Imaging issues specific to hadrontherapy (proton, carbon, helium therapy and other charged particles) for radiotherapy planning, setup, dose monitoring and tissue response assessment

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Spécificités de l'imagerie pour l'hadronthérapie (protonthérapie, thérapie par ions carbone, hélium et autres particules chargées) pour la planification, le repositionnement, le contrôle de la dose et l'évaluation de la réponse tissulaire

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Abstract

Imaging is critical to each step of precision radiation therapy, i.e. planning, setup, delivery and assessment of response. Hadrontherapy can be considered to deliver more precise dose distribution that may better spare normal tissues from intermediate low doses of radiation. In addition, hadrontherapy using high linear energy transfer ions may also be used for dose escalation on biological target volumes defined by functional imaging. However, the physical characteristics of hadrontherapy also make it more demanding in terms of imaging accuracy and image-based dose calculation. Some of the developments needed in imaging are specific to hadrontherapy. The current review addresses current status of imaging in proton therapy and the drawbacks of photon-based imaging for hadrons. It also addresses requirements in hadrontherapy planning with respect to multimodal imaging for proper target and organ at risk definition as well as to target putative radioresistant areas such as hypoxic ones, and with respect to dose calculation using dual energy CT, MR-proton therapy, proton radiography. Imaging modalities, such as those used in photon-based

radiotherapy (intensity modulated and stereotactic radiotherapy), are somewhat already implemented or should be reaching "routine" hadrontherapy (at least proton therapy) practice in planning, repositioning and response evaluation optimizable within the next five years. Online monitoring imaging by PET, as currently developed for hadrontherapy, is already available. Its spatiotemporal limits restrict its use but similar to prompt gamma detection, represents an area of active research for the next 5 to 10 years. Because of the more demanding and specific dose deposit characteristics, developments image-guided hadrontherapy, such as specific proton imaging using tomography or ionoacoustics, as well as delivery with MR-proton therapy, may take another 10 years to reach the clinics in specific applications. Other aspects are briefly described such as range monitoring. Finally, the potential of imaging normal tissue changes and challenges to assess tumour response are discussed.

Keywords

hadrontherapy, particle therapy, proton therapy, carbon, range, imaging, planning, response

Résumé

L'imagerie est essentielle à chaque étape de la radiothérapie de précision, et en particulier la planification, la vérification du repositionnement en salle, la vérification de la dose et l'évaluation de la réponse. Certains des développements nécessaires en imagerie sont spécifiques à l'hadronthérapie du fait des caractéristiques du dépôt de dose et des interactions dans la matière. Cette brève revue porte sur l'état actuel de l'imagerie en protonthérapie et sur les inconvénients de l'utilisation d'une imagerie X pour les hadrons. Elle décrit les exigences de la planification de l'hadronthérapie en ce qui concerne l'imagerie multimodale pour la définition de la cible et des organes à risque, ainsi que les pistes actuellement identifiées pour cibler spatialement et temporellement l'hypoxie tumorale. Le calcul de la dose par tomodensitométrie à double énergie, la protonthérapie-IRM et la radiographie par protons sont des voies de recherche actuelles en imagerie pour réduire les incertitudes liées à l'imagerie X dans le calcul de la dose. Les modalités d'imagerie utilisées en radiothérapie classique par photons en planification, repositionnement et évaluation de la réponse sont globalement toutes transposables ou déjà présentes et optimisables en hadronthérapie dans un horizon de 5 ans. L'imagerie de contrôle en ligne, actuellement spécifique à l'hadronthérapie, par TEP est déjà disponible. Ses limites spatiotemporelles restreignent son usage mais sont une voie de recherche active, comme la détection de gamma prompts, pour les 5-10 années à venir. Les problématiques de radiothérapie guidée par l'image spécifiques à l'hadronthérapie, plus requérante du fait du dépôt de dose "fini", telles que la tomographie par protons ou la ionoacoustique, le seront probablement dans un horizon de 10 ans dans des applications particulières. Les aspects de vérification du parcours des hadrons sont brièvement décrits. Enfin, le potentiel de l'imagerie pour analyser des effets infracliniques dans les tissus normaux et les défis liés à l'évaluation de la réponse tumorale sont discutés.

Mots clés

hadronthérapie, protonthérapie, carbone, parcours, imagerie, planification, réponse

1. Introduction

Hadrontherapy corresponds to the field of therapeutic irradiation using particles composed of quarks (subatomic elements involved in the strong interaction force present in neutrons and protons of the nucleus). Neutrons have been abandoned because of their poor spatial distribution as neutral particles and high biological efficacy resulting in unnecessary toxicities; neutrons will not be reported in the current review. Hadrontherapy *de facto* excludes electrons and photons used in "conventional radiation therapy". Hadrontherapy currently mainly includes protons and carbon ions. Other hadrons are being studied for therapeutic use and this is the purpose of the French-European ARCHADE program based in Caen to study multi-ion therapy, with corresponding developments in accelerator technology, instrumentation and models of radiation effects in order to offer personalized radiation therapy. Combined multi-ion therapy (even photons - hadrons) may be thought as a way to overcome tumour radioresistance while preserving healthy tissues.

Due to the physical and biological characteristics of the dose deposition of charged particles used in hadrontherapy, a new field of applications is opening up for imaging for planning, setup/repositioning, range monitoring and response assessment. Unlike photons, the path of particles is finite in depth depending on the initial energy and the tissues traversed. As a result, the dose can be delivered in the tumour with a generally reduced number of more precisely imaged beams. This requires high resolution imaging in order to both better predict and control the dose deposition.

Several issues are common to protons and carbons with additional specificities of carbons, linked to differences in biological efficacy, lateral penumbra and distal fragmentation, which will be briefly explained. The current review addresses the current state of the art of imaging in hadrontherapy and further requirements that may contribute to deliver irradiation more optimally.

2. Material et methods

It is a non-systematic analysis of the literature and feedback on the specificities of imaging for planning, setup, monitoring and response, as summarized in figure 1.

3. Planning

3.1. Delineation

Optimal exploitation of the geometric advantage of proton therapy (and other hadrontherapy modalities) requires the use of planning imaging with excellent spatial resolution. Complex shape and radioresistant tumours near critical serial organs are typically treated with proton therapy. Careful target delineation is therefore critical given the proximity of normal tissues. Computerized tomography (CT) scan should be systematically performed with and without injection. Because of the steep gradients obtained with hadrontherapy, accurate tumour delineation is even more critical than with conventional irradiation to avoid geometric misses and tumour relapse. Adding larger margins around the tumour may be performed but would result in irradiation of larger healthy tissue volumes, increased toxicity and loss of one of the major advantages of hadrontherapy. It may be recommended to double-check delineated structures (tumour and serial organs in particular). CT scan slices should be 1 to 1.25 mm to improve delineation precision, especially if pencil beam scanning is used. Because of the risk of dose error calculation critical in hadrontherapy, artefacts in CT scans should be corrected by specific softwares. Range errors can reach 5% in the abdomen and 11% in the head (1, 2).

If a multimodal imaging can differentiate tumour from inflammatory tissues, it should be used (i.e. magnetic resonance imaging [MRI], positron emission tomography [PET]-CT, etc.) and the coregistration step should be extremely accurate. For example, an MRI is essential for the treatment of chordoma and chondrosarcoma of the skull base because of the dose gradient needed (74 Gy_relative biological efficacy [RBE] for chordomas to 55 Gy for the brain stem in less than 1 cm) Due to the low tissue contrast that exists between the brain stem and adjacent soft tissues or tumour on CT alone, it would not be not safe not to use an MRI. The sequences are at least T1w, contrast-enhanced T1w and T2w with a three-dimensional (3D) sequence and reconstruction in thin sections over a sufficiently large acquisition volume to allow reliable co-registration. 3 T MRI and functional diffusion-weighted imaging (DWI) sequences can provide other relevant information to distinguish between tumours requiring different dose prescription levels (3). MRI distortions should be corrected for, as they may induce critical delineation uncertainties.

Hadrontherapy may also allow dose escalation or biological target volumes through dose painting of metabolically and/or functionally active tumour subvolumes which can be further analysed by PET-CT. The prerequisite for tumour heterogeneity characterization and spatially selective dose delivery is that imaging could identify areas of radioresistance with a high spatial resolution. Various radiopharmaceuticals are available in research or routine and PET-CT is a technique with very high potential for hadrontherapy. Beyond an evaluation of hypermetabolic foci with fluorodeoxyglucose (FDG)-PET, proliferation markers ([^{18}F]-fluorothymidine ([^{18}F]-FLT), amino-acid markers ([^{11}C]-methionine ([^{11}C]-Met, O-(2-[^{18}F]fluoroethyl-)-L-tyrosine ([^{18}F]-FET), FET-PET), 3,4-dihydroxy-6-

(^{18}F)-fluoro-l-phenylalanine ([^{18}F]-FDOPA)) or hypoxia markers (3-[^{18}F]fluoro-1-(2-nitro-1-imidazolyl)-2-propanol ([^{18}F]-FMISO), [^{18}F]-fluoroazomycin arabinoside [^{18}F]-FAZA, etc.) have been developed to characterize tumour regions at risk for radioresistance and recurrence. For example, in the context of glioma, in a retrospective study, Met-PET volumes were compared to target volumes based on CT or MRI of patients receiving carbon ion radiotherapy, with the authors concluding that Met-PET may be predictive of survival, regional control, and distant control times following carbon ion radiotherapy (4). Similarly, in supratentorial anaplastic astrocytoma or glioblastoma, the Shanghai Proton and Heavy Ion Centre recently developed a phase I/III clinical trial investigating the use of carbon ion boost following initial proton irradiation with concurrent temozolomide. A phase I study was also designed with a carbon ion boost directed to the residual gross disease defined with the contrast enhancement on fluid-attenuated inversion recovery (FLAIR) MRI, and tumour areas presented on Met/FET-PET and magnetic resonance spectroscopy (5). Hypoxia targeting is currently the aim of two proton therapy trials (NCT02802969 and NCT00713037). Hypoxia, a well-recognized factor of radioresistance with X-rays (i.e. using photons), can also be targeted with carbon ions to overcome the oxygen effect taking advantage of the minimal oxygen effect with high lineal energy transfer (LET) hadrontherapy. While in a normal tissue, partial oxygen pressure ranges from 30 to 70 mmHg of O_2, partial oxygen pressure in solid tumours often ranges between 0 and 10 mmHg. Hypoxia results from a gradient of oxygenation deprivation from the nearest perfused blood vessel (a situation referred as diffusion-limited hypoxia or chronic hypoxia) or from perfusion-limited hypoxia (also termed cycling hypoxia), which refers to oxygen deprivation along the vascular tree. Cycling hypoxia results in temporal partial oxygen pressure instability with intermittent periods of reoxygenation., In carbon ion therapy, hypoxia targeting should rely on non-invasive imaging modalities with a high spatial resolution and that allow repeatability measurements to account for temporal patterns of hypoxia during the course of irradiation. PET tracers of hypoxia using (^{18}F)-labelled molecules, such as ([^{18}F]-FMISO) and ([^{18}F]-FAZA) may be used in addition to FDG-PET for carbon ion therapy planning. After cell penetration by passive diffusion, these tracers are reduced in a two-step process, with the first step being reversed if oxygen is present and with the tracer becoming irreversibly trapped in the absence of oxygen. So, tracer uptake be can used as an estimate of partial oxygen pressure and the energy of ^{18}F isotopes allows to map hypoxia with a resolution of less than 4 mm in clinical routine. Recently, more hydrophilic tracers have been designed with the potential advantages of shorter acquisition times. However, formal validation in clinical situations is required. One of the main drawbacks with PET is its relatively poor spatial resolution relative to other biomedical imaging modalities such as MRI .While it raises question about interpretation due to partial volume effects, it also raises the question for radiotherapy and more especially for hadrontherapy for which a millimetric dose deposition is achievable and there are no mature data to demonstrate the relevance of such an approach in the clinics. MRI has also emerged as a promising tool to address the question of hypoxia imaging. It can be achieved through a blood-oxygen-level-dependent (BOLD)-based MRI method for

the measurement of relative oxygen extraction Fraction, or through oxygen-enhanced-MRI (OE-MRI), based on the correlation between hypoxia and the variation in longitudinal relaxation rate during oxygen challenge. BOLD-based MRI are considered as an indirect reflection of ptO$_2$ but have a greater spatial resolution than PET and may thus be more relevant to hadrontherapy. Radiomics of precision radiotherapy and hypoxia are awaited in the field of hadrontherapy (6).

3.2. Dose calculation

The physical benefit due to the spatial dose distribution of proton therapy, compared with photon therapy (intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT)), can contribute to proper tumour coverage while better limiting the dose to normal tissues more effectively. Hadrontherapy planning today is however based on single-energy CT (SECT). The stoichiometric method consists in measuring pairs of CT Hounsfield units and stopping power ratio (SPR) values for various tissues (7). The range of protons in the human body can be controlled to better than ±1.1% of the water equivalent range in soft tissue and ±1.8% in bone, which translates into a range precision of about 1 to 3 mm in typical treatment situations (8). However, some tissues and implanted material compositions, as well as tissue changes in various conditions, have not been well characterized and may be misestimated. To account for these uncertainties in range due to stoichiometric issues, optimization uses a robust 3% uncertainty approach around the clinical target volume. However, to further ensure full clinical exploitation of the theoretical advantages of protons, these uncertainties in proton range prediction from CT can be minimized using spectral scanner, also known as dual energy CT or multienergy CT (9). Dual energy CT may be used for setup imaging and replanning in hadrontherapy. Voxel-wise dual energy CT-based stopping power ratio prediction approaches are subject to intensive research activities and should soon be integrated into commercial treatment planning systems (TPS). Further, dual energy CT may allow to change practice from a systematic precautionary principle that consists in avoiding placing serial organs at risk (such as the brainstem or spinal cord) distally from the beam because of range uncertainties to taking advantage of the Bragg peak at the beam distality. However, placing them in the lateral penumbra (or passing through them) may limit the possibility of steep gradients, potentially reducing the advantages of proton therapy, unless the high linear energy transfer areas are placed within the tumour (10, 11). Dual energy CT will probably be implemented in hadrontherapy planning in the next 2 to 5 years. Other approaches, including MRI-based pseudo (also called synthetic)-CT, are being studied to bypass the calibration step but may not eliminate calibration issues (12). Moreover, beyond range uncertainties, multiple scattering in variable medium including metals and for large ranges is less documented. Multiple scattering can induce other sources of dose uncertainty transversely to beam direction, especially for protons. Additionally, nuclear events depend on chemical composition of tissues which is only partially known from CT numbers.

4. In room imaging for patient setup and repositioning

Image guidance in hadrontherapy has lagged behind image guidance for photon irradiation modalities (IMRT, SBRT) in the last 20 years (13). However, proton therapy was one of the first radiation modalities to employ in-room imaging for setup correction. Orthogonal X ray images were used for ocular tumours at Massachusetts General Hospital and Lawrence Berkeley Laboratory before the early photon linear accelerators used any image guidance, and was rapidly adopted by most proton therapy centres in the 1960's. High energy beams (greater than 250 MeV protons) were unavailable for transmission body imaging and image quality of proton radiography was insufficient. The fact that accelerators were located outside hospitals and were very few, may be among the several reasons for the slower developments for in room imaging for hadrontherapy. Most in-room equipment of proton therapy currently rely on orthogonal bidimensional kilovoltage (kV)/kV imaging only for daily repositioning. Although they achieve highly precise reproducibility with appropriate immobilizing devices, they do not allow 3D imaging and soft tissue characterization (14). In France, the three proton therapy centres use two daily orthogonal bidimensional kV images (with or without implanted fiducials) and their planning CT to account for tissue changes and perform adaptive proton therapy when needed. Volumetric acquisition in the treatment room is however feasible through cone beam CT (CBCT) or CT on rail (15). Rapid implementation of the use of cone beam CT for automatic adaptive treatment, particularly for head and neck and lung cancer is ongoing (16,17). Similarly, surface imaging has been implemented in the proton therapy room for breast cancer (18). Motion management, particularly with four-dimensional (4D) imaging (4D cone beam CT, also accounting for time by acquiring images at different breathing phases, for example), is another area for imaging developments in hadrontherapy. Organ motion is even more critical with active scanning (including layer repainting to adjust the dose) and intensity modulated proton therapy (multifield optimization) as these delivering modalities can result in significant interplay and geometric misses. They are less robust and cannot be compensated by robust optimization. Thus, developments in immobilization devices and 4D imaging in the hadrontherapy room are warranted. Several techniques have been used to control motion such as fluoroscopy, internal fiducial markers, fiducial electromagnetic transponders, external surrogates, CT motion prediction, novel proton CT and ultrasonic tumour location but each presents issues limiting their use in particle therapy (19).

Because X-based setup imaging technologies intrinsically include the same uncertainties as planning CT for ion therapy planning, ion-based imaging appears to be a more reliable method to verify the path of protons or ions through tissues. A realistic in room approach of proton radiography (i.e. at a current stage of development allowing passage from prototype to clinical use within 2 to 5 years) requires the use of passing through protons, of sufficient energy and on selected beam angles (such as those passing through aerial cavities) on the path of range uncertainties along given beams (through sinonasal tract for example) (20). For instance, the potential of proton CT for pretreatment positioning

was assessed in a recent experimental study, that used a head phantom (21). The residual errors in image registration were lower than 1 mm and 1° of magnitude regardless of the anatomic directions and imaging dose. This approach does not currently allow to reconstruct a proton tomography but could be one practical in-room proton radiography to check for interfraction range variations within 5 years (22). Proton tomography may also be used, ideally, at the planning step (and replanning), but more technological developments are awaited. Given the physical advantages of helium over protons, prototypes are also being designed with helium (with specific accelerators).

Suboptimal and irradiating setup imaging modalities warrant developments for proton therapy and hadrontherapy in general. Magnetic resonance (MR)-linear accelerators (relying on X-based IMRT) seem to outperform current setup and adaptive IGRT modalities in the clinics. They will allow adaptive proton therapy and daily replanning. MR-proton therapy goes a step further by avoiding the drawbacks of using poorly distributed uncharged particles and combining the advantages of high resolution, in room, source of setup imaging with a therapeutic (ionizing) irradiation that spreads less dose to the normal tissues (23). Prototypes may be designed to reach the clinics within the next 15 years.

Similarly, PET-linear accelerators, which belong to the field of emission-guided radiation therapy and molecular imaging-guided radiation therapy planning to improve the delineation of target volumes. PET-linear accelerators are currently reaching clinical maturity with a first clinical proof of concept using a commercial solution, the RefleXion[R] (Hayward, California, USA) system in 2018 at American Society of Radiation Oncologists (ASTRO) meeting. PET-linear accelerators currently rely mostly on FDG-based tumour tracking but other tracers could be used as done in diagnostic procedures. Their advantage compared tocoregistration with diagnostic PET-CT is that they can guide dose delivery directly. Emission-guided proton therapy equipment have not yet reached the clinics but a patent was deposited in 2015. The latter include a proton delivery unit to direct protons to a target area, a PET system having a detector unit to scan for radiotracers introduced into the patient's body, a processing unit to localize information corresponding to the target based on the scanned radiotracer, a guidance unit to receive the location information from the PET system and to instruct the proton delivery unit to direct protons to the target area according to the location information.

5. Range monitoring

In hadrontherapy, unlike photons that pass through the patient, the protons or ions stop without exiting, which is an advantage to limit the integral delivered dose but leads to an impossibility of portal dosimetry. Moreover, since the end-point of particle range corresponds to a maximum of deposited dose, the precise control of the range remains one of the main challenges for quality assurance. A solution may come from nuclear reactions, occurring –almost- all along the ion path in patient tissues, and generating secondary particles that may come out. During these reactions, some

target nuclei fragment, as well as the projectile if it is an ion. Secondary protons, neutrons and prompt-gamma are emitted during the fragmentation and the return to equilibrium level of the excited nuclei. Therefore, Prompt-Gamma Imaging and secondary particle imaging can be used for a real-time control of the range. The resultant nuclei may be radioactive, and in particular positron emitters may be localized by PET imaging. Other imaging systems, not based on nuclear reactions, are also feasible (proton and ion radiography, ionoacoustics) to monitor ion range.

The motivation for the development of imaging techniques for proton and ion Bragg peak localization comes from the fact that, although their ballistic is very advantageous, the sum of the uncertainties related to the definition of the patient (non-uniqueness CT Hounsfield units calibration to proton stopping powers, metal implants artefacts, anatomical changes of the patient during treatment, etc.) requires the addition of safety margins (robustness parameters integrated in the optimization phase) of the order of 3% of the range. This prevents the use of the steep distal gradient of the Bragg peak as protection of the organs at risk and may also affect the tumour volume coverage.

The concept of using patient's outgoing **Prompt Gammas** to image the beam track and deduce the range in proton therapy was reported first in 2003. Many studies have followed and a first camera was installed in the clinic in 2016 (24). According to an *in silico* study, the prompt Gamma detection technique could be sensitive enough to detect changes in tumour coverage between proton therapy (using active delivery such as pencil beam scanning (PBS) delivery) sessions (25). The Prompt Gamma emission in times inferior to 1 ns could allow a corrective feedback online. Non-imaging techniques (spectroscopy, timing or integral counting) are also considered for prompt-gamma detection. Beyond range localization, dose characterization can be considered and research is very active the field (25, 26). **PET monitoring** through the use of tissue activation on proton or ion beam tracks is certainly the most mature technique for Bragg peak localization in the clinic (27, 28). The radioelements produced in greater abundance (^{12}N, ^{15}O, ^{10}C, ^{11}C) have periods of a few tens of milliseconds to a few tens of minutes, which allows inline or offline PET processing. The offline aspect is controlled (29), although restricted to *a posteriori* verification, and limited by the available statistics and metabolic washout. The inline aspect requires the emergence of « openfield » detector type to facilitate its integration into treatment room and make compatible a simultaneity between beam shoot and PET acquisition and analysis. Moreover, PET acquisition is possible only between beam pulse deliveries due to Prompt-Gamma background. A recent study carried out with proton and carbon beams shows possible dose mapping issued from PET data (30). Spatial resolution is another limitation to the current use of inline PET. In the case of heavier ions than protons, **secondary proton imaging** (tracking technique) showed promising results and will be implemented at Centro Nazionale Adroterapia Oncologica (CNAO) centre in Pavia, Italy (INSIDE project). A recent *in silico* study showed that secondary neutrons could also be a solution for inline range information of a proton beam of treatment (31). Thermoacoustic waves, i.e. **ionoacoustics,** produced by the energy deposition of

protons or ions in tissues are also a way to image dose deposition and to localize the Bragg peak (32). The first results recorded in a clinical facility indicate submillimetric accuracy. The method is well suited to soft tissues but seems more difficult to implement for other tissues. Ionoacoustics have the advantage of being cost effective and not requiring bulky detectors. **Proton and ion radiography** consist of acquiring a proton or ion radiography giving a patient range image (33). Then, compared to a Monte Carlo calculation that uses the patient's CT images, it can be used to produce a simulated radiography. Range differences between measured and simulated images reflect the uncertainties associated with CT. This can be done with only a few singular beams called "range probes", and prototypes have recently reached the clinics. Multiple scattering can also be an issue especially with tissues of higher densities.

More generally, online range verification modalities are technically dependent on the beam delivery mode (beam species, intensity and pulse-time structure, fixed beamline or gantry), which makes their development and clinical use quite specific to each irradiation modality.

6. Assessment of tissue responses following hadrontherapy

Tissue changes have been reported after irradiation in symptomatic patients with radionecrosis and in asymptomatic patients during follow-up. Assessment of **normal tissue or tumour responses** shows differences between photon-based radiation modalities (linear energy transfer linear energy transfer of about 0.2 keV/µm) and particle therapy.

Adipose changes in vertebral bone marrow have been a classical observation after spinal 3D photon-based irradiation but may show more spatially accurate dose deposit with protons (34, 35). It is yet uncertain whether tissue changes are more frequent than with photons or are more detectable because of a more finite dose deposit where dose is not blurred (35, 36), in contrast to IMRT, which uses multiple beam entries and shows substantial dose exit in normal tissues diluted through the use of multiple beams. Tissue changes occur within weeks to years, but it is uncertain whether early tissue changes could be surrogates for symptoms or will resolve over time. Significant changes are observed after proton therapy (which is considered low linear energy transfer irradiation of 0.2 – 10 keV/µm). Tissue changes are also observed after carbon ions (linear energy transfer 10-100 keV/µm) more frequently than with protons (37). Such changes have been reported in the recent literature at an increasing pace using various imaging modalities. They may be used for *in vivo* offline monitoring of dose deposit. Moreover, as they appear early after irradiation, such changes may become useful to assess uncertainties and to reoptimize proton therapy plans in a near future (38). As MRI seems the most sensitive imaging modality to detect such changes (39-41), MRI-proton therapy could be an interesting area of practical research. Imaging tissue response could also contribute to a better understanding of the mechanisms of cellular and tissue effects and might be used to improve current radiobiological models (37).

Different patterns between photon or proton therapy either by passive scattering or pencil beam scanning of normal tissue changes have been reported for the bone marrow when irradiating vertebrae, the brain, the liver, the lung, but not for the oesophagus, etc. However, these have little or not translated in different toxicity profiles. Data from CT studies show quantitative changes in volume and shape, as well as density, in the irradiated liver and brain that seem to differ between proton therapy than IMRT (41, 42). Due to different dose distribution patterns and smaller low/intermediate dose bath, proton therapy might favour compensatory liver hypertrophy more as compared to SBRT in patients who have proper initial hepatic reserve (42). Similarly, reduction of grey and white matter was observed after photon irradiation but not after proton therapy. This was likely due to better sparing of the healthy hemisphere from low/intermediate doses (41). However, most evidence of tissue changes arises from MR follow-up images because of the better spatial resolution and functional sequences of MRI (39, 40). Dose–volume effect relationships may thus be more accurately described to build more reliable normal tissue complication probability (NTCP) models. Anatomic MR images can show alterations of functional subvolumes depending on the cells that they are made of. Their description is quite aspecific. For example, temporal lobe reactions are detected on T1-weighted post-gadolinium MR-images but no more defined nor quantified (37). Further, radiation-induced of endothelial cells, inflammation, fibrosis, necrosis and hypoxia may be further investigated on functional MRI sequences. Cell killing following hadrontherapy translates into large variations of the diffusion of molecules detectable on quantitative parameter mapping (diffusion, anisotropic changes…). PET can also be used to image early tissue changes, including proliferation arrest. For example, radionecrosis can be confused with tumour progression and may require diffusion-weighted imaging, perfusion-weighted imaging and MR-spectroscopy (40).

Single-photon emission CT/CT changes that also illustrate of imaging to assess functional outcomes (43). Based on patient-specific variations in dose-response, the authors estimated that imaging could identify patients with poor baseline liver function and increased sensitivity to radiation therapy. Dose response effects have also been reported in other clinical settings (37, 44-46) and may guide particle therapy planning better than anatomic CT and / or MRI.

Proton therapy-induced macroscopic tissue damages have been mostly attributed to underestimated RBE values, resulting from the historical and controversial use of an average RBE value of 1.1 that does neither account for higher values in the distal fall-off (up to 1.7) nor for linear energy transfer values (from 0.2 to 6.5 keV/μm) along the beam path (47). However, linear energy transfer maps and avoidance of stopping the distal edge of proton beams in serial organs (48) argue against the accountability of uncertainties to explain the toxicities observed in paediatric series. As underlined by Merchant *et al*, clinical damages after proton therapy may be similar to those of similar populations treated with photons (unpublished data, PTCOG 2018).

Imaging the beam trace in tissues might provide ways to optimize the delivery of hadron beams, by using the distal fall off rather than the lateral penumbra of protons. For carbon ions, imaging of tissue effects of secondary particles might be useful to improve biophysical modelling and provide safer estimates of clinical effects.

Contrary to the prescription of protontherapy, which uses a constant RBE value of 1.1, the prescription of carbon ion therapy is based on biomathematical models that implement radiobiological effects based on cellular death curves in their treatment planning systems. Recent data indeed suggest that the differences between the different versions of biomathematical models (local effect models I to IV, for example) or between the microdosimetric kinetic model and local effect models, may have clinically relevant consequences (37, 49). Linear energy transfer and RBE mapping using specific softwares may provide more data to correlate tissue changes with physical and radiobiological parameters (50). Highly sensitive imaging modalities following carbon ion therapy may also contribute to a better understanding of post-therapeutic changes. Except for cases of radionecrosis, systematic data on post carbon ion therapy are still lacking. However, at the cellular level *ex vivo*, differential expression of several signalling pathways, including those involved in inflammation and hypoxia, has been shown between photons, protons and carbon ions. Additionally, the higher biological efficacy of carbon ions seems to be associated with higher rates of radionecrosis and pseudoprogression (40, 51). Pseudoprogressions may also be more frequent after proton therapy than photon therapy (52). In such cases, specific imaging, including functional radiolabelled amino acid PET and diffusion-weighted MRI, may be needed to distinguish between progression and necrosis (53, 54). Similarly, assessment of tumour response appears to be quite complex after carbon ion therapy of bone tumours (55). Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 may not be sufficient and response in soft tissues may be used to interpret response in bone, as suggested by a recent retrospective study (55).

7. Conclusion

Imaging in hadrontherapy has lagged behind imaging in X-based radiation therapy modalities but recent advances are considerable. Current developments in imaging for hadrontherapy cover the needs in planning and setup, with the specific need for equivalent stopping power determination, online control of the particle range that relies mostly on nuclear reactions, and they also contribute to a better understanding (and prediction) of particle effects and to better targeting of radioresistant areas. Finally, imaging modalities, such as those used in IMRT and SBRT, are somewhat already implemented or should be reaching "routine" hadrontherapy (at least proton therapy) practice in planning, repositioning and response evaluation optimizable within the next five years. On-line monitoring imaging by PET, as currently developed for hadrontherapy, is already available. Its spatiotemporal limits restrict its use but similar to prompt gamma detection, represents an area of active research for

the next 5 to 10 years. Because of the more demanding and specific dose deposit characteristics, developments image-guided hadrontherapy, such as specific proton imaging using tomography or ionoacoustics, as well as delivery with MR-proton therapy, may take another 10 years to reach the clinics in specific applications.

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Figure legend

Figure 1. imaging issues specific to hadrontherapy and putative developments (arrows). LET: linear energy transfer; DECT: dual energy computerized tomography; 4D: four dimensional including time for moving tumours; IGRT: image-guided radiotherapy; MRI: magnetic resonance imaging; PET: positron emission tomography; pCT: proton CT; 3D: three-dimensional.

MULTIMODAL IMAGING

Targeting of radioresistant areas w/ high LET hadrontherapy / dose painting using PET tracers and MRI

DOSE CALCULATION

Minimization of calibration uncertainties (DECT, MRI-PT, pCT)

NORMAL TISSUE EFFECTS

CT monitoring, morphologic and functional tissues changes, radiobiological effects

TUMOR RESPONSE

Specific functional MRI sequences and PET tracers for pseudoprogression / radionecrosis, radiobiological modelling

SETUP IMAGING

In room 3D and 4D X-based imaging, range probes

ADAPTIVE

In room imaging with rapid replanning / MRI proton therapy

RANGE UNCERTAINTIES

Prompt gammas, inline / offline PET, secondary neutrons, ionoacoustics

PROTON ION RADIOGRAPHY

Minimization of calibration uncertainties (pCT)

PLANNING

IGRT

IMAGING ISSUES SPECIFIC TO HADRONTHERAPY

RESPONSE

MONITORING