to achieve tumor control, but would otherwise be limited due to normal tissue tolerance, for example patients with skull base chordoma or primary or secondary liver.
5) Tumor geometry and surrounding anatomy must be evaluated to estimate the potential benefit of proton therapy. For example, a 2 year old patient requiring flank radiation for Wilms tumor may have not benefit with proton therapy, whereas an 18 year old with a paravertebral Ewing's sarcoma may have significant advantage with proton therapy.
6) Patient set up, tissue uncertainties, external devices or implanted need to be evaluated to minimize the risk of uncertainties and disruption in the proton dosimetry.
7) Proton therapy may be a good option for re-irradiation in selected patients.In summary, proton therapy can be an excellent option to provide better local control and/or reduced toxicities in selected patients.

SP-0010
Selection of patients for proton therapy: a physicists view

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Intensity Modulated Proton therapy (IMPT) is a highly promising approach for radiation treatment of cancer patients due to its increased potential to reduce side effects and improve quality of life compared to contemporary radiation therapy techniques, such as IMRT. However, IMPT is associated with high costs and hence limited availability. Ideally, patient selection for IMPT should be based on the highest expected complication reduction compared to IMRT.
For a given patient, it is possible to predict the risk of side effects for proton and photon therapy by applying Normal Tissue Complication Probabilities (NTCP) models to optimized dose distributions. Only patients with clinically relevant reductions in NTCP exceeding minimum pre-defined thresholds will then qualify for proton therapy. While this approach should guarantee effective use of proton therapy, there are several concerns that will be discussed in this presentation:
1. The generation of a radiotherapy treatment plan is a complex procedure and its quality is highly dependent on the planner skills. To enable unbiased comparisons between IMPT and IMRT for each patient, automation of the treatment planning process is imperative.
2. IMPT is highly susceptible to inaccuracies in patient setup, anatomic changes, and to uncertainties in the calculation of the proton range. In IMRT, uncertainties in dose delivery are accounted for in the CTV-to-PTV margin. In IMPT, however, the PTV concept is not applicable. Alternatively, robust treatment planning can be used to take into account patient setup and range uncertainties. However, it is currently unknown which robustness settings need to be used to achieve an adequate target coverage for given population-based distributions of setup and range errors.
3. Image-guidance technology improves the accuracy of radiation therapy delivery, however its impact and current state-of-the-art may vary for proton and photon radiotherapy due to the physical differences between protons and photons and for historical reasons. The applied image-guidance technology will have an impact on the magnitude of NTCP reduction and hence on the selection of patients qualifying for proton therapy.

SP-0011
Future selection practice for proton therapy: selection of patients based on treatment planning comparison and NTCP-modelling

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The last decade, many new radiation delivery techniques have been clinically introduced without being subjected to randomized controlled trials. Many of these new techniques have been introduced in order to reduce the dose to the healthy tissues and subsequently to prevent radiation-induced side effects. Due to its superior beam properties, radiotherapy with protons compared to photons enables similar dose administration to the target volume with substantially lower dose to the normal tissue. In the Netherlands, we applied a 4-step model-based approach to select patients for proton therapy and to validate the benefit of protons compared to photons with regard to reducing the risk on radiation-induced side effects.
Step 1 consists of the development and validation of multivariable Normal Tissue Complication Probability (NTCP) models. NTCP models describe the relationship between radiation dose distribution parameters and the probability of a given side effect (NTCP-value). One of the output parameters of this step are the most relevant Dose Volume Histogram (DVH) parameters that can be used to optimize radiation treatment.
Step 2 includes in silico planning comparative studies. In this phase protons are compared with photons with regard to their ability to reduce the most relevant DVH-parameters resulting from step 1 (ΔDose).
Step 3: Integration step 1 and 2. By integrating the results of the individual in silico planning comparison into the validated NTCP-models, the differences in dose can be translated into a difference in NTCP-value in each individual patient

(ΔNTCP). In the Netherlands, a national consensus has been reached regarding the threshold for (ΔNTCP
Finally, the potential benefits of protons can be clinically validated in step 4, based on external validation of the NTCP-models when patients are treated with protons. The model-based approach is an evidence-based methods for selection and validation of new radiation technologies.

Symposium: Mitigating normal tissue toxicity

SP-0012
The use of ACE inhibitors to attenuate thoracic irradiation-induced cardiopulmonary toxicity.
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Synopsis:
In thoracic irradiation, the maximum radiation dose is restricted by the risk of radiation-induced cardiopulmonary damage and dysfunction limiting tumor control. Unfortunately, current clinical practice does not include preventative measures to attenuate radiation-induced lung or cardiac toxicity. Inhibition of the renin-angiotensin system (RAS) seems to be an alluring strategy for attenuating radiation-induced cardiopulmonary dysfunction.
Interestingly, angiotensin-converting enzyme inhibitors (ACEi) have been shown to reduce the risk of radiation-induced respiratory dysfunction in preclinical (1) and clinical studies (2). More recently a study in rats showed that ACEi reduces respiratory dysfunction indirectly by reducing acute heart damage (3).
So far, the mechanisms of the protective effect of ACEi on radiation-induced toxicity are not clear. Apart from their hypotensive action, ACEi are known to have other properties such as an anti-inflammatory action. Further, it has been suggested that the sulfhydryl group in the molecular structure of captopril confers in a free radical scavenger activity. All these effects can account in part for its radioprotection. Besides, it might act as an antioxidant to reduce inflammatory reactive oxygen species and thus mitigate radiation-induced toxicity.
To conclude, ACE inhibitors have been shown to mitigate radiation-induced cardio-/pulmonary toxicity in (pre)clinical models. However, the mechanisms of action are not clear. As such the use of ACE inhibitors should be further evaluated as a strategy to reduce cardiopulmonary complications induced by radiotherapy to the thoracic area.
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SP-0013
Radiation-induced musculosqueletic late damages: possible clinical cure or simple mitigation?
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RI musculo-squeletic sequelae combine opposite tissular aspects of fibrosis and atrophy in an heterogeneous patchwork comprising concomitant active cellular and sclerotic matricial areas. Tissue remodeling follow early, subacute, chronic inflammatory changes, then fibrosis and necrosis, that provides signaling pathways through growth factors and their receptors.
In medicine, clinical cure of a chronic disease is never binary or surgical, if exists, because of the pathologic underground network well-established in the tissues.
Cure for radiation-induced (RI) late damages should be approach by a strategy using a hierarchical control of accurate protagonists. During last decades, each therapeutic intervention has illustrated successively one of the facets of this fibrotic process:
- In seventies, STEROIDS, then non anti-inflammatory drugs, showed able to stop acute RIF progression and are always required today as the first treatment in all sequelae, while anti-collagenic drugs were too toxic.
- In eighties, vascular approach revealed antithrombotic help in some acute aspects (HEPARIN), and interesting role of PENTOXIFYLLINE (speed healing) or HBO.
- In nineties, successful clinical use of superoxide dismutase (SOD) allowed to bring to light reactive oxygen species (ROS)
- fibroblasts and their related anti-oxidant strategy, then PENTOXIFYLLINE-VITAMIN E (PE) combination. The fibrotic clinical regression was slow but measurable, followed by convincing "preclinical" studies (histological reversion, in vitro modulation): first cases of fibrotic clinical cure [1,2].
- Then anticytokines (TGFβ, CTGF, …).
- After 2000, adding clodronate, in a PENTOCLO combination, allowed speeder and durable clinical RI responses, highlighting its anti-macrophagic effect on bone necrosis : first cases of osteoradionecrosis clinical cure [3]. However, therapeutic range of these drugs is tight, related to bisphosphonate absence of specificity and the bivalent macrophagic action (M1/M2 populations).
Clinical cure is a difficult art: it should take in account all these several facets. In the future, controlled trials and preclinical studies are necessary to identify best antifibrotic agents (phenotypic revesion of deficient cells), and organ specific targeted drugs and/or stem cell therapy (compensate tissular depletion after cell death), to obtain regular clinical cure if any.
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