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Positron-emission tomography-guided radiation therapy: ongoing projects

and future hopes

Radiothérapie guidée par la tomographie par émission de positrons : projets actuels et espoirs futurs

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Radiothérapie ; Oncologie clinique ; Imagerie fonctionnelle ; Radiothérapie guidée par l'image

Abstract

Radiation therapy has undergone significant advances these last decades, particularly thanks to technical improvements, computer science and a better ability to define the target volumes via morphological and functional imaging breakthroughs. Imaging contributes to all three stages of patient care in radiation oncology: before, during and after treatment. Before the treatment, the choice of optimal imaging type and, if necessary, the adequate functional tracer will allow a better definition of the volume target. During radiation therapy, image-guidance aims at locating the tumour target and tailoring the volume target to anatomical and tumoral variations. Imaging systems are now integrated with conventional accelerators, and newer accelerators have techniques allowing tumour tracking during the irradiation. More recently, MRI-guided systems have been developed, and are already

active in a few French centres. Finally, after radiotherapy, imaging plays a major role in most patients' monitoring, and must take into account post-radiation tissue modification specificities. In this review, we will focus on the ongoing projects of nuclear imaging in oncology, and how they can help the radiation oncologist to better treat patients. To this end, a literature review including the terms « Radiotherapy », « Radiation Oncology » and « PET-CT » was performed in August 2019 on Medline and ClinicalTrials.gov. We chose to review successively these novelties organ-by-organ, focusing on the most promising advances. As a conclusion, the help of modern functional imaging thanks to a better definition and new specific radiopharmaceuticals tracers could allow even more precise treatments and enhanced surveillance. Finally, it could provide determinant information to artificial intelligence algorithms in "-omics" models.

Résumé

La radiothérapie a connu des avancées significatives ces dernières décennies, liées notamment aux améliorations techniques, à l'informatique et à une meilleure capacité à définir les volumes cibles grâce aux progrès en imagerie morphologique et fonctionnelle. L'imagerie est essentielle aux trois temps du traitement de radiothérapie i.e. avant, pendant et après le traitement du patient. Avant l'irradiation, le choix du bon type d'imagerie ainsi que, le cas échéant, du radiotraceur optimal, permettront une meilleure définition du volume. Au cours de la radiothérapie le guidage par l'image a pour but de localiser la cible tumorale et d'adapter le volume à traiter aux variations anatomiques et tumorales en cours de traitement. Ces systèmes d'imagerie s'intègrent désormais aux accélérateurs classiques, et les nouveaux accélérateurs possèdent des techniques permettant de suivre la tumeur pendant l'irradiation. Plus récemment, des accélérateurs avec IRM embarquée ont été développés, et sont déjà actifs dans quelques centres français. Enfin, après la radiothérapie, l'imagerie joue un rôle majeur dans le suivi de nombreuses pathologies cancéreuses, et doit prendre en compte les spécificités des tissus après irradiation. Dans cette revue, nous nous concentrerons sur les projets actuels de l'imagerie nucléaire en oncologie et la manière dont ils peuvent aider le radiothérapeute à mieux traiter ses patients. Dans cette optique, une revue de la littérature incluant les termes "Radiotherapy", "Radiation Oncology" et "PET-CT" a été réalisée en août 2019 sur Medline et ClinicalTrials.gov. Nous avons choisi d'aborder successivement ces nouveautés organe par organe, en nous concentrant sur les avancées les plus prometteuses. En conclusion, l'apport de l'imagerie fonctionnelle moderne, via une meilleure définition et le développement de nouveaux traceurs radiopharmaceutiques spécifiques, pourrait permettre des traitements encore plus précis ainsi qu'une surveillance améliorée. Enfin, elle pourrait fournir des informations déterminantes aux algorithmes d'intelligence artificielle des modèles « -omiques ».

1. Introduction

Radiation oncology, which uses ionizing radiations to treat cancer, is a mixed discipline on the border between clinical and technical features, and has benefited from the forefront of advances in medical imaging which helped shaping modern radiotherapy.

With the appearance and development of linear accelerators, the notion of dose calculation and treatment planning emerged, leading eventually to computer-based dose calculation rapidly evolving through the last decades. Three-dimensional dose calculation on computerized tomography (CT) scans allowed advanced radiotherapy: more accurate dose distribution, dose optimization, more precise visualization of tumour targets and organs at risk, as well as better patient positioning control. These were the necessary elements that allowed the development of techniques that aim to better conform the irradiation: intensity-modulated radiotherapy (IMRT), volumetric modulated arctherapy, image-guided radiotherapy, etc. [1]. The availability of ultraprecise imaging is also a mandatory requirement, along with rigorous systems of radiation focalization, for stereotactic body radiotherapy which can deliver very high doses in small volumes.

Currently, radiotherapy planning is completely computerized. The combination of modern conformation techniques and ultra-qualitative imaging modalities allows treatment accuracy of the order of a few millimetres. Improvements can still be made in the definition of target volumes which is sometimes difficult on CT alone, as some specific CT limitations exist, for instance suboptimal tissue contrast and subpar definition for certain areas of the body and lack of functional information. To this end, radiation oncologists often fuse pretherapeutic magnetic resonance imaging (MRI) and positronemission tomography (PET) sequences with the dosimetric scanner to better define the volumes. CT remains compulsory, mainly because it allows physicists to identify mass attenuation or attenuation characteristics which are critical parameters for precise dose calculation.

PET/CT can provide additional information, by allowing the identification of abnormal metabolic areas, guiding delineation and possibly dose escalation to these areas ("dose-painting") [2-3]. While (¹⁸F)-fluorodeoxyglucose (FDG) remains the most commonly used tracer, new radiopharmaceutical tracers are being evaluated for a range of diseases, aiming to be more informative, sensitive and/or specific.

In this article, we will successively review recent advances and ongoing trials combining PET-CT and radiation therapy, following an organ-after-organ pattern. For each organ we will review the pretherapeutic, pertherapeutic and/or post-therapeutic hopes of future progress in the field of nuclear medicine applied to Radiat Oncol This review was made after an extensive research conducted in August 2019 on Medline and ClinicalTrials.gov. The terms « Radiotherapy », « Radiation Oncology » and « PET-CT » were included. Articles and ongoing trials were then chosen for their relevance to the subject.

2. Brain malignancies: pretherapeutic imaging

For most brain tumours, radiation treatment is guided by MRI acquisition fused to the dosimetric scan. FDG PET/CT are rarely useful, because of the vivid physiological glucose metabolism uptake of brain cells. Functional imaging using (¹⁸F)-L-dihydroxyphenylalanine ([¹⁸F]-dopa) is being tested in a Mayo Clinic pilot study (NCT02104310) to treat gliomas. Indeed, tumour delineation is a difficult task in regions beyond areas of contrast enhancement where infiltrative disease can extend, due to the non-specific nature of T2 signal abnormalities, which can also include gliosis and peritumoral oedema [4]. (¹⁸F)-dopa has shown promising results in being able to better distinguish tumour from normal brain tissue, as well as discriminating tumour recurrence and radiation-induced changes. It could also assist the radiation oncologist in identifying the most aggressive regions of the tumour possibly leading to dose escalation of these areas [5].

3. Head and neck malignancies

3.1. Pretherapeutic imaging

Technological developments, in particular intensity-modulated radiotherapy, have paved the way to innovative therapeutic prospects and functional organs preservation for head and neck malignancies [6-8]. Innovations in nuclear medicine contribute to these therapeutic changes, especially as guidance on metabolic areas available to potential dose escalation. For instance, the RADPAINT trial (NCT03847480) investigates the safety of FDG PET/CT-guided radiotherapy using a volumetric modulated arctherapy simultaneous integrated boost plan with a maximum point dose of 83Gy (73Gy and 78Gy minimum doses to two PET-guided gross tumour volumes inside the conventional 68Gy gross tumour volume). The investigators expect to keep the level of side effects on the normal tissue within the level of conventional radiotherapy. Having the same purpose, UPGRADE-RT (NCT02442375) is a phase III trial that has been opened since June 2016 which questions whether deescalation of radiation doses guided by PET/CT with dose reduction to the elective neck (35Gy versus 45Gy) and 60Gy intermediate dose levels can safely be used for newly diagnosed stage T2-4 N0-2 M0 squamous cell carcinomas of the oropharynx, hypopharynx or larynx without compromising the efficacy [9]. The RIDPAINT trial (NCT02921581) explores dose-painting methods when reirradiation (relapse or second head and neck cancer) is needed. For concomitant chemoradiotherapy, the ARTFORCE phase III trial (NCT01504815) aims to explore the impact of PET information for adaptive high dose radiotherapy (up to 84Gy maximum in 7 weeks on 50% uptake gross tumour volume) compared to conventional 70Gy in 7 weeks (with concomitant cisplatin in both cases) on locoregional, recurrence-free survival and toxicity for patients with locally advanced HNSCC. This study is estimated to be fulfilled by September 2021 [10]. Finally, TRIMODAL (NCT03897166) is a French trial using a combination of pretherapeutic FDG PET, MRI and CT imaging for 60 patients

with head and neck cancers to test a synergistic effect of these modalities to gross tumour volume delineation and to explore anthropometric and radiomic parameters.

3.2. Pertherapeutic imaging

Response to radiation therapy depends on a number of biological factors, such as tumour proliferation, number of clonogenic cells or hypoxia [11-13]. Recently, various markers of hypoxia have been explored. Studies have shown that patients with head and neck squamous cell carcinomas whose tumours are hypoxic after 2 weeks of primary chemoradiotherapy have a significantly lower chance of locoregional control [14]. INDIRA-MISO (NCT03865277) is a new phase II trial evaluating the value of radiation dose escalation based on hypoxia detection by (¹⁸F)-misonidazole (F-miso) PET/CT. Patients with tumours classified as hypoxic with this new radiotracer are randomized after 2 weeks of chemoradiotherapy to completion of standard chemoradiotherapy (70Gy) or chemoradiotherapy with escalated radiation dose (77Gy), in order to evaluate tumour control 2 years after treatment. An additional interventional arm includes a carbon ion boost. Results are expected in 2024. HYPONECK is another ongoing French phase II trial (NCT04031534) using F-miso PET imaging, this time in a preoperative setting for squamous cell carcinomas of the oropharynx. It combines a quasi simultaneous evaluation of preoperative PET/MRI images in order to compare PET and MRI indicators of hypoxia, then combining them to anatomic pathology features to analyse the correlation between hypoxia and one-year recurrence free survival in a second part of the study. This could lead to stimulate research on multimodal imaging-guided radiation dose-escalation to hypoxic tumour areas.

4. Oesophageal malignancies

4.1. Pertherapeutic imaging

PET scan is a major asset in the pre-therapeutic management of oesophageal tumours, and is becoming an early therapeutic evaluation tool, especially for poor early responders. Phase II/III trial SCOPE2 (NCT02741856) will compare the effects of standard dose radiotherapy (50Gy in 25 fractions) to a dose escalation (60Gy in 25 fractions) for patients with oesophageal cancer. Patients are PETreassessed after two weeks of induction chemotherapy consisting of cisplatin and capecitabine. According to response to this induction chemotherapy, patients will receive standard radiotherapy dose or high dose with standard (cisplatin and capecitabine) or alternative (carboplatin and paclitaxel) regimen of induction chemotherapy. Inclusions have started since November 2016 with estimated primary results in 2021.

Nuclear imaging is also used to guide induction chemotherapy in a phase II study (NCT03791905), aiming to evaluate whether changing the induction chemotherapy regimen during radiation based on PET response to induction chemotherapy (combining oxaliplatin, leucovorin, and 5-fluorouracile or cisplatin and paclitaxel) can improve clinical complete response in patients with unresectable

oesophageal squamous cell carcinomas. A second PET is performed on days 36-42 and changes in maximum standard uptake value (SUV_{max}) compared to baseline are assessed. Using a predefined cutoff value of a 35% decrease in SUV_{max}, PET responders continue the same induction chemotherapy regimen during radiotherapy, whereas PET non-responders cross over to an alternative regimen. First results are also expected in 2021.

4.2. Intermodal research

For locally advanced oesophageal cancer, the standard treatment relies on a neoadjuvant chemoradiotherapy followed by surgery if possible [15]. The PRIDE trial (NCT03474341), which has been including patients since 2018, hopes to develop a multimodal model that predicts the probability of pathological complete response to neoadjuvant chemoradiotherapy in oesophageal cancer, by integrating diffusion-weighted MRI and dynamic contrast enhanced MRI in conjunction with combined FDG PET/CT scans acquired prior to, during and after administration of neoadjuvant chemoradiotherapy. The underlying ideas are that patients with pathological complete response may not have benefited from surgery, and that an early identification of non-responders would be beneficial to explore other treatments. Finally, the PreSINO trial (NCT03937362) explores the ability of FDG PET/CT to detect residual disease after neoadjuvant chemoradiotherapy. Ultimately, the goal is to offer a possibility of active surveillance instead of esophagectomy in patients with a complete response after neoadjuvant chemoradiotherapy.

5. Lung malignancies

5.1. Pertherapeutic imaging

Chemoradiotherapy is widely used in the treatment strategy of patients with locally advanced lung malignancies. Accurate tumour delineation is crucial for an effective treatment. FDG PET/CT is an interesting tool for delineating the tumour volume [16], and many trials are being conducted to study the value of PET/CT for dose painting in pre- and pertherapeutic situations. For instance, the French trial entitled "RTEP7" (NCT02473133) aims to study the benefit of personalized radiotherapy dose in patients with locally advanced non-small cell lung cancer. The goal is to investigate the individual tumour heterogeneity on FDG PET during chemoradiotherapy at 42Gy in order to reduce the radiation volume to a biological target that could receive a higher total dose of 74Gy in 6.6 weeks. Therefore, a significant reduction in FDG uptake and/or volume (metabolic response) would suggest that the radiotherapy target volume could be reduced during radiotherapy, possibly improving organs at risk tolerance. Conversely, a lack of metabolic response may justify treatment intensification before the end of radiotherapy) is the primary objective. Another trial, entitled "REPAINT" (NCT03481114), is designed to evaluate patient-reported outcomes during and after concurrent chemoradiotherapy for locally advanced non-small cell lung cancer. Patients will be randomized to a standard 6-week

radiotherapy course or a 4-week radiotherapy course using dose painting based on pretreatment PET findings (55Gy in 20 fractions for lesions with metabolic tumour volume exceeding 20 cm³, 48Gy in 20 fractions otherwise) thus offering the chance for a shorter and more personalized treatment course using PET imaging. Finally, a Danish phase III trial (NCT02354274) aims to investigate a radiation dose escalation (as high as possible taking the tolerance of the normal tissue into consideration) to tumour and lymph nodes based on an inhomogeneous dose distribution based on FDG-PET positive areas, compared to a standard homogeneous dose spread (66Gy in 33 fractions).

Single photon emission computed tomography may also have a role to play in the radiotherapy planning for lung cancer. A pilot study trial (NCT02492867) explores response-driven adaptive radiotherapy for patients with locally advanced non-small cell lung cancer, applying functional imaging, FDG-PET and ventilation/perfusion single photon emission CT, before and during treatment to determine if it helps predict treatment response and pertherapeutic lung function with ventilation/perfusion single photon emission CT, possibly reducing toxicity. Ventilation/perfusion single photon emission CT could also be useful for stereotactic body radiotherapy, helping to avoid critical volumes of functional areas of the lungs in patients with often limited respiratory function [17]. In the same way, the study entitled "FLARE radiotherapy" (NCT02773238) is a phase II trial that studies how PET/CT imaging mid-way through treatment of stage IIB-IIIB non-small cell lung cancer could accurately predict treatment efficacy, and single photon emission CT/CT imaging may be able to tell which parts of the lung tissue are healthier than others. Treatment adjustments may then be made to improve survival and decrease toxicity. In this study, patients undergo functional avoidance radiotherapy during weeks 1-3, with FDG PET/CT evaluations at baseline, 3 weeks, and 3 months post treatment, and single photon emission CT/CT at baseline and 3 months postradiation therapy. Patients not responding to treatment at three weeks will receive an escalated dose of radiation. Finally, the "HI-FIVE" study (NCT03569072) is being performed to assess the feasibility of using ventilation/perfusion PET/CT scans to adapt radiotherapy plans using volumetric modulated arctherapy to avoid regions of functional lung and deliver a higher dose to the primary tumour. Secondarily, this study aims to assess the incidence of acute and late radiotherapy toxicity, to quantify regional ventilation loss and regional perfusion loss on post-treatment ventilation/perfusion PET/CT.

Conventional FDG PET imaging highlights the glucose metabolism of lesions, usually quantified by the SUV from a static acquisition, which is still a controverted way of quantification. Besides the lack of data on the binding kinetics of FDG by tumour cells, some studies have reported significant variation in standard uptake value measures in non-small cell lung cancer lesions for repeated PET examinations in untreated patients [18]. This is where the investigators of the PARAPET trial (NCT02821936) suggested a new approach to obtain the parametric information in PET: average percentage of metabolized or unmetabolized FDG and time required to metabolize 80% of FDG. They aim to evaluate the concordance between parametric PET versus standard PET for the one-year

prognosis of patients with non-small cell lung cancer treated by chemoradiation. An ancillary study will evaluate the interest of parametric PET imaging during treatment (around 42Gy) to detect local relapse in order to suggest treatment replanification or intensification.

FDG is not the only tracer that may be used in the radiotherapy strategy for lung cancers: new tracers are being studied, such as hypoxia and cell proliferation tracers. A pilot trial (NCT02456246) is investigating the feasibility of using 3'-(¹⁸F)-deoxy-3'-fluorothymidine (FLT) PET/CT in non-small cell lung cancer treated by stereotactic body radiation for the detection of cancer recurrences compared to regular CT scans. FLT is a thymidine analogue, used to assess the integration of thymidine into DNA as a surrogate of cell proliferation. Conceptually, increased DNA synthesis is correlated to tumour aggressiveness and response to therapy, more so than glucose utilization. Another novel tracer is the (¹⁸F)-arabinofuranosylguanine ([araG], NCT04052412) which biodistribution and kinetics are studied in patients with non-small cell lung cancer undergoing immunotherapy with and without adjuvant radiotherapy. One of this study's aims is to correlate the potential change in (¹⁸F)-araG uptake within the tumour or draining lymph nodes with clinical and pathologic response in these patients treated with immunotherapy. Finally, hypoxia tracers, like F-miso, are also being studied on non-small cell lung cancer: for instance, an ongoing trial (NCT02016872) is trying to determine if F-miso can predict treatment response and disease relapse.

5.2. Intermodal imaging

Heart sparing is one of the cornerstones of lung cancer radiotherapy. RICT-LUNG (NCT03416972) aims to detect radiation-induced cardiac toxicity after non-small cell lung cancer radiotherapy using hybrid PET/MRI. This non-invasive technique can perform simultaneous metabolic, functional and tissue imaging, avoiding the need of histological biopsy and its complications. The primary objective is to assess acute changes in heart function and to measure inflammation before and six weeks after non-small cell lung cancer radiotherapy. The findings of this study will help designing new studies to reassess dose escalation for locally advanced non-small cell lung cancer while limiting the risk of heart toxicity.

6. Anorectal malignancies

6.1. Pretherapeutic imaging

Radiotherapy is a common component in the strategy of locally advanced rectal cancer treatment. FDG PET/CT is an efficient way to assess treatment response, but the place of other tracers and PET/MR hybrid imaging still remains unexplored. In the RECTOPET trial (NCT03846882), PET/MR is compared with other imaging modalities (PET/CT, CT and MRI) to evaluate its additional staging value for local tumour proliferation, lymph node metastasis and other important prognostic factors (mesorectal fascia involvement, extramuscular vascular involvement). Another primary outcome of this study is to assess tumour regression following CRT in rectal cancer with FDG PET/MR compared to MRI or FDG PET/CT.

6.2. Pertherapeutic imaging

AIDA-RE-1 (NCT03479814) is an interventional prospective trial that aims to evaluate the achievement of pathological complete response in high-risk rectal cancer treated with neoadjuvant chemoradiotherapy. 45Gy are delivered to the clinical target volume (rectum and locoregional lymph nodes), and after 2 weeks of treatment, patients are evaluated with a FDG PET/CT allowing the delineation of the additional target volume for a sequential boost of 5Gy (in two fractions).

6.3. Intermodal imaging

The clinical trial entitled "TEP (⁶⁴Cu)-ATSM-Rectum" (NCT03951337) is a French phase II trial that aims to evaluate early and late tumour uptake of a novel radiotracer, (⁶⁴Cu)-labelled diacetylbis(N4methylthiosemicarbazone (ATSM), in predicting histological response to neoadjuvant chemoradiotherapy treatment in patients with locally advanced rectal cancer. Patients receive pretherapeutic CT scan, pelvic MRI and FDG PET/CT scan within 45 days before enrolment. A (⁶⁴Cu)-ATSM PET/CT is then achieved before the chemoradiotherapy starts, with two acquisition sequences performed at 1 h and 23 to 25 h after injection in order to evaluate early and late tumour uptake of the tracer. Patients are then treated for 5 weeks by capecitabine combined to a 50Gy radiotherapy. Pelvic MRI is performed 4 weeks after the end of this sequence in order to evaluate the treatment efficacy. Surgery is scheduled 6 to 8 weeks after chemoradiotherapy.

Anal canal cancer is a relatively rare disease, however the incidence has increased considerably over the past three decades. The standard treatment is an exclusive chemoradiotherapy [19,20]. Early assessment of the initial extension of the tumour, its therapeutic response and early detection of relapses are determining factors in the management of the disease. The French IFACT trial (NCT02697084) is evaluating whether a post-treatment FDG PET/CT at 2 months could be useful to predict locoregional or metastatic recurrence in patients treated by chemoradiation, distinguishing two groups (low and high risk of 2-year recurrence) of patients based on the metabolic response.

7. Prostate malignancies: intermodal imaging

The future of nuclear medicine and radiotherapy for prostate cancer will undoubtedly rely on (⁶⁸Ga)-PSMA-11 PET/CT. Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein enzyme which can be up to 1000-fold overexpressed in prostate cancer cells. Because of its high specificity, (⁶⁸Ga)-PSMA-11 PET/CT could assist physicians in disease localization in case of biochemical recurrence, and also help staging and restaging of the disease [21,22]. (⁶⁸Ga)-PSMA-11 PET/CT could select patients for PSMA-targeted molecular radiotherapy, which is being studied in two trials. The first one is the Canadian trial entitled "PSMA-PETgRT" (NCT03525288), expected to end in 2026, where conventional staging-guided radiotherapy is compared to radiotherapy informed by PSMA-PET findings (up to five avid sites distant from the prostate gland can be included in the radiotherapy plan) with 5-year failure free survival or time to failure event being the primary outcome. The second one is the "PSMA-SRT" trial (NCT03582774), which seeks to evaluate the success rate of salvage radiation therapy for recurrence of prostate cancer after prostatectomy with and without planning based on PSMA PET/CT. Indeed, target volume delineations for prostate cancer salvage radiation therapy after radical prostatectomy are usually drawn in the absence of visibly recurrent disease. PSMA PET/CT detects recurrent prostate cancer with superior sensitivity than standard imaging at serum prostate specific antigen (PSA) concentration values low enough to impact routine salvage radiation therapy planning. It could allow finding patients with M1 disease (extr-pelvic disease is seen in at least 13% of patients with [PSA] <1.0 ng/ml) and improving the coverage of recurrent lesions by the pelvic radiation fields (out-of-field pelvic disease is seen in at least 7% of patients) [23,24].

To conclude, hypoxic markers such as F-miso are also being investigated, for instance in the French trial entitled "HYPOXProstat" (NCT01898065), which recruitment status is complete. This trial uses functional imaging to characterize changes in hypoxia before and during radiotherapy. The aim is to allow dose escalation to radioresistant areas inside the tumour volume.

8. Lymphomas

8.1. Pertherapeutic imaging

Lymphoma is a heterogeneous group of cancers that affect cells of the immune system, primarily those involved in the lymphatic system. PET/CT has become a standard for initial staging and assessment of treatment response for most lymphomas.

A study led by the Memorial Sloan Kettering Cancer Center (NCT03179917) is currently assessing the safety and effectiveness of pembrolizumab followed by involved-site radiotherapy in relapsed or refractory early stage classical Hodgkin lymphoma, to decrease toxicity or further treatments (chemotherapy, stem cell transplant). The patients undergo an initial PET/CT to evaluate the extent of disease, repeated 14 to 21 days after four cycles of pembrolizumab, with involved-site radiotherapy doses guided by PET and CT responses. Also evaluating immunotherapy for lymphomas, the phase I RaDD trial (NCT03610061) hopes to determine the safety profile of concurrent radiotherapy and durvalumab for relapsed diffuse large B cell lymphoma, the most common non-Hodgkin lymphoma. One of the secondary objectives is to assess the biodistribution of new PET/CT tracers, (⁸⁹Zr)-labelled durvalumab and (⁸⁹Zr)-labelled anti-human CD8 probe IAB22M2C.

For Hodgkin lymphomas, EuroNet-PHL-C2 (NCT02684708) is an international, multicentre, randomized trial. It aims to compare an experimental treatment (induction chemotherapy without

radiotherapy or restricted radiotherapy) to conventional treatment (induction chemotherapy and radiotherapy) in order to reduce radiotherapy indications. Indeed, patients with a negative PET/CT after two cycles of induction chemotherapy will not receive radiotherapy.

8.2. Intermodal imaging

New tracers are being investigated in lymphomas as well. For example, like for lung cancer, FLT imaging is studied as a predictor of treatment response in a secondary objective of a pilot clinical trial (NCT03422731) focusing on bone marrow changes in patients with acute myeloid leukaemia undergoing total body radiotherapy and induction chemotherapy. Eligible patients will receive a FLT PET/CT at baseline, on days 30 and 100, at 1 year, and at the time of relapse.

9. Sarcomas

9.1. Pertherapeutic imaging

An ongoing trial (NCT03076333) is investigating, in patients with high-grade sarcomas, the ability to predict neoadjuvant radiotherapy response combining MRI with tumour functional exploration at the midpoint of radiotherapy. Quantitative measures from PET and MRI will then be computed: PET tumour-mean standard uptake value variation and tumour size as assessed by MRI, from pre- to post-treatment, and from pre- to midtreatment. The image-based quantitative measures will be correlated with the pathology outcomes (completeness of resection and percent of necrosis) to evaluate predictability of the image measures for treatment response.

9.2. Intermodal imaging

FDG imaging is a helpful modality in the follow-up of sarcoma patients to evaluate relevant responses, and to provide predictive information for patient outcome. New tracers are nevertheless being evaluated, like (¹⁸F)-fluoroazomycin arabinoside (Faza), a hypoxic marker. In a Canadian single centre study (NCT03418818), the use of Faza PET in combination with MRI is being investigated, as hypoxia in sarcoma has been consistently associated with poor treatment outcomes [25]. Parameters such as diffusion, microperfusion, and contrast enhancement (as a surrogate marker for viable tumour tissue) can be simultaneously compared with the Faza-derived pattern. The study is being conducted to measure the volume of hypoxic tumour in high-risk sarcoma patients, using Faza-PET/MRI, before and after neoadjuvant chemoradiotherapy.

Finally, an early phase I American study (NCT03613259) explores the use of FLT PET in patients with intermediate or high grade soft tissue sarcoma. Change in FLT standard uptake value peak/mean values as response to therapy and correlation to mitotic index and MRI enhancement may provide useful information about the tumour's response to treatment and may give early results that would better help to plan the postsurgical therapy.

10. Conclusion

The future of imaging in radiotherapy planning is promising, with always improving imaging resolutions and development of more sensitive and specific oncological imaging markers. Specifically, higher definition PET/CT and high magnetic field MRI have the ability to improve the visualization of tumours even to the level of microscopic disease extension. Emerging algorithms for automatic imaging fusion will also be more accurate and allow faster fusion process and verification.

Ongoing trials in nuclear medicine applied to oncology focus on three main aspects. Firstly, apart from the historical FDG, new radiotracers are being investigated in order to evaluate their ability to achieve better sensitivity and specificity to identify tumours. As hypoxia plays a major role in the resistance of tumours to oncological treatments especially radiotherapy, hypoxia markers, like FLT, ATSM, and F-miso, that can better define regions of hypoxia, oxygen metabolism, microscopic disease, and high metabolism inside the tumour are often cited for numerous malignancies [26]. As tumours are often heterogeneous, these new tracers could help mapping the tumour according to each subpart specific properties. Secondly, existing proven radiotracers like FDG have the ability to help radiation therapists better delineate tumour volumes based on functional data, or even influence treatment planning with dose heterogeneity ("dose painting") according to the metabolic activity. Pertherapeutic intermediate PET/CT evaluations could help identifying more aggressive (FDG) or radioresistant (hypoxia markers) areas and residual disease, potentially directing towards radiation boosting of these areas and improved avoidance of organs at risk. Thirdly, new radiotracers could allow more sensitive and specific follow-up, for instance PSMA for prostate malignancies highlighting otherwise undetected early relapses. Ongoing trials in French centres can be found in Table 1.

Finally, this overall improved performance in morphological and functional imaging brings increasing data waiting to be harvested in big data and artificial intelligence algorithms. Indeed, in the race for personalized treatment based on an individual portrait issued from "-omics" (genomics, proteomics, etc.), imaging data ("radiomics") could also bring crucial information [27].

In conclusion, the future of image-guided treatment planning is boundless and its continuous innovations should ultimately lead to higher cure rates and less treatment-associated toxicity.

Author contributions

Conception or design of the work: NG, GP, HR, DT and PV.

Data collection and drafting the article: NG, GP, HR and DT.

Critical revision of the article: GP, HR, DT and PV.

Final approval of the version to be published: NG, GP, HR, DT and PV.

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Table 1. Ongoing clinical trials combining positron-emission tomography and radiotherapyin French centres.

ClinicalTrials	Organ	Radiotracer	Description	Inclusion	French centres
.gov				start	involved
Identifier					
(study title)					
NCT0150481	Head	(¹⁸ F)-	Prechemoradiothe	March	Institut
5	and	fluorodeoxygl	rapy, PET-guided	2012	Gustave-
(ARTFORCE)	neck	ucose	radiotherapy dose		Roussy,
			painting		Villejuif
NCT0389716	Head	(¹⁸ F)-	Multimodal	January	Centre Henri-
6	and	fluorodeoxygl	PET/MRI for	2019	Becquerel,
(TRIMODAL)	neck	ucose	radiomic and		Rouen
			anthropometric		
			preradiotherapy		
			evaluation		
NCT0403153	Head	(¹⁸ F)-	Multimodal	March	Centre Henri-
4	and	misonidazole	PET/MRI	2019	Becquerel,
(HYPONECK	neck		pretreatment		Rouen
)			hypoxia evaluation		
NCT0247313	Lung	(¹⁸ F)-	PET-guided	July	Centre Henri-
3 (<i>RTEP7</i>)		fluorodeoxygl	radiotherapy dose	2015	Becquerel,
		ucose	painting at 42Gy of		Rouen
			chemoradiotherapy		(sponsor)

					29 centres
					opened in
					08/2019
NCT0282193	Lung	(¹⁸ F)-	Evaluation of new	May	Centre Henri-
6 (PARAPET)		fluorodeoxygl	parametric PET	2016	Becquerel,
		ucose	imaging; detection		Rouen;
			of local relapse at		APHM,
			42Gy of		Marseille
			radiotherapy		
NCT0395133	Rectu	(⁶⁴ Cu)-	PET evaluation of	April	Institut de
7 (TEP ⁶⁴ Cu-	m	diacetylbis(N4	histological	2019	cancérologie
ATSM-		-	response to		de l'ouest,
Rectum)		methylthiosem	neoadjuvant		centres René-
		icarbazone	chemoradiotherapy		Gauducheau,
		(ATSM)			Saint Herblain
					et centre Paul-
					Papin, Angers;
					CHU de Brest;
					centre Eugène-
					Marquis,
					Rennes
NCT0269708	Anal	(¹⁸ F)-	Post-	Novembe	Centre
4 (IFACT)	canal	fluorodeoxygl	chemoradiotherapy	r 2014	Antoine-
		ucose	PET prediction of		Lacassagne,
					Nice
1	1		1	1	1

			locoregional and		
			metastatic relapse		
NCT0189806	Prosta	(¹⁸ F)-	PET evaluation of	June	CHU de
5	te	misonidazole	hypoxia before and	2012	Poitiers;
(HYPOXProst			during	(recruitm	Institut de
at)			radiotherapy	ent	cancérologie
				complete	de l'ouest,
				d)	centre René-
					Gauducheau,
					Saint-Herblain

MRI: magnetic resonance imaging; PET: positron-emission tomography; CHU: university hospital.