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Review

PET monitoring of hadrontherapy

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Abstract

Imaging techniques for in-vivo verification of the ion beam range and treatment delivery are increasingly receiving a considerable attention, as they hold the promise to enable full clinical exploitation of the improved tumour-dose conformality offered by ion beams. Although promising novel techniques have recently been proposed and are being investigated in fundamental pre-clinical research, Positron-Emission-Tomography (PET) still offers the only technically feasible method for a volumetric non-invasive verification of the ion treatment during or shortly after daily dose delivery. This contribution discusses examples of clinical implementation of PET imaging, with special focus on the experience in in-beam and offline monitoring of carbon ion and proton therapy at the GSI Helmholtzzentrum für Schwerionenforschung in Germany, the Massachusetts General Hospital in USA, and the Heidelberg Ion Beam Therapy Center in Germany. In particular, it highlights the encouraging clinical results but also the encountered major limitations. Finally, it addresses the most promising ongoing developments aiming to achieve optimal exploitation of the surrogate PET signal for in-vivo quality assurance of high precision ion beam therapy.
Key words: Positron-Emission-Tomography, ion beam therapy, treatment verification

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Introduction

The favourable physical properties of ion beam interaction in matter with the characteristic dose maximum in depth known as "Bragg peak" (Figure 1) offer the possibility of superior tumour-dose conformality with better sparing of surrounding critical organs and healthy tissue in comparison to conventional radiation in external beam radiotherapy. However, these advantages come at the expense of an increased sensitivity to uncertainties in the dose delivery, especially due to inter- and intra-fractional changes of the patient position and anatomy over the course of fractionated therapy. In particular, the praised finite range of ion beams (correlated with the position in depth of the Bragg peak) is a major source of uncertainty in the patient [1–3], hampering full clinical exploitation of the ion ballistic properties. Therefore, clinical practice of ion beam therapy still tends to rely on the less sharp but better controllable lateral penumbra of the beam (cf. Figure 2), rather than stopping the Bragg peak in front of critical structures. Although treatment uncertainties can be mitigated by the introduction of cautious safety margins and the careful choice of the beam incident directions, in-vivo and non-invasive validation of the actual dose delivery and, in particular, of the ion beam range during the fractionated course of radiotherapy would be highly beneficial.

Over the last years, increasing interest has been devoted to in-vivo quality assurance of high precision ion beam therapy. In this context, very promising novel concepts of real-time range verification exploiting prompt (with respect to the time of beam interaction in matter) emitted neutral or charged radiation have recently been proposed and started being investigated [4–6]. Nevertheless Positron-Emission-Tomography (PET) still offers the only technically feasible method for a volumetric non-invasive verification of the ion treatment during or shortly after daily dose delivery. This method, originally proposed for the imaging of im-

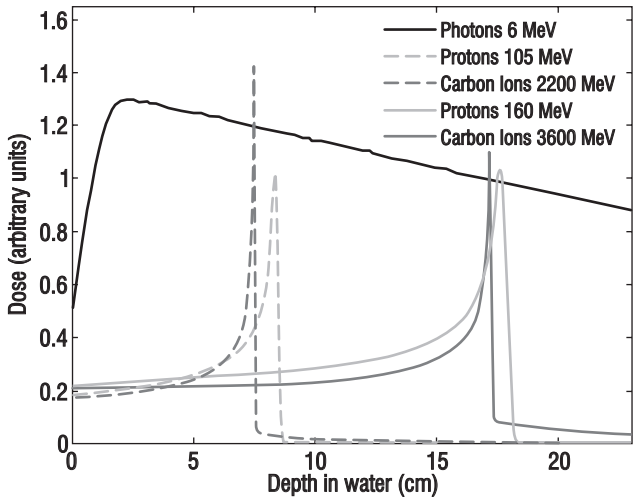

Figure 1. Calculated depth-dose deposition in water for monoenergetic photon, proton and carbon ion beams in the energy range of therapeutical relevance. For the photon beam, an additional filtering layer of 2 mm aluminium was included in the calculation prior to the entrance in the water target. Taken from [1]

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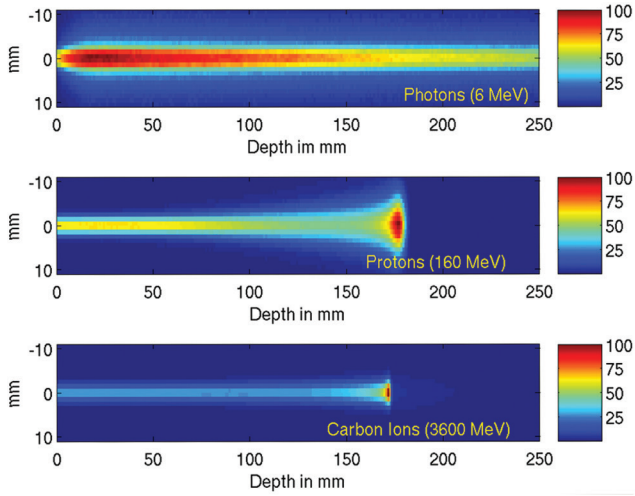

Figure 2. Calculated 2D dose distributions for a collimated photon beam (top, square transversal profile of 4 mm edge) with respect to proton (middle) and carbon ion (bottom) Gaussian-shaped pencil-like beams (3 mm FWHM) in the therapeutically relevant energy range (cf. the corresponding laterally integrated depth-dose distributions in Figure 1). The beams enter the water target from the left. The colour map indicates percentages of the maximum dose. The less sharp lateral penumbra with respect to the steeper distal fall-off at the Bragg peak is evident for ion beams, especially for protons. Taken from [1]

planted radioactive beams [7], has been extensively investigated in the case of therapy with the more easily accessible stable ion beams. To date, several examples of clinical implementations of PET-based treatment verification have been reported worldwide, exploiting different types of installation to measure the signal induced by actively- or passively-shaped ion treatment fields during or shortly after irradiation. This contribution will review the basic principle of the method and give an exemplary overview of different implementations and clinical experiences. These include in-beam and offline PET monitoring of carbon ion and proton therapy at the GSI Helmholtzzentrum für Schwerionenforschung in Germany, the Massachusetts General Hospital in USA, and the Heidelberg Ion Beam Therapy Center in Germany.

Material and methods — the principle of PET-based treatment verification

The unconventional application of PET imaging to the monitoring of ion therapy with stable beams is based on the detection of the transient $\beta+$-activation which is induced in nuclear interactions between the ions and the irradiated tissue. Depending on the primary ion beam species, the mechanism of $\beta+$-activation may include either target fragmentation only or the formation of both target and projectile positron-emitting fragments. The mechanism of production mainly affects the shape of the ion-induced activity and its correlation to the deposited dose (Figure 3). In fact, activated target nuclei stay almost at rest in the place of interaction, while positron-emitting projectile fragments travel further and accumulate at their end of range, resulting in a peaked activity signal. The latter is located shortly before the Bragg peak for the most frequent positron-emitting isotopes of the primary therapeutic ion beam, such as ^{11}C and ^{10}C from a primary ^{12}C ion beam. Regardless of the formation mechanism, dose deposition and irradiation-induced activation remain different quantities due to the different underlying electromagnetic and nuclear processes, respectively. Hence, treatment verification can be obtained either by comparing the actual PET measurement with a reference measurement taken at the beginning of the treatment course to assess reproducibility [9], or with an expectation based on the treatment plan and the time course of irradiation and imaging to assess accuracy [10].

Due to the intrinsically delayed radioactive decay according to the half-lives of the typical reaction products (e.g. ^{10}C, ^{15}O, ^{11}C), ranging from few seconds up to several minutes, the PET signal can be measured during or shortly after beam delivery. In particular, three major implementations have been so far clinically explored, which utilize either dedicated limited angle detectors integrated in the beam-delivery, or full ring scanners located inside or outside the treatment room. In particular, "in-beam" implementations refer to data acquisition during the irradiation, which has been so far only achieved in the pauses of pulsed beam delivery due to the considerable prompt radiation background

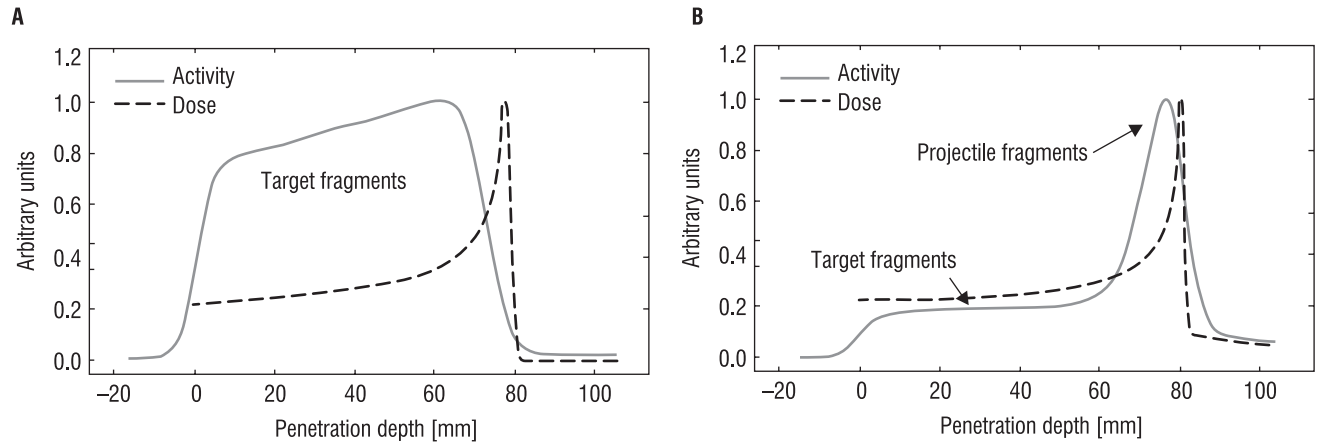

Figure 3. In-beam PET measurements of $\beta+$-activity depth profiles (solid line) for proton (**A**) and carbon ion (**B**) irradiation of Polymethyl methacrylate (PMMA) targets at 110 MeV and 212.12MeV/u, respectively. The different pattern of activation either due to positron-emitting target fragments only (left) or including also the peaked contribution from positron-emitting projectile fragments (right) is evident. The dotted line shows the corresponding calculated dose distributions. Adapted from [8, 18]

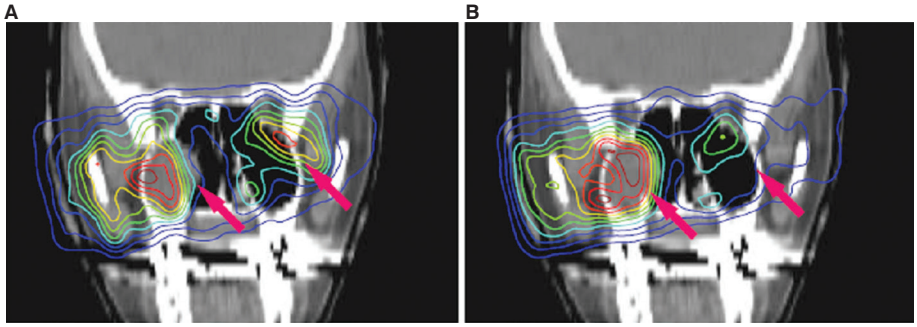

Figure 4. Measured (**A**) and predicted (**B**) β+-activity distributions (displayed by coloured isolines normalised to the maximum within the imaged plane) for an oblique treatment field entering the patient from the right side (left in figure). The arrows point at discrepancies suggesting a local tissue reduction in the beam path. Taken from [17]

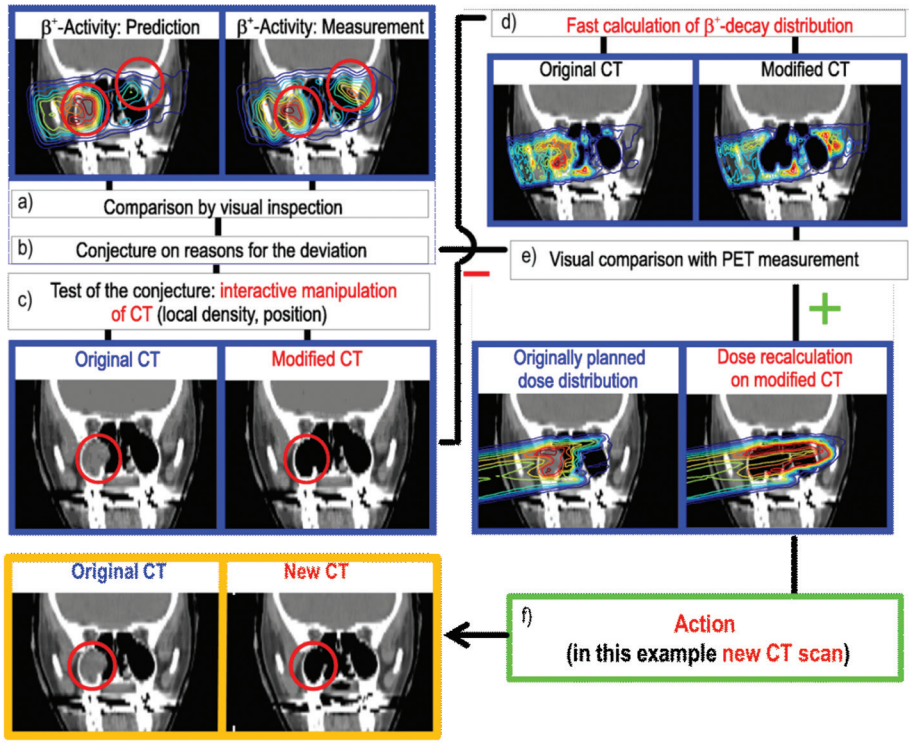

Figure 5. Flow chart of the interactive approach developed in [17] for local dose quantification from PET images in routine monitoring of carbon ion therapy at GSI Darmstadt. Figure adapted from [17, 18]

during the real beam-on time [11, 12]. "In-room" installations may include on-board detectors starting acquisition immediately after the end of the therapeutic irradiation [9], or full-ring scanners moved to the patient (or vice-versa) for a few minutes delayed acquisition after treatment [13]. "Offline" imaging refers to the acquisition using a full-ring scanner installed outside of the treatment room [14, 15]. Examples of these three concepts with related initial clinical experience are recalled and discussed in the next session.

Results and discussion — examples of clinical implementation and experience

The most extensive clinical experience has been so far reported for the in-beam PET monitoring of scanned carbon ion therapy in the pilot therapy project at GSI Darmstadt [10]. The daily dose fraction of over 400 patients mostly treated for head and neck tumours could be imaged using a dedicated dual-head positron camera directly integrated in the treatment site [11]. Despite the shortcomings of limited angle detection and the lack of quantitative imaging, important conclusions on the actual beam delivery could be inferred from the comparison of the daily measured activity with a corresponding prediction for the first delivered treatment field. In particular, the method gave an essential contribution in reducing the systematic error of the semi-empirical calibration of the patient Computed Tomography (CT) data into ion range, consistently used by the treatment planning system and the PET calculation engine [16]. Additional random errors due to patient mispositioning or local anatomical modifications could also be detected (Figure 4), and the impact on the actual dose delivery could be in first approximation quantified prior to the application of the next treatment fraction for a possible treatment adaptation (Figure 5).

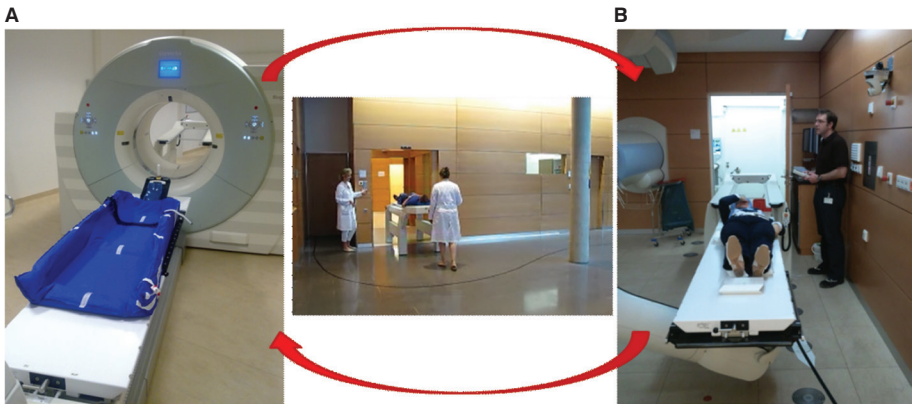

Figure 6. Example (with volunteers) of the dedicated shuttle solution allowing to share the same table top (with related immobilization device) between the PET/CT scanner (**A**) and the robotic treatment table (**B**) for easy transport between the imaging and treatment room (cf. central image). An example of clinical workflow starts with volumetric CT imaging for positioning, transport to the treatment room for therapy, and transport back for post-radiation in-vivo verification. Adapted from [20, 21]

Despite the promising results achieved in the GSI project, the considerable development and integration efforts and costs prevented the spread of similar solutions at other treatment centers. Here, more viable approaches could benefit from the advent of commercial combined PET/CT scanners to overcome the major limitations encountered with stand alone off line PET scanners [14]. In fact, PET/CT devices offer additional anatomical information to reduce the unavoidable uncertainties of patient repositioning at the remote sites outside of the treatment room. At MGH Boston, a pilot clinical study with a total of 23 patients was conducted using a commercial PET/CT installation in the department of radiology, at more than 10 min walking distance from the proton center [15, 19]. The relatively long time (15 min on average) elapsed between passively scattered proton irradiation and imaging with the consequent significant loss of counting statistics needed to be compensated with a long PET scan time of 30 min (in single bed position). Still, inherent drawbacks of off line imaging were encountered, such as the missed contribution of short-lived emitters (especially the most abundant ^{15}O with a half-life time of ca. 2 min) and the degraded spatial correlation between activity and dose due to biological washout processes. The latter had to be for the first time accounted in the simulation process for a more reliable comparison with the measurement [15]. Despite the extremely low activity signal and the above mentioned shortcomings, irradiation-induced activation could be demonstrated for different treatment sites, with encouraging results of millimetric in-vivo range confirmation in low perfused bony structures of intracranial and cervical spine tumour patients. Severe limitations for accurate in-vivo range verification were instead encountered in the case of abdominopelvic tumors, which were attributed to biologic washout effects, co-registration, motion and limitations of CT stoichiometric calibrations for tissue classification in CT-based Monte Carlo simulation of the expected activity patterns [19]. As most of these challenges were ascribed to the suboptimal imaging implementation rather than the PET technique itself, clinical research was then continued with a prototype neurological PET scanner on wheel for in-room imaging shortly after the patient treatment [13]. The first experience with two patient cases confirmed the expected improvements in counting statistics [13]. This enables scan times below 5 minutes in order to avoid too long prolongation of the treatment session in the treatment room for the sake of acceptable patient throughput. Moreover, the most relevant ^{15}O emitter could be detected for visualisation of soft tissue activation, exhibiting better spatial correlation with the high-dose region and steeper distal fall-off for improved range verification, at the expense of a less well understood biological washout [13]. The major encountered technical obstacle was the co-registration accuracy between the in-room PET acquisition and the planning CT, which is essential for the comparison of PET measurements with CT-based simulated predictions. Thus, future studies are planned at a next generation "neuroPET" prototype integrating a CT scanner to overcome the co-registration issue. However, due to the limited bore opening of the device, this promising low-cost and high-sensitivity modality is limited to the monitoring of cranial sites or pediatric patients.

As neither in-beam nor in-room commercial solutions existed yet, at the more recent Heidelberg Ion Beam Therapy Center a dedicated commercial PET/CT scanner was installed just outside of the treatment sites. For an efficient workflow, a novel shuttle solution has been implemented to preserve the patient immobilisation and positioning between the treatment and imaging site (Figure 6) [20, 21]. This can be advantageous with respect to the walking and repositioning of the patient especially in the case of challenging anatomical locations requiring complex immobilisation devices. The scanner is currently being used in a major clinical study aiming to investigate the benefit of post-treatment PET/CT verification on a large population of patients being treated with scanned proton or carbon ion beams [22]. The initial clinical experience (cf. Figure 7) is going to be reported soon, together with a description of the ongoing efforts for further methodological improvements [23]. These feature improvements in the modelling of the irradiation-induced activity [24] and in the dedicated software developed to support the PET-verification clinical workflow towards a semi-automated range assessment [25].

In addition to the cited examples, more and more institutions are actively investigating the clinical usage of dedicated or commercial PET scanners for the purpose of in-situ verification of ion therapy treatment (e.g. [26–28]). Despite the generally encouraging results, all experiences reported so far seem to suf-

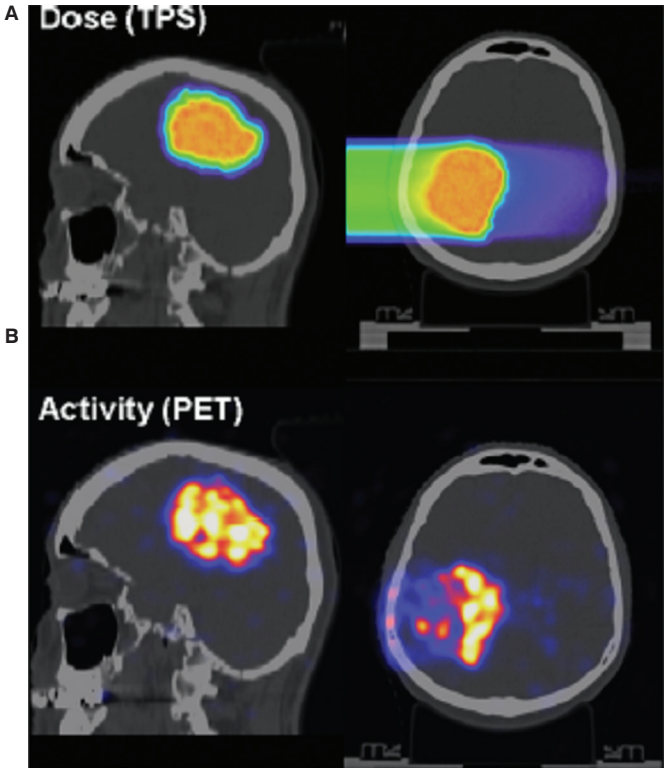

Figure 7. Patient treated for a primary brain tumour with a carbon ion boost (**A**, planned dose distribution overlaid onto the planning CT), undergoing a PET/CT measurement (**B**) shortly after scanned ion irradiation at HIT. Taken from [22]

fer from the suboptimal PET instrumentation, mostly adapted or directly taken from established conventional nuclear medicine or small animal imaging.

Prototype in-beam or on-board solutions offer the advantage of imaging in the treatment room with the patient immobilised in the same treatment position, with no or only minor impact on the patient throughput. Drawbacks are the limited angle imaging artifacts, as well as the considerable development and integration costs. In-room solutions with full-ring tomographs could offer a good compromise in terms of image quality, acceptable workflow and moderate integration efforts [13, 29], provided that accurate co-registration is ensured. "Offline" imaging using a commercial scanner installed outside of the treatment rooms is the cheapest and easiest approach, not interfering at all with the patient treatment throughput. The drawback is the need of long scan times to compensate for the activity decay in the time elapsed between irradiation and imaging, together with the loss of short-lived emitter contributions (especially the most important) ^{15}O and the degraded correlation between activity and dose due to biological washout.

In all implementations, imaging performances are challenged by the extremely weak (less than 10 kBq/Gy/ml [1]) activation signal induced by the therapeutic irradiation, which is order of magnitude below the typical tracer concentrations administered in nuclear medicine applications. Therefore, major improvements can be expected by the ongoing technological developments towards new geometrical arrangements for in-beam full ring scanners [30] or next generation ultra-fast time-of-flight in-beam PET detectors for artifact-free on-the-fly imaging [31], as being explored by several institutions and international collaborations including the European project ENVISION (European NoVel Imaging Systems for ION therapy) [32]. Further challenges of the PET-based verification approach being tackled are the modeling of the expected PET images [33–35] (including the physiological clearance especially remarkable in offline imaging), the co-registration between imaging and treatment positions (for in-room and offline implementations implying the movement of the patient) as well as organ motion [36] (strongly depending on the anatomical location and the duration of the PET scan).

It can be concluded that despite the proof-of-concept and promising initial clinical experience reported so far, the full potential of the PET verification approach has not yet been reached. Nevertheless, there are strong reasons to believe that the several technological and methodological developments being currently investigated will enhance the role of this imaging modality for in-vivo verification of range, and possibly, dose delivery of high precision ion beam therapy in the near future. Improved instrumentation could also open the possibility of exploiting the irradiation-induced signal in correlation with functional modifications over the course of fractionated treatment, as already suggested by retrospective analysis of in-beam PET data at GSI [37].

Conclusion

Full clinical exploitation of the superior selectivity offered by ion beam therapy requires in-vivo imaging of a "surrogate" signal (e.g. from escaping secondary radiation) correlated to the beam range and delivered dose, as well as a reliable computational tool for accurate modeling of the "surrogate" signal in relation to the range/dose deposition. PET is a mature imaging technique which has been already clinically investigated for in-vivo treatment verification of proton and carbon ion therapy at several institutions and with different instrumentation. Despite the encouraging results reported so far for in-vivo visualization of the treatment area and confirmation of the beam range within few millimeters in favorable anatomical locations (e.g. skull base), technological and methodological improvements are still desirable for optimal usage of the minor amount of irradiation-induced $\beta+$-activity correlated with the dose delivery. In this respect, major advances can be expected from the usage of next generation dedicated instrumentation tailored to this specific application, as being currently pursued by several groups. Eventually, it can be expected that in-vivo verification of ion therapy will benefit from a variety of complementary imaging techniques, most of which — unlike PET — are still at the basic research and development level.

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