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aPROMISE: A Novel Automated-PROMISE platform to Standardize Evaluation of Tumor Burden in 18F-DCFPyL (PSMA) images of Veterans with Prostate Cancer

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ABSTRACT

Rationale: Standardized staging and quantitative reporting is necessary to demonstrate the association of ^{18}F-DCFPyL PET/CT (PSMA) imaging with clinical outcome. This work introduces an automated platform to implement and extend the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria - aPROMISE. The objective is to validate the performance of aPROMISE in staging and quantifying disease burden in patients with prostate cancer who undergo PSMA Imaging.

Methods: This was a retrospective analysis of 109 Veterans with intermediate and high-risk prostate cancer, who underwent PSMA imaging. To validate the performance of aPROMISE, two independent nuclear-medicine physicians conducted aPROMISE-assisted reads, resulting in standardized reports that quantify individual lesions and stage the patients. Patients were staged as having local only disease (miN0M0); regional lymph node only (miN1M0), metastatic disease only (miN0M1), and with both regional and distant metastatic disease (miN1M1). The staging obtained from aPROMISE-assisted reads was compared with the staging by conventional imaging. Cohen's pairwise kappa agreement was used to evaluate the inter-reader variability. Correlation coefficient and ICC was used to evaluate the inter-reader variability of the quantitative assessment (miPSMA-index) in each stage. Kendall Tau and t-test was used to evaluate the association of miPSMA-index with PSA and Gleason Score.

Results: All PSMA images of 109 veterans met the DICOM conformity and the requirements for the aPROMISE analysis. Both independent aPROMISE-assisted analyses demonstrated significant upstaging in patients with localized (23%; N=20/87) and regional tumor burden (25%; N=2/8). However, a significant number of patients with

bone metastases identified on conventional imaging (NaF PET/CT) were downstaged (29%; N=4/14). The comparison of the two independent aPROMISE-assisted reads demonstrated a high kappa agreement - 0.82 (miN0M0), 0.90 (miN1M0), and 0.77 (miN0M1). The Spearman correlation of quantitative miPSMA-index was 0.93, 0.96 and 0.97, respectively. As a continuous variable, miPSMA index in the prostate (miT) was associated with risk groups defined by the PSA and Gleason..

Conclusion: Here we demonstrate consistency of the aPROMISE platform between readers and observed substantial upstaging in PSMA imaging compared to the conventional imaging. aPROMISE may contribute to the broader standardization of PSMA imaging assessment and to its clinical utility in management of prostate cancer patients.

Key Words: ^{18}F-DCFPyL; PSMA; aPROMISE; segmentation; quantification; standardization; Prostate Cancer

INTRODUCTION

Prostate cancer is the most common solid tumor in men, with nearly 192,000 incidence cases and nearly 30,000 deaths in the United States annually. The accurate staging of a patient with prostate cancer is critical for selection of appropriate treatment strategies, especially as applied to differentiating between those with localized or regional disease who can be treated with curative intent versus those with metastatic disease. Whether or not surgery, radiation, and systemic hormone and/or chemotherapy are appropriate for a given patient is driven in large part by the clinical stage.(*1*) According to the recent updated National Comprehensive Cancer Network guidelines, 99mTc-phosphonate bone scintigraphy (bone scan) and computed tomography (CT) or magnetic resonance imaging MRI scans remain the standard imaging modalities used for prostate cancer staging. However, bone and CT scans have demonstrated limited diagnostic accuracy in earlier disease settings (*2,3*) which in turn limits accurate staging necessary for optimal prostate cancer management.

Accurate detection of metastatic disease is a particularly important goal because metastatic prostate cancer requires a different treatment approach and carries a significantly worse prognosis as compared to local disease. Positron Emission Tomography (PET) is a noninvasive technique that can image bone and soft tissue in a single modality, evaluate high-grade tumors that may not produce PSA, and provide a quantifiable data using the standardized uptake value (SUV). However, in prostate cancer PET tracers that image metabolic pathways, such as C-11 choline, C-11 acetate, and F-18-deoxyglucose (FDG) suffer from suboptimal sensitivity and specificity in detection of regional and distant metastatic disease. Recently, small ligands for PET-imaging have

been developed which target the cell surface protein Prostate Specific Membrane Antigen (PSMA), which is overexpressed in prostate cancer cells, but also expressed to some extent in other organs and blood vessels.(*4*) The radiopharmaceuticals based on the PSMA ligands have demonstrated high diagnostic accuracy for the detection of both regional and distant metastatic prostate cancer. The proPSMA trial demonstrated that PSMA PET/CT has greater staging accuracy than conventional imaging consisting of bone scan and CT for initial staging of patients with high-risk prostate cancer.(*5*) This supports the use of a single PSMA PET/CT rather than two conventional imaging modalities in this setting.

Recent efforts in standardizing the assessment of PSMA scans have resulted in a number of PSMA PET evaluation and reporting systems, including PSMA-RADS, EANM, and Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE).(*6-8*) While all the proposed criteria are focused on the characterization of individual PSMA lesions based on the location and the definition of significant uptake, the PROMISE standard is also proposing a patient level staging (miTNM), which is based on the detection and location of the disease in the PSMA PET/CT image. A Recent study comparing such standardized assessment has shown that they have a high inter-reader reproducibility.(*9,10*)

However, the adoption and implementation of PROMISE criteria in routine clinical practice and investigational studies is limited by the fact that it must be done manually and is labor-intensive. The manual work can be greatly facilitated through automation by deep learning image analysis. The structural radiological processes including the segmentation of anatomical structures (from CT) can be automated to contextualize and

characterize the functional imaging. The application of deep learning in automating the whole-body segmentation in PET/CT is the foundational framework of automating the PROMISE criteria. In this study, we introduce and evaluate the analysis of PSMA-PET images through aPROMISE, a deep learning platform to both automate standardized staging as well as generate a fully quantitative assessment of PSMA defined disease burden at the lesion and patient level.

MATERIALS AND METHODS

Patient Population

The purpose of our study was to evaluate the performance of the aPROMISE technology in standardizing the staging and quantification of prostate cancer disease. This investigation was a retrospective analysis of 109 Veterans with unfavorable intermediate and high-risk primary prostate cancer who underwent ^{18}F-DCFPyL PET/CT (PSMA) under clinical trial NCT03852654. NCT03825654 is a single arm trial of PSMA PET/CT in Veterans who also underwent conventional imaging with bone scan, CT or MRI. The study was approved by the local institutional review board at Veterans Affairs (VA) hospital (PCC 2018-100989), with waiver for individual informed consent.

Study Design

To validate the performance of aPROMISE, two independent board-certified nuclear medicine physicians -(three years of clinical experience) reviewed the PSMA images with the assistance of aPROMISE. No prior instructions were given, and the readers solely and independently relied on the aPROMISE workflow (detailed below). In summary, the

aPROMISE provides the reader with automated segmentation and quantification of lesions with pre-selected miTNM type. The reader can choose to accept or override the aPROMISE automated selections at the level of each individual lesion. A final report is auto-generated based on the aPROMISE assisted read.

First, the aPROMISE-assisted staging was evaluated against the conventional image staging obtained from the routine clinical reports. Conventional imaging in every patient included: ^{99m}Tc-methyl diphosphonate bone scan or ^{18}F-Sodium Fluoride PET/CT (NaF), and computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvis. Second, we evaluated the reproducibility of the staging and lesion quantification between the two independent aPROMISE-assisted reads. Finally, we evaluated the clinical association of quantitative PSMA uptake (miPSMA-index) with baseline clinical variables – Gleason Score, and PSA values. All patients were staged in four distinct categories:

1. Patients with localized disease and absence of regional lymph node or distant metastatic disease – miN0M0,
2. Patients with regional lymph node disease but absence of distant metastatic disease – miN1M0;
3. Patients with absence of regional lymph node but presence of distant metastatic disease – miN0M1;
4. Patients with presence of both regional lymph node and distant metastatic disease – miN1M1.

aPROMISE and miPSMA index

The aPROMISE v1.1 is a web-application, a class II software as a medical device (SaMD) developed by EXINI Diagnostics AB, Lund Sweden to standardize and quantify PSMA imaging in prostate cancer. aPROMISE is enabled with deep learning that automatically analyzes the CT image to segment anatomical regions in detail, including individual vertebrae, ribs, pelvic bones, and soft tissue organs including the prostate (**Figure 1**). The anatomical contextualization of the molecular image (mi) is used to stage the patient based on location and extent of the disease in the primary prostate tumor (miT), local/regional pelvic lymph node disease (miN) and distant metastasis (miM). Subsequently, the PET image is analyzed to detect target lesions. aPROMISE technology enables implementation of standard guidelines like PROMISE in standardizing PSMA assessment.(*6*) Merging the target lesion information with the anatomical location, each target lesion is quantified in terms of both intensity and volume and summarized by tissue type to generate the miPSMA index. The aPROMISE report is created automatically with both aggregated information as well as detailed information on a per lesion basis. Manual controls are provided as fallback to augment automatic analysis.

In the PROMISE criteria, Eiber et al. defined the miPSMA score of a lesion as 0 when uptake is below aorta, 1 when uptake is between aorta and liver, 2 when uptake is between liver and the parotid gland, and 3 when uptake is above parotid gland. The miPSMA lesion index is a continuous extension of this, defined by linear interpolation from the lesion SUVmean and the aorta and liver SUV references as follows:

$$\boldsymbol{LesionSUV_{mean}} \leq \boldsymbol{AortaSUV_{ref}}:$$
$$LesionIndex = \frac{LesionSUV_{mean}}{AortaSUV_{ref}}$$

$$\boldsymbol{AortaSUV_{ref} \leq LesionSUV_{mean} \leq LiverSUV_{ref}}:$$

$$LesionIndex = 1 + \frac{LesionSUV_{mean} - AortaSUV_{ref}}{AortaSUV_{ref}}$$

$$\boldsymbol{LiverSUV_{ref} \leq LesionSUV_{mean} \leq 2 \times LiverSUV_{ref}}:$$

$$LesionIndex = 2 + \frac{LesionSUV_{mean} - LiverSUV_{ref}}{LiverSUV_{ref}}$$

$$\boldsymbol{2 \times LiverSUV_{ref} \leq LesionSUV_{mean}}: LesionIndex = 3$$

The use of the parotid gland as a threshold has been replaced by 2 times liver reference since it is not certain that the parotid glands are included in all PSMA PET/CT scans. For each miTNM type, lesion uptake is aggregated into the Intensity-weighted Total Lesion uptake Volume (ITLV). This PSMA-index is defined as:

$$ITLV_{miX} = \sum_{Lesion of type miX} LesionIndex \times LesionUptakeVolume,$$

where miX can be any of miT, miN, miMa/b/c.

Statistical Analysis

Descriptive statistics were used to compare the aPROMISE staging to that of the conventional imaging. Cohen's pairwise kappa agreement was used to evaluate the inter-reader variability of aPROMISE-assisted staging - miN0M0, miN1M0, and miN0M1. Spearman and Kendall correlation coefficient was used to evaluate the inter-reader variability of the quantitative assessment (miPSMA-index) of each stage. Student's t-test

was used to evaluate the miPSMA-index values (in tumor) in the risk groups defined by the PSA and the Gleason Score. All statistical analyses were carried out using R version 4.0.2.

RESULTS

109 consecutive patients were included in the analysis. Baseline characteristics of the patients are detailed in **Table 1**. Conventional Imaging staged 87 of the 109 patients as localized disease with no regional lymph node or distant metastasis (N0M0), 8 patients with regional lymph node disease (N1M0), 14 patients with metastatic disease without regional lymph node disease (N0M1), and no patients with both regional and distant metastatic disease (N1M1). Of the 14 patients identified as N0M1, all were conventionally staged with bone metastasis (N0M1b) by ^{18}F Sodium Fluoride PET/CT scan and did not undergo ^{99m}Tc-methyl diphosphonate bone scan.

The duration of the aPROMISE assisted read, from selecting a patient to generating a complete report, was recorded at a mean of 3.2 minutes (range 1.8 – 5.1 minutes) per scan for reader 1 and 3.4 minutes (range 2.3 to 5.8 minutes) for reader 2. The comparative assessment of conventional against the aPROMISE assisted PSMA staging is detailed in **Table 2a and Table 2b**. Both aPROMISE assisted PSMA analyses demonstrated significant upstaging in patients with localized and regional tumor burden and downstaging of patients that were positive for distant bone metastasis by NaF PET/CT. In aPROMISE-assisted read-1, of the 87 patients who were determined to be negative for local (N1) or distant (M1) metastatic disease by conventional imaging, 20 (23%) were upstaged in PSMA imaging assessment to have regional lymph node (N=13)

and distant metastatic disease (N=6). Similarly, of the 8 patients staged as having pelvic nodal local only disease (N1), 2 (25%) were upstaged to having distant metastatic disease. Notably, a significant population with bone metastatic disease (by conventional imaging), were down staged by the aPROMISE-assisted PSMA imaging – 4/14 (29%). Examples of the down staged aPROMISE-assisted PSMA read against the NaF is demonstrated in **Figure 2**. The aPROMISE-assisted read-2 had similar observations against the conventional imaging (**Table 2b)**.

Inter-observer reproducibility of aPROMISE-reads: A comparison of the two independent aPROMISE-assisted read is detailed in **Table 3**. The kappa agreement between the two aPROMISE-assisted reads was 0.82 for categorization of patients with miN0M0, 0.90 for patient with miN1M0, and 0.77 for patients with miN0M1b. Among all the stages, the relatively modest discrepancy in aPROMISE-associated reads was most notable for isolated low intensity bone lesions. The quantitative reproducibility of miPSMA index in the cases that were categorized the same in the two independent aPROMISE-assisted reads, miN0M0 (N=66), miN1M0 (17), miN0M1(N=12), is illustrated in **Figure 3**. The spearman correlation was at 0.93, 0.96 and 0.97, respectively.

aPROMISE miPSMA index: As a continuous variable, miPSMA index in the prostate (miT) of all patients (N=109) was correlated with PSA values ($t=0.30$; $p<0.0001$). **Figure 4** shows the miPSMA index values in the prostate, stratified in risk groups defined by the PSA and separately by the Gleason Score. There was a significant difference in the PSMA index values of patients with PSA of ≤10ng/ml (median=17.61; IQR 8.75 – 44.63) compared to that observed in patients with ≥20ng/ml (median=54.63; IQR 27.55 – 80.79), $p=0.05$. Similarly, the PSMA-index values of prostate tumors with Gleason of 3+3

(median=19.45; IQR 9.97 – 23.54) was significantly lower compared to tumors with Gleason grade ≥4+3 (median=32.74; IQR 15.38 – 54.63), p=0.01.

DISCUSSION

The aPROMISE-assisted independent staging and the quantitative assessments of total disease burden were found to be consistent and reproducible between readers. Integrating PSMA assessment tools in the clinical workflow could allow for automation to provide efficiency, consistency, and accuracy in the staging and quantification of PSMA PET/CT. This study also demonstrated that the aPROMISE-assisted reads for PSMA PET/CT detected significantly more regional and metastatic lesions that were suspicious of disease than identified by the conventional imaging.

The ability of PSMA imaging to detect a greater number of suspicious metastatic lesions in comparison to conventional bone scan or CT has been evident across multiple studies.(*11-14*) The frequency of upstaging in nodal and distant metastasis by PSMA PET/CT compared to conventional imaging in this cohort of patients with intermediate and high-risk prostate cancer was in line with previous reports. Notably, the biological dimension of PSMA in evaluating suspected metastatic disease was particularly apparent when comparing findings from NaF to PSMA imaging. Of the 14 patients categorized as M1b through NaF scan, four (29%) were called negative in aPROMISE-assisted reads of their respective PSMA scan. As a bone metabolic scan NaF scan is known to be susceptible to non-pathophysiological features in bone like trauma, degenerative changes, fibrous dysplasia, etc. Of these four patients with lesions called on NaF image but not PSMA PET/CT, two demonstrated what appear to be more likely benign lesions

on PSMA PET/CT that were called positive on the corresponding NaF imaging. The other two patients with discordant findings in between NaF and PSMA imaging had suspicious appearing sclerotic bone lesions that were not picked up on the aPROMISE reads due to low lesion PSMA intensity. One of these two patients underwent curative intent radical prostatectomy and remains free of biochemical recurrence almost one-year post surgery without additional therapy. The other patients delayed treatment and instead underwent a repeat NaF imaging six months later that was without interval change in the bone lesion, however imaging demonstrated progression within soft tissue. In these two cases, clinical follow-up was more consistent with the PSMA PET staging rather than NaF imaging. A more comprehensive comparison of PSMA and NaF imaging is beyond the scope of this study but will be followed up in a separate analysis.

The inter-reader agreement on the interpretation of PSMA PET/CT has been evaluated mostly using ^{68}Ga-PSMA11 PET/CT. Fendler et. al evaluated inter-reader agreements in 50 patients with primary disease and after biochemical recurrence and found agreement $\kappa = 0.62$ (for primary tumor), 0.74 (for nodes), and 0.88 (for bone lesions).(*15*) In a more homogenous biochemically recurrent patient population consisting of patients with PSA levels up to 0.6 ng/ml, Miksch et al. demonstrated $\kappa = 0.76$ (for primary tumor), 0.73 (for nodes), and 0.58 (for bone lesions).*(16)* In one study, focused exclusively on 50 patients who underwent ^{18}F-DCFPyL PET, an intra-class correlation coefficient of 0.79 was derived for nodal disease.(*17*) Similarly, the manual reproducibility of following the PROMISE classification has been reviewed and reported by Toriihara, A et al. JNM 2020, which demonstrated a moderate inter-reader agreement (0.67) for miTNM classification in PSMA PET/CT.*(9)* The agreements between the aPROMISE-

assisted reads in our study compare favorably against these prior evaluations (Cohen's Kappa agreement >0.75), with a notable quick reading time (mean 3.2 and 3.4 minutes per scan). Notably, one reader in our study had considerably more prior experience in interpretation of PSMA PET/CT than the other. Still, a high degree of agreement was noted. Readers in our study did not get any strict guidance on lesion detection nor formal training on PROMISE criteria. The findings may suggest that an aPROMISE- assisted read, which involves automated segmentation, localization and lesion pre-selection, may nudge readers towards a moderately high agreement irrespective of their prior experience. This hypothesis warrants a multi-center multi-reader study for validation.

Quantitative metrics of disease burden may further enhance prognostic and predictive power of imaging. Currently, the automated bone scan index (aBSI) is the only FDA cleared SaMD that has been prospectively validated in a registration study as a prognostic imaging biomarker for metastatic prostate cancer.(*18*) The STAMPEDE trial investigated addition of radiation to the primary in M1 patients. In a post-hoc analysis that used aBSI to assess disease burden, aBSI was predictive of response to prostate radiotherapy.(*19*) The aBSI employs a machine learning algorithm that pre-selects and segments the lesions in bone and automatically computes a quantitative total tumor burden in Tc99m planar bone scans.(*20*) In some sense, the miPSMA index for quantification of disease burden defined by PSMA PET/CT can be considered a three-dimensional analog of aBSI.

However, the automated miPSMA index offers a far more comprehensive assessment of disease burden. The miPSMA index is a continuous extension of the miPSMA score proposed in the PROMISE criteria. Like the miPSMA score, the miPSMA

index is the PSMA quantification of an individual lesion in relation to the mean uptake in reference organs. The result is a linear quantification of PSMA burden for each lesion that can be summarized by each tissue type – miT, miN, $miM_{a/b/c}$. Our study showed an association between miPSMA-Index in the primary tumor and both Gleason grade and PSA value. This is consistent with prior studies reporting PSMA expression in the primary tumor is associated with higher Gleason grade and recurrence risk.(*21,22*) We hypothesize that miPSMA index may be useful for selecting patients for PSMA targeted radiotherapy, where current trials largely use qualitative assessments of PSMA expression as inclusion criteria. Moreover, there is a potential role for the miPSMA-index in conjunction with morphologic findings as a quantitative response assessment post-treatment.

The purpose of our hypothesis generating study was to evaluate the performance of the aPROMISE technology for subsequent prospective clinical investigations. The findings here enable future investigations to evaluate any additive benefits of aPROMISE-assisted reads over manual reads of PSMA PET/CT and to evaluate enhanced diagnostic performance of PSMA PET/CT when employing the aPROMISE software. Our study was limited in the number of independent reads and in its retrospective design. Therefore, the findings and the hypothesis presented here should be validated in a prospectively designed multi-reader and multi-institutional study design. In addition, lesions selected by aPROMISE have not been histopathologically validated. However, high specificity of PSMA-PET has been demonstrated in several recent studies.

Despite these limitations, our study demonstrates the performance of aPROMISE in an independent assessment. The incorporation of aPROMISE and miPSMA index in

subsequent clinical investigational can further explore its clinical context of use for prospective validation.

CONCLUSION

aPROMISE-assisted PSMA PET/CT reads generate detailed imaging reports at the whole patient and lesion level within minutes. aPROMISE-assisted reads of PSMA PET/CT upstages patients as compared to conventional imaging. Moreover, aPROMISE-assisted reads may standardize PSMA evaluation and reduce inter-reader variability, even amongst readers of differing baseline levels of experience. Prospective studies and direct manual comparison studies are required to validate these findings. The miPSMA index is a quantitative measure of lesion volume and relative intensity, is associated with Gleason grade and PSA, and describes overall and tissue-specific tumor burden. Evaluation of the miPSMA index as an imaging biomarker of disease burden is warranted in order to assess prognostic value.

KEY POINTS

Question

Can the aPROMISE platform generate a consistent and standardized evaluation of PSMA scans?

Pertinent Findings

The comparison of the two independent aPROMISE-assisted reads demonstrated a high kappa agreement in staging of patients in each present. As a continuous variable, miPSMA index in the prostate was associated with risk groups defined by the PSA values and Gleason Score.

Implication for patient care

aPROMISE-assisted reads may standardize PSMA evaluation and reduce inter-reader variability, even amongst readers of differing baseline levels of experience. The miPSMA index is a quantitative measure of lesion volume and relative intensity, is associated with Gleason grade and PSA, and describes overall and tissue-specific tumor burden.

Conflict of Interest Disclosures: Drs J. Brynlofsson, and K. Johnsson are employees of EXINI Diagnostics AB. Drs. A. Anand and P. Borelli has received honorary support from EXINI Diagnostics AB. All other authors have no disclosures to declare.

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Tables

Table 1. Patient Characteristics (N=109)

Age		**Gleason Score**	**N (%)**
average	70	3+3	13 (7%)
median	69	3+4	28 (23%)
minimum	55	4+3	24 (18%)
maximum	86	≥4+4	49 (36%)
Race	**N (%)**	**Diagnosis PSA**	**Value (ng/ml)**
White	54 (49%)	average	20.4 ng/mL
African American	44 (41%)	median	13.55 ng/mL
Hispanic	7 (7%)	minimum	3.03 ng/mL
Asian Pacific Islander	3 (2%)	maximum	167.92 ng/mL
Native American	1 (1%)		
Clinical T Stage	**N (%)**	**Percent of Positive Core**	**N (%)**
cT1/2	62 (57%)	<25%	18 (17%)
cT3	47 (43%)	25% - 50%	28 (26%)
		51% - 75%	14 (13%)
		>75%	28 (26%)
		Unknown	11 (10%)

Table 2a. aPROMISE-PSMA Staging read 1 vs. Conventional Imaging; N=109

		Local and Distant Metastatic Staging by **Conventional Imaging**			
		N0 M0 (N=87)	N1 M0 (N=8)	N0 M1a/b (N=14)	N1 M1a/b (N=0)
aPROMISE-PSMA Staging read 1	miN0M0 (N=71)	**67**	0	4	0
	miN1M0 (N=19)	**13**	**6**	0	0
	miN0 M1a/b (N=15)	**6**	**0**	**9**	0
	miN1M1a/b (N=4)	**1**	**2**	**1**	**0**

Table 2b. aPROMISE-PSMA Staging read 2 vs. Conventional Imaging; N=109

		Local and Distant Metastatic Staging by **Conventional Imaging**			
		N0 M0 (N=87)	N1 M0 (N=8)	N0 M1a/b (N=14)	N1 M1a/b (N=0)
aPROMISE-PSMA Staging read 2	miN0M0 (N=72)	**68**	0	4	0
	miN1M0 (N=18)	**12**	**6**	0	0
	miN0M1a/b (N=15)	**6**	**0**	**9**	0
	miN1M1a/b (N=4)	**1**	**2**	**1**	**0**

Table 3. aPROMISE-PSMA Read against aPROMISE-PSMA Read 2; N=109

		Local and Distant Metastatic Staging by **aPROMISE-PSMA Read 1**			
		miN0M0 (N=71)	miN1M0 (N=19)	miN0M1a/b (N=15)	miN1M1a/b (N=4)
aPROMISE-PSMA Read 2	miN0M0 (N=72)	**67**	2	3	0
	miN1M0 (N=18)	1	**17**	0	0
	miN0M1a/b (N=15)	3	0	**12**	0
	miN1M1a/b (N=4)	0	0	0	**4**

Figures

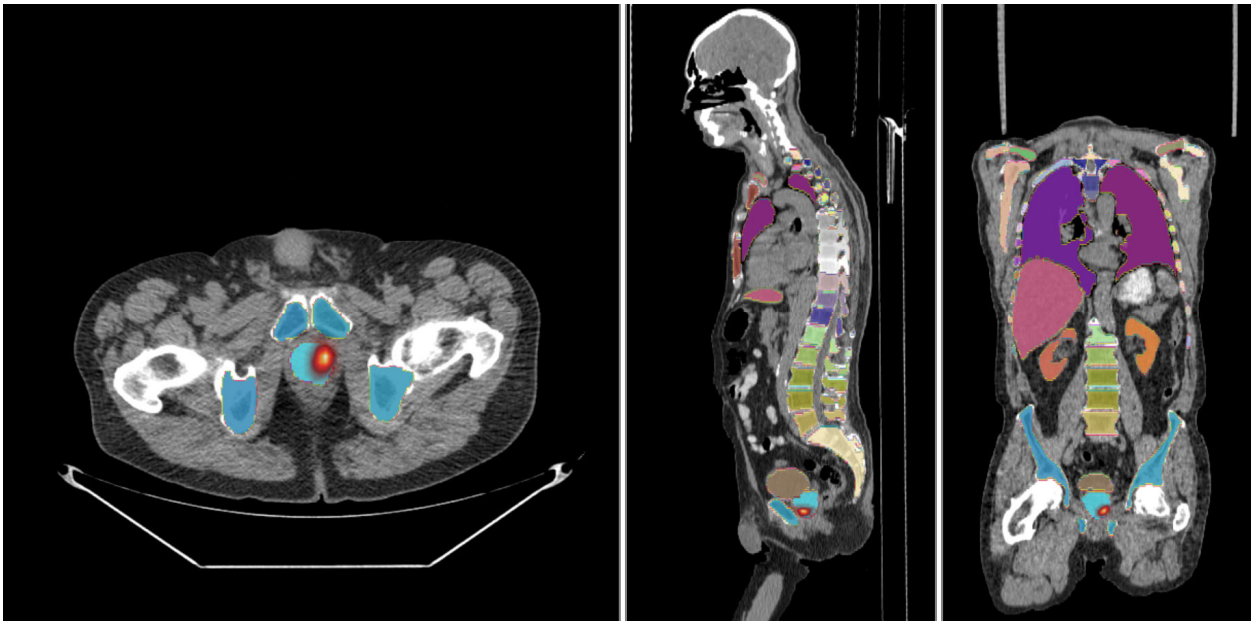
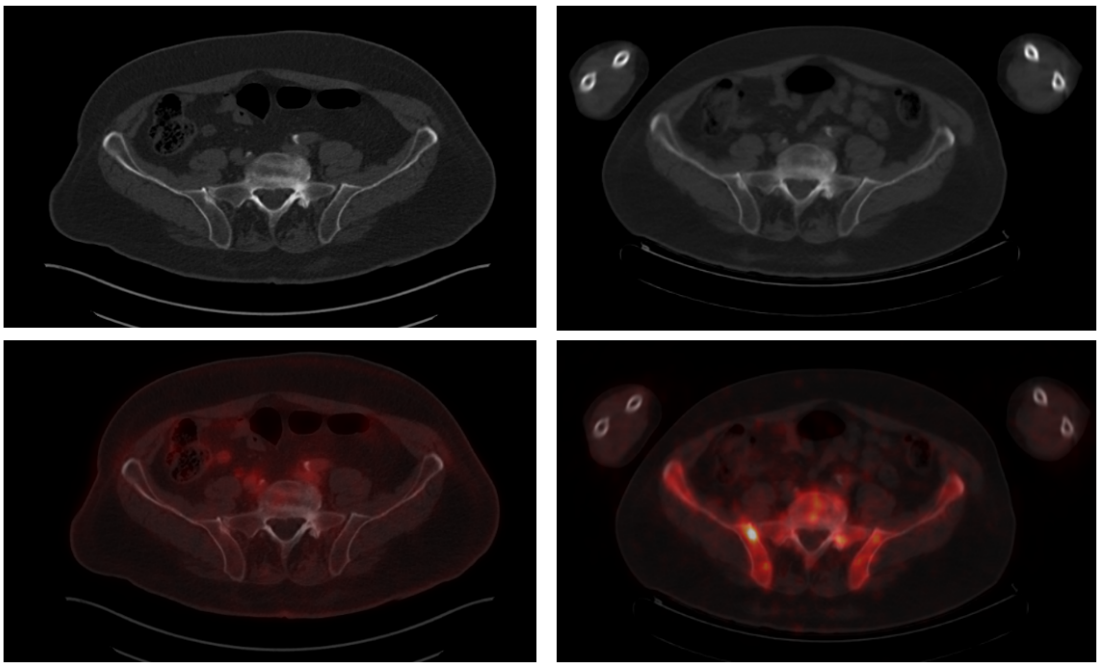


Figure 1. Deep learning enabled segmentation of anatomical context in low dose CT of PET/CT. Individual color represents the respective segmented organ. The aPROMISE technology enables automated segmentation of reference organs, and anatomical delineation of the disease in the prostate (miT), regional lymph nodes (miN), and distance metastases (miM).

A (Pt# 94 ^{18}F-DCFPyL) **B** (Pt# 94 Na^{18}F)



C (Pt# 28 ^{18}F-DCFPyL) **D** (Pt# 28 Na^{18}F)

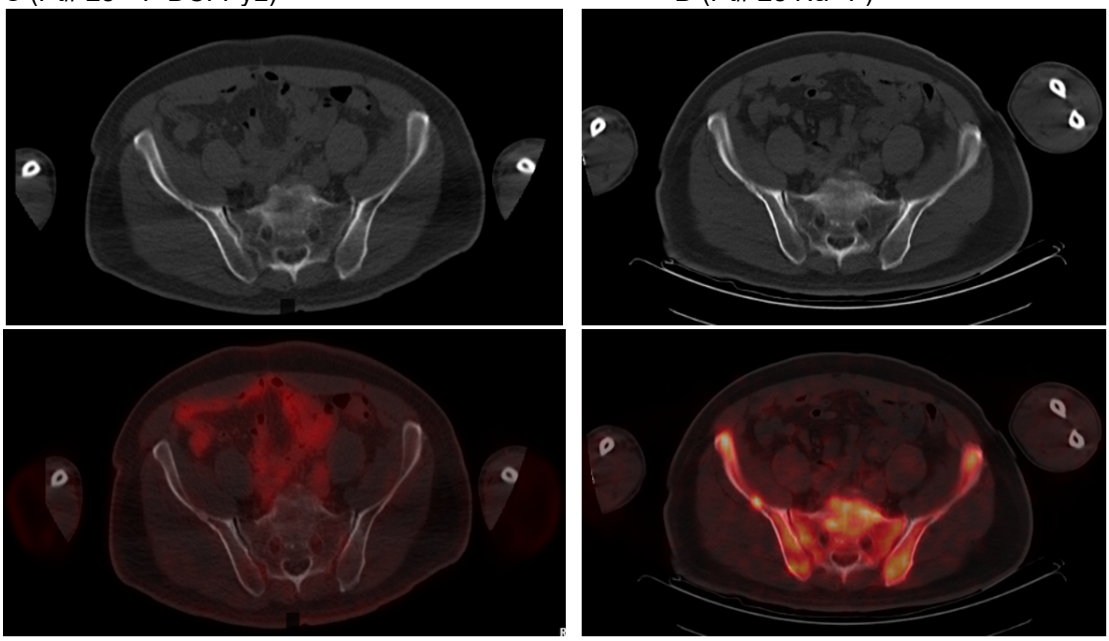


Figure 2. Example of cases (Pt# 94 and Pt#28) that were negative in the aPROMISE-assisted reads in ^{18}F-DCFPyL scan (A and C) compared to the Na^{18}F (B and D) and were down staged from N0M1 to N0M0.

A

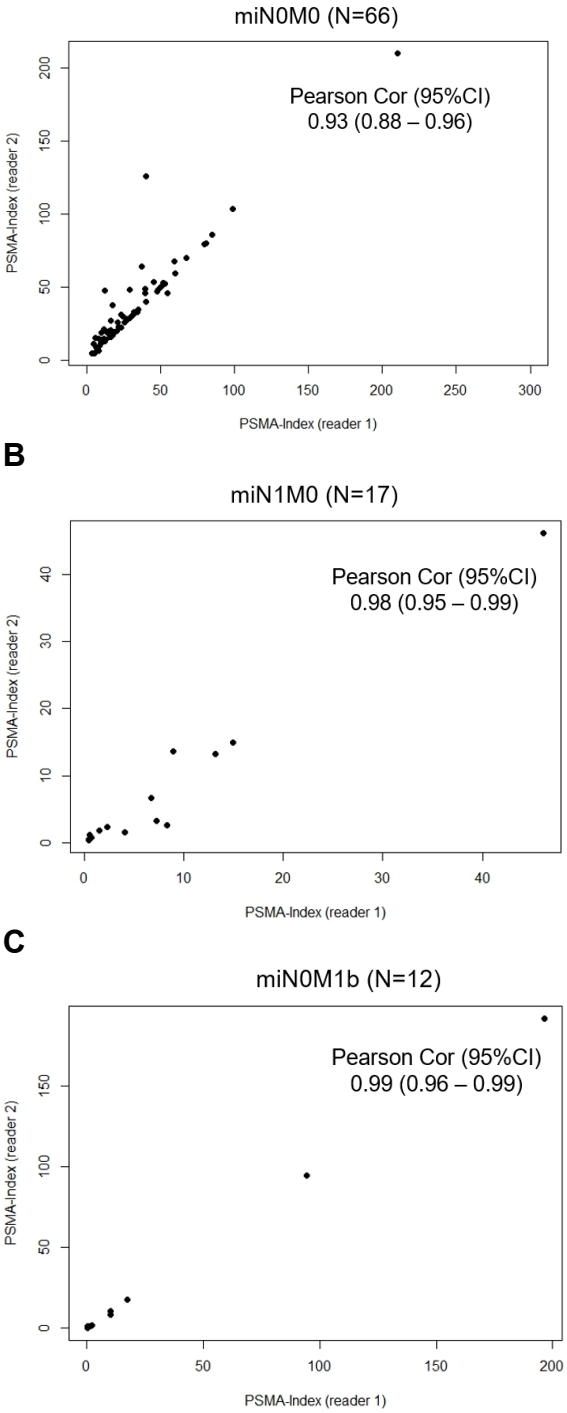
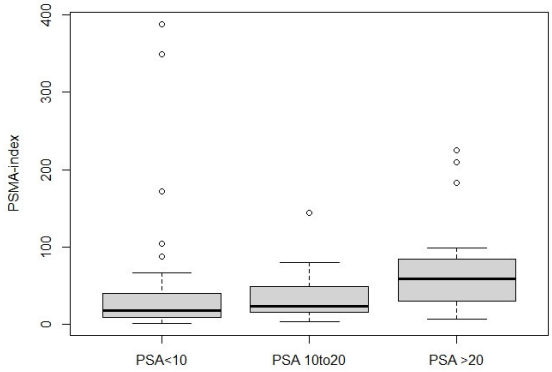
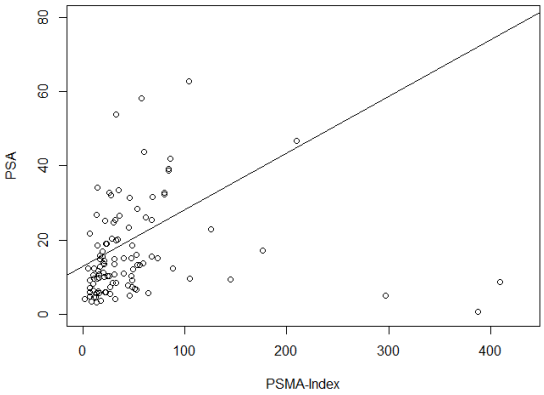


Figure 3. The quantitative reproducibility of the miPSMA-index in cases that were categorized the same in the two independent aPROMISE-assisted reads – miN0M0* (A), miN1M0 (B), and miN0M1(C). *One patient was excluded due to a manual segmentation error that incorporated the bladder.

A.



B.



C.

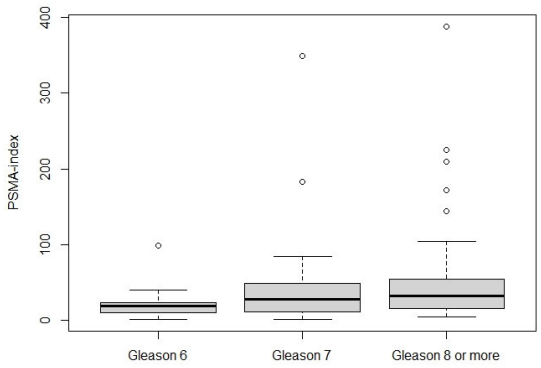


Figure 4. miPSMA-index values in the prostate, stratified by PSA (4A and 4B) and separately by Gleason grade (4C).