Prostate Cancer Imaging with ^{18}F-DCFPyL PET and multiparametric MRI

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Conclusion & Future Perspectives

CONCLUSIONS

PART 1

The use of multiparametric MRI in primary prostate cancer is rising. It can be performed prior to prostate biopsy, or after biopsy to aid treatment planning. In both scenarios a local tumour stage is assigned. In **Chapter 1** of this thesis, we evaluated the accuracy of such staging information in a multicentre, retrospective study (*n*=430 patients). The radiologic T-stage from mpMRI was compared to pathology results following radical prostatectomy (reference T-stage). We found a poor sensitivity (45%, CI 37-54%) and moderate specificity (75%, CI 71-81%) for locally advanced prostate cancer (T-stage 3-4), in line with results from other research groups[1]. The implications of erroneous staging were further explored. Even with mpMRI available, a third of all patients with pathology-confirmed locally advanced disease (T-stage 3-4) had not received the indicated lymph node dissection or had been operated with a potentially hazardous nerve-sparing approach. Finally, radiologic accuracy did not improve over time (2013-2016), although the use of mpMRI expanded. This challenges the idea that increasing radiologic exposure naturally enhances diagnostic performance[2, 3].

In **Chapter 2** we studied the hypothesis that individual radiologic (or clinical) predictors may be insufficient to classify disease stages, but that multiple predictors can be combined to provide more reliable tumour assessment. Although mpMRI seems insufficient for tumour staging as stand-alone modality, it may still improve diagnostic accuracy in combination with other, clinical parameters. We added the radiologic stage from mpMRI to two clinical nomograms (the MSKCC and Partin nomogram), using the same patients as in Chapter 1. The overall accuracy to predict locally advanced disease increased only marginally, however (the AUC of the receiver operating characteristic curve increased by 1% when mpMRI was added to the MSKCC nomogram; 4% when mpMRI was added to the Partin nomogram).

Preoperative detection of locally-advanced tumours may prevent oncological unsafe nerve-sparing surgery, resulting in less tumour-positive surgical margins. The staging sensitivity of mpMRI appears limited, but its reasonable specificity (75% in Chapter 1; 91% in prior studies[1]) may help to reduce the incidence of positive surgical margins. To test this hypothesis, we analysed a series of 523 patients undergoing robot-assisted radical prostatectomy in a single reference centre (2013-2017), **Chapter 3**. In 118/523 patients (23%) a preoperative mpMRI had been available. The patients with preoperative mpMRI had identical clinical characteristics as patients without mpMRI. We found that surgical radicality was not associated with the availability of preoperative mpMRI: 34/118 patients with mpMRI (29%) had positive margins, compared to 109 of 402 patients without mpMRI (27%, *p*=0.69).

Taken together, in Part 1, we found limited evidence for the value of tumour staging with mpMRI in primary prostate cancer in current clinical practice.

PART 2

Upon clinical introduction of a new PET radiopharmaceutical, thorough analysis of the technical parameters influencing image-quality, scan interpretation and the pharmacokinetic profile are required. In Part 2, we performed such 'technical validation' for ^{18}F-DCFPyL PET/CT. The results promote standardized image interpretation (reducing interobserver variability), optimal lesion detection and the use of quantitative ^{18}F-DCFPyL PET measurements as an imaging-biomarker.

Healthy tissues with limited tracer uptake variability between patients can serve as reference regions for standardized PET interpretation, meaning the uptake in these tissues is taken as thresholds to classify suspicious lesions. Examples of such standardized interpretation include the PERCIST[4] and Deauville classifications for ^{18}F-FDG PET/CT[5]. **Chapter 4** describes the uptake variability of ^{18}F-DCFPyL, ^{68}Ga-PSMA, ^{18}F-fluoromethylcholine, and ^{18}F-dihydrotestosterone in healthy tissues. For ^{18}F-DCFPyL, the blood pool and liver had the least variable uptake across patients. For ^{68}Ga-PSMA, only the blood pool appeared a candidate reference tissue. Both the blood pool and liver are proposed reference regions in the recent PROMISE protocol for standardized PSMA PET interpretation[6]. Our results support the use of blood-pool uptake, but raise concern regarding the use of liver uptake for ^{68}Ga-PSMA PET evaluation. As a secondary outcome, this study provided reference ranges for healthy tissue uptake (population ranges). These may be used as image-based quality control for future PET scans, as any uptake outside this ranges points to flaws in image-acquisition.

In **Chapter 5** we investigated whether advanced image-reconstruction algorithms for ^{18}F-DCFPyL PET/CT could improve detection of prostate cancer recurrence and interobserver agreement. Twenty-four patients with biochemically recurrent prostate cancer and a current PSA <2.0ng/mL were included, as lesion detection in this group may still be improved (current localization rates 11-80%)[7-9]. Four image-reconstruction algorithms were used for every PET acquisition, generating four different PET scans per patient. These included a scan with 4mm voxels (reference standard) and a scan with 2mm voxels. Both the 4mm and 2mm PET scans were consequently reconstructed including *Point-Spread Functions* (PSF) modelling, a technique to improving image contrast. All scans were independently reviewed by four experienced nuclear medicine physicians. Detection of prostate cancer recurrence was based on consensus analysis (agreement of at least 3 readers per scan), as well as on all individual scan readings. Based on the consensus analysis, the advanced reconstruction methods did not affect the detection of recurrent cancer compared to the 4mm reconstruction (localization rates of 63-67% versus 63%, respectively). However, based on the individual readings

(*i.e.* clinical reality), recurrent prostate cancer was more frequently detected on the 2mm (74%, CI 65-83%) and the 2mm+PSF PET scans (75%, CI 66-84%) compared to the 4mm scans (66%, CI 56-75%, $p<0.03$). Additionally, a higher number of lesions was detected on the 2mm (median 2 lesions) compared to 4mm scans (median 1 lesion; $p=0.008$). The higher number of detected lesions did not include an upsurge in false-positivity. Applying advanced reconstructions did not significantly increase interobserver agreement (81-85%), compared to the 4mm scans (76%, $p>0.08$).

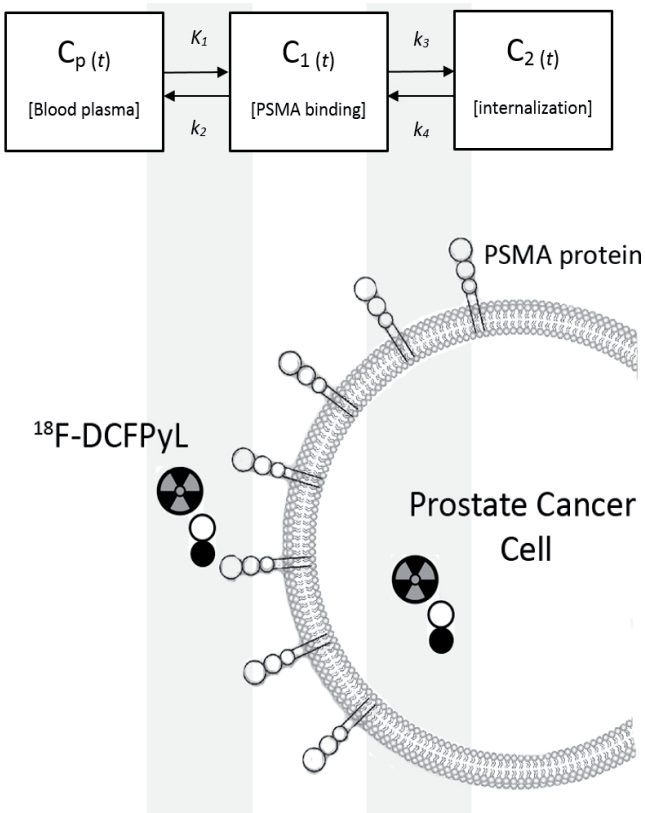
Chapter 6 describes the pharmacokinetic properties of ^{18}F-DCFPyL in prostate cancer metastases. Eight patients with metastasised prostate cancer were included. Dynamic PET acquisitions were made from injection of ^{18}F-DCFyL until 120 minutes post-injection, while arterial blood sampling was performed. The uptake of ^{18}F-DCFPyL in metastases was measured over time and defined as a function of the tracer's bioavailability in the blood pool (the blood input curve). Standard pharmacokinetic tissue-compartment models were used, defining the kinetic behaviour of a tracer in rate constants (k) (Figure 1). A reversible two-tissue compartment model (with a fixed, small k_4) best described the kinetic behaviour of ^{18}F-DCFPyL. In this model K_1 and k_2 may explain the transport and (un)binding of ^{18}F-DCFPyL from blood to prostate cancer cells. After binding the extracellular part of the target, PSMA-ligands are known to be internalized into the cell[10]. This process may be described by the observed k_3 and k_4 constants. See Figure 1.

Pharmacokinetic modelling is the reference method for tracer uptake quantification, but is not suited for clinical routine. Hence, *simplified methods for quantification* of ^{18}F-DCFPyL were validated. We established that an image-based measurement of tumour uptake, normalized to the blood activity concentration, accurately represent the pharmacokinetics of ^{18}F-DCFPyL. This image-based *Tumour-to-Blood ratio* can be easily obtained from clinical PET scans. Such simplified quantitative analysis of ^{18}F-DCFPyL PET/CT may be used as an imaging biomarker for histologic grade and disease progression. Further, it could allow monitoring of treatment response, as changes in the Tumour-to-Blood ratio may imply therapeutic response or failure.

To monitor treatment response in patients, it is needed to understand the intrinsic variability of the quantitative PET measurements. In **Chapter 7** we thus performed a repeatability analysis of ^{18}F-DCFPyL PET/CT measurements. Twelve patients received two ^{18}F-DCFPyL PET/CT scans within median 4 days' time. We observed that the daily variation in Tumour-to-Blood ratio (TBR) does not exceed 32%: greater variation may be interpreted as treatment effect or disease progression. Additionally, we found that the patient-based PET-delineated *Total Tumour Volume* is appropriate for follow-up, for this metric was highly repeatable and robust to different image-reconstructions.

In busy clinical routine, measuring only tumour uptake (Standardized Uptake Values, SUV) might be preferred over deriving a TBR. Moreover, the repeatability of SUV is better

Figure 1: Pharmacokinetic properties of ^{18}F-DCFPyL, described by a two-tissue tissue compartment model.



(the blood measurements used in TBR increase variability). In using SUV, one assumes that input functions (e.g. the activity concentration of ^{18}F-DCFPyL in blood over time) are equal in shape and size across patients. In Chapter 1, we hypothesized that this assumption is invalid for ^{18}F-DCFPyL, for patients with large tumour volumes had lower activity concentrations of ^{18}F-DCFPyL in their blood. Further evidence the presence of this so-called *sink-effect* is presented in in **Chapter 8**. We reviewed a patient with metastasised castration-resistant prostate cancer, who underwent ^{18}F-DCFPyL PET/CT before and after starting a systemic therapy (abiraterone). The patient's baseline and follow-up PSA levels were 1436 ng/mL and 1936 ng/mL, indicating progressive disease under treatment. On follow-up PET, a substantial increase in tumour volume was apparent, accompanied by decreasing normal tissue uptake. A discrepancy between SUV and TBR was noted: tumour SUV had decreased by 13%, while the Tumour-to-Blood ratio increased by +75%. TBR thus seemed to correct for the sink-effect and adequately reflected the clinically observed disease progression. We concluded that ^{18}F-DCFPyL uptake should be quantified using TBR, instead of SUV. The effect of tumour volume on PSMA uptake could be especially relevant for patients scheduled for PSMA-targeted

radioligand therapy (^{177}Lu-PSMA), who are often heavily metastasised. Personalized dosimetry might be needed in these patients, accounting for the sink-effect.

To conclude, in PART 2 we identified reference regions for standardized interpretation of ^{18}F-DCFPyL (blood; liver). We observed potential benefit of using high resolution PET-images (2mm) for lesion detection, but not for interobserver agreement. Lastly, we validated simplified methods to quantify ^{18}F-DCFPyL uptake in clinical practice (Tumour-to-Blood ratio, not SUV) and assessed the repeatability of these measures for therapy response monitoring.

PART 3

In PART 3 we summarize the first clinical results with ^{18}F-DCFPyL PET/CT in patients with recurrent prostate cancer. **Chapter 9** assessed the efficacy of lesion detection with ^{18}F-DCFPyL in 248 patients with biochemically recurrent prostate cancer, included in two hospitals. Suspected metastases were identified in the majority (86%) of all PET examinations and even at PSA values <0.5 ng/mL lesions were observed in 59% of the patients. These findings support the recent EAU guidelines, recommending PSMA PET upon first signs of biochemical recurrence after radical prostatectomy (PSA >0.2 ng/mL). Moreover, ^{18}F-DCFPyL PET/CT frequently revealed prostate cancer lesions outside of the prostatic fossa, also at low PSA values. These findings are clinically relevant, for patients with biochemical recurrent disease after prostatectomy are candidates for local salvage radiotherapy on the prostatic fossa. This treatment may likely be ineffective in the presence of (lymph node) metastases.

The diagnostic results with ^{18}F-DCFPyL PET/CT appear equivalent to ^{68}Ga-PSMA PET/CT in patients with PSA values >2.0 ng/mL (*i.e.* 95% lesion detection with both tracers). Potentially improved detection is observed in patients with a PSA value <2.0 ng/mL [11]. See Table 1. Recently, another ^{18}Fluorine-labelled tracer has been introduced: ^{18}F-PSMA-1007[12]. ^{18}F-PSMA-1007 is minimally excreted via the urinary tract, which potentially improves visualisation of cancer lesions in the prostatic fossa. Our results with ^{18}F-DCFPyL PET/CT appear grossly in line with the diagnostic efficacy found with ^{18}F-PSMA-1007 PET/CT in two recent studies[12, 13](Chapter 9). In terms of detection of local recurrence specifically, no evident benefit of ^{18}F-PSMA-1007 is seen compared to our ^{18}F-DCFPyL results[13, 14].

In **Chapter 10** we report on using PSMA PET for patients with a rising PSA after curative radiotherapy, who did not meet the Phoenix criteria for biochemically recurrent disease (*i.e.* a PSA rise of ≥2 ng/mL above the PSA nadir[15, 16]). The Phoenix criteria were drawn up in 2005, when detection of prostate cancer recurrences was based on CT, bone scan, or prostate biopsies. The diagnostic sensitivity of PSMA PET imaging is likely superior to these techniques. We reviewed 315 patients scanned with PSMA PET/CT (both

Table 1: Lesion detection in patients with biochemically recurrent prostate cancer with various PSMA radiotracers

Publication	Tracer	*N*	Detection rates per PSA strata (ng/mL)			
			<0.5	*0.5-<1.0*	*1.0-<2.0*	*≥2.0*
Perera[11] 2019	^{68}Ga-PSMA-11	4790	45%	59%	75%	95%
			<0.5	*0.5-<1.0*	*1.0-<2.0*	*≥2.0*
Giesel[13] 2018	^{18}F-PSMA-1007	251	62%	74%	91%	94%
			≤0.5	*0.51-≤1.0*	*1.1-≤2.0*	*>2.0*
Rahbar[14] 2018	^{18}F-PSMA-1007	100	86%	89%	100%	100%
			<0.5	*0.5-<1.0*	*1.0-<2.0*	*≥2.0*
This thesis 2019	^{18}F-DCFPyL	248	59%	69%	85%	96%

^{18}F-DCFPyL and ^{68}Ga-PSMA) after curative radiotherapy in three centers (2015-2018). In total, 63 patients (20.0%) were scanned before meeting the Phoenix criteria. Although these patients are officially considered to be disease-free, prostate cancer lesions were found in the great majority (84%) of cases. These worrisome outcomes question whether the Phoenix criteria are still adequate in the era of PSMA PET. The Phoenix criteria defined biochemical recurrent disease based on the presence of metastases; such definition appears inherently dependent on the precision of available diagnostic techniques. We urge for re-evaluation of the criteria for biochemical recurrence after radiotherapy.

The early detection of prostate cancer recurrences with ^{18}F-DCFPyL PET/CT, as found in PART 3, shows clear improvement to previous diagnostic techniques. Timely detection of metastases may be clinically relevant as it refines patient selection for salvage therapies, metastases-directed therapies, or the start of systemic treatment. It is crucial to realize however, that the clinical outcomes of none of these PSMA PET-based decisions have been sufficiently studied in prospective clinical trials yet[15, 17, 18].

FUTURE PERSPECTIVES

Multiparametric MRI

The use of multiparametric MRI has recently been incorporated in the Dutch, as well as the European, clinical guidelines as standard-of-care for patients with suspect prostate cancer, primarily to guide targeted prostate biopsies. If prostate cancer is detected, however, a tumour-stage is assigned as well[19]. This radiologic staging is not without consequence (PART 1). Given the dubious diagnostic accuracy, the question arises if radiologists should even continue providing a T-stage.

To improve T-staging, confining mpMRI interpretation to expert centres is often advocated[3, 20], though this may not appear feasible given the expected rise in mpMRI scans (following the new EAU guidelines). We cannot assume that just performing more mpMRI scans will ensure sufficient radiologic learning either (Chapter 1). Further (sub) specialization of radiologists within the local centres may be stimulated, but it is unclear if the staging sensitivity will truly become dependable.

The specificity of mpMRI for locally advanced cancer (75-91%) may be valuable, however. If the specificity could be improved to a minimum of 92%, a positive prediction value of 75% will be reached (if the prevalence of locally advanced disease is 33%, Chapter 1). This lower threshold appears acceptable to refrain from nerve-sparing surgery, promoting radical tumour dissection. To ensure adequate specificity, radiologists could be encouraged to indicate their staging certainty (similar to the 5-point PI-RADS classification for *detection* of prostate cancer). A more radical alternative is to only describe the presence of T3 tumours only when reasonably certain; in other cases, T-staging with mpMRI is likely of limited value.

Alternatively, PSMA PET/CT may provide information on the local tumour stage. The anatomical resolution of PET is much lower compared to mpMRI, but the (bright) PSMA uptake is often unambiguous. Especially for detection of seminal vesical invasion, PSMA PET provides encouraging first results (specificity >90%)[21-23]. Increasing PET-resolution may further improve these outcomes. Lastly, PET and MRI can also be acquired simultaneously, leveraging the qualities of both techniques. The availability of PET/MRI systems is currently constricted to expert imaging centres, and some technical challenges remain. This should not hold back enthusiasm for the technique's superior visual quality, however. A prospective study investigating local tumour staging with ^{18}F-DCFPyL PET/MRI vs. mpMRI is currently undertaken (the *ProStaPET* study).

^{18}F-DCFPyL PET/CT

Currently, PSMA based PET diagnostics appear the most adequate imaging modality for detecting prostate cancer metastases[24-26]. Various PSMA-radiotracer have been developed (^{68}Ga-PSMA, ^{18}F-DCFPyL, and ^{18}F-PSMA-1007); superiority has not conclusively been proven for any of the tracers yet. ^{18}Fluorine-labelled ligands potentially outperform ^{68}Ga-PSMA in restaging of patients, though data on ^{18}F-PSMA is limited and coming from renowned diagnostic centres only. Compared to ^{18}F-DCFPyL, ^{18}F-PSMA-1007 theoretically improves visualization of tumours close to the bladder, but clinical confirmation is lacking. Furthermore, frequent off-target ^{18}F-PSMA-1007 uptake in bone is problematic (false-positive findings)[27, 28]. As it currently stands, there appears to be a future for ^{18}F-DCFPyL PET/CT.

Ultimately, the choice for any of the PSMA tracers may be driven more by product availability, pricing, and regulatory aspects (drug registration), than by subtle differences in diagnostic performance. Moreover, the impact of diagnostics differences in PSMA radiotracers should not be overestimated in terms of real clinical value. Adequate translation of the increased diagnostic sensitivity into effective therapeutic management is difficult (all prior clinical trials are based on conventional imaging). So far, no studies have yet established real improvement in patient outcomes (e.g. cancer-specific survival) by using PSMA PET in clinical decision making. Therefore, future research should not be focused on finding the 'best' PSMA tracer; proper (re)evaluation of clinical decisions based upon any PSMA PET will likely inform urologists or (radiation) oncologists more. This notion is supported by the consensus recommendation of the EORTC, advocating to integrate modern imaging techniques in clinical trials – without emphasis on the specific modality used (PSMA PET, choline PET, whole-body MRI)[17].

Still, newer radiotracers will likely be developed, potentially offering ever increasing diagnostic precision. To keep up with these diagnostic advances, dynamic research schemes are desired in which novel developments can be continuously introduced. This concept is effectively implemented in the famous STAMPEDE trials for metastatic prostate cancer[29], using a single control arm to compare multiple alternative treatments with. The trial is continuous and new treatment arms may be opened – the prior arms naturally serving as a comparator. A similar protocol could be followed with different imaging modalities, e.g. for restaging prostate cancer. Identical therapeutic decision should be undertaken in each diagnostic arm, upon detection of recurrences (e.g. irradiation of lesions, initiation of systemic treatments). Only then, the impact of different imaging outcomes may be quantified in terms of patient outcomes (e.g. time to castration resistance; cancer-specific survival; quality of life).

Besides optimizing the choice of tracer, diagnostic quality could be improved by ongoing technical optimization. With the arrival of digital PET/CT systems increasingly high image-resolutions will be possible. The results of Chapter 3 certainly encourage to investigate these developments. Higher resolution may increase diagnostic sensitivity, but comes at the risk of false-positive findings. To validate new imaging results, a good reference standard (pathology) is thus required. The prospective studies on PSMA PET in patients undergoing pelvic lymph node dissection (e.g. the SALT study[30], the OSPREY study[31]) provide valuable cohorts to this purpose. Moreover, these studies show lower than expected sensitivity for lymph node metastases in primary prostate cancer (40-45%) – even more reason to continue the search for technical improvements. Lastly, advanced quantitative analysis of PSMA PET scans could enhance prediction of (lymph node) metastases. Hundreds of *radiomics features* can be extracted from primary tumours. Combined with powerful statistical analysis (machine learning), adequate prediction of metastatic disease may be possible. Our results on ^{18}F-DCFPyL

PET radiomics-based prediction appear promising (AUC 0.86 ±0.14)[32]).

The clinical value of PSMA PET for follow-up of patients with metastatic prostate cancer is yet unknown. Here, radiographic progression is used as a measure for treatment response and a predictor of disease progression (survival). The use of PSMA PET as a predictor for clinical outcomes should be compared to follow-up based on conventional imaging. Conventional imaging is far less costly, but potentially less sensitive to changes in disease. The added sensitivity of PSMA PET imaging may be especially relevant for follow-up of therapies that are associated with significant toxicity and financial costs.

The last chapter of this thesis beholds potentially the biggest change in current clinical standards. A large number of patients treated with curative radiotherapy revealed metastasised disease on PSMA PET, prior to official diagnosis of recurrent disease. This calls for re-evaluation of the diagnostic paradigm and is an excellent opportunity to define clinical impact of PSMA PET imaging. A randomized trial may be initiated, in which patients are examined with PSMA PET upon any rising PSA (*i.e.* a PSMA based diagnostic paradigm) versus the standard diagnostic workup (the Phoenix criteria). Similar treatment should be agreed upon (*i.e.* metastasis-directed treatment, criteria for initiation of systemic treatment). Such design would establish the effect of early detection of recurrences on clinical outcomes, including time to castration-resistance, (cancer-specific) survival, but also evaluate the burden of additional treatment and diagnostic tests.

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