SP-0498
Modern imaging and radiotherapy in lymphoma

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Abstract not received

Joint Symposium: ESTRO-PTCOG: ART in particle therapy

SP-0499
The need for adaptive approaches in proton therapy (compared to photons).

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The large scale introduction of soft-tissue imaging (e.g. via computed tomography) and the multiyear experience in its use paved the way, at least in radiotherapy with photons, for the development of adaptive treatments, where image datasets acquired during the treatment cycle are used to evaluate and tune the dose distributions actually delivered to the patient.

In proton therapy the presence of range uncertainties, and their effect in terms of dose perturbations, has been tackled so far mostly looking at source of range and dose uncertainties other than anatomy deformation, e.g. range error due to imperfections in the CT scan calibration and setup errors. However, neither improved CT calibration nor the use of sophisticated planning approaches such as robust optimization are coping with dose perturbations due to anatomy changes. As a consequence, proton therapy has for quite some time approached the issue in a defensive way, i.e. focusing on dose indications where anatomy changes are not expected (e.g. the skull) or at least choosing beam directions going through regions of the body where such changes are less likely.

The broadening of the indications considered to be suitable for proton therapy and the increased availability of soft tissue image guidance in proton therapy treatment rooms is slowly allowing for more proactive approaches, where repeat CT scans are actually used to modify the treatment parameters.

Starting from clinical cases, we'll see how adaptive therapy with protons has some peculiarities with respect to adaptive with photons, such as:
- A more prominent impact of anatomy deformation on the dose distribution. The finite range of protons makes the dose distribution sensitive even to anatomy variations that would not be of concern in photons
- Adaptive proton therapy needs to rely on high quality imaging for dose recalculation and optimization. Since CT calibration is an issue even with diagnostic quality CT, any further deterioration of the image quality will in principle impact the accuracy in dose distribution, thus potentially making the treatment adaptation less relevant.
- Given the strict correlation between anatomy and dose distribution, it remains to be seen whether approaches that are successful in photons (e.g. the use of plan libraries) are safe and effective with protons too.

SP-0500
Cone beam CT for adaptive proton therapy

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Daily volumetric imaging is essential in adaptive radiation therapy (ART) due to patient related uncertainties which may occur during the course of radiation treatment. The in room Cone-Beam CT (CBCT) imaging has been considered a viable option for photon ART, while CBCT just recently emerged in proton therapy. CBCT deployment in proton therapy has been slow due to technical challenges for design and implementation, lower image quality and more importantly less HU accuracy relative to CT imaging due to scattered x-rays. Therefore, the clinical deployment of CBCT in proton therapy is still in an early phase and currently is limited to treatment setup and detection of potential changes in patient anatomy generated by tissue deformation, weight loss, physiological changes and tumor shrinkage. The HU accuracy of CBCT is more critical in adaptive proton therapy (APT) relative to photon ART, as even small differences in HU could cause significant range and absolute dose errors. As a result, the integrity of the proton dose calculation may be easily compromised. Studies showed that photon dose calculation discrepancy caused by CBCT HU error can be over 10% for raw CBCT image data sets and be within 1% for scatter corrected CBCT. However, no study up to date has demonstrated the feasibility of proton clinical dose calculation or treatment planning on raw CBCT data sets and therefore currently the primary role of CBCT in APT is to trigger the need for CT rescanning for dose adaptation. However, there are two major approaches explored to overcome current CBCT image data sets limitations. The first one employs deformable image registration of the treatment planning CT to the daily verification raw CBCT to generate a CBCT based stopping power distribution. This method has been explored mostly for head and neck dose adaptation. The second one aims to improve the raw CBCT data accuracy via scatter corrections and in its current stage explored the feasibility of raw CBCT based planning on an anthropomorphic phantom. As these methodologies are developing and new ones emerge, CBCT imaging may further evolve and holds the potential to become a viable tool for APT.

SP-0501
Adaptive practice and techniques in proton therapy of the lung

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Adaptive radiation therapy is the practice of modifying initial treatment plan in order to accommodate the changes in a patient's anatomy, organ motion, and biological changes during course of treatment. Within this scope of definition, it can be further classified based on different time scale going from offline (between fractions) to online (prior to a fraction), and to real time (during fraction) modification in beam delivery. The dose distribution of proton is "non-static" relative to the change in patient anatomy because the finite path length of protons is tissue density dependent. Therefore the adaptive radiation therapy is more relevant for proton than photon. For the same reason, for moving target in particular, online or real time adaptation may become more important for proton therapy. During initial treatment planning phase, proton ranges in patient must be determined precisely in order to take the advantage of Bragg peak. Changes in water equivalent thickness along the beam path due to breathing motion must be accounted by robust planning strategies. Any significant changes in proton range from what was calculated should be detected and prompt for an adaptive re-plan. Treatment sites that are likely to change in anatomy during the course of treatment or during treatment are particularly important. In this regard, lung cancer is one of the most relevant sites to practice adaptive proton therapy. Over 40% of lung tumors move more than 5 mm and 10% moves greater than 10 mm [1] with possibility of changes in breathing pattern during the course of treatment. The change in tumor shape or density and decrease in tumor volume as tumors respond to the radiation also raise another challenge for proton therapy. The protons can travel further without the tumor tissues to stop them in lung. Previous studies found that on average from 0.6 to 2.4% of tumor volume can be reduced per day [2]. Adaptive radiation therapy requires modification in treatment plan through changing contours of targets or organs at risk and beam

parameters accordingly and any quality assurance checks that are deemed necessary. Therefore the adaptive radiation therapy requires more resources when compare to the conventional image-guided radiation therapy. In fact, image-guidance can be considered the first step in adaptive practice as it triggers the initial decision to adapt and provide the 3D volumetric images that are necessary for adaptive re-plan. There have been efforts to create techniques and technologies that can facilitate the adaptive planning. In this presentation, we will first discuss the state of art practice of adaptive proton therapy including the experience at our institution. We will review studies assessing the magnitude of intra- and inter-fractional changes and its impact on delivered proton dose distribution with and without adaptive practice. Secondly, we will present the cutting edge ideas and techniques that are developed specifically for adaptive proton lung therapy in the most recent literature.

[1] Liu HH, Balter P, Tutt T, et al. Assessing respiration-induced tumor motion and internal target volume using 4DCT for radiation therapy of lung cancer. Int J Radiat Oncol Biol Phys 2007;68:531-540

[2] Sonke JJ, Belderbos J. Adaptive Radiotherapy for lung cancer. Semin Radiat Oncol 2010 Apr; 20(2):94-106.

SP-0502
In-vivo range estimation and adaptive particle therapy
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The finite range of protons is a two-edged sword. On one side, it is the *raison d'etre* of proton therapy, on the other, a potential source of uncertainties in-vivo. As such, both in-vivo range estimates and adaptive therapy are being proposed and pursued for mitigating such uncertainties. However, sources of in-vivo range uncertainties are many, ranging from systematic uncertainties in the calibration of CT Hounsfield units to proton stopping power and inaccuracies in dose calculations (for convenience defined here as type I uncertainties) to variations in patient positioning and anatomy changes during the course of treatment (type 2). Whereas, for good quality CT data, type 1 uncertainties can result in range uncertainties of a few percent or millimeters (about 3% or 6mm in the worst case,) type 2 can result in range changes of the order of centimeters. In addition, type 1 uncertainties will, to a good approximation, be similar across all patients of a particular indication and will remain the same throughout the duration of a patient's treatment. Type 2 on the other hand will be patient and (potentially) treatment day dependent. So, what are the roles of in-vivo range measurement and adaptive therapy for dealing with these? It seems to this author that in-vivo range verification perhaps has a role to play in reducing type 1 uncertainties, whereas the best approach to type 2 has to be adaptive therapy. Adaptive therapy (based on regular, if not daily, imaging) must be pro-active (i.e. the treatment should ideally be adapted *before* delivery), whereas in-vivo range verification can only be (at best) reactive (e.g. may be able to provide a reason to interrupt a delivery if an error is detected). As such, the best use of in-vivo range estimation seems to be as part of a population based (commissioning) approach in order to verify that CT calibration and dose calculations are more and more precise, such that type 1 uncertainties resulting from pre-treatment imaging (necessary to mitigate type 2 errors) can then be reduced as much as possible. Such an approach however puts stringent demands on the accuracy and precision of in-vivo range estimates, with in-vivo resolutions in the millimeter range being required in order to significantly improve these uncertainties. Will this ever be achievable?

SP-0503
European strategy
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One of the most exciting areas of basic, translational and clinical research in radiation oncology today is radiotherapy with particles, i.e. with protons or heavier ions. The main advantage of radiotherapy with protons compared to state-of-the-art radiotherapy with photons is a decrease of the volume of normal tissues irradiated to intermediate and low doses, while irradiation of normal tissues to high doses or the conformality of the dose to the tumor are usually similar for protons and photons. Exceptions include situations where critical normal tissues can be excluded by proton therapy from the irradiated volume completely or to a large extent. The most relevant clinical research question is therefore to investigate whether sparing of normal tissue by proton therapy leads to clinical relevant benefits which balance the higher costs of this treatment. After demonstration of relevant sparing of normal tissues, further clinical studies on utilizing dose intensification strategies may become another important research avenue in those tumors where local or locoregional tumor control today are unsatisfactory.

At present only few centers (often with different technologies and patient populations) are active in clinical research using protons, which makes fresh thinking on study design in radiation oncology necessary, as large scale randomized trials will not be feasible in many situations. Model-based approaches are a major component of the trial methodological portfolio, but alternatives (including multicenter stepwise randomized trials, pseudo-randomized trials and prospective matched pair trials) may be superior in different clinical situations. All of these approaches necessitate dedicated clinical research infrastructures and complex high-level network formation to reach the power for meaningful clinical trials. This also plays an important role in terms of radiotherapy stratified by biological parameters, which is anticipated to become a clinical reality in the near future for several tumor entities.

Proton (or other particle) therapy holds particular promise to further advance personalized radiation oncology. However obstacles in trial design, data sampling and integration, or analysis may dilute the effects to such an extent that it may not be possible to demonstrate it according to generally accepted scientific standards. This would be a major hurdle for further implementation and reimbursement of this auspicious technology, and also for sound medical stratification of access of patients in need for this therapy.

The lecture will discuss opportunities and problems of proton therapy in the context of high precision personalized as well as biologically stratified radiation oncology, thereby also touching trial design, technology development and the importance of network formation on a European level.

Symposium: Small animal irradiation

SP-0504
Preclinical radiotherapy technology, dosimetry and treatment planning
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Small animal image guided irradiation platforms are revolutionizing the field of preclinical radiobiology by facilitating the delivery of clinically relevant irradiation