UNCONVENTIONAL IMAGING IN ION BEAM THERAPY: STATUS AND PERSPECTIVES

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Owing to their favorable physics interaction properties, ion beams can offer unprecedented ballistic accuracy for highly conformal irradiation of complex-shaped tumour volumes, with excellent sparing of surrounding healthy tissue and critical organs. However, these advantageous dosimetric properties also bear enhanced sensitivity to uncertainties in treatment planning and delivery, calling for an increasing need of advanced imaging to ensure safe application of the intended dose to the targeted area during the entire course of fractionated therapy. Although it is common perception that in-room image-guidance of particle therapy is still lagging behind modern integrated solutions of photon therapy, new technological developments are being pursued by several groups to exploit the unique features of ion beam interaction in matter for innovative image-guidance concepts, with particular focus on *in vivo* verification of the ion beam range.

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1. Introduction

The physical and radiobiological properties of light ion beams (*i.e.*, protons and heavier ions up to charge $Z \leq 10$) enable a selective concentration of radiation damage in the characteristic Bragg peak at their end of range (figure 1), opening the perspective of a highly precise and biologically effective radiation therapy [1, 2]. Therefore, radiotherapy with ion beams, particularly protons and carbon ions, is a rapidly emerging treatment modality worldwide, promising improved clinical outcome with reduced toxicity for various tumour sites in comparison to conventional radiotherapy with photons and electrons. However, the favorable physical selectivity of ion beams comes at the expense of enhanced sensitivity to uncertainties in the calculation of the planned treatment as well as inter- and intra-fractional changes of the actual patient anatomy with respect to the planned one. In particular, the longitudinal dimension of the dose delivery, which is related to the

finite ion beam range in tissue, is strongly influenced by the radiological pathlength, determining accurate placement of the Bragg peak in the tumour. Hence, full clinical exploitation of the therapeutic advantages of ion beams requires dedicated imaging techniques not only capable of assessing patient position and anatomy at the treatment site, but also to visualize *in vivo* the actual beam range and, ideally, enable reconstruction of the dose delivered to the patient. To this aim, several groups are working on the development and evaluation of unconventional imaging modalities able to provide dedicated image-guidance solutions for particle therapy.

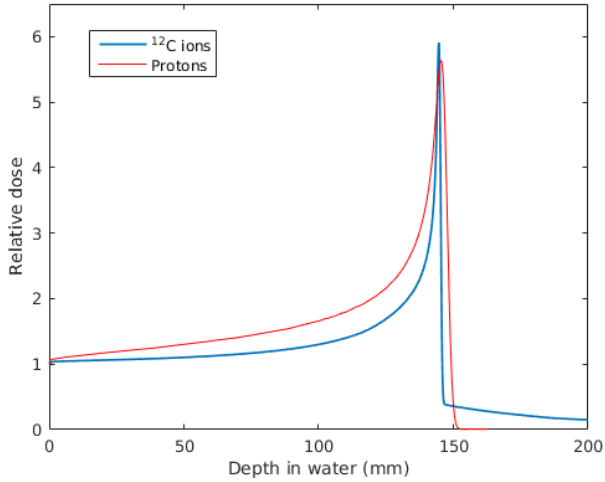

Fig. 1. Example of Bragg peaks for mono-energetic proton (gray/red line) and ^{12}C ion (black/blue line) beams in water at an intermediate therapeutic energy.

2. Material and methods

Clinical experience reported so far has been restricted to indirect *in vivo* visualization of beam range via Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI), after individual or cumulated treatment fractions, respectively [3]. PET imaging exploits the transient amount of β^+-activation which is produced in nuclear interactions between the primary ions and the penetrated tissue. The spatial pattern of irradiation-induced activity, carrying the correlation to the beam range and deposited dose, strongly depends on the ion beam species, the properties of the irradiated tissue (elemental composition and physiological clearance or so-called "biological washout"), and the time course of irradiation and data acquisition. Depending on the PET installation, this β^+-activity can be imaged during or after treatment delivery, using instrumentation directly integrated

in the treatment site (in-beam) or located closeby, inside (in-room) or outside (off-line) the treatment room [4]. Conversely, MRI has been found able to visualize physiological changes induced by ionizing radiation, *e.g.*, fatty replacement of irradiated bone marrow [5]. As these processes can become manifest only after a certain dose threshold, in particular anatomical locations such as the spine and the liver, this method does not lend itself to verification of single treatment fractions and, even less, real-time imaging. Therefore, for the more ambitious goal of on-site imaging directly during treatment delivery, ongoing detector development efforts aim at *in vivo* range verification via visualization of secondary radiation emerging either from delayed radioactive decays of β^+-activated isotopes (PET imaging) or from prompt de-excitation products (prompt gamma and charged particle imaging) of nuclear fragmentation reactions [3]. For facilities able to provide sufficiently high beam energies to completely penetrate through the patient body, all these (quasi) real-time techniques could be complemented by radiographic or tomographic transmission imaging of energetic ion beams prior to, or even "in-between", treatment [3, 6, 7]. The emerging interest in ion-based transmission imaging is due to its potential to decrease range errors via direct determination of the tissue stopping power ratio relative to water, which is roughly independent of the beam energy used for imaging or therapy as well as the ion species. Moreover, ion-based imaging is less prone to artefacts from metal/dental implants and might be ultimately used to complement or even replace in-room X-ray imaging for daily low-dose image guidance and, if necessary, treatment adaptation.

3. Results

Despite the usage of suboptimal instrumentation adapted from conventional whole-body and small-animal PET scanners, and workflow implementations most often unable of in-beam imaging, encouraging results of PET-based treatment verification have been reported by different groups, indicating the possibility to identify treatment delivery inaccuracies from interfractional anatomical modifications or patient mis-positioning in well-fixated anatomical locations of negligible activity washout [8–10]. Moreover, few groups recently reported first promising experiments on the potential of in-beam and off-line time-resolved (4D) PET imaging for assessment of motion-mitigated scanned beam delivery to moving targets [11, 12]. Optimal choice of reconstruction algorithms and parameters has also proven to be useful for achieving an improved image quality at the typically encountered extreme scenarios of low counting statistics [13], and ongoing efforts aim at refined modeling of activity prediction and establishment of robust data processing for automated evaluation of measured and calculated activity to

infer treatment quality [14–16]. However, the largest impact is expected from the promising next-generation PET instrumentation relying either on full-ring ("openPET") or dual-head (with fast time of flight) designs specifically tailored to low-statistics in-beam imaging, as successfully demonstrated in proof-of-principle experiments with first dedicated prototypes [17–19].

In addition to advances in PET imaging, different new concepts have been proposed for detection of neutral or charged prompt secondary radiation originating from nuclear interaction of the therapeutic beam in the patient. Prototypes of prompt gamma imaging perpendicular to the main beam direction span from one-dimensional (1D) visualization of the last few centimeters of beam penetration through a massive knife-edge collimator [20, 21] to the more challenging 3D detection relying on the Compton kinematics [22]. The single slit camera design of [21] has just entered clinical testing in proton therapy, and promising 3D prompt gamma data have just been acquired in phantom experiments by a Compton camera prototype operated at clinical proton beam intensities [23]. Imaging of charged particles, with special focus on secondary protons from impinging carbon ion beams, has been demonstrated with tracking systems inspired by particle physics experiments, using solid state detectors or drift chambers followed by absorbers, placed at different angles from the main-beam direction [24, 25]. Finally, recent implementations of ion transmission imaging include particle-by-particle tracking with residual energy measurement for broad proton and carbon ion beams, as well as range assessment from integral measurements, especially for scanned carbon ion beams, either of transmission through thin planar detectors or of the entire Bragg peak stopped in stacked large area detectors (range telescopes) [3, 7, 26].

4. Discussion and conclusion

The rapidly increasing spread of ion beam therapy facilities worldwide is being accompanied by an increasing interest in unconventional imaging techniques able to provide information on the actual *in vivo* beam range and dose delivery, aiming to reduce treatment uncertainties and foster optimal clinical usage of ion beams. Whereas a limited number of clinical investigations have been so far reported for PET- and MRI-based range assessment after individual or cumulated treatment fractions, several groups are pioneering new detector developments aiming at (quasi) real-time on-site imaging of radioactive or prompt nuclear reaction products, possibly complemented by morphological imaging with the same radiation quality but higher energy than for therapy. Although most of the new developments are still at the research and development level or just at the beginning of clinical evaluation, it is expected that some of these new concepts will be deployed

for routine clinical usage in the near future. From the different nature of the underlying signals, the novel imaging modalities are expected to provide often complementary information and perform differently in dependence of the ion species and anatomical site. On the other hand, even when neglecting cost issues, it could be challenging and even unpractical to integrate all discussed techniques at the treatment site to complement standard X-ray anatomical imaging (figure 2). Therefore, hybrid detector concepts [27, 28], fulfilling multiple detection purposes likely traded with compromises in image quality, might be a viable solution for the future. Additional challenges will include synchronization of the new detector developments with motion monitoring sensors for anatomical locations subject to physiological motion, for example from respiration, and optimal integration in the clinical workflow for routine usage.

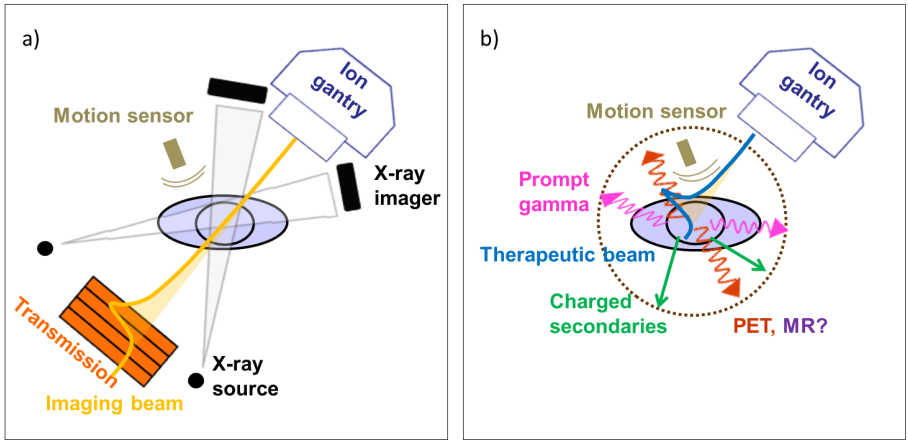

Fig. 2. Example of pre-treatment (a) and in-beam (b) image guidance, including the novel concepts of transmission and emission imaging discussed in the text.

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