Acta Oncologica, 2015; 54: 1254–1258

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COMMENTARY

Imaging in particle therapy: State of the art and future perspective

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Several imaging and image guidance reviews are present in the literature for both photon and proton (ion) [1–9] beam therapy. In the present commentary we discuss imaging technology presently available for proton and ion therapy in a three-stage approach that can guide the application new/old imaging technology to proton and carbon ion centers:

Stage 1: Pre-treatment imaging
Stage 2: In-room image-guidance
Stage 3: Post-treatment imaging

The three stages are represented by three numbers "**1**", "**2**" and "**3**" to represent the overall impact the imaging procedures can have on the quality of the treatment, where "**1**" has the highest impact while "**3**" has the lowest impact.

Stage 1: Pre-treatment imaging is the most important stage in the imaging procedure, as it will be needed by both clinicians and physicists to generate the best feasible and robust treatment plan. In addition, the images generated during Stage 1 will be used as reference images during the course of treatment (Stage 2) and for the post-treatment (Stage 3) assessments.

Stage 2: In-room image-guidance is fundamental for patient daily positioning, treatment delivery and intra-fraction evaluation of anatomical and physiological changes due to radiation therapy. Daily image guidance is fundamental to guaranteeing accurate delivery of the planned radiation dose.

Stage 3: Post-treatment imaging is an important stage in the imaging procedure, since it involves patient follow-up and post-treatment assessment that can provide valuable input to other future treatments.

Stage 1: Pre-treatment imaging

Presently available pre-treatment imaging

Single energy computed tomography (SECT) is the work horse of any radiation therapy department (photons or protons) and provides not only anatomically information for contouring but also stopping power estimates needed for proton and ion beam treatment planning (electron density in the case of photon therapy). Most radiation therapy departments use 140 kV x-rays, although some may use 120 kV or 100 kV for better contrast of specific anatomical sites. Accurate stopping power estimate and excellent tumor-to-surrounding contrast are required to allow proton/ion range calculations and treatment planning for each individual patient.

Presently, state-of-the-art stopping power estimation is based on SECT scans of the patient [10], where the measured Hounsfield Units (HU) are converted to stopping power, via a calibration curve usually obtained in water-equivalent plastic phantoms. The proton/ion range uncertainties may have many sources of error, from organ and patient motion, to metal artifacts, dose calculation approximations, systematic CT inaccuracies, etc [11,12], where one of the largest contributor is the HU-to-Stopping-Power calibration. The overall systematic uncertainty can be as large as 3.5% in biological materials [11–13]. Given the dosimetric-importance of the systematic range-uncertainty to proton beam therapy, a variety of different approaches have been proposed in the literature and reviewed by Knopf and Lomax [13], such as: 1) positron emission tomography (PET); 2) dual energy CT (DECT); 3) proton CT (pCT) or proton radiography (pRAD);

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(Received 10 June 2015; accepted 19 June 2015)

ISSN 0284-186X print/ISSN 1651-226X online © 2015 Informa Healthcare
DOI: 10.3109/0284186X.2015.1075665

4) prompt gamma; 5) magnetic resonance imaging (MRI); and 6) implantable dosimeters for direct Bragg peak evaluation. These imaging modalities will be addressed in the section of *In-room image guidance*.

Tumor contouring in radiation therapy is still predominantly done based on either SECT, MRI, single photon emission computed tomography (SPECT) or PET imaging. SECT is the dominant imaging modality used for contouring, while MRI has been used predominantly in regions where tumor-to-soft tissue contrast is poor in SECT images, like in the brain. SECT has been used also in time-resolved modality [also known as four-dimensional (4D)CT] to account for tumor motion in extra-cranial sites, such as in lung and liver. It has been shown that a 4D treatment plan can significantly reduce motion effects in active scanning beam modality, especially when the tumor motion is larger than 1 cm [14,15]. More generally, 4D imaging can be employed to plan gated treatments or to better delineate the target volume [16]. PET scanning is used mostly to identify hypoxic radio-resistant or metabolic regions within the tumor or nodes (using FDG or Fmiso) which may require radiation dose boosting, and it is usually acquired by means of hybrid PET/CT scanners that allow attenuation correction and enhanced anatomical localization of metabolic active regions.

Recent development of the hybrid imaging modality of PET/MRI, combines excellent soft tissue contrast, high spatial resolution, multifunctional imaging, such as spectroscopy, functional MRI, and arterial spin labeling of an MRI with quantitative physiologic information from the PET [17]. Although the hybrid PET/MRI imaging system is still not readily available in many proton or ion therapy centers, it has great potential for tumor evaluation and contouring to reduce inter-observer variability and may provide an excellent tool to assess in vivo biochemical responses of the tumor and healthy organs to radiation therapy.

Future of pre-treatment imaging

Recent improvements in dual-energy CT, DECT, may make this imaging technology the new workhorse of proton and ion-therapy departments. DECT acquires patient images with x-rays at two voltages (mostly at 80 kV and 140 kV) from which electron density and Z_{eff} maps of the patient can be generated. The combined maps have been shown to yield significantly better in vivo proton and ion stopping maps, reducing range uncertainties from 3.5% to the order of 1–1.5% [12,18–20]. However, the limiting factor at the moment is the high level of noise present in DECT images, where HU estimates have standard deviations of up to 60–70 HU, which is three times the 20 HU for SECT, values obtained at General Electric (GE) CT scanners at our hospital. An alternative to DECT are pCT or pRAD, where the stopping power is directly measured in vivo using the therapeutic particle. The pCT/pRAD technology has not matured and is not readily available at any center.

Stage 2: In-room image-guidance

Presently available in-room image-guidance

The role of in-room imaging involves at least three aspects of the therapy: patient set-up, range verification, plan adaptation.

Patient alignment and tumor setup at many of the proton therapy centers is performed using tattoos on the patient's skin in conjunction with a laser localizer or by acquiring daily 2D x-ray radiographs which are compared to digitally reconstructed radiographs (DRRs) from the treatment plan CT. However, many of the newer proton therapy centers have adopted photon-imaging in-room technologies such as stereoscopic planar x-ray kV images, cone-beam (CB) CT, or sliding CT unit. Planar imaging allows fast patient set-up based on bony anatomy or implanted fiducials and has the advantage that it can be used in fluoroscopic mode for real time tumor tracking in extra-cranial sites. Volumetric imaging using CBCT can perform daily alignment of the patient reproducibly to within a few millimeters at the cost of an added 5–8 minutes to total treatment time [21–23]. Some centers proposed the use of optical localizer as standalone technology or in conjunction with x-ray imaging for patient set-up and tumor tracking [24]. These technologies are based on the acquisition of external surface of the patient (thorax or abdomen, depending on the region to treat) or surrogate physical markers placed on the skin. The main advantage is that they are non-invasive for the patient and they can provide a good estimate of internal tumor motion, especially when gated treatment is required [25]. A unique situation is currently available at Paul Scherrer Institute (PSI, Switzerland), where a fluoroscopy unit has been integrated into the proton gantry along beam eye's view (BEV) and a sliding CT scanner is available for patient positioning [26]. pRAD has also been proposed as an ultimate imaging frontier for tumor set-up in simulation studies [27–29]. The main benefit would be that the target region would be visualized from the BEV thus allowing accurate positioning and possibly real time tumor tracking. Methods to enhance soft tissue identification in pRAD are also available [30].

Several during-treatment range verification approaches have been investigated over the past 10–15 years [13,31–33]. The most widely available is based on PET imaging of positron-emitting

radioactive elements such as ^{11}C, ^{13}N, and ^{15}O, which are produced through nuclear interactions. In the case of proton therapy, the activity measured by the PET is solely a consequence of the activation of the target elements, such as carbon and oxygen. While in the case of carbon ions the measured activity can be from both target activation and incident particle activation. In addition, the activity distribution present during and immediately after irradiation is dependent on the timing of the PET images, due to both the different half-lives of the various positron emitters and the biological wash-out from perfused tissues. As pointed out in Knopf [13], all these factors prevent direct range verification by comparing dose and activity profiles; a modeled activity is required via Monte Carlo algorithm. PET imaging can either be performed online with the focus on measuring predominantly the ^{11}C activity (half-life 2 minutes) or offline with the focus on measuring predominantly the ^{15}O activity (half-life 20 minutes). For head-and-neck patients, range verification accuracy is on the order of 1–2 mm [28] for well registered bony structures. However, due to among other things wash-out, the PET approach cannot provide millimetric accuracy range verification at every position of the tumor [13]. Moteabbed et al. [34] compared PET to prompt gamma, for range verification of proton passive- and active-scanning beams. They showed that prompt gamma imaging is capable of avoiding some of the inherent limitations of PET (such as biological washout).

Large anatomical inter-fractional changes which could jeopardize the treatment plan can usually be detected through volumetric imaging such us CBCT [35–37]. Dose recalculation can be performed by means of deformable registration or repeated CT where the plan is completely recomputed.

Future of in-room Image-Guidance

Lu [38–40] demonstrated that for passive-scattered proton beams the time-dependence of a delivered SOBP is unique at every point in depth and thus encodes the depth information. Thus if the time dependence can be acquired in the patient at any specific location, the residual range of the proton beam can be computed. The use of implantable dosimeters allows for direct range measurements on a beam-per-beam basis. However, a limitation is the limited number of points that can be acquired. Presently, this method is being investigated for prostate cancer where the diodes are inserted via a rectal a balloon filled with water, and with approximately 12 diodes (4×3 cm^2 array).

An alternative for in vivo proton range verification is prompt gamma imaging, which can potentially perform range verification to better than 1 mm [30], because of the ability to measure the proton dose in real time, mitigating wash-out effects. Several approaches have been proposed in the literature [41–45], varying from the use of different scintillating crystals to the detector and collimator arrangement using either slit or Compton cameras. Most of the prompt gamma detectors are fluence-based detectors, while some are able to distinguish the energy or the time of flight of each prompt gamma. Energy and timing selection of the arriving prompt gammas has been shown to potentially allow in vivo range verification to better than 1 mm [45], however, the major limitation of this system is the cost of the LaBr3 scintillating crystals.

Stage 3: Post-treatment imaging

Presently available post-treatment imaging

Several follow-up images are commonly acquired to allow clinical evaluation of the patient and the treatment. The first follow-up imaging post-treatment is done using mainly CT or MRI, approximately 9–12 weeks after the end of treatment. While, a second follow-up review of the patient and of the radiation treatment is commonly done 1–2 years after the end of treatment. If the patient is part of a clinical trial further imaging is performed regularly during this period and/or after the second follow-up images. However, if the patient is not part of a clinical trial, then no subsequent follow-ups images are taken unless the patient is considered to have high risk of recurrence. For these cases, the radiation oncologist may propose annual to bi-annual follow-up images up to 5–10 years post-treatment.

Future of post-treatment imaging

MRI offers the possibility of generating in vivo biological range maps of the proton or carbon ion beams, taken 7–10 days post-therapy. MRI generated range maps have been generated for: 1) pediatric crania-spinal [46,47]; and 2) liver [48,49] cancers. Further research is required to generalize the use of MRI to other sites. MRI for post-therapy dose/range imaging of the proton or ion beam therapy is still in the infancy of development. A combined approach using PET/MRI can potentially provide functional and anatomical post-therapy information on the treatment outcome.

Discussion

Imaging in protons and ion therapy is vital to guarantee that the dose is delivered correctly and accurately to the tumor, where a small shift in the Bragg

Table I. Review of *present* and *future* imaging technology used in proton and ion therapy centers.

Present	Future
Pre-treatment imaging	
Single energy CT (SECT), PET, MRI, SPECT	Dual energy CT (DECT), PET/MRI
In-room image-guidance	
2D x-ray radiograph, CBCT, PET	Prompt gamma, implantable dosimeters
Post-treatment imaging	
CT, MRI for standard follow-up imaging	MRI or PET/MRI for dose/range imaging to evaluate proton/ion therapy and patient response

peak can have lead to large variations in the final delivered dose. In Table I, we review all the "**Present**" and "**Future**" imaging.

At present, proton and ion clinics are heavily dependent on SECT imaging. A future trend will be to incorporate the use of DECT and PET/MRI into daily therapy pre-treatment assessments. In addition, during-treatment assessments in most proton and ion clinics lag behind most photon therapy centers, where it is common to use CBCT for daily alignment and positioning. In order to deal with the additional range uncertainties from proton and ion beams, a future trend will be adopt into daily routine the use of either prompt gamma, PET or even implantable dosimeters (where possible). These will allow a significant reduction of range uncertainties. In the case of post-treatment assessment, physicists/physicians working in radiation therapy centers usually do not follow patients beyond the two years after treatment. Patient follow-up is vital to evaluate if the treatment was yield long-term complications and allow the correlation of these with range uncertainties.

In addition, imaging should always be "SERENE" to avoid any additional stress to the patient that is ultimately not important to the treatment itself, where

S-Safe for the patient, with minimal required imaging dose, according to ALARA principle;
E-Efficient to reduce imaging time that may impact patient immobilization and comfort;
R-Redundant to provide accurate anatomical/functional information of organs and tumor for contouring;
E-Exact for patient positioning and setting up during treatment;
N-Normalized to electron density (photon) or Stopping Power (proton/ions) for dose calculation;
E-Effective at identifying possible patient responses to radiation therapy during- and post-treatment.

ALARA is an acronym for As Low As Reasonably Achievable. This is a radiation safety principle for minimizing radiation doses and releases of radioactive materials by employing all reasonable methods.

The "SERENE" concept highlights the importance of considering also the consequences of imaging procedures on patients, which in many cases can be much debilitated from the cancer. "SERENE" imaging, will allow patient-specific imaging at minimal dose and side effects, while providing the required anatomical and stopping power (or electron) density information needed for dose calculation.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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