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PET and MRI guided adaptive radiotherapy: rational, feasibility and benefit

Radiothérapie adaptative guidée par la TEP et l'IRM: rationnel, faisabilité et bénéfices

Sebastien Thureau¹, Aurelien Briens², Pierre Decazes³, Joel Castelli⁴, Anais Barateau⁴, Robin Garcia⁵, Juliette Thariat^{6,7,8}, Renaud de Crevoisier⁹

1. Département de Radiothérapie et de Physique Médicale, Centre Henri Becquerel, QuantIF EA 4108, Université de Rouen, 76000 Rouen, France
2. Département de radiothérapie, centre Eugène Marquis, rue de la Bataille-Flandres-Dunkerque, CS 44229, 35042 Rennes cedex, France
3. Département de Médecine Nucléaire, Center Henri Becquerel, QuantIF EA 4108, Université de Rouen, Rouen, France
4. Département de radiothérapie, centre Eugène Marquis, rue de la Bataille-Flandres-Dunkerque, CS 44229, 35042 Rennes cedex, France; CLCC Eugène Marquis, Inserm, LTSI-UMR 1099, université de Rennes, 35000 Rennes, France
5. Service de physique médicale, Institut Sainte-Catherine, 84918 Avignon, France
6. Department of Radiation Oncology, Centre François Baclesse, 14000 Caen, France
7. Laboratoire de Physique Corpusculaire IN2P3/ENSICAEN-UMR6534-Unicaen-Normandie Université, 14000 Caen, France
8. ARCHADE Research Community, 14000 Caen, France
9. Département de radiothérapie, centre Eugène Marquis, rue de la Bataille-Flandres-Dunkerque, CS 44229, 35042 Rennes cedex, France; CLCC Eugène Marquis, Inserm, LTSI-UMR 1099, université de Rennes, 35000 Rennes, France

Résumé

La radiothérapie adaptative (ART) correspond à diverses stratégies de replanification visant à corriger les variations anatomiques survenant au cours de la radiothérapie. L'objectif de l'article est de préciser la rationalité, la faisabilité et les avantages de l'utilisation de la TEP et/ou de l'IRM pour guider cette stratégie dans diverses localisations tumorales.

En effet, les modifications anatomiques définies par le scanner en prenant en compte la mobilité tumorale et la variation de volume ne sont pas toujours suffisantes pour optimiser le traitement. L'apport de l'imagerie fonctionnelle par TEP ou la précision des tissus mous par IRM permet d'envisager une ART optimisée. Aujourd'hui, les données les plus importantes, tant pour la TEP que pour l'IRM, concernent les cancers du poumon, de la tête et du cou, du col de l'utérus et de la prostate.

L'ART guidée par TEP et/ou IRM semble faisable et sûre, mais dans une expérience clinique très limitée. Des études de phase I/II doivent encore être réalisées, avant de proposer des essais randomisés prenant en compte le coût de cette technique et de l'utiliser en pratique courante.

Abstract

Adaptive radiotherapy (ART) correspond to various replanning strategies aiming to correct for anatomical variations occurring during the course of radiotherapy. The goal of the article was to report the rational, feasibility and benefit of using PET and/or MRI to guide this ART strategy in various tumor localizations.

The anatomical modifications defined by scanner taking into account tumour mobility and volume variation are not always sufficient to optimise treatment. The contribution of functional imaging by PET or the precision of soft tissue by MRI makes it possible to consider optimized ART. Today, the most important data for both PET and MRI are for lung, head and neck, cervical and prostate cancers.

PET and MRI guided ART appears feasible and safe, however in a very limited clinical experience. Phase I/II studies should be therefore performed, before proposing cost-effectiveness comparisons in randomized trials and before using the approach in routine practice.

Key words : PET, MRI, ART

Mots clés : TEP, IMR, radiothérapie adaptative

1. Introduction

The aim of radiotherapy is to deliver the maximum dose to the tumour while sparing organs at risk. Intensity Modulated Radiotherapy (IMRT) has made it possible to reduce the dose to organs at risk but initial IMRT planning may need replanning in case of volumetric changes of tumor, organs at risk or the patient. Improvements in tumor definition include the use of multimodal imaging (Computed Tomography (CT scan), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET)) and tumor targeting during radiotherapy through Image-guided radiotherapy (IGRT) using advanced in-room setup imaging such as cone-beam CT (CBCT) and further, MRI-linac. Currently, MRI-linac allows adaptive radiotherapy (ART) based on the anatomy of the day. ART has also been developed using PET and various tracers to account for interfractional changes in tumor biology. A recent concept of emission-guided radiotherapy (EGRT) has also emerged by using PET-linac [1]. The ultimate step is ART with dose painting. Even though this concept has been validated, its clinical impact remains to be demonstrated. This article focusses on PET and MRI-based ART for lung, head and neck, cervix and prostate tumors.

2. PET tracers for ART

PET-CT is currently indispensable in oncology for diagnosis, radiotherapy planning and follow-up. Many PET tracers can guide radiotherapy (Tables 1, 2). The glucose analogue [18F] fluoro-2-deoxy-D-glucose (FDG) is the most widely used tracer to guide radiotherapy, exploiting the increased metabolic rate of tumour cells. The mechanisms underlying FDG labelling not only depend on increased glycolysis and glucose

transporter density but also on cell proliferation, hypoxia or activation of oncogenic signaling pathways [2]. Oxygen deprivation (hypoxia) is an important factor in radiotherapy resistance and poor survival. Specific tracers have been developed to define hypoxic areas in various cancers including head and neck or lung cancer. The most common PET hypoxia tracer is 18F-fluoromisonidazole (FMISO) [3]. However, limitations of F-MISO include slow diffusion, tumour accumulation and washout, resulting in low hypoxic contrast imaging. 18F- fluoroazomycin-arabinoside (18F-FAZA), a more hydrophilic marker, is associated with poor disease-free survival in 18F-FAZA-positive tumours [4]. F-flortanidazole (18F-XH4), 18F-labeled fluoroerythronitroimidazole (FETNIM) or 18F-2-nitroimidazol-pentafluoropropyl acetamide (18F-EF5) are interesting surrogate markers of radioresistance [5]. Finally, other radiopharmaceuticals have exploited the lipophilic properties of copper (^{64}Cu) mainly coupled with diacetyl-bis(N4-methylthiosemicarbazone) (ATSM) to identify areas of tumour hypoxia. The latter has good sensitivity but poor specificity to predict treatment response [6]. Its perfusion-dependent distribution seems to limit its accuracy in defining hypoxic areas.

Tumour proliferation is also a poor prognostic factor. FDG PET/CT shows poor correlation between FDG uptake (metabolism) and Ki-67 proliferation index [7]. [18F]Fluorothymidine (FLT), a pyrimidine analogue, is phosphorylated by thymidine kinase-1 during the S phase of the cell cycle and then trapped inside cells. Methionine is an essential amino-acid whose increased consumption is often correlated with cell proliferation. ^{11}C -methionine PET/CT shows divergent results compared to FDG PET/CT [8].

3. ART in lung tumors

Radiochemotherapy is standard treatment for locally advanced lung cancers but with a risk of recurrence and significant toxicities. Increasing the dose across the entire volume is deleterious as demonstrated by RTOG 0617 trial [9]. One option, therefore, is to increase the dose only in areas of radioresistance, but these may change from one fraction to another. Tumor shrinkage during radiotherapy and adaptation to tumor volume per-treatment is not easy and there is no correlation between volume changes during radiotherapy and patient prognosis [10]. Today, ART for lung cancers has mostly been developed using PET.

3.1 PET tracers in lung cancer

3.1.1 Metabolism tracers

Aerts et al. [11] and Calais et al. [12] showed that high FDG-uptake areas on pre-therapeutic FDG PET/CT scans were highly correlated to sites of local relapse or persistent abnormalities on post-therapeutic CT scans. These findings led to consider dose escalation on smaller sub-volumes, allowing better local disease control while minimising early and late toxicity. Nestle et al. demonstrated in a randomized trial (PET plan) that it was possible to increase the dose without increased toxicity based on pre-treatment PET. This was confirmed in the European PET boost study. [13] Per-radiotherapy FDG PET/CT uptake can also be a volume of interest [14]. FDG-PET can be performed without artefacts (lung inflammation) and the persistence of 42 Gy pathologic fixation is pejorative [15]. As a result, we proposed a French multicenter study with dose increase on per-radiotherapy FDG volume (RTEP7, NCT02473133). American study RTOG 1106 is also underway based on encouraging preliminary results by Kong et al. in a phase 2 as opposed to study RTOG 0617 [16].

The definition of BTV (Biologic Target Volume) during radiotherapy is a crucial step but requires a consensus on the method of segmentation and current recommendations do not clearly answer the question for both pre- and per-therapeutic volumes [17]. Previous studies defined dose levels to areas at risk according to TCP models or a predefined dose. Dose painting strongly depends on PET (3D averaged, 4D gated, 4D MIP) acquisition and segmentation methods (automatic with gradient, manual, fixed...) [18]. Resolving motion patterns of lung tumors for accurate dose calculation can be complex with tumor movement, size and deformation, which are dependent on tumor location. Motion artifacts caused by respiratory movements can be reduced by 4D PET acquisitions and ITV (Internal target volume) definition [19]. Respiratory function defined by SPECT can also change during radiotherapy [20]. Current radiotherapy techniques allow functional area sparing, but it is necessary to take into account changes in healthy tissue and tumour during radiotherapy.

3.1.2 Hypoxia tracers

In a phase 2 study, increasing the dose of radiotherapy up to 86 Gy resulted in no excess toxicity at 3 years [21] with similar local control despite twice as large volumes. Correlation between hypoxia and FDG hot spots is unclear [22].

3.1.3 Others tracers

3'-[18F]fluoro-3'-deoxythymidine (18F-FLT) may be used to select patients for increased dose or modified fractionation on subvolumes with high density of actively proliferating cells [22]. 18F-FDG and 18F-FLT correlate with Ki-67 labeling index in pulmonary lesions, but correlation of 18F-FLT is stronger, confirming its link with tumor cell

proliferation in lung cancer. In areas with significant proliferation, ^{18}F -FLT fixation decreases rapidly during radiotherapy, which does not make this tracer optimal for ART [23].

Anti-angiogenic therapy targeting tumor neovasculature is one of the promising approaches in treating lung cancer. ^{68}Ga -labeled dimerized-RGD (^{68}Ga -RGD2) is a tracer of Integrin $\alpha\text{v}\beta3$. This tracer has already been tested to evaluate anti-angiogenic drugs but not radiotherapy [24].

3.2 MRI and lung cancer

Thoracic MRI has had limited role in lung cancers due to low lung density and the resulting low signal-to-noise ratio, as well as the presence of respiratory and cardiac movements. MRI/linacs may change indications for MRI in lung ART. Indeed, CT scan (CT or CBCT) is often not very informative for ART and hypoxia PET is little accessible. The use of 1.5T MRI/linacs should allow functional sequences such as BOLD (blood oxygenation level dependent). The reproducibility of these sequences (BOLD or others as TOLD (tumour oxygenation level dependent)) will have to be confirmed, particularly for mobile tumors [25]. The incorporation of motion data to RT planning also needs further investigation [26].

4. PET and MRI guided ART in head and neck cancer

ART for squamous head and neck cancer (HNSCC), aiming to correct for anatomical variations occurring during the treatment course, is mostly based on CT or CBCT. The main clinical goals of ART is to decrease toxicity by sparing OARs, in particular the

parotid gland, and to increase local control using accurate dose escalation, based on PET.

4.1. Anatomical and metabolism variations during the treatment course justifying ART in head and neck cancer

During the HNSCC radio-chemotherapy course, morphological changes take place both in target volumes and organs at risk (OAR). GTV decreases by about 70% and parotids by 30%, which may go with position variations, due to volume variations and weight loss during treatment, of the order of 5 kg [27].

ART aims to minimize deviations from initially planned dose distributions based on the principle of replanning during treatment [27]. However, whereas morphological imaging allows only geometrical adaptations considering mostly OARs, functional imaging can, in addition, be used to adapt/increase the dose by highlighting significant areas for tumour control.

In HNSCC, FDG PET/CT is increasingly used both for diagnosis and response to treatment. To target FDG avid tumour regions [28], volume-based metabolic parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) appear to have superior performance in identifying patients at risk than standardized uptake value (SUVmax) [29]. However, it is unknown whether increased dose as a boost in these sub-volumes, can translate into increased tumour control probability. Therefore, which volumes should be targeted? Most loco-regional recurrences after radio(chemo)therapy in HNSCC occur within metabolic volumes ± 10 mm [30]. Until now, identification of tumor sub-volumes is not reliable enough to serve for large-scale spatially selective dose escalation trials. A phase 1 dose-escalation trial to 82 Gy reported long-term toxicity issues [31]. More accurate definition of the volumes at risk of recurrence could be achieved through voxel-scale analysis using radiomics techniques [(clinicaltrials.gov/NCT02469922) [32].

Monitoring metabolic parameters during radiochemotherapy with SUVmax and TLG decrease while the extent of MTV decreases or increases (notably due to peritumoral inflammation), could be interesting [33]. Persistent hypermetabolism during treatment is

a pejorative prognostic factor [33]. Metabolic imaging for ART is therefore promising to target hypermetabolic regions. Two kinds of dose-escalation regimens can be developed. The first consists of delivering a boost to a hypermetabolic volume within the anatomic-clinical target volume designated as the biological target volume. The second, referred to as "dose-painting by numbers", consists of delivering different doses at the voxel scale according to FDG uptake values [34]. Dose escalation up to 80.9 Gy seems feasible with dose-painting by numbers, but increases the risk of late mucosal ulcers [35]. ART with metabolic imaging improves the sparing of the OARs [36]. It yields local, regional and distant control rates as with conventional IMRT. ART FDG-PET/CT-based dose escalation is being investigated in a phase II trial conducted by the Ghent team and a phase III trial by the Netherland Cancer Institute [37] while ART dose de-escalation is investigated in HPV-positive patients [38].

4.2. Hypoxia-re-oxygenation targeted in PET based ART in head and neck cancer

Hypoxia is a well-known risk factor of failure to radiotherapy. Non-invasive imaging with FMISO and FAZA hypoxia tracers shows significant decrease in most patients during treatment, thus revealing re-oxygenation [39,40]. Moreover, persistence of hypoxic areas during treatment is a strong risk factor for loco-regional recurrence [39,40]. Hypoxia imaging in a dose-painting by numbers approach, compared to conventional IMRT, could increase tumor control probability from 55.9 to 70.4% [41], without excess toxicity. ART with FMISO PET/CT is also used for dose de-escalation (from 70 to 60 Gy) in HPV-positive patients [42] without pre-therapeutic hypoxia or with hypoxia resolving after 1 week of radiotherapy. Interestingly, none of the 10 patients treated by dose de-escalation experienced 2-year recurrence while one patient with hypoxic tumor undergoing metastatic progression [42].

4.3. Proliferation targeted in PET based ART in head and neck cancer

Rapid proliferation of clonogens surviving radiotherapy, referred to as accelerated repopulation, is a known cause of failure in HNSCC. Proliferation imaging, mainly with FLT PET/CT, is a good surrogate of accelerated repopulation [43]. Intensity of FLT labelling decreases from about 50% after 2 weeks of treatment to 70% after 4 weeks. These kinetics have significant prognostic value on loco-regional control, disease-free survival and overall survival. FLT PET/CT could even perform better than FDG PET/CT [44]. Dose-escalation strategies could be designed to boost proliferating FLT-PET/CT positive volumes. However, more correlative data on proliferation imaging and patterns of failure are needed to propose ART strategies.

3.1.4. Other tracers

Epidermal growth factor receptor (EGFR) is one of the main players in cell proliferation in HNSCC and a therapeutic target for cetuximab. The use of radiolabeled antibodies targeting EGFR is limited by their large size, low diffusion capacity and slow clearance, affecting their sensitivity and specificity. Smaller EGFR-targeting peptide probes are in preclinical stage [45]. Programmed Cell Death-1/Ligand-1 (PD-1/PD-L1) imaging using immuno-labelled antibodies, mainly with radioactive Zirconium (^{89}Zr), are investigated to predict immunotherapy response in 2 clinical trials in HNSCC [46]. Finally, tumour angiogenesis is a crucial process in tumour development and progression. Targeting $\alpha\beta3$ integrins with radiolabeled RGD (arginine-glycine-aspartic) peptides, such as ^{18}F -Galacto-RGD or RGD-K5 seems to be the most interesting strategy in HNSCC [47].

3.5. Remaining issues of PET based ART in head and neck

PET based ART poses at least three main challenges.

1: Optimal timing of PET imaging in ART is uncertain. Adapting radiotherapy too early could deprive information about treatment response and accurate identification of areas at risk of recurrence. On the contrary, later adaptation limits the impact of adaptive strategies and poses the technical problem of the correct delineation of target volumes whose identification is altered by inflammatory phenomena. This optimal timing varies between studies from 1 to 3 weeks [48]. Indeed, the prognostic value of intra-treatment

FDG-PET may be greatest at 3 weeks from the start of treatment [49]. Variations in FDG PET parameters are greater in the first 10 fractions than in subsequent fractions [50]. Lastly, the increase in FDG uptake related to inflammatory processes could be significant after week 3 [51]. Another important issue regarding the timing concerns the number of re-imaging and consequent re-planning during treatment. These issues are being addressed in an ongoing prospective trial, TEMPORAL, evaluating the predictive value of FDG PET scans at weeks 2 and 4 of radiotherapy (clinicaltrials.gov/NCT02469922) [33].

Another issue concerns the correct delineation of target volumes, in particular because of the FDG uptake by the surrounding tissues, either physiologically (e.g. vocal cords) or due to inflammatory phenomena. It seems therefore necessary to develop standardized delineation methods and among them, the good accuracy of gradient-based delineation methods appears to be of particular interest [52].

2: Replanning is time-consuming (up to a full working day). Automation of treatment plan adaptation by deformable image coregistration method addresses this problem. ART guided by functional imaging also encounters issue of day-to-day consistency of PET images in the same patient, reported as moderate to good.

3: Finally, the technical limitations of PET, such as spatial resolution, restrict the performances of PET-based radiotherapy.

3.6. MRI guided ART in head and neck

MRI provides superior soft tissue contrast in comparison with CT, allowing better definition of tumour and OARs. The lack of additional radiation exposure is another attractive feature for intra-treatment monitoring. MRI can be used at diagnostic, delineation, prediction of treatment response, treatment response, or treatment planning and morphological and functional MRI in an ART workflow for HNSCC patients [53].

3.6.1. Morphological MRI guided ART in head and neck

HNSCC ART studies with CT have demonstrated the dosimetric benefit of replanning for OAR sparing. MRI could be used instead of CT for replanning. MRI replanning can be

performed with an independent MRI-only workflow or using MRI-linac. The main issue of MRI (re)-planning is the lack of electron density information, necessary for dose calculation. To overcome this issue, methods have generated synthetic CT, also called pseudo-CT (pCT), from MRI. For HNSCC MRI-dose calculation, recent deep learning methods provided dose uncertainties lower than 2%. These methods used one or several MRI sequences, mainly T2 weighted sequence or Dixon reconstruction [54].

Recent MRI-linac devices allow MRI acquisition before each treatment delivery. Daily plan treatment adaptation is therefore available. Chen et al. reported their initial clinical experience of MRI-guided radiotherapy for 18 patients [55]. A TrueFISP sequence for daily MRI acquisition can be used and anatomic and dosimetric changes quantified (N=6) [56].

3.6.2. Functional MRI guided ART in head and neck

Functional MRI sequences are able to characterize tumour biology by providing quantitative functional parameters such as tissue cellularity, vascular perfusion/permeability and hypoxia. Diffusion-weighted MRI (DW-MRI) examines water diffusion through apparent diffusion coefficient (ADC, in mm^2/s). ADC is inversely correlated with tumour cellularity. Dynamic contrast-enhanced (DCE-)MRI examines vascularity. DW and DCE-MRI in HNSCC radiotherapy [57] could be used to guide RT adaptation and dose escalation [58]. However, the geometry of DW-MRI in HNSCC is complex due to air cavities causing large magnetic field inhomogeneities. Using conventional DW-MRI, acquired with echo planar imaging (EPI), geometric distortions in ADC maps can be up to one centimeter [59]. The development of geometrically accurate DW-MRI sequences on an MRI-linac system is ongoing [60].

In total, PET imaging seems to be more explored than MRI to guide ART in HNSCC. Dose-painting approaches may however use combined functional MRI and PET imaging in an ART perspective [59].

5. ART in cervical cancer

Radio-chemotherapy of locally advanced cervical cancer (LACC) faces several technical difficulties. One of them is the concordance between the planned and the delivered treatment. Indeed, during radiotherapy, important morphological variations may occur for both target volumes and OARs. The uterus exerts rocking movements that modify the position of the uterine fundus of up to 5 cm in the anterior-posterior plane. Translational movements of up to 2 cm occur related to variations in rectal distention. Finally, the tumour volume decreases by an average of 2/3 during treatment [61]. In order to take into account all these modifications and to adapt radiotherapy as well as possible, ART protocols have been developed, mainly based on treatment plan libraries. Several treatment plans are computed on CT scans, with different bladder fillings for example. At each fraction, the most suitable plan is selected from IGRT (CT, cone-beam CT or MV-CT). Such strategy enables better target volume coverage and significant dose reduction in the bladder and GI structures [61]. PET and MRI may also be used to guide ART strategies.

5.1 PET guided ART in cervical cancer

In addition to morphological characteristics, assessment of functional parameters using PET/CT metabolic imaging is an important part of cervical cancer staging and follow-up. Indeed, in locally advanced cervical cancers (LACC), FDG PET/CT improves lymph node assessment compared to MRI or contrast-enhanced CT [62]. Performing an FDG PET/CT as part of the initial extension work-up of LACC modifies the initial management of about 1/3 of the patients, and is therefore recommended by European Society of Gynaecological Oncology (ESGO), European Society of Radiotherapy and Oncology (ESTRO) and European Society of Pathology (ESP) [62]. It also modifies the radiotherapy fields. However, as in other tumour localisations, the risk of false positives must be pointed out, linked, for example, to ovarian or uterine physiological fixations. The low spatial resolution is associated with a risk of false negatives, for example, in

lymph node micro-metastases or low FDG avidity of some tumours (e.g. mucinous tumours).

FDG PET/CT has important prognostic value, not only by allowing proper staging, but also by revealing metabolic characteristics. Volume-based metabolic parameters such as metabolic tumour volume (MTV) and total lesion glycolysis (TLG) on baseline FDG PET/CT appear to be better predictors than maximum standardized uptake value (SUVmax). However, elevated nodal SUVmax is a pejorative prognostic factor for recurrence and survival [62]. Using a “radiomics” approach, intra-tumoral FDG heterogeneity appears as a consistent negative predictor of recurrence, progression-free survival (PFS) and overall survival (OS) [63].

As for HNSCC, the kinetics of response to radiochemotherapy assessed by FDG PET during treatment increases the prediction capability of PET, each patient being his/her own reference. Early complete metabolic response, in the 3rd week of treatment, is a significant positive prognostic factor [64]. The prognostic value of partial metabolic response is more difficult to establish. However, low MTV and TLG values during radiochemotherapy are associated with better OS [65] and have better prognostic value than SUVmax [66]. MTV decreases by 65% and TLG by 85% at week 4 of treatment. The determination of these parameters by adapted thresholds (55% of SUVmax for MTV and 32% for TLG) provides a good predictive value for survival [67]. Like in HNSCC, optimal timing is uncertain. Kidd et al showed that the predictive value of FDG PET CT was better at week 4 than week 2 during treatment [68]. However, week 4 appears too late to adapt chemoradiotherapy, as it is usually administered in 5 weeks. Nevertheless, it can be of great value in tailoring brachytherapy following external beam radiotherapy. Thus, two potential implications of intra-treatment FDG PET/CT in an ART approach can be envisaged in LACC. First, it identifies patients with a favourable prognosis, who could be candidate for dose de-escalation. On the contrary, the persistence of poor prognostic metabolic parameters such as high MTV or TLG values could support dose escalation protocols in the primary tumour or lymph nodes. However, information on the correlation between patterns of failure and metabolic imaging parameters is still unknown and there is no consensus about the optimal threshold for delineation from FDG PET/CT. Thus, to

our knowledge, only ART strategies based on morphological imaging have been tested in cervical cancer to date. The metabolic information offered by FDG PET/CT in this strategy could further improve the prognosis in these patients.

5.2 MRI guided ART in cervical cancer

In cervical external-beam radiotherapy, MRI is used at different steps [69]: diagnostic, delineation, treatment planning or treatment response. MRI is recommended as the imaging method of choice in brachytherapy, due to the excellent soft-tissue contrast and tumour visualization [70] and morphological and functional MRI could be used in an ART workflow for patients with cervical cancer.

5.2.1 Morphological MRI guided ART in cervical cancer

MRI allows more accurate and reproducible contouring in cervical cancer than CT imaging. Moreover, MR acquisitions during treatment course may allow management of inter- and intra-fraction variations. Two studies proposed ART with weekly MRI acquisitions. Oh et al. [71] combined weekly MRI (T2-weighted fast spin echo)-guidance for error correction with off-line replanning. Kerkhof et al. [72] proposed a planning study simulating a MRI-linac online adaptive technique to model tracking and/or treating inter- and intra-fractional motion during treatment. They acquired weekly MR images and found significant dose reductions to OARs, while preserving PTV coverage. No study with online ART for cervical radiotherapy with MRI-linac has yet been reported to our knowledge.

In the aim of MRI (re) planning, only one study reported pseudo-CT generation from MRI in cervical radiotherapy [73]. In this study, three-dimensional fast spoiled gradient-echo dual echo with a Dixon reconstruction (fat and water separation) was used. A deep learning network (conditional GAN) was trained with prostate CT and MR images. Dose differences between reference CT planning and pCT planning were within 2%. Using MRI-linac, intra-fraction movements can be managed thanks to gating with cine-MRI sequence. Such strategy allows CTV-PTV margin reduction, resulting in better OAR dose sparing. In case of large variations, online replanning can be performed.

5.2.2 Functional MRI guided ART in cervical cancer

DCE-MR is an interesting image modality for tumour response prediction. Mayr et al. [74] established functional risk volumes from DCE-MRI that could predict outcomes as early as 2-5 weeks of treatment. Based on DW-MRI, ADC was identified as a biomarker of tumour response and early response (at mid-treatment) [75]. Implementation of functional sequences in MRI-linac should allow adaptive workflow. ART strategies could be set according to treatment response and higher doses could be delivered to hypoxic tumour areas [76].

In total, MR-guided radiotherapy is a promising tool for cervical cancer since it allows to daily monitor a dose to critical structures, adapt for anatomical variations, and potentially reduce toxicity to OARs while simultaneously increasing the delivered dose to tumour.

6. ART in prostate cancer

A dose-effect relationship has been demonstrated for prostate cancer radiotherapy, both in terms of biological control for the most aggressive diseases (in the absence of androgen deprivation) and in terms of digestive and urinary toxicities. If highly conformal techniques such as intensity modulated radiotherapy have historically improved patient outcome, the accuracy of any radiotherapy delivery is however limited by multiple factors: CT scan based organ delineation, set up error and inter-/intra-fraction organ motion, rotation and deformation. Indeed, if IGRT and the recent hypofractionated SBRT techniques correct for prostate displacements by performing a rigid registration, these techniques cannot take however in account large rotations and organ deformations occurring in the seminal vesicles and in most of the organs at risk (bladder, rectum and small bowel) during the treatment course. A systematic population-based PTV definition exposes the patients to an increased risk of toxicity if the margins are too large and to an increased risk of recurrence if they are too small. The historical ART approach, using standard fractionation, was based on off-line CT scan-based strategies, not solving the

issues of organ visualization and on-line correction. Modifying the standard single CT-based planning radiotherapy or this historical ART approach toward a more complex MRI based hypofractionated ART appears an attractive new strategy to solve these issues.

6.1 First approaches of prostate cancer ART based on CT scan and CBCT

The inter/intra-fractionation deformations occurring during prostate radiotherapy are well quantified . For instance, 200 CBCT images matched for 10 patients to planning CT images using deformable registration identified large prostate deformations, mainly in the anterior direction with a maximum of 10 mm, 5 mm and 3 mm in 1%, 17% and 76% of cases, respectively [77]. RT can induce an initial increase in prostate size, followed by a constriction at the end of RT [78]. With SBRT, prostate swelling can persist even after radiotherapy [79]. SV deformations can be large, with changes in the posterior direction of >5 mm and >3 mm in 7.5% and 44.9% of cases [77]. Considerable inter-fraction deformation can also occur for the bladder. Using elastic registration methods, differences in mean dose reached 7 Gy in average (up to 18 Gy) for the bladder and 2 Gy (up to 4 Gy) for the rectum [80]. ART in prostate cancer has been used for years using CT or CBCT strategies. An offline adaptive process, i.e. using information from the first three to five treatment fractions to provide feedback for future deliveries, has been first historically used to correct systematic variations. Indeed, adapted personalized reduced PTV reduced OAR irradiation and toxicity, while allowing dose escalation, in non-randomized trials. More recently, 3D CBCT imaging has been used for fraction adaptation by including non-rigid deformations and dose mapping. One of the main limitations is the low quality of tissue visualization with CBCT.

6.2 Rational and feasibility for direct MRI-based planning and MRI only workflow

Uncertainties in anatomical structure visualization/delineation is a critical because generating systematic errors can deteriorate patient outcomes. If CT-scan is reference imaging for radiotherapy planning, and electron density for dose calculation, CT-scan

depicts poor soft tissue contrast, leading to inaccuracy in tumor and OAR delineation as well as patient repositioning. CT-scan overestimates by 30% the prostate volume [81], the tumor is not visualized and anatomical structures involved in erectile function (such as the penile bulb) are not well visualized. MRI improves organ delineation [82]. Unfortunately, diagnostic MRI cannot be directly used for delineation due to complex anatomical variations between CT-scan and MRI, even with rigid/elastic registration. In this context, direct MRI planning appears as an appealing modality. However, MRI does not provide electron density for dose calculation. Several methods based on advanced image processing have led to the generation of synthetic or pseudo-CT from MRI, finally allowing dose calculation [83,84]. These methods can be divided into four categories: bulk density methods [85,86], probabilistic methods [87], atlas-based methods [88,89], and more recently machine learning methods such as patch-based methods including random forest modeling [90,91] and deep learning methods [92]. These methods can now be used for dose calculation in a clinical workflow as demonstrated recently in four studies [93,94].

For MR-only planning to be implemented, MR images are also required for patient position verification purposes prior to treatment. 3D CBCT based patient treatment positioning has been investigated using manual fiducial marker registration [95] and automatic bone and grey-value registration methods of Elekta's XVI system [96]. Synthetic-CT to CBCT registrations were comparable to planning CT to CBCT registrations (mean differences <1mm) indicating that synthetic-CT datasets can replace CT datasets, for manual or automatic registrations, for patient setup. In total, MRI can be used straight for pre-treatment planning or replanning, without the need for CT scans.

6.3 MRI guided ART in prostate cancer

MR-Linacs allow prostate radiotherapy guidance with MR imaging, identifying the prostate accurately, the tumor and surrounding OARs in real time whilst delivering radiotherapy, with a reduction in radiation exposure. MR-linacs allow hypofractionated stereotactic ART strategies, and address both systematic and random errors. In practice, even if challenging, adaptive re-planning does not need to start completely

from scratch. An initial plan fully optimized from the planning images for the same patient can be adapted to the anatomy of the day thanks to image registration, automatic segmentation and plan optimization algorithms [97]. With online ART, prostate CTV-PTV margins can be reduced to 3 mm. Moreover, the MR-Linac system is designed to be able to track/monitor prostate motion in real-time on 2D (cine) MRI during radiotherapy delivery, allowing further reduction of PTV margins. Indeed, the radiation beam can be paused, via gating, if prostate motion is detected outside a pre-defined range, and can be resumed if the prostate moves back into the range. Assessment of prostate intrafraction motion can be done through automatic fiducial marker tracking on 3D cine-magnetic resonance (MR) images with high spatial and temporal resolution [98]. In total, reduction in PTV margin around 1 to 2 mm should reduce both toxicities and recurrence by allowing a safe escalated dose delivery in the whole prostate or tumor. Furthermore, deformable dose accumulation/monitoring for OARs in MR-guided prostate SBRT appears feasible and accurate [99]. Such dose-guided approach can guide plan adaptation/replanning based on cumulative dose during fractionated treatment, instead of systematic replanning at each fraction. Finally, in a more advanced perspective, MRI sequences could also be used as surrogates of tumour response to adapt the total dose to the tumor response (i.e. dose escalation in the tumor index to non-responders). Longitudinal diffusion MRI analysis (every 2-5 fractions) appears feasible using the 0.35 T ViewRay MRI [100]. The apparent diffusion coefficient values from DWI has been shown to increase after treatment, with the greatest changes seen in patients with better outcomes [101].

Clinical data of MRI-guided ART are limited due to the novelty of the approach, with only two published studies to the best of our knowledge. Preliminary data of 25 prostate cancer patients, undergoing 1.5 T MR-guided adaptive SBRT, reported optimal safety and excellent tolerability, without grade ≥ 3 events [102]. The PTV consisted of CTV + 5mm margins in each direction, except for 3mm posteriorly. Two “adaptive” strategies were used. An “adapt-to-position” modality consists of only modifying the (isocenter) position in the pre-treatment CT, without daily delineation. An “adapt-to-shape” modality consisted in recontouring the daily MRI to adapt the plan of the day. Another phase II

study enrolled 101 patient with T1-3bN0M0 prostate cancer [49]. MRI-guided adaptive SBRT delivered 5 fractions of 7.25 Gy to the target volume using daily plan adaptation with simultaneous relative sparing of the urethra to a dose of 6.5 Gy per fraction. The $PTV_{prostate}$ for treatment was derived after the addition of a 3 mm margin to the CTV, with subtraction of the $PTV_{urethra}$. Before each fraction, a new high-resolution MRI scan was performed and rigidly registered to the simulation MRI scan by aligning on the CTV. A reoptimized plan used the same number and direction of intensity modulated radiation therapy beams as with baseline plan. The maximum cumulative grade ≥ 2 early GU and GI toxicity measured by any symptom at any study time point was 23.8% and 5.0%, respectively. No early grade 3 GI or GU toxicity was observed.

In total, MRI-guided hypofractionated ART appears feasible and safe, in small patient series with short follow-up. Other phase II studies are warranted before proposing cost-effectiveness comparisons in randomized trials.

7. Conclusions

In total, ART is a recent RT strategy aiming to correct for anatomical variations occurring during the treatment course. Improving the tumour targeting while better sparing the OARs allows reducing PTV, and therefore hypofractionated treatments, depending on tumour localization. The clinical expected benefits are to decrease toxicity and to increase local thanks to dose escalation. The ART approach has been based first historically on per-treatment CT scan and/or CBCT images. PET and MRI guided ART open the possibilities to correct for both morphological and functional variations within a dose painting perspective and are also indispensable during many steps of cancer management.. The approach appears particularly indicated in lung, cervix and prostate cancers. PET/MRI guided ART strategies are however currently at the step of feasibility and prospective clinical data are missing. These complex and expensive treatments should not be proposed in routine but in clinical trials comprising strong quality controls.

8. References

- [1] Fan Q, Nanduri A, Mazin S, Zhu L. Emission guided radiation therapy for lung and prostate cancers: a feasibility study on a digital patient. *Med Phys*. 2012;39(11):7140-7152. doi:10.1118/1.4761951
- [2] Hoeben BAW, Bussink J, Troost EGC, Oyen WJG, Kaanders JHAM. Molecular PET imaging for biology-guided adaptive radiotherapy of head and neck cancer. *Acta Oncol* 2013;52:1257–71. <https://doi.org/10.3109/0284186X.2013.812799>.
- [3] Marcu LG, Moghaddasi L, Bezak E. Imaging of Tumor Characteristics and Molecular Pathways With PET: Developments Over the Last Decade Toward Personalized Cancer Therapy. *Int J Radiat Oncol* 2018;102:1165–82. <https://doi.org/10.1016/j.ijrobp.2018.04.055>.
- [4] Mortensen LS, Johansen J, Kallehauge J, Primdahl H, Busk M, Lassen P, et al. FAZA PET/CT hypoxia imaging in patients with squamous cell carcinoma of the head and neck treated with radiotherapy: results from the DAHANCA 24 trial. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2012;105:14–20. <https://doi.org/10.1016/j.radonc.2012.09.015>.
- [5] Komar G, Lehtiö K, Seppänen M, Eskola O, Levola H, Lindholm P, et al. Prognostic value of tumour blood flow, [18F]EF5 and [18F]FDG PET/CT imaging in patients with head and neck cancer treated with radiochemotherapy. *Eur J Nucl Med Mol Imaging* 2014;41:2042–50. <https://doi.org/10.1007/s00259-014-2818-3>.
- [6] Lopci E, Grassi I, Rubello D, Colletti PM, Cambioli S, Gamboni A, et al. Prognostic Evaluation of Disease Outcome in Solid Tumors Investigated With 64Cu-ATSM PET/CT. *Clin Nucl Med* 2016;41:e87-92. <https://doi.org/10.1097/RLU.0000000000001017>.
- [7] Meyer H-J, Gundermann P, Surov A. Associations between FDG-PET and Ki 67-index in head and neck cancer: A meta-analysis. *Medicine (Baltimore)* 2019;98:e17472. <https://doi.org/10.1097/MD.00000000000017472>.

- [8] Quartuccio N, Caobelli F, Di Mauro F, Cammaroto G, Young AIMN Working Group. Non-18F-FDG PET/CT in the management of patients affected by HNC: state-of-the-art. *Nucl Med Commun* 2016;37:891–8. <https://doi.org/10.1097/MNM.0000000000000530>.
- [9] Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16(2):187-199. doi:10.1016/S1470-2045(14)71207-0
- [10] Woodford C, Yartsev S, Dar AR, Bauman G, Van Dyk J. Adaptive radiotherapy planning on decreasing gross tumor volumes as seen on megavoltage computed tomography images. *Int J Radiat Oncol Biol Phys*. 2007;69(4):1316-1322. doi:10.1016/j.ijrobp.2007.07.2369
- [11] Aerts HJ, van Baardwijk AA, Petit SF, Offermann C, van Loon J, Houben R et al. Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy (18)Fluorodeoxyglucose-PET-CT scan. *Radiother Oncol*. 2009;91(3):386-392. doi:10.1016/j.radonc.2009.03.006
- [12] Calais J, Thureau S, Dubray B, Modzelewski R, Thiberville L, Gardin I et al. Areas of high 18F-FDG uptake on preradiotherapy PET/CT identify preferential sites of local relapse after chemoradiotherapy for non-small cell lung cancer. *J Nucl Med*. 2015;56(2):196-203. doi:10.2967/jnumed.114.144253
- [13] Nestle U, Schimek-Jasch T, Kremp S, Schaefer-Schuler A, Mix M, Küsters A et al. Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial. *Lancet Oncol*. 2020;21(4):581-592. doi:10.1016/S1470-2045(20)30013-9
- [14] Feng M, Kong FM, Gross M, Fernando S, Hayman JA, Ten Haken RK. Using fluorodeoxyglucose positron emission tomography to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. *Int J Radiat Oncol Biol Phys*. 2009;73(4):1228-1234. doi:10.1016/j.ijrobp.2008.10.054

- [15] Vera P, Mezzani-Saillard S, Edet-Sanson A, Menard JF, Modzelewski R, Thureau S et al. FDG PET during radiochemotherapy is predictive of outcome at 1 year in non-small-cell lung cancer patients: a prospective multicentre study (RTEP2). *Eur J Nucl Med Mol Imaging*. 2014;41(6):1057-1065. doi:10.1007/s00259-014-2687-9
- [16] Kong FM, Ten Haken RK, Schipper M, Frey KA, Hayman J, Gross M et al. Effect of Midtreatment PET/CT-Adapted Radiation Therapy With Concurrent Chemotherapy in Patients With Locally Advanced Non-Small-Cell Lung Cancer: A Phase 2 Clinical Trial. *JAMA Oncol*. 2017;3(10):1358-1365. doi:10.1001/jamaoncol.2017.0982
- [17] Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging*. 2015;42(2):328-354. doi:10.1007/s00259-014-2961-x
- [18] Thomas HM, Kinahan PE, Samuel JJE, Bowen SR. Impact of tumour motion compensation and delineation methods on FDG PET-based dose painting plan quality for NSCLC radiation therapy. *J Med Imaging Radiat Oncol*. 2018;62(1):81-90. doi:10.1111/1754-9485.12693
- [19] Scarsbrook A, Ward G, Murray P, Goody R, Marshall K, McDermott G, et al. Respiratory-gated (4D) contrast-enhanced FDG PET-CT for radiotherapy planning of lower oesophageal carcinoma: feasibility and impact on planning target volume. *BMC Cancer*. 2017 Oct 4;17(1):671. doi: 10.1186/s12885-017-3659-9. PMID: 28978306; PMCID: PMC5628433.
- [20] Lee E, Zeng J, Miyaoka RS, Saini J, Kinahan PE, Sandison GA, Wong T, et al. Functional lung avoidance and response-adaptive escalation (FLARE) RT: Multimodality plan dosimetry of a precision radiation oncology strategy. *Med Phys*. 2017;44(7):3418-3429. doi:10.1002/mp.12308
- [21] Vera P, Mihailescu SD, Lequesne J, Modzelewski R, Bohn P, Hapdey S et al. Radiotherapy boost in patients with hypoxic lesions identified by 18F-FMISO PET/CT in non-small-cell lung carcinoma: can we expect a better survival outcome without toxicity? [RTEP5 long-term follow-up]. *Eur J Nucl Med Mol Imaging*. 2019;46(7):1448-1456. doi:10.1007/s00259-019-04285-9

- [22] Thureau S, Modzelewski R, Bohn P, Hapdey S, Gouel P, Dubray B et al. Comparison of Hypermetabolic and Hypoxic Volumes Delineated on [18F]FDG and [18F]Fluoromisonidazole PET/CT in Non-small-cell Lung Cancer Patients. *Mol Imaging Biol*. 2020;22(3):764-771. doi:10.1007/s11307-019-01422-6
- [23] Vera P, Bohn P, Edet-Sanson A, Salles , Hapdey S Gardin I et al. Simultaneous positron emission tomography (PET) assessment of metabolism with ¹⁸F-fluoro-2-deoxy-d-glucose (FDG), proliferation with ¹⁸F-fluoro-thymidine (FLT), and hypoxia with ¹⁸fluoro-misonidazole (F-miso) before and during radiotherapy in patients with non-small-cell lung cancer (NSCLC): a pilot study. *Radiother Oncol*. 2011;98(1):109-116. doi:10.1016/j.radonc.2010.10.011
- [24] Kang F, Wang Z, Li G, Wang S, Liu D, Zhang M et al. Inter-heterogeneity and intra-heterogeneity of $\alpha\beta3$ in non-small cell lung cancer and small cell lung cancer patients as revealed by ⁶⁸Ga-RGD2 PET imaging. *Eur J Nucl Med Mol Imaging*. 2017;44(9):1520-1528. doi:10.1007/s00259-017-3696-2
- [25] O'Connor JPB, Robinson SP, Waterton JC. Imaging tumour hypoxia with oxygen-enhanced MRI and BOLD MRI. *Br J Radiol*. 2019;92(1095):20180642. doi:10.1259/bjr.20180642
- [26] Kumar S, Liney G, Rai R, Holloway L, Moses D, Vinod SK. Magnetic resonance imaging in lung: a review of its potential for radiotherapy. *Br J Radiol*. 2016;89(1060):20150431. doi:10.1259/bjr.20150431
- [27] Gensheimer MF, Le Q-T. ART for head and neck cancer: Are we ready to put it into routine clinical practice? *Oral Oncol* 2018;86:19–24. <https://doi.org/10.1016/j.oraloncology.2018.08.010>.
- [28] Pugachev A, Ruan S, Carlin S, Larson SM, Campa J, Ling CC, et al. Dependence of FDG uptake on tumor microenvironment. *Int J Radiat Oncol* 2005;62:545–53. <https://doi.org/10.1016/j.ijrobp.2005.02.009>.
- [29] Schwartz DL, Harris J, Yao M, Rosenthal DI, Opanowski A, Levering A, et al. Metabolic tumor volume as a prognostic imaging-based biomarker for head-and-neck

cancer: pilot results from Radiation Therapy Oncology Group protocol 0522. *Int J Radiat Oncol Biol Phys* 2015;91:721–9. <https://doi.org/10.1016/j.ijrobp.2014.12.023>.

[30] Mohamed ASR, Cardenas CE, Garden AS, Awan MJ, Rock CD, Westergaard SA, et al. Patterns-of-failure guided biological target volume definition for head and neck cancer patients: FDG-PET and dosimetric analysis of dose escalation candidate subregions. *Radiother Oncol* 2017;124:248–55. <https://doi.org/10.1016/j.radonc.2017.07.017>.

[31] Rasmussen JH, Håkansson K, Vogelius IR, Aznar MC, Fischer BM, Friborg J, et al. Phase I trial of ¹⁸F-Fludeoxyglucose based radiation dose painting with concomitant cisplatin in head and neck cancer. *Radiother Oncol* 2016;120:76–80. <https://doi.org/10.1016/j.radonc.2016.03.005>.

[32] Beaumont J, Acosta O, Devillers A, Palard-Novello X, Chajon E, de Crevoisier R, et al. Voxel-based identification of local recurrence sub-regions from pre-treatment PET/CT for locally advanced head and neck cancers. *EJNMMI Res* 2019;9:90. <https://doi.org/10.1186/s13550-019-0556-z>.

[33] Min M, Lin P, Lee M, Shon IH, Lin M, Forstner D, et al. ¹⁸F-FDG PET-CT performed before and during radiation therapy of head and neck squamous cell carcinoma: Are they independent or complementary to each other? *J Med Imaging Radiat Oncol* 2016;60:433–40. <https://doi.org/10.1111/1754-9485.12439>.

[34] Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. *Lancet Oncol* 2005;6:112–7. [https://doi.org/10.1016/S1470-2045\(05\)01737-7](https://doi.org/10.1016/S1470-2045(05)01737-7).

[35] Madani I, Duprez F, Boterberg T, Van de Wiele C, Bonte K, Deron P, et al. Maximum tolerated dose in a phase I trial on adaptive dose painting by numbers for head and neck cancer. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2011;101:351–5. <https://doi.org/10.1016/j.radonc.2011.06.020>.

[36] Berwouts D, Olteanu LAM, Duprez F, Vercauteren T, De Gersem W, De Neve W, et al. Three-phase adaptive dose-painting-by-numbers for head-and-neck cancer: initial results of the phase I clinical trial. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2013;107:310–6. <https://doi.org/10.1016/j.radonc.2013.04.002>.

- [37] Berwouts D, Madani I, Duprez F, Olteanu AL, Vercauteren T, Boterberg T, et al. Long-term outcome of 18F-fluorodeoxyglucose-positron emission tomography-guided dose painting for head and neck cancer: Matched case-control study. *Head Neck* 2017;39:2264–75. <https://doi.org/10.1002/hed.24892>.
- [38] Adaptive Radiation Treatment for Head and Neck Cancer - Full Text View - ClinicalTrials.gov 2020. <https://clinicaltrials.gov/ct2/show/NCT01504815> (accessed April 26, 2020).
- [39] Rischin D, Hicks RJ, Fisher R, Binns D, Corry J, Porceddu S, et al. Prognostic significance of [18F]-misonidazole positron emission tomography-detected tumor hypoxia in patients with advanced head and neck cancer randomly assigned to chemoradiation with or without tirapazamine: a substudy of Trans-Tasman Radiation Oncology Group Study 98.02. *J Clin Oncol Off J Am Soc Clin Oncol* 2006;24:2098–104. <https://doi.org/10.1200/JCO.2005.05.2878>.
- [40] Bollineni VR, Koole MJB, Pruim J, Brouwer CL, Wiegman EM, Groen HJM, et al. Dynamics of tumor hypoxia assessed by 18F-FAZA PET/CT in head and neck and lung cancer patients during chemoradiation: Possible implications for radiotherapy treatment planning strategies. *Radiother Oncol* 2014;113:198–203. <https://doi.org/10.1016/j.radonc.2014.10.010>.
- [41] Thorwarth D, Eschmann S-M, Paulsen F, Alber M. Hypoxia dose painting by numbers: a planning study. *Int J Radiat Oncol Biol Phys* 2007;68:291–300. <https://doi.org/10.1016/j.ijrobp.2006.11.061>.
- [42] Lee N, Schoder H, Beattie B, Lanning R, Riaz N, McBride S, et al. Strategy of Using Intratreatment Hypoxia Imaging to Selectively and Safely Guide Radiation Dose De-escalation Concurrent With Chemotherapy for Locoregionally Advanced Human Papillomavirus-Related Oropharyngeal Carcinoma. *Int J Radiat Oncol Biol Phys* 2016;96:9–17. <https://doi.org/10.1016/j.ijrobp.2016.04.027>.
- [43] Li C, Zhang X, Pang L, Huang Y, Gao Y, Sun X, et al. Spatial Concordance of Tumor Proliferation and Accelerated Repopulation from Pathologic Images to 3'-[18F]Fluoro-3'-Deoxythymidine PET Images: a Basic Study Guided for PET-Based

Radiotherapy Dose Painting. *Mol Imaging Biol* 2019;21:713–21. <https://doi.org/10.1007/s11307-018-1292-x>.

[44] Hoshikawa H, Mori T, Yamamoto Y, Kishino T, Fukumura T, Samukawa Y, et al. Prognostic value comparison between (18)F-FLT PET/CT and (18)F-FDG PET/CT volume-based metabolic parameters in patients with head and neck cancer. *Clin Nucl Med* 2015;40:464–8. <https://doi.org/10.1097/RLU.0000000000000652>.

[45] Marcu LG, Moghaddasi L, Bezak E. Imaging of Tumor Characteristics and Molecular Pathways With PET: Developments Over the Last Decade Toward Personalized Cancer Therapy. *Int J Radiat Oncol* 2018;102:1165–82. <https://doi.org/10.1016/j.ijrobp.2018.04.055>.

[46] Verhoeff SR, Heuvel MM van den, Herpen CML van, Piet B, Aarntzen EHJG, Heskamp S. Programmed Cell Death-1/Ligand-1 PET Imaging: A Novel Tool to Optimize Immunotherapy? *PET Clin* 2020;15:35–43. <https://doi.org/10.1016/j.cpet.2019.08.008>

[47] Mena E, Thippsandra S, Yanamadala A, Redy S, Pattanayak P, Subramaniam RM. Molecular Imaging and Precision Medicine in Head and Neck Cancer. *PET Clin* 2017;12:7–25. <https://doi.org/10.1016/j.cpet.2016.08.009>.

[48] Garibaldi C, Ronchi S, Cremonesi M, Gilardi L, Travaini L, Ferrari M, et al. Interim 18F-FDG PET/CT During Chemoradiation Therapy in the Management of Head and Neck Cancer Patients: A Systematic Review. *Int J Radiat Oncol* 2017;98:555–73. <https://doi.org/10.1016/j.ijrobp.2017.02.217>.

[49] Martens RM, Noij DP, Ali M, Koopman T, Marcus JT, Vergeer MR, et al. Functional imaging early during (chemo)radiotherapy for response prediction in head and neck squamous cell carcinoma; a systematic review. *Oral Oncol* 2019;88:75–83. <https://doi.org/10.1016/j.oraloncology.2018.11.005>.

[50] Subesinghe M, Scarsbrook AF, Sourbron S, Wilson DJ, McDermott G, Speight R, et al. Alterations in anatomic and functional imaging parameters with repeated FDG PET-CT and MRI during radiotherapy for head and neck cancer: a pilot study. *BMC Cancer* 2015;15:137. <https://doi.org/10.1186/s12885-015-1154-8>.

- [51] Hentschel M, Appold S, Schreiber A, Abramyuk A, Abolmaali N, Kotzerke J, et al. Serial FDG-PET on patients with head and neck cancer: Implications for radiation therapy. *Int J Radiat Biol* 2009;85:796–804. <https://doi.org/10.1080/09553000903039180>.
- [52] Geets X, Lee JA, Bol A, Lonneux M, Grégoire V. A gradient-based method for segmenting FDG-PET images: methodology and validation. *Eur J Nucl Med Mol Imaging* 2007;34:1427–38. <https://doi.org/10.1007/s00259-006-0363-4>.
- [53] Wong KH, Panek R, Bhide SA, Nutting CM, Harrington KJ, Newbold KL. The emerging potential of magnetic resonance imaging in personalizing radiotherapy for head and neck cancer: an oncologist's perspective. *Br J Radiol* 2017;90:20160768. <https://doi.org/10.1259/bjr.20160768>.
- [54] Qi M, Li Y, Wu A, Jia Q, Li B, Sun W, et al. Multi-sequence MR image-based synthetic CT generation using a generative adversarial network for head and neck MRI-only radiotherapy. *Med Phys* 2020. <https://doi.org/10.1002/mp.14075>.
- [55] Chen AM, Hsu S, Lamb J, Yang Y, Agazaryan N, Steinberg ML, et al. MRI-guided radiotherapy for head and neck cancer: initial clinical experience. *Clin Transl Oncol* 2017. <https://doi.org/10.1007/s12094-017-1704-4>.
- [56] Raghavan G, Kishan AU, Cao M, Chen AM. Anatomic and dosimetric changes in patients with head and neck cancer treated with an integrated MRI-tri- 60 Co teletherapy device. *Br J Radiol* 2016;89:20160624. <https://doi.org/10.1259/bjr.20160624>.
- [57] Leibfarth S, Winter RM, Lyng H, Zips D, Thorwarth D. Potentials and challenges of diffusion-weighted magnetic resonance imaging in radiotherapy. *Clin Transl Radiat Oncol* 2018;13:29–37. <https://doi.org/10.1016/j.ctro.2018.09.002>.
- [58] Wong KH, Panek R, Dunlop A, Mcquaid D, Riddell A, Welsh LC, et al. Changes in multimodality functional imaging parameters early during chemoradiation predict treatment response in patients with locally advanced head and neck cancer. *Eur J Nucl Med Mol Imaging* 2018;45:759–67. <https://doi.org/10.1007/s00259-017-3890-2>.

- [59] Teng F, Aryal M, Lee J, Lee C, Shen X, Hawkins PG, et al. Adaptive Boost Target Definition in High-Risk Head and Neck Cancer Based on Multi-imaging Risk Biomarkers. *Int J Radiat Oncol* 2018;102:969–77. <https://doi.org/10.1016/j.ijrobp.2017.12.269>.
- [60] Houweling AC, Wolf AL, Vogel WV, Hamming-Vrieze O, van Vliet-Vroegindeweij C, van de Kamer JB, et al. FDG-PET and diffusion-weighted MRI in head-and-neck cancer patients: Implications for dose painting. *Radiother Oncol* 2013;106:250–4. <https://doi.org/10.1016/j.radonc.2013.01.003>.
- [61] Briens A, Castelli J, Barateau A, Jaksic N, Gnep K, Simon A, et al. [ART: Strategies and benefits depending on tumor localization]. *Cancer Radiother J Soc Francaise Radiother Oncol* 2019;23:592–608. <https://doi.org/10.1016/j.canrad.2019.07.135>.
- [62] Gandy N, Arshad MA, Park W-HE, Rockall AG, Barwick TD. FDG-PET Imaging in Cervical Cancer. *Semin Nucl Med* 2019;49:461–70. <https://doi.org/10.1053/j.semnuclmed.2019.06.007>.
- [63] Lucia F, Visvikis D, Desseroit M-C, Miranda O, Malhaire J-P, Robin P, et al. Prediction of outcome using pretreatment 18 F-FDG PET/CT and MRI radiomics in locally advanced cervical cancer treated with chemoradiotherapy. *Eur J Nucl Med Mol Imaging* 2018;45:768–86. <https://doi.org/10.1007/s00259-017-3898-7>.
- [64] Bjurberg M, Kjellén E, Ohlsson T, Bendahl P-O, Brun E. Prediction of Patient Outcome With 2-Deoxy-2-[18F]fluoro-D-Glucose-Positron Emission Tomography Early During Radiotherapy for Locally Advanced Cervical Cancer. *Int J Gynecol Cancer* 2009;19. <https://doi.org/10.1111/IGC.0b013e3181c00359>.
- [65] Carpenter DJ, Jacobs CD, Wong TZ, Craciunescu O, Chino JP. Changes on Midchemoradiation Therapy Fluorodeoxyglucose Positron Emission Tomography for Cervical Cancer Are Associated with Prognosis. *Int J Radiat Oncol Bull Biol Bull Phys* 2019;105:356–66. <https://doi.org/10.1016/j.ijrobp.2019.06.2506>.

- [66] Khili S, Muratet J-P, Roche S, Pointreau Y, Yossi S, Septans A-L, et al. Use of Metabolic Parameters as Prognostic Factors During Concomitant Chemoradiotherapy for Locally Advanced Cervical Cancer. *Am J Clin Oncol* 2017;40:250–5. <https://doi.org/10.1097/COC.0000000000000159>.
- [67] Leseur J, Roman-Jimenez G, Devillers A, Ospina-Arango JD, Williaume D, Castelli J, et al. Pre- and per-treatment 18F-FDG PET/CT parameters to predict recurrence and survival in cervical cancer. *Radiother Oncol* 2016;120:512–8. <https://doi.org/10.1016/j.radonc.2016.08.008>.
- [68] Kidd EA, Thomas M, Siegel BA, Dehdashti F, Grigsby PW. Changes in Cervical Cancer FDG Uptake During Chemoradiation and Association With Response. *Int J Radiat Oncol* 2013;85:116–22. <https://doi.org/10.1016/j.ijrobp.2012.02.056>.
- [69] Cree A, Livsey J, Barraclough L, Dubec M, Hambrock T, Van Herk M, et al. The Potential Value of MRI in External-Beam Radiotherapy for Cervical Cancer. *Clin Oncol* 2018;30:737–50. <https://doi.org/10.1016/j.clon.2018.08.002>.
- [70] Dimopoulos JCA, Petrow P, Tanderup K, Petric P, Berger D, Kirisits C, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy. *Radiother Oncol* 2012;103:113–22. <https://doi.org/10.1016/j.radonc.2011.12.024>.
- [71] Oh S, Stewart J, Moseley J, Kelly V, Lim K, Xie J, et al. Hybrid ART with on-line MRI in cervix cancer IMRT. *Radiother Oncol* 2014;110:323–8. <https://doi.org/10.1016/j.radonc.2013.11.006>.
- [72] Kerkhof EM, Raaymakers BW, van der Heide UA, van de Bunt L, Jürgenliemk-Schulz IM, Lagendijk JJW. Online MRI guidance for healthy tissue sparing in patients with cervical cancer: An IMRT planning study. *Radiother Oncol* 2008;88:241–9. <https://doi.org/10.1016/j.radonc.2008.04.009>.
- [73] Maspero M, Savenije MHF, Dinkla AM, Seevinck PR, Intven MPW, Jürgenliemk-Schulz IM, et al. Dose evaluation of fast synthetic-CT generation using a generative adversarial network for general pelvis MR-only radiotherapy. *Phys Med Biol* 2018;63:185001. <https://doi.org/10.1088/1361-6560/aada6d>.

- [74] Mayr NA, Huang Z, Wang JZ, Lo SS, Fan JM, Grecula JC, et al. Characterizing Tumor Heterogeneity With Functional Imaging and Quantifying High-Risk Tumor Volume for Early Prediction of Treatment Outcome: Cervical Cancer as a Model. *Int J Radiat Oncol* 2012;83:972–9. <https://doi.org/10.1016/j.ijrobp.2011.08.011>.
- [75] Hameeduddin A, Sahdev A. Diffusion-weighted imaging and dynamic contrast-enhanced MRI in assessing response and recurrent disease in gynaecological malignancies. *Cancer Imaging* 2015;15. <https://doi.org/10.1186/s40644-015-0037-1>.
- [76] Hoskin PJ. Hypoxia dose painting in prostate and cervix cancer. *Acta Oncol* 2015;54:1259–62. <https://doi.org/10.3109/0284186X.2015.1061692>.
- [77] Mayyas E, Kim J, Kumar S, Liu C, Wen N, Movsas B, et al. A novel approach for evaluation of prostate deformation and associated dosimetric implications in IGRT of the prostate. *Medical physics* 2014;41:091709.
- [78] King BL, Butler WM, Merrick GS, Kurko BS, Reed JL, Murray BC, et al. Electromagnetic transponders indicate prostate size increase followed by decrease during the course of external beam radiation therapy. *International journal of radiation oncology, biology, physics* 2011;79:1350-1357.
- [79] Gunnlaugsson A, Kjellen E, Hagberg O, Thellenberg-Karlsson C, Widmark A Nilsson P. Change in prostate volume during extreme hypo-fractionation analysed with MRI. *Radiat Oncol* 2014;9:22.
- [80] Nassef M, Simon A, Cazoulat G, Dumenil A, Blay C, Lafond C, et al. Quantification of dose uncertainties in cumulated dose estimation compared to planned dose in prostate IMRT. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2016;119:129-136.
- [81] Christie DRH Sharpley CF. How Accurately Can Prostate Gland Imaging Measure the Prostate Gland Volume? Results of a Systematic Review. *Prostate cancer* 2019;2019:6932572.
- [82] Pathmanathan AU, McNair HA, Schmidt MA, Brand DH, Delacroix L, Eccles CL, et al. Comparison of prostate delineation on multimodality imaging for MR-guided radiotherapy. *The British journal of radiology* 2019;20180948.
- [83] Edmund JM Nyholm T. A review of substitute CT generation for MRI-only radiation therapy. *Radiat Oncol* 2017;12:28.
- [84] Johnstone E, Wyatt JJ, Henry AM, Short SC, Sebag-Montefiore D, Murray L, et al. Systematic Review of Synthetic Computed Tomography Generation Methodologies

for Use in Magnetic Resonance Imaging-Only Radiation Therapy. International journal of radiation oncology, biology, physics 2018;100:199-217.

[85] Lambert J, Greer PB, Menk F, Patterson J, Parker J, Dahl K, et al. MRI-guided prostate radiation therapy planning: Investigation of dosimetric accuracy of MRI-based dose planning. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2011;98:330-334.

[86] Chin AL, Lin A, Anamalayil S Teo BK. Feasibility and limitations of bulk density assignment in MRI for head and neck IMRT treatment planning. Journal of applied clinical medical physics / American College of Medical Physics 2014;15:4851.

[87] Gudur MS, Hara W, Le QT, Wang L, Xing L Li R. A unifying probabilistic Bayesian approach to derive electron density from MRI for radiation therapy treatment planning. Physics in medicine and biology 2014;59:6595-6606.

[88] Guerreiro F, Burgos N, Dunlop A, Wong K, Petkar I, Nutting C, et al. Evaluation of a multi-atlas CT synthesis approach for MRI-only radiotherapy treatment planning. Phys Med 2017;35:7-17.

[89] Persson E, Gustafsson C, Nordstrom F, Sohlén M, Gunnlaugsson A, Petruson K, et al. MR-OPERA: A Multicenter/Multivendor Validation of Magnetic Resonance Imaging-Only Prostate Treatment Planning Using Synthetic Computed Tomography Images. International journal of radiation oncology, biology, physics 2017;99:692-700.

[90] Aouadi S, Vasic A, Paloor S, Torfeh T, McGarry M, Petric P, et al. Generation of synthetic CT using multi-scale and dual-contrast patches for brain MRI-only external beam radiotherapy. Phys Med 2017;42:174-184.

[91] Largent A, Barateau A, Nunes JC, Lafond C, Greer PB, Dowling JA, et al. Pseudo-CT Generation for MRI-Only Radiation Therapy Treatment Planning: Comparison Among Patch-Based, Atlas-Based, and Bulk Density Methods. International journal of radiation oncology, biology, physics 2019;103:479-490.

[92] Largent A, Barateau A, Nunes JC, Mylona E, Castelli J, Lafond C, et al. Comparison of Deep Learning-Based and Patch-Based Methods for Pseudo-CT Generation in MRI-Based Prostate Dose Planning. International journal of radiation oncology, biology, physics 2019;105:1137-1150.

[93] Tenhunen M, Korhonen J, Kapanen M, Seppala T, Koivula L, Collan J, et al. MRI-only based radiation therapy of prostate cancer: workflow and early clinical experience. Acta Oncol 2018;57:902-907.

[94] Kerkmeijer LGW, Maspero M, Meijer GJ, van der Voort van Zyp JRN, de Boer HCJ van den Berg CAT. Magnetic Resonance Imaging only Workflow for Radiotherapy Simulation and Planning in Prostate Cancer. Clin Oncol (R Coll Radiol) 2018;30:692-701.

- [95] Tyagi N, Fontenla S, Zhang J, Cloutier M, Kadbi M, Mechalakos J, et al. Dosimetric and workflow evaluation of first commercial synthetic CT software for clinical use in pelvis. *Physics in medicine and biology* 2017;62:2961-2975.
- [96] Korhonen J, Kapanen M, Sonke JJ, Wee L, Salli E, Keyrilainen J, et al. Feasibility of MRI-based reference images for image-guided radiotherapy of the pelvis with either cone-beam computed tomography or planar localization images. *Acta Oncol* 2015;54:889-895.
- [97] Pathmanathan AU, van As NJ, Kerkmeijer LGW, Christodouleas J, Lawton CAF, Vesprini D, et al. Magnetic Resonance Imaging-Guided Adaptive Radiation Therapy: A "Game Changer" for Prostate Treatment? *International journal of radiation oncology, biology, physics* 2018;100:361-373.
- [98] de Muinck Keizer DM, Kerkmeijer LGW, Maspero M, Andreychenko A, van der Voort van Zyp JRN, van den Berg CAT, et al. Soft-tissue prostate intrafraction motion tracking in 3D cine-MR for MR-guided radiotherapy. *Physics in medicine and biology* 2019;64:235008.
- [99] Bohoudi O, Lagerwaard FJ, Bruynzeel AME, Niebuhr NI, Johnen W, Senan S, et al. End-to-end empirical validation of dose accumulation in MRI-guided ART for prostate cancer using an anthropomorphic deformable pelvis phantom. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2019;141:200-207.
- [100] Yang Y, Cao M, Sheng K, Gao Y, Chen A, Kamrava M, et al. Longitudinal diffusion MRI for treatment response assessment: Preliminary experience using an MRI-guided tri-cobalt 60 radiotherapy system. *Medical physics* 2016;43:1369-1373.
- [101] Decker G, Murtz P, Gieseke J, Traber F, Block W, Sprinkart AM, et al. Intensity-modulated radiotherapy of the prostate: dynamic ADC monitoring by DWI at 3.0 T. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2014;113:115-120.
- [102] Alongi F, Rigo M, Figlia V, Cuccia F, Giaj-Levra N, Nicosia L, et al. 1.5 T MR-guided and daily adapted SBRT for prostate cancer: feasibility, preliminary clinical tolerability, quality of life and patient-reported outcomes during treatment. *Radiat Oncol* 2020;15:69.

Ways of actions of the tracers	Tracers	Use
Carbohydrate metabolism tracer	¹⁸ F-FDG, ¹¹ C-Glucose, ¹⁸ F-FDM...	Therapeutic evaluation and extension of many cancers Also used outside oncology: neurodegenerative pathologies, inflammatory and infectious pathologies...
Membrane renewal tracers	¹⁸ F-Choline, ¹¹ C-Choline	Prostatic cancer
Specific membrane tracers	⁶⁸ Ga-PSMA	
Somatostatin receptor tracers	⁶⁸ Ga-DOTA-TOC (–TATE / –NOC)	Neuroendocrine tumors
Amino acid tracers	¹⁸ F-FET ¹¹ C-Méthionine	Essentially glioblastoma
Synthesis of neurotransmitters and hormones	¹⁸ F-DOPA	Brain tumours, medullary thyroid carcinoma, Also used outside cancerology: Neurodegenerative pathologies (Parkinson's disease; Lewy body dementia...)
Nucleic acid tracers	¹⁸ F-FLT	Head and neck cancer, esophageal cancer, lung cancer, brain tumours
Bone metabolism	¹⁸ FNa	Bone metastasis
Hypoxia	¹⁸ F-MISO, ¹⁸ F-FAZA, ...	Head and neck cancer, lung cancer, brain tumours
Hormone tracers	¹⁸ -FES ¹⁸ F-FDHT	Breast Prostate

Tableau 1 : Principales indications de la TEP selon le type de traceurs utilisés.

Table 1 : Main indications of PET by type of tracers used

Tableau 2 : Rôle de la TEP selon le type lésions et le type de traceurs (en gras, les indications recommandées)

Table 2 : Role of PET by lesion type and tracer type (in boldface, recommended indications)

Localisations	Tracers	Utility in radiotherapy
Lung Cancer	FDG	<ul style="list-style-type: none"> - Staging of locally advanced cancers (metastatic and lymph node involvement) - Delineation (including atelectasis exclusion and mediastinal targets) - Adaptive radiotherapy - Assessment of response to treatment - Definition of areas at risk of recurrence / Dose painting
	FMISO, FAZA	<ul style="list-style-type: none"> - Definition of Poor Prognosis Patients - Definition of areas at risk of recurrence / Dose painting
Head and neck cancer	FDG	<ul style="list-style-type: none"> - Staging of locally advanced cancers (metastatic and lymph node involvement) - Search for a primitive lesion in case of adenopathies without primitive lesion - Delineation - Adaptive radiotherapy - Assessment of response to treatment - Definition of areas at risk of recurrence
	FMISO, FAZA, Cu-ATSM	<ul style="list-style-type: none"> - Definition of Poor Prognosis Patients - Definition of areas at risk of recidivism - Adaptive radiotherapy
Cervical cancer	FDG	<ul style="list-style-type: none"> - Staging of locally advanced cancers - Adaptive radiotherapy - Assessment of response to treatment
	FMISO, FAZA	<ul style="list-style-type: none"> - Definition of Poor Prognosis Patients - Definition of areas at risk of recurrence / Dose painting
Prostatic cancer	Choline, PMSA	<ul style="list-style-type: none"> - Staging in case of biological recurrence - Dose painting
	FMISO	<ul style="list-style-type: none"> - Dose painting