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Interest of positron-emission tomography and magnetic resonance imaging for radiotherapy planning and control

Intérêt de la tomographie par émission de positrons et de l'imagerie par résonance magnétique pour la planification et le contrôle de la radiothérapie

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Abstract

Computed tomography (CT) in the treatment position is currently indispensable for planning radiation therapy. Other imaging modalities, such as magnetic resonance imaging (MRI) and positron emission-tomography (PET), can be used to improve the definition of the tumour and/or healthy tissue but also to provide functional data of the target volume. Accurate image registration is essential for treatment planning, so MRI and PET scans should be registered at the planning CT scan. Hybrid PET/MRI scans with a hard plane can be used but pose the problem of the absence of CT scans. Finally, techniques for moving the patient on a rigid air-cushioned table allow PET/CT/MRI scans to be performed in the treatment position while limiting the patient's movements exist. At the same time, the advent of MRI-linear accelerator systems allows to redefine image-guided radiotherapy and to propose treatments with daily recalculation of the dose. The place of PET during treatment remains more confidential and currently only in research and prototype status. The same development of imaging during radiotherapy is underway in proton therapy.

Résumé

La tomodensitométrie en position de traitement est actuellement indispensable pour la planification de la radiothérapie. D'autres modalités d'imagerie, comme l'imagerie par résonance magnétique (IRM) et la tomographie par émission de positons (TEP), peuvent être utilisées pour améliorer la définition de la tumeur et/ou des tissus sains mais également donner des données fonctionnelles du volume cible. Un recalage précis des images étant indispensable pour la planification thérapeutique, l'IRM et la TEP doivent être recalées à la scanographie de planification. La TEP/IRM hybride avec un plan dur, peut être utilisée mais pose le problème de l'absence de scanographie. Enfin, des techniques de déplacement du patient installé sur une table rigide sur coussin d'air permettent de réaliser des TEP/scanographie/IRM en position de traitement en limitant les mouvements du patient existents. En parallèle l'apparition d'accélérateurs avec IRM embarquée permet de redéfinir la radiothérapie guidée par l'image et de proposer des traitements avec recalcul quotidien de la dose. La place de la TEP au cours du traitement reste plus confidentielle et actuellement uniquement au statut de recherche et de prototype. Ce même développement de l'imagerie en cours de radiothérapie est en cours en protonthérapie.

1. Introduction

Radiotherapy is an essential treatment for more than 50% of cancers in both the curative and palliative phases. Current treatments have presented major advances in the field of drugs with a range of less toxic and more effective systemic therapies (targeted therapies, immunotherapies). In surgery, the arrival of minimally invasive techniques has made it possible to significantly reduce the morbidity. The greatest advances in improving local control and reducing the side effects and sequels of radiotherapy are based on advances in medical physics and imaging [1].

Image-guided radiotherapy is widespread and used for the treatment of the majority of cancers using low (kilovolt) or high (megavolt) energies including onboard imaging systems to improve targeting accuracy before or during the session from a direct or indirect target that may be a bone target, implanted fiducial markers or soft tissues [2]. For several cancers, such as prostate cancer, image-guided radiotherapy has established itself as a technique that reduced toxicity and hypofractionated treatments. Image-guided radiotherapy is also essential for certain tumours considered radioresistant that can now be treated with stereotaxis [3, 4]. Despite these advances, radiotherapy, guided by x-ray images and delivered by a low or high energy source, remains a technique that still suffers from several limitations and disadvantages: irradiating techniques, difficulty in managing movement, over- or underestimation of the target volume related to the quality of the computed tomography (CT) image by cone beam reconstructed in three dimensions (3D), artefacts related to prostheses or air in the intestines, adaptation to the response to radiotherapy.

Due to its excellent spatial resolution and high soft tissue contrast, magnetic resonance imaging (MRI) has become a reference anatomical imaging tool for tumour staging and remote extension. This non-irradiating, repeatable technique also has the advantage of performing functional measurements (multiparametric MRI) in order to study tissue function (diffusion or dynamic infusion sequence). It thus combines the advantages of optimal anatomical imaging with a strong contrast between tissues, bones and fat while giving major information on the mapping, behaviour and aggressiveness of the tumour.

Positron emission tomography coupled with CT (PET/CT) has also significantly altered the diagnosis and staging of several cancers (lung, haematological, prostate, etc.). This technique has a more limited spatial resolution but allows detection of distant lesions in order to optimize the therapeutic strategy but can also give functional information about the tumour (hypoxic zones, proliferative zones, etc.), notably to consider therapeutic adaptations (escalation, de-escalation, pertherapeutic imaging).

2. What role for PET/MRI in radiotherapy planning?

The use of MRI and PET is becoming increasingly common in radiotherapy planning. The integration of these two modalities ideally requires the performance of examinations in the processing position,

followed by an adjustment of the PET and MRI images on the dosimetric scanner. These different steps can generate biases in image registration and have important consequences on the contouring of target volumes.

Hybrid PET/MRI, with its digital PET detectors insensitive to magnetic field, allows simultaneous acquisition of both modalities. Hybrid PET/MRIs are relatively new equipment, the first installations took place in 2010 to be used for clinical or research purposes [5]. The theme of oncology dominates the indications, particularly prostate cancer, brain or head and neck tumours. Hybrid systems concentrate recent technological developments in PET detection systems: time of flight (TOF) correction, modelling of detector response function (point spread function, PSF), new reconstruction methods (Bayesian method), and compensation for respiratory movements [6].

In clinical practice, PET/MRI has shown superior performance to PET/CT when MRI was used for diagnostic purposes, particularly in the identification of bone metastases of breast cancers, staging of colorectal cancers, and recurrence of pelvic tumours [7]. The 2017 International Workshop in Tübingen, Germany, discussed the potential of PET/MRI to monitor therapeutic responses and adapt therapeutic targets during radiotherapy [8]. However, in 2019, an international workshop mentioned benefits in terms of patient comfort and improved image registration, but the interest in radiotherapy was not mentioned [9]. By the simultaneous acquisition of both modalities, hybrid PET/MRI could facilitate image shift and improve radiotherapy planning [10].

The first applications of PET/MRI contribution for radiotherapy were published in 2011, reporting a clinical case of meningioma treatment by intensity-modulated irradiation: the planning target volumes measured on MRI and PET separately, were significantly different, from a planning target volume measured on simultaneous PET/MRI acquisition [11]. A German team subsequently developed a prototype treatment table, on which MRI antenna supports (6-channel body antennas) were attached for PET/MRI imaging of the head and neck region in the thermoformed mask treatment position [12]. The authors demonstrated the technical feasibility of the system, with good MRI image quality, even if the "signal-to-noise" ratio of the images is reduced by about 20 to 30% compared to diagnostic MRI; they also showed a good quantification of the PET signal, provided that the attenuation caused by the immobilization equipment is corrected, using an attenuation map generated by a scanner.

Another prototype, for whole body imaging, has been developed by a Swedish team [13]. In this study, the authors observed a relative decrease of 30 to 50% in the signal-to-noise ratio in MRI, compared to the PET/MRI performed in the diagnostic position, requiring an adjustment of MRI protocols and probably an increase in examination time. Other authors mention the possibility of doing without the dosimetry scanner, by performing only a PET/MRI scan in the treatment position, and by constructing a pseudo CT from MRI images to perform pretherapeutic dosimetry, this technology could have a major interest in prostate or head and neck cancers [14].

PET/MRI therefore has a definite potential in radiotherapy planning, justified above all by the improvement of intermodality registration through the optimization and better definition of therapeutic target volumes. However, this potential remains limited due to the small number of machines available and the high cost of the devices.

The alternative to PET/MRI is to perform both examinations under the same conditions and in the treatment position. This system should make it possible to reduce the misalignments between images and to benefit from the PET/CT scanner in the absence of validation of the pseudo CT that could be created from the PET/MRI. This system can be envisaged using General Electric® equipment (PET/CT Discovery™ GE710 and an Optima™ MR450w MRI). Both examination rooms should be equipped with centring lasers and rigid tabletops. Patient transfer from one modality to the other is performed using a rigid Zephyr XL (Diacor®) tabletop. This air-cushioned device, which is multimodality compatible, makes it possible to move the patient while keeping him/her in the treatment position. The acquired images are aligned using the "Integrated Alignment" module of the AW Server 3.2 (General Electric®) software. Zephyr XL in the context of trimodality for radiotherapy allows for a reduction in image registration uncertainties for the different modalities, thus improving the definition of dosimetric volumes.

3. What role for PET/MRI in radiotherapy?

This imagery remains underutilized and often associated with CT imaging, and will require training for our teams if we want to disseminate it and improve:

- the management and handling of these machines in the environment of a particle accelerator;
- the identification and selection of the acquisition sequences best adapted to the pathology to be treated;
- the interpretation of images.

During planning, MRI produced for diagnostic or performed in the treatment position ("fused" MRI) remains the most widely used technique. During processing, some linear accelerator manufacturers offer image-guided radiotherapy, based on the same principle by integrating a real-time MRI fusion management platform to adapt the positioning or distribution of the dose to the MRI shift. These techniques suffer from several disadvantages that add uncertainties in the definition of the target volume:

- quality of the registration: automatic, semi-automatic, manual (cognitive);
- image distortion management;
- different MRI acquisition time from treatment planning CT acquisition time that may decrease the likelihood of reproducing the patient's or tumour's anatomy.

The integration of an MRI coupled with a particle accelerator offers multiple advantages: better definition of target volumes, non-irradiant examination that can be repeated or used in four-dimensional (4D) cinema mode during the session, ease of integration into an adaptive radiotherapy clinical program. Internal physiological movements during irradiation imply the use of additional margins to manage these uncertainties (an "internal margin" which added to the "set up margin" can lead to planning target volumes of 3 to 15 mm classically). The introduction of MRI to a radiotherapy accelerator should make it possible to reduce the target volume and improve its definition and, above all, reduce the irradiation of the organs at risk around it and reduce the "internal margin" to a value close to zero. At the same time, multiple technical constraints exist requiring complex engineering and quality assurance of physics associated with the distribution of emitted dose from the beam under a magnetic field of variable intensity.

4. Equipment

Currently four MRI machines exist, two of which are marketed after obtaining a CE marking in France: the MRidian® from ViewRay® (Oakwood village, Ohio) and the Unity™ from Elekta™ (Stockholm, Sweden). The main characteristics of these two machines are summarised in Table 1.

4.1. MRidian®

This system was developed with its MRI-guided adaptive radiotherapy solution "plug and play". The robustness and speed of implementation of this system in routine operation are linked to the use of a low-energy magnetic field to reduce the constraints of image distortion and the return effect of electrons under a magnet. The first machine installed to treat patients dates back to 2014 at Washington University in Saint Louis (Missouri, USA), since then approximately 5,000 patients have been treated worldwide. More than fifty machines are installed worldwide, including three MRidian® in France: Marseilles, Dijon and Montpellier.

Tumours treated with this machine are mainly abdominopelvic: pancreatic cancer, liver cancer, prostate cancer but also breast, thorax or head and neck cancers [15, 16].

MRidian® allows adaptive radiotherapy with gating of the tumour position by MRI. This adaptive radiotherapy is based on the anatomy of the day (intrafractional movements of the tumour and interfractional movements of organs at risk) on sagittal T1 or T2 sequences and will soon be available in all three planes [17]. The major disadvantages are a heavier service organization and a treatment time that remains long, 30 to 60 minutes, with the required presence of a doctor, a physicist and a manipulator during each session [18]. More recent work seems to show that dose and/or volume adaptive radiotherapy based on response should be possible thanks to the technical feasibility of 0.35 T diffusion sequences [19].

4.2. Unity™

This system has been developed by the UMC Utrecht team who succeeded in integrating a 1.5 T MRI (Philips®, Best, Netherlands) with an Elekta™ particle accelerator (Stockholm, Sweden) delivering 6MV X-photons. The proof of concept was established and published in 2008 and 2009 [20, 21].

Currently the system has evolved to include a 7 MV accelerator. The integrated MRI can also evaluate the movements and anatomical position of the tumour and surrounding organs, as well as their deformation before and during each session [22, 23]. Replanning based on MRI is also possible. Unity™ therefore makes it possible to envisage the integration of real-time imaging biomarkers to evaluate the response to irradiation between sessions and adapt irradiation volumes and/or doses. The first treatments were carried out in 2018 in Utrecht on pelvic lymph node relapses of prostate cancer and to evaluate the analgesic response to vertebral radiotherapy of spinal metastases [24]. Treatment times were less than 60 minutes. Soft tissue contour tracking appears to be feasible with a precision close to that of fiducial marker tracking (less than 1mm) [25]. Uncertainty still exists on the clinical impact of the electron return effect with 1.5 T MRI, responsible for areas of over or under dosage at the interface of low and high density areas (lungs, airway, soft tissue, bone) [26]. Approximately 40 machines are installed worldwide, with a first machine planned in France in 2021 in Lyon.

4.3. PET–linear accelerator

A prototype (not commercialized) combining a PET scanner and a linear accelerator, RefleXion™ X1, is being developed by RefleXion™ (Hayward, California, USA).

The concept of this machine compared to the current low or high energy image-guided, or MRI-guided radiotherapy systems is completely different. It introduces a new concept: biologically guided radiotherapy. The rotary gantry combines a linear particle accelerator delivering 6 MV X-rays with a flow rate of up to 800 UM/min and a multiblade collimator of 2 x 64 blades and a double PET detector, positioned on the rotary gantry at 90° from the accelerator, allowing to guide the radiotherapy according to the metabolism detected after injecting the patient with a radiotracer. Positron emission from the tumour generates two photons at 180°. The emission of these two photons at 180° causes response lines which are detected by the accelerator in 250 ms and allow dynamic targeting, in real time (tracking), of multiple metabolically active mobile lesions [27, 28]. The advantages could therefore be multiple: no need for trustees, no need for gating and internal target volume, possibility of treating multiple lesions in the same session over short treatment times.

This PET–linear accelerator prototype may have clinical potential for optimizing radiation therapy for metastatic whole body disease due to its ability to detect the whole body and the possibility of treating multiple targets at the same time and large volumes with helical radiation therapy. A major limitation

to this technology is the need to inject a radiotracer prior to each session, which severely limits the number of sessions to target tumour metabolism.

5. What role for PET/MRI in protontherapy?

5.1. MRI and protontherapy

Protontherapy and MRI–linear accelerator are quite regularly opposed in current debates in oncology. There are actually several aspects to the issue: the first is probably strategic. In a context of constrained health expenditure and the attractiveness or competitiveness of health care centres, access to the latest innovation is a strong decision-making factor in the choice of investments. Another aspect of the question is the degree of innovation of these two technologies. MRI–linear accelerator systems represents 2.5 to 3 times the cost of a modern accelerator, and proton therapy is of the order of 10. Reimbursement for procedures is not valid for either technique. The other aspects of this question are more debatable. Indeed, a non-irradiating image guidance modality associated with a photon irradiation modality is compared to a charged particle irradiation modality allowing to limit the irradiated volumes outside the tumour target without precision on the associated image-guided radiotherapy modality.

Is the clinical question relevant? These two technologies have a common objective: that of reducing toxicities with tumour control at least equivalent or even better by allowing hypofractionation and/or dose escalation.

However, it should be noted that the advantage of a non-irradiating image guiding system would be even more clinically relevant with a volume-saving irradiation modality. Cancer patients have a 36% higher risk than the general population to have a second cancer (French national cancer institute [INCa] report 2019): individual genetic susceptibility, role of environment and lifestyle, aging population and/or susceptibility to chemotherapy and radiotherapy? The impact of low doses of intensity-modulated radiotherapy will remain a point of vigilance for the occurrence of secondary cancers in the coming decades. In this context, the development of hadrontherapy, at least through the reduction of irradiated volumes, could ideally be coupled with a non-irradiating image guidance modality.

The concept of protontherapy MRI has been described from 2015 [29]. The deflection of protons in magnetic fields is well controlled since it is on these magnetic fields that the principle of active scanning is based. It remained to take into account the interaction of the magnetic fields of the onboard MRI with the elements of the beam line. Feasibility and resolution have been shown to be compatible with clinical use. The first clinical prototypes should be available within the next 5 years.

5.2. PET and protontherapy

PET is currently being developed as a way of online monitoring of the course and dose of hadrontherapy. One of the limits of use is the lifetime of the emitted elements. Online or offline approaches are being developed, each with their own advantages and disadvantages.

In a completely different direction, diagnostic PET imaging on board of a particle accelerator could be particularly useful for the dynamic measurement of hypoxia. Indeed, although data are relatively rare, a number of elements suggest that hypoxia is a dynamic phenomenon during radiotherapy. In hadrontherapy, the production of oxygen on the trace of charged heavy particles of high transfer linear energy [30].

The failure of intensity-modulated radiation dose-painting strategies based on imaging of hypoxia may be due in part to changes in hypoxia during fractional radiotherapy. The choice of tracer and the order of magnitude of insufficient dose escalation (+10% in photons) for oxygen enhancement ratio values of the order of 3 in hypoxic tumours could be other explanations. It is therefore potentially a field to investigate for radioresistant tumours due to hypoxia treated with hadrons, which would be facilitated by an online PET scan. Other features of varying tumour aggressiveness during irradiation, such as proliferation, could theoretically be targeted with tracers such as fluorothymidine. On the other hand, the problem of repeated dose in PET is an unavoidable limiting factor.

6. Conclusion

Precision radiotherapy requires high-precision imaging, which initially focused on pretherapeutic imaging. In this context, the use of multimodality has become a standard in the management of patients, particularly for cerebral, head and neck, pelvic or lung cancers. This imaging is still highly dependent on images obtained from diagnostic examinations, which poses problems of registration and fusion, image orientation (strict axial), distortions, MRI sequences, organ mobility, etc.

In this context, the appearance of examinations dedicated to radiotherapy makes it possible to resolve many of the limitations of multimodality. The appearance of PET/MRI is a major opportunity for radiotherapy to combine very high-resolution images and functional information. The use of these images remains limited by the lack of development of antennas dedicated to radiotherapy and compatible with thermoplastic masks. Specific patient transfer systems between PET and MRI can also be used and allow the patient to benefit in addition to the scanner from PET/CT. However, these more complex systems pose the same problem with respect to dedicated antennas.

Adaptive radiotherapy has developed little since its introduction, mainly due to problems with pretherapeutic imaging and dose recalculation. These problems seem to be being resolved and allow for daily replanning. The first MRI-linear accelerator scanners have demonstrated the capacity for daily rescheduling but their therapeutic impact remains to be demonstrated. Alternative solutions

based on CT imaging are also possible and would make it possible to treat patients in about 15 minutes while adapting the dose on a daily basis without any problems thanks to artificial intelligence.

Finally, the same problem arises for proton therapy and seems to be solvable. The problem of multiple image processing and verification systems may make future clinical studies and validation of such systems difficult

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Table 1. Image-guided radiotherapy: main characteristics of the MRI–linear accelerator systems on the market.

Trade name (manufacturer)	Magnetic field	Ring size	Beam energy	Beam size	Collimator
Mridian® (Viewray®)	0.35 T	70 cm	6 MV flattening filter free	27.4 × 24.1 cm	138 blades
Unity™ (Elekta™)	1.5 T	70 cm	7 MV flattening filter free	57,4 × 22 cm	160 blades