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REVIEW

Molecular imaging of PARP in cancer: state-of-the-art

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ABSTRACT

Introduction: Poly-ADP-ribose-polymerase inhibitors (PARPi), which exploit the processes of so-called 'synthetic lethality,' have been successfully implemented in oncological practice. However, not all patients respond to PARPi, and there is an unmet need for noninvasive biomarkers suitable for patient selection and monitoring during PARPi therapy.

Areas covered: The first clinical applications of molecular imaging with positron emission tomography/computed tomography (PET/CT) with [18F]-FluorThanatrace ([18F]-FTT) and [18F]-PARPi, highly effective PARP-ligands, in patients with several malignancies (head and neck, ovarian, prostate, and breast cancer) are covered, with a particular focus on its potential for pre-treatment selection and follow-up.

Expert opinion: By a search made on the most common database, such as PubMed and Google Scholar in a period from January 2010 and 2023, first clinical evidence suggests that PET/CT with [18F]-FTT and [18F]-PARPi might represent a reliable tool for in vivo imaging and quantification of PARP-1 expression in ovarian, prostate, breast, head, and neck cancer, supporting their potential usefulness for patient selection before PARPi-therapies. In addition, a reduction in [18F]-FTT uptake has been registered after therapy initiation and seems to be correlated with patient outcome after PARPi-based regimens. Further studies are needed to better address the value of PARPI-radiolabeled PET imaging in these clinical settings, especially as it concerns technical features such as optimal scan modality (dynamic vs. static) and timing.

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Molecular imaging; PARP, ovarian cancer; prostate cancer; breast cancer; PET/CT

1. Background

Cancer, the leading cause of death in most of the Western Countries, is a genetic disorder caused by an accumulation of mutations in DNA sequences that control cell differentiation, proliferation, and survival [1]. In this perspective, it can be considered as the result of an unbalanced ratio between natural genomic variability (DNA damage deriving from endogenous and exogenous sources) and the efficiency of the enzymes capable of repairing DNA anomalies and restoring genome integrity [2]. The importance of DNA repair mechanisms was clear from the very beginning, since as early as in 1974, Francis Crick, the 'father' of the double helix along with James Watson, remarked: 'Nowadays, one could hardly discuss mutation without considering repair at the same time' [3].

DNA damage repair (DDR) genes play an important role in preserving human genome integrity by recognizing potential DNA damage and activating DNA repair pathways, including either homologous recombination (HR) or non-homologous end joining (NHEJ). DDR defects play a crucial role in enhancing genome instability, therefore representing a crucial feature in cancer. In a recently published analysis of DDR deficiency carried out on more than 10,000 cancer specimens, the most commonly mutated DDR genes were ATM (19.13%), BRCA2 (17.16%), BRCA1 (10.92%), RAD50 (8.92%), and ATR (7.8%), which were more frequently detected in endometrium, prostate, and bladder cancer [4]. DDR gene mutations present a relevant therapeutic implication since they have been identified as effective biomarkers for patient selection prior to targeted therapy with poly-ADP-ribose-polymerase inhibitors (PARPi) [5,6]. PARPi are a unique class of anti-neoplastic drugs exploiting the mechanism of the so-called 'synthetic lethality' occurring when PARPi and either another agent (e.g. platinum chemotherapy) or an underlying genetic alteration (i.e. a DDR defect) together determine irreversible DNA damage and ultimately cell death [5]. However, cells with dysfunctional BRCA1 or BRCA2 are dramatically more sensitive to PARP inhibitors.

The PARP protein family encompasses at least 17 different members, whose biological functions are not completely understood yet but are all characterized (except for PARP-3) by the ability to catalyze the transfer of ADP-ribose to substrates. Among the various members of the PARP family, PARP-1 and PARP-2 are the most extensively studied. In particular, single-stranded DNA breaks were found to activate PARP-1 as an early response to genotoxic damage [7]. In this

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Article highlights

- An *in vivo* tool able to quantify novel pharmacodynamics of PARP-inhibitors could aid in the early evaluation of their efficacy.
- Both [18F]-FTT and [18F]-PARPi are in clinical translational as imaging agents used in humans to assess *in vivo* the expression of PARP-1 in oncological patients.
- In ovarian cancer, [18F]-FTT has both a diagnostic and predictive meaning, potentially enhancing the efficacy of PARP therapy in a selected group of patients.
- In prostate cancer, BRCA-2 genomic alterations are associated with intense [18F]-FTT uptake at baseline PET.
- In breast cancer and in head and neck cancer, radiolabeled PARP-inhibitors should be further tested, although preliminary data are encouraging.

perspective, PARP-1 expression can be considered as a DNA damage sensor.

In 2014 the Food and Drug Administration (FDA) approved the first PARPi, namely Olaparib (an inhibitor targeting both PARP-1 and PARP-2), to treat patients with advanced ovarian cancers, bearing mutations in BRCA1/2. The implementation of Olaparib in clinical practice represented a keystone in the development of so-called 'precision medicine' and was then followed by the authorization of other PARPis (e.g. rucaparib, niraparib) also for malignancies other than ovarian cancer such as breast, pancreas, and prostate [8]. However, not all patients bearing DDR detects (i.e. BRCA 1/2) respond to PARPi therapy and, most importantly, about 40–70% of patients present a tendency to develop resistance over time [9]. Therefore, several efforts have been made to identify patients who are more likely to benefit from PARPis. Positron emission tomography/computed tomography (PET/CT) offers the unique opportunity to get an insight into pathological processes at a cellular and molecular level by employing dedicated imaging agents (i.e. radiopharmaceuticals) [10]. As concerns PARP-targeted imaging, first encouraging results were obtained by employing two olaparib-derivative compounds radiolabeled with the positron-emitter fluorine-18 ([18F]), namely [18F]-BO and [18F]-PARP-FL [11,12]. More recently, [18F]-FluorThanatrace ([18F]-FTT), a highly effective PARP-ligand, was synthesized and tested with promising results in pre-clinical and preliminary clinical studies [13]. Particularly, in breast cancer, it was discovered that [18F]-FTT pre-clinical uptake in tumor cells and xenografts was linked with the level of PARP-1, with specific binding to PARP-1 relative to other PARP family enzymes [14]. Similarly, another PARP ligand, known as [18F]-PARPi, was synthesized from the small molecule AZD2281 (Olaparib) and effectively evaluated as an imaging agent in mice carrying orthotopic glioblastoma models [15]. Furthermore, PARPi can be conjugated with fluorescent probes, such as PARPi-FL, enabling the high-contrast visualization of orthotopic glioblastoma xenografts in fluorescence optical imaging compared to the adjacent normal tissue [16].

The purpose of this special report is to present a thorough overview of the initial clinical uses of PARP-targeted imaging while attempting to identify its constraints, potential, and necessary next steps for its widespread adoption in daily clinical practice. For these endpoints a search on PubMed and Google Scholar in a period from January 2010 and 2023 was made.

2. Clinical applications

The main clinical applications of [18F]-FTT PET in prostate, ovarian, and breast cancer, as well as [18F]-PARPi in head and neck cancer, are summarized in Table 1.

2.1. Prostate cancer

Metastatic castration-resistant prostate cancer (mCRPC) represents the last phase of the natural history of PCa, with a median overall survival (OS) of 13.2 months [17]. In the last few years, PARPi has been included in the roster of available treatments for mCRPC in patients with mutations of BRCA1/2 and/or ATM, following the results of the PROfound trial [18,19]. Nevertheless, there is still much room for improvement regarding PARPi in the treatment of mCRPC. This is mainly due to the short time since their approval in this clinical setting and the fact that only a relatively small percentage of these patients present DDR gene mutations and can be candidates for treatment [20]. In this context, [18F]-FTT PET should be investigated as an *in vivo* biomarker for selecting PCa patients to address PARPi therapy. Dehdashti et al. [21], in a recently published pilot study, used [18F]-FTT PET aiming to assess PARP-1 expression in 9 patients affected by both metastatic hormone-sensitive prostate cancer (mHSPCa) and mCRPC with and without HRR (Homologous Recombination Repair) genomic alterations. As expected, patients with DDR gene mutations had a significantly higher uptake of [18F]-FTT in PET images compared to those without any mutations. Moreover, no significant differences in the median tracer uptake were found between bone, lymph node, or visceral metastases. Interestingly, patients harboring BRCA-2 genomic alterations showed more intense [18F]-FTT uptake at baseline. Furthermore, in the same subgroup of BRCA2-mutated patients, [18F]-FTT PET and PSA (Prostate-Specific Antigen) trend showed an agreement in the response to PARPi therapy. This suggests that [18F]-FTT PET could also have a potential use to evaluate the response to PARPi therapy, which is still an unsolved question not only for PARPi but also for other treatments in patients affected by PCa [22] (Figure 1).

2.2. Ovarian cancer

Three papers explored the role of [18F]-FTT PET/CT as a biomarker of PARP expression in patients with ovarian cancer. The first study, conducted by Makvandi et al. [23], included 2 patients with ovarian cancer and mutations in BRCA1/2. PET images with [18F]-FDG and [18F]-FTT were compared. While [18F]-FTT showed biliary excretion with limited bladder activity, in contrast to [18F]-FDG biodistribution, both agents were considered complementary. [18F]-FDG detected the presence of peritoneal metastasis, whereas [18F]-FTT better identified primary lesions or recurrent ones in the pelvis. The authors demonstrated that the accumulation of [18F]-FTT after platinum

Table 1. Summary of the studies with ^{18}F-FFT or ^{18}F-PARPi in patients affected by ovarian or prostate or breast cancer.

Author, ref	Year of publication (country)	Tracer	Type of cancer	N of patients*	PET protocol	Results
Makvandi et al.	2018 (U.S.A.)	^{18}F-FFT	Ovarian cancer	10	Dynamic scan for 60 min + late scans after 90 and 180 min from the RF injection	^{18}F-FTT is a noninvasive biomarker of PARP-1.
Young et al.	2020 (U.S.A.)	^{18}F-FFT	Ovarian Cancer	18	Dynamic scan for 60 min + late scans after 90 and 180 min from the RF injection	SUV calculated after 60 min from the RT injection can be considered a robust parameter for predicting PARP1 expression.
Schöder et al.	2020 (U.S.A.)	^{18}F-PARPi	Had and neck cancer	11	Dynamic scan for 30 min + late scans at 30, 60 and 120 min	Administration of ^{18}F-PAPi was safe. ^{18}F-PARPi PET was positive in all patients, correlated with PARP-1 expression at histology and outperformed ^{18}F-FDG for the detection of nodal metastases.
Pantel et al.	2023 (U.S.A.)	^{18}F-FFT	Ovarian Cancer	16	Dynamic scan for 20–25 min + late scans after 60 and 90 min from the RF injection	The reduction of SUV > 50% is associated with a better PFS and to a reduction > 50% in CA 125 value.
Dehdashti et al.	2022 (U.S.A.)	^{18}F-FFT	Prostate Cancer	9	Dynamic scan for 60 min + late scan after 60 min	Patients harboring DDR gene mutations had a significantly higher uptake of ^{18}F-FTT at PET images as compared to those without any mutations
McDonald et al.	2021 (U.S.A.)	^{18}F-FFT	Breast Cancer	13	Static 20-min PET image at 60 min post injection	^{18}F-FTT PET is a promising tool for quantification of PARP expression as well as to assess drug-target engagement during PARPi treatment

*final population; DDR: DNA damage repair; PET: positron emission tomography; ^{18}F-FTT: ^{18}F-fluorthanatrace.

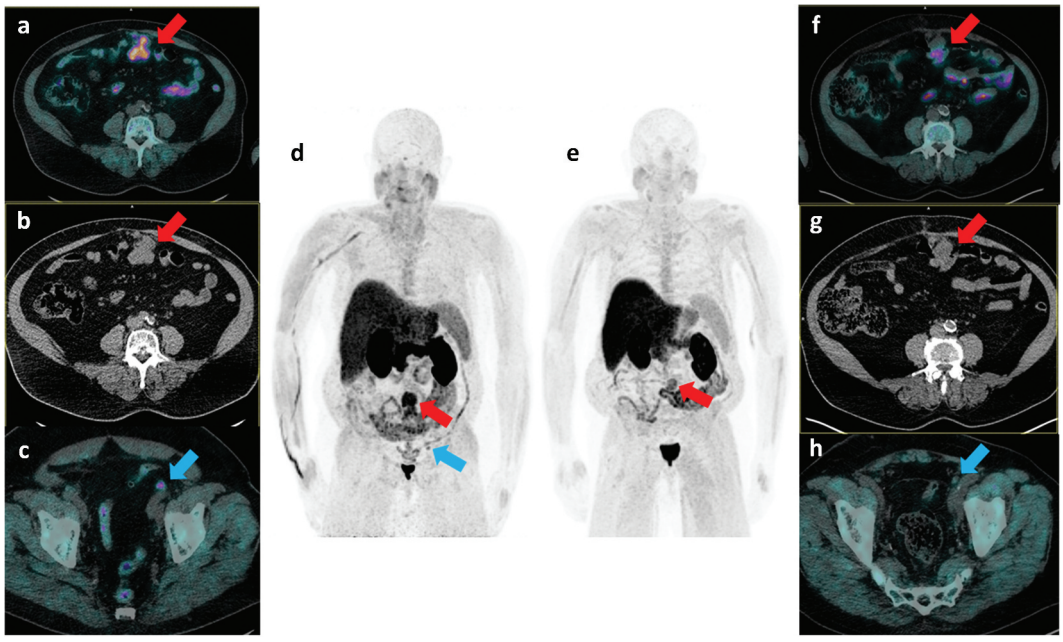

Figure 1. A 72-year old mCRPC patient (ISUP grade 4) treated with Olaparib + abiraterone after progression to Docetaxel. Baseline [$^{[18F]}$]F-choline PET/CT (A-D: transaxial fused, CT, transaxial fused and MIP images respectively), showed a large peritoneal mass with an intense radiotracer uptake (PCa localization confirmed with laparoscopic biopsy – red arrow) and an area of focal uptake corresponding to a left external iliac lymph node (blue arrow). PSA was 41 ng/ml. The patient performed a second [$^{[18F]}$]F-choline PET/CT (E-H: MIP, transaxial fused, CT and transaxial fused images respectively) 3 months after starting PARPi therapy. The exam showed an evident reduction of the uptake intensity and of the size of the peritoneal mass (red arrow) and the complete normalization of the pathological uptake in correspondence of the left external iliac lymph node metastasis (blue arrow). A standardized tool to assess response to oncological treatments in PCa is still an unmet clinical need. [$^{[18F]}$]F-choline and PSMA-ligands PET/CT are often used in daily clinical practice, although they are still not included in most updated guidelines for therapy response assessment, mainly due to the low quality of scientific evidence on support. Therefore, $^{[18F]}$-FTT PET could have a rising relevance for this indication if validated by prospective trials.

treatment was a predictive biomarker of poor response, providing information on viable tissue. Additionally, [18F]-FTT showed a positive correlation with PARP-1 expression, unlike [18F]-FDG, supporting the different molecular imaging targets.

Young et al. [24] enrolled 20 patients with recurrent or metastatic ovarian cancer. Eighteen patients were definitively enrolled, with 14 of them receiving a dynamic PET scan for 60 minutes after [18F]-FTT injection, followed by 2 later scans. SUVmax and SUVpeak values calculated within 60 minutes from the tracer injection showed a good relationship with the expression of PARP-1. However, late scans demonstrated a continuing increase in SUVs, suggesting the irreversible binding of [18F]-FTT in the cells and a potential trapping of PARP-1 in the cells. Nevertheless, a well-designed study is needed to confirm these assumptions.

In the most recent available papers by Pantel et al. [25], the researchers enrolled 16 patients affected by ovarian cancer, each with different mutational patterns. Patients underwent a baseline [18F]-FTT PET scan and a subsequent PET scan within 7–14 days from the start of PARPi. The reduction in SUV from baseline to post-therapy was categorized into < 50% and > 50% and correlated with progression-free survival (PFS) and CA-125 levels. Patients with a reduction of > 50% in SUV had better PFS than those with a reduction < 50%; however, a similar correlation was also found using RECIST criteria as a biomarker of response. Conversely, the reduction in SUV was associated with the reduction of CA-125, while RECIST did not show such a correlation. Moreover, no correlation was found between baseline [18F]-FTT uptake and PFS, indicating that baseline expression of the drug target is not a prognostic biomarker itself, but a high occupancy by the PARPi is also required. One more result about this study is worthy of mention. Two patients underwent [18F]-FTT PET/CT after progression to PARPi and still showed tracer uptake. They were consequently enrolled into an ongoing clinical trial (CAPRI trial, NCT03462342), proposing a combination with PARPi and ataxia-telangiectasia inhibitor (ATRi), with clinical benefits. This finding suggests that patients who become resistant to PARPi may still express PARP-1 and, therefore, may still benefit from treatment with a different PARPi, alone or in combination with ATRi.

2.3. Breast cancer

BRCA1 and BRCA2 are two of the most commonly involved mutations in breast cancer (BC) patients, and they are associated with aggressive diseases and worse prognosis compared to the sporadic counterpart [26]. Specifically, BRCA1 mutations are more frequently associated with high grade and triple-negative (TN) BC, while BRCA2 mutations usually induce BC with a higher histological grade than sporadic cases [27].

In a feasibility study, McDonald et al. [28] used [18F]-FTT PET to quantitatively test PARP expression *in vivo* in 13 patients affected by BC. At baseline PET, the tracer uptake was heterogeneous, with axillary lymph nodes showing the highest SUVmax (standardized uptake value). Of note, [18F]-FTT uptake was reported both in patients with TNBC and estrogen receptors positive (ER+) BC, providing the evidence of PARP-1 expression also in ER+ patients. Subsequently, 9 out of 13 patients underwent surgery, and their PARP expression was correlated ex vivo using another analog radiopharmaceutical with a longer half-life – [125I]KX1. The results showed an 82% reduction in uptake intensity after introducing olaparib in the tissue samples. The remaining 4 patients were not suitable for surgery, with 3 of them receiving PARPi therapy, showing a negative [18F]-FTT PET at restaging. The last patient, who exhibited no significant uptake of [18F]-FTT at baseline PET, experienced rapid disease progression and passed away after 1 year. The authors concluded that [18F]-FTT PET should be further investigated for *in vivo* quantification of PARP expression and to assess drug-target engagement during PARPi treatment. This could help early identification of patients with treatment resistance mediated by downregulation of PARP-1.

2.4. Head and neck cancer

A Phase I clinical trial explored the safety and feasibility of [18F]-PARPi in 11 patients diagnosed with oral and oropharyngeal cancer, concurrently examining the correlation between [18F]-PARPi findings and histopathology, as well as the conventional [18F]-FDG imaging used in standard patient care [29]. In the initial six patients, a dynamic PET scans were performed, with a field of view encompassing the heart, lungs, liver, and kidneys to investigate the biodistribution and clearance of the tracer. Additionally, in all instances, three static PET/CT scans were performed at 30, 60, and 120 minutes, respectively. No adverse events were documented in association with the injection of [18F]-PARPi, and all patients displayed tracer uptake in both primary tumors and metastatic lymph nodes, consistently with the high PARP-1 expression detected at histological examination. Notably, the administered activity cleared rapidly in healthy tissues (mostly through renal and hepatobiliary excretion), while it exhibited prolonged persistence in tumors and metastatic nodes, resulting in an optimal tumor-to-background signal at the 120-minute mark. In comparison to [18F]-FDG, the two tracers produced consistent results for primary tumors, but [18F]-PARPi exhibited superior performance in detecting nodal metastases. Additionally, the overall equivalent dose for [18F]-PARPi ranged from 3.9 mSv to 5.2 mSv, which is lower than the reported dose for [18F]-FDG (8.1 ± 1.2 mSv).

2.5. Other solid cancers

Pancreatic cancer, melanoma, lung cancer and gastrointestinal cancer can be associated with the mutation in BRCA-1/2 genes. The pancreatic cancer with a mutational status account for 5–7% of cases. The results of the POLO trial [30] showed that a germinal BRCA1/2 Pathogenic/Likely Pathogenic Variants (PV/LPV) represent a predictive marker of PARP inhibitors' sensitivity for the maintenance treatment of the metastatic disease, previously treated with platinum-based therapy. The role of germline BRCA1/2 alterations in melanoma susceptibility has been controversial for a long period, but strong evidence suggested that PARP-inhibitors in association with

other chemotherapeutical agents can beuseful for the treatment of melanoma patients [31]. Germline BRCA1/2 PVs/LPVs have been shown to be associated with 5% of all lung cancer cases. In clinical trial, only PARP-inhibitors therapy has demonstrated poor results, while the combination of temozolomide plus Olaparib and other has improved patient outcomes. Gastroesophageal tumors show a BRCA1/2 alteration in 3–12% of cases, mainly involving BRCA2 gene, while HR genes are involved in 12% of cases. Clinical trials aiming to test the utility of PARP-inhibitors in combination with other agents are still ongoing, therefore without providing already definitive evidence.

3. Expert opinion

In the era of precision medicine, predicting the *in vivo* efficacy of treatments has become crucial for engaging targeted drugs. Among these drugs are PARPi, which have shown the ability to increase OS in patients with specific solid tumors [19,32,33]. In addition to well-known PARPi like olaparib, rucaparib, niraparib, and talazoparib, newer and more effective drugs targeting PARP expression are in development. Having an *in vivo* tool to quantify novel pharmacodynamics could aid in the early evaluation of their efficacy.

Currently, both [18F]-FTT and [18F]-PARPi are in clinical translational as imaging agents used in humans to assess *in vivo* the expression of PARP-1 in oncological patients. Although the current literature evidence on this is scarce, preliminary data are promising. In a study involving 44 ovarian cancer patients, [18F]-FTT showed a positive correlation with PARP-1 expression. Furthermore, in 16 of these patients, the reduction in [18F]-FTT uptake was correlated with progression-free survival (PFS) and the changes in Ca125 values. This opens the possibility of considering [18F]-FTT as both a diagnostic and predictive biomarker in this aggressive oncological disease, potentially enhancing the efficacy of PARP therapy in a selected group of patients. However, more evidence is needed to support these findings. Similarly, [18F]-PARPi showed high diagnostic accuracy in patients with head and neck cancer, outperforming [18F]-FDG for the detection of nodal metastases, showing strong correlation with PARP-1 expression revealed by histology.

Recently, two clinical trials, namely PROFound and TRITON-2 [19,33], have demonstrated that prostate cancer patients with alterations in homologous recombination repair (HRR) genes, such as BRCA1/2, respond better to PARPi therapy than those with different gene alterations. Therefore, identifying HRR gene mutations is essential in selecting prostate cancer patients likely to respond to PARP therapy. Currently, the evaluation of BRCA1/2 alterations requires specific laboratory tests, which can cause delays in identifying suitable candidates for PARPi therapy. Additionally, the availability of laboratories capable of performing these examinations is limited globally. Consequently, the role of HRR genomic aberrations in accurately predicting PARPi response remains unclear, making an *in vivo* biomarker desirable for understanding the physiopathological effects. Preliminary data in prostate cancer show that BRCA-2 genomic alterations are associated with intense [18F]-FTT uptake at baseline PET. Moreover, [18F]-FTT uptake and PSA trends seem to align with the response to PARPi therapy, at least in BRCA-2 patients.

Likewise, the potential of [18F]-FTT PET in breast cancer patients should be further explored as a means of *in vivo* quantification of PARP expression and assessing drug-target engagement during PARPi treatment. There are several ongoing clinical trials investigating [18F]-FTT PET/CT in breast,

Table 2. Summary of the ongoing clinical trials investigating ^{18}F-FTT and ^{18}F-PARPi PET in tumors.

NCT identifier	Tumor	Tracer	Study Type	Patient population	Outcomes	Recruitment Status
NCT05226663	Breast cancer	^{18}F-FTT	Interventional Phase II	Known primary breast cancer, with a target lesion size of 1.0 cm or greater on at least one type of standard clinical imaging	Correlation of ^{18}F-FTT uptake with PARP expression	Recruiting
NCT03846167	Breast cancer	^{18}F-FTT	Observational Prospective	Known or suspected primary or metastatic breast cancer, with target lesion size (for primary breast cancer) of 1.0 cm or greater on at least one type of standard imaging	*Primary outcome*: PARP-1 Activity in Breast Cancer *Secondary outcomes*: Correlation of ^{18}F-FTT uptake with: 1) PARP-1 activity in tissue; 2) hormone receptor status; 3) change after therapy	Recruiting
NCT03083288	Breast cancer	^{18}F-FTT	Interventional	Known or suspected primary or breast cancer, with target lesion size (for primary breast cancer) of 1.0 cm or greater on at least one type of standard imaging	To correlated ^{18}F-FTT PET/CT uptake with pathology measures and treatment response	Active, not recruiting
NCT02469129	head and neck squamous cell cancer (HNSCC) and other malignancies	^{18}F-FTT	Interventional	Patients with HNSCC or lung cancer or other malignancies suitable for platinum-based chemotherapies + Healthy volunteers for dosimetric studies	*Primary outcome*: doses to critical organs for ^{18}F-FTT PET in healthy individuals *Secondary outcomes*: SUVmax and Distribution volume ratio (DVR) of ^{18}F-FTT in tumors, PARP enzyme activity and positive PARP-cells at immunohistochemistry	Enrolling by invitation

(*Continued*)

Table 2. (Continued).

NCT identifier	Tumor	Tracer	Study Type	Patient population	Outcomes	Recruitment Status
NCT03492164	Pancreatic cancer	^{18}F-FTT	Interventional Early Phase 1	Patients with stable disease after platinum chemotherapy, eligible for PARPi-based therapies	*Primary outcome*: Baseline and post-therapy PET/CT scans will be performed to evaluate whether the PARP inhibitor therapy decreases ^{18}F-FTT uptake	Recruiting
NCT05636540	Pheochromocytoma or paraganglioma	^{18}F-FTT	Interventional Early Phase 1	Patients with pheochromocytoma or paraganglioma, diagnosed by biochemical and imaging studies (standard of care germline genetic testing performed)	^{18}F-FTT PET will be used to evaluate PARP-1 expression before surgery	Not still recruiting
NCT04221061	Glioblastoma	^{18}F-FTT	Interventional Early Phase 1	Patients with a diagnosis of glioblastoma and enrolled in the companion treatment trial, IRB 832,694.	*Primary outcome*: To assess ^{18}F-FTT uptake in glioblastoma after initiation of tumor treating fields (TTFields) *Secondary outcomes*: To correlate ^{18}F-FTT uptake with DNA damage defect genes, to determine changes in ^{18}F-FTT uptake after TTFields and PARPi-therapies, to correlate ^{18}F-FTT uptake with histology	Recruiting
NCT03334500	Prostate cancer	^{18}F-FTT	Interventional Early Phase 1	Patients with prostate cancer eligible for indicated radical prostatectomy or oligometastectomy	To compare ^{18}F-FTT uptake with PARP-1 expression in tumor samples	Active, not recruiting
NCT05242744	Prostate cancer	^{18}F-FTT	Observational Prospective	Patients with metastatic prostate cancer, considered a candidate for new therapy or change in therapy	*Primary outcome*: To determine change in ^{18}F-FTT uptake before and after systemic therapy *Secondary outcomes*: Correlation between ^{18}F-FTT uptake and PARP-1 expression on immunohistochemistry, prediction of response	Recruiting
NCT02637934	Ovarian cancer	^{18}F-FTT	Phase 1	Patients with known or suspected epithelial ovarian, fallopian tube, or primary peritoneal cancer, with at least one lesion ≥1.0 cm that is seen on standard imaging	*Primary outcome*: To assess PARP-1 activity by ^{18}F-FTT PET *Secondary outcomes*: To correlate ^{18}F-FTT uptake with mutational status and PARP-1 expression in tumors, to perform dosimetry analysis	Recruiting
NCT03604315	Ovarian cancer or other solid tumors	^{18}F-FTT	Phase 1	Patients with ovarian cancer or other solid tumors, with at least one lesion ≥1.0 cm that is seen on standard imaging	*Primary outcome*: To assess PARP-1 activity by ^{18}F-FTT PET *Secondary outcomes*: To correlate ^{18}F-FTT uptake with mutational status and PARP-1 expression in tumors, to assess change in ^{18}F-FTT after therapy	Recruiting
NCT04173104	Brain cancer	^{18}F-PARPi	Observational	Patients with newly diagnosed or recurrent brain tumors with at least one brain lesion size >/ = 1.5 cm diameter	*Primary outcome*: To assess ^{18}F-PARPi updtake in lesions, quantified by standard SUVmax measurements from PET/MR scans	Recruiting
NCT03631017	Head and neck cancer	^{18}F-PARPi	Interventional, Phase I	Patients with oral carcinoma, at least 1 lesion of 1.5 cm minimum diameter	*Primary outcome*: To determine the biodistribution of this imaging agent in normal organs as well as the kinetics of uptake in squamous cell carcinomas of the head and neck	Recruiting

PET: positron emission tomography; PARP: Poly (ADP-ribose) polymerases; ^{18}F-FTT: ^{18}F-fluorthanatrace.

ovarian, pancreatic, brain, and prostate cancers, as well as [18F]-PARPi in brain tumors and head and neck cancer (Table 2).

However, there are still some unresolved issues regarding PARP-targeted imaging. Firstly, both radiotracers currently undergoing the first 'in-human' clinical trials exhibit intense hepato-biliary excretion, which could potentially hinder the detection of abdominal lesions. In this regard, a recently synthesized PARP-ligand, [18F]-PyPARP, showed a significantly reduced liver-to-kidney ratio during late-time acquisitions, thus holding the promise of facilitating the detection of foci of pathological tracer accumulation located in the upper abdomen [29]. Secondly, a significant heterogeneity in technical protocols (dynamic, static) and the timing of PET/CT acquisition was

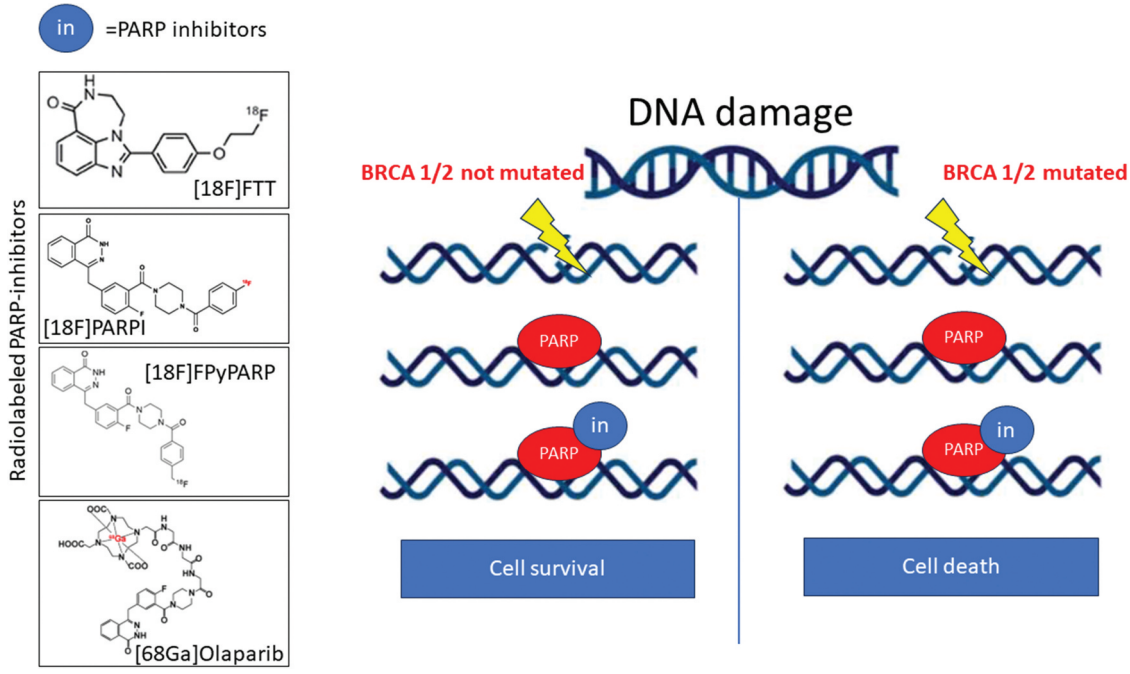

Figure 2. A schematic representation of PARPI inhibitors' mechanism of action (right) and the available radiopharmaceuticals (left).

observed among the various studies, although late scans appeared to offer better image contrast. Third, the implementation of PET with PARP ligands will depend on the cost and availability of tracers, which are still to be determined.

Additional radiopharmaceutical agents are now under evaluation, by using 68 Ga or [18F] as radioisotope. The preclinical study by Wang et al [34] has demonstrated the potential utility of 68 Ga-Olaparib for monitoring ovarian cancer tissues with elevated PARP expression and detecting abdominal tumor metastases, thanks to the high contrast imaging, thus overpassing the limitations of the available tracers. The study by Stotz et al [35], moreover, compared the biodistribution and pharmacokinetics of three agents, such as [18F]PARPi, [18F]FTT and [18F]FPyPARP in mice. The authors underlined the different peculiarities from the three agents. Indeed, [18F]PARPi has the highest initial tumor-to-muscle ratio, [18F]FPyPARP demonstrated an improved clearance from liver tissue and sufficient tumor uptake, and [18F]FTT showed continuously increasing tumor uptake due to the long blood retention time. However, only [18F]PARPi and [18F]FTT have already been tested in humans, but both 68 Ga-Olaparib and [18F]FPyPARP seem promising in solving some issues relative to the clinical conditions. A strong effort is required in drawing specific clinical trials. In Figure 2 is reported a scheme of the PARPis' function and the available tracers.

In conclusion, PARPi offers a significant therapeutic alternative for patients with aggressive tumors, such as ovarian cancer. However, their efficacy can sometimes be limited. Identifying a predictive biomarker could significantly impact the management and prognosis of these patients. Further studies are required to address these issues comprehensively.

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Author contributions

Luca Filippi, Luca Urso, Laura Evangelista: designed the review study; Luca Filippi, Luca Urso and Laura Evangelista performed the literature research and data extraction; all authors: wrote the paper; all authors: supervised the paper.

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