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Review – Prostate Cancer

Second Version of the Prostate Cancer Molecular Imaging Standardized Evaluation Framework Including Response Evaluation for Clinical Trials (PROMISE V2)

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Abstract

Context: Prostate-specific membrane antigen (PSMA) targeting positron emission tomography (PET) is emerging to become a reference imaging tool for the staging and restaging of patients with prostate cancer for both clinical routine and trials. The prostate cancer molecular imaging standardized evaluation (PROMISE) criteria have been proposed as a framework for whole-body staging (molecular imaging TNM staging, denoted miTNM staging) to describe the prostate cancer disease extent on PSMA-PET.
Objective: To create a comprehensive and integrated framework for PSMA-PET image interpretation and reporting.
Evidence acquisition: We propose the PROMISE V2 framework, which integrates an updated miTNM system, improved assessment of local disease, and a slightly modified PSMA-expression score for clinical routine. We have added a response monitoring

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PSMA-RADS
Prostate cancer molecular imaging standardized evaluation

framework defining qualitative and quantitative parameters to be recorded for a longitudinal assessment in clinical trials.
Evidence synthesis: We provide a comprehensive literature review on the current use of the PROMISE framework in clinical research and prospective trials. PROMISE variables demonstrate a clear association with survival. PSMA expression assessed by the PSMA-expression score was used in several trials, and a low PSMA-expression score is a negative prognosticator of overall survival after ^{177}Lu-PSMA radioligand therapy. The proposed imaging parameters recorded for response assessment in clinical trials can be utilized to determine response according to PSMA-PET progression (PPP) or Response Evaluation Criteria in PSMA-PET/Computed Tomography (RECIP) frameworks, but also future response criteria.
Conclusions: PROMISE V2 offers standardized reporting of disease extent for clinical routine and research. Parameters recorded within clinical trials facilitate objective response assessment.
Patient summary: Prostate-specific membrane antigen (PSMA) targeting positron emission tomography (PET) has become a standard imaging examination for prostate cancer. We propose a comprehensive framework for the analysis and reporting of PSMA-PET findings that will improve the communication between imaging experts and uro-oncologists.

1. Introduction

Prostate-specific membrane antigen (PSMA) targeted positron emission tomography (PET) demonstrates high accuracy for staging and restaging of patients with prostate cancer. Prospective clinical studies led to the Food and Drug Administration's approval of [68Ga]Ga-PSMA-11 and [18F]F-DCFPyL since 2020 and 2021, respectively [1–4]. A large body of evidence supports PSMA-PET use in several indications leading to its integration into clinical guidelines, for example, by the National Comprehensive Cancer Network or the European Association of Urology. Reproducible and standardized reporting of PSMA-PET is crucial for clinical implementation.

To facilitate standardized reporting, the first version of the prostate cancer molecular imaging standardized evaluation (PROMISE) was published in 2018 as a living framework and has already received >200 citations [5]. PROMISE provides standardized reporting of disease extent in histologically confirmed prostate cancer. Recently, the E-PSMA initiative for a European standardized reporting recommendation developed a template for a structured report including the molecular imaging TNM (miTNM) staging system proposed by PROMISE [6].

Here, we present the updated PROMISE V2 framework in accord with current experience and evidence from the literature [5]. PROMISE V2 comes with two standardized hierarchical levels of assessment (Fig. 1A): (1) an updated miTNM whole-body staging system and (2) reporting of the PSMA-expression score as a tool to annotate certainty of diagnosis and potential eligibility for PSMA radioligand therapy.

Furthermore, patterns of PSMA expression in the prostate were recently described to detect clinically significant prostate cancer in biopsy-naïve patients [7]. Patterns can be summarized in a 5-point scoring system (PRIMARY score) validated by a post hoc analysis of the prospective PRIMARY trial [8]. The updated PROMISE framework now integrates the PRIMARY score for the assessment of the prostate gland.

To account for the increasing use of PSMA-PET for treatment response assessment, recommendations for reporting of sequential examinations were integrated. The location of metastases (eg, locoregional vs systemic and visceral) significantly impacts the outcome [9]. Growing evidence supports PSMA-PET–derived tumor volume as a metric for treatment response. The use of PSMA-PET tumor volume is currently not suited for routine clinical use, but standardized assessment of organ-specific tumor volumes for clinical trials is of growing importance. We therefore provide recommendations for volume assessment and interpretation.

Finally, PROMISE V2 includes a reporting scheme for response parameters in clinical trials integrating lesion distribution and tumor volume. This reporting scheme serves as a common ground for defining measurable parameters in PSMA-PET that can be used as inputs for current or future models to assess a response or prognosis. For example, this reporting scheme enables the application of existing PSMA-PET response metrics such as the PSMA-PET Progression (PPP) criteria and the Response Evaluation Criteria in PSMA-PET/CT (RECIP) framework [10,11]: PPP focuses on the response of single lesions in PSMA-PET and is therefore used to assess the limited disease extent seen in metastatic hormone-sensitive prostate cancer (mHSPC). In contrast, the RECIP framework relies on the PSMA-PET–derived total tumor volume and is more appropriate for extensive disease. It has been established and validated in the metastatic castration-resistant prostate cancer (mCRPC) setting of patients receiving ^{177}Lu-PSMA radioligand therapy.

2. Evidence acquisition

2.1. Standardized reporting of PSMA-PET in clinical routine

The initial PROMISE framework proposed a standardized reporting scheme for a single time point assessment [5]. In PROMISE V2, we updated staging recommendations (miTNM), integrated the PRIMARY score to facilitate

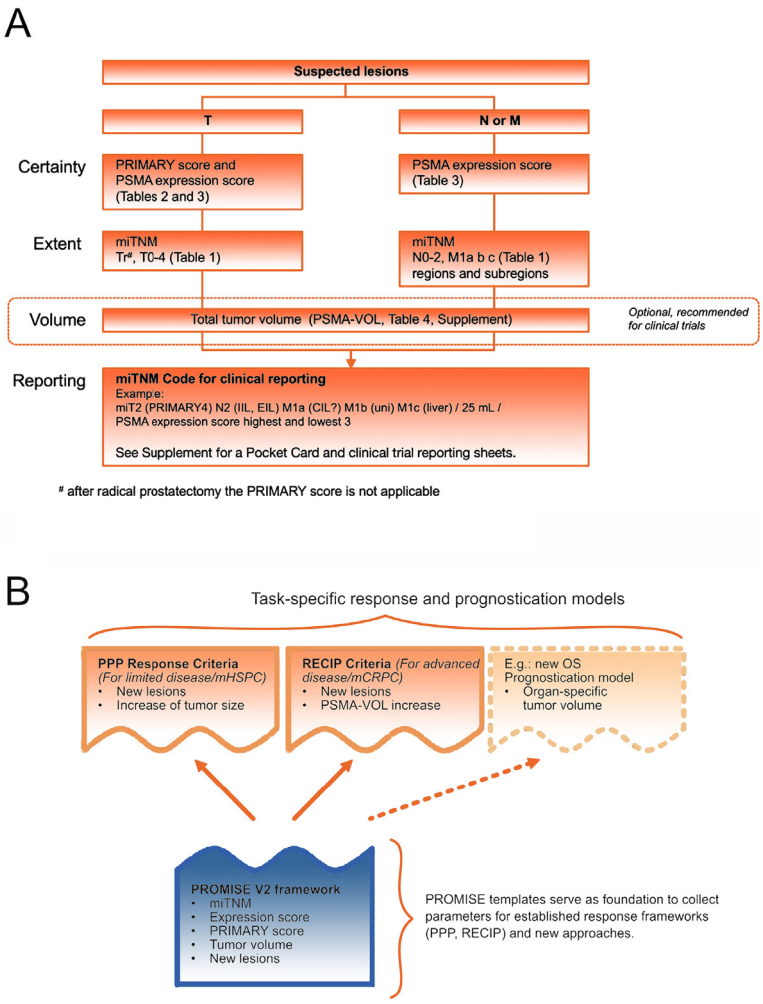

Fig. 1 – PROMISE V2 framework.Assessment within the PROMISE V2 framework for one timepoint in clinical routine (A) and role of PROMISE V2 as framework for standardized response assessment (B).

reporting of primary prostate cancer, and propose minor modifications of the PSMA-expression score. A pocket card was added to provide a quick reference for routine practice (Supplementary material).

2.1.1. *miTNM*

The miTNM system enables standardized reporting of PSMA-PET. The following modifications for lesion location assignment have been made (Table 1):

2.1.1.1. Tumor staging. The miT2–4 categories to characterize local tumor extent and miTr to describe local recurrence after radical prostatectomy are retained unaltered (Table 1 and Supplementary Fig. 1). The initial attempt to report local tumor extent on a sextant base was regarded as inconsistent between readers and unreliable in clinical practice, and was thus removed. High accuracy of PSMA-PET for intraprostatic lesion extent was reported previously [12–14]. The accuracy of PSMA-PET in detecting seminal vesicle infiltration was 86%, and the accuracy in detecting extension beyond the capsule was 71% [15]. Addition of PSMA-PET to multiparametric magnetic resonance imaging enhances sensitivity for extracapsular disease but slightly reduces specificity [16].

2.1.1.2. Nodal staging. The definition of pelvic lymph nodes is now aligned with the American Joint Committee on Cancer staging manual [17]: Only lymph nodes in the true pelvis are regarded as regional (Table 1 and Supplementary Figs. 1 and 2). Anatomically, the true pelvis is defined by the pelvic brim. Therefore, lymph node metastases in the common iliac region are now reported in the miM1a category.

2.1.1.3. Distant metastasis staging. The main categories for distant lymph node metastases (miM1a), bone metastases (miM1b), and visceral metastases (miM1c) are retained (Table 1 and Supplementary Fig. 2). In PROMISE V2, inguinal and other extrapelvic lymph node metastases are now classified as distant lymph node metastases (miM1a). The miM1c category for visceral metastases includes but is not limited to the liver, lung (including pulmonary lymphangiosis), adrenals, and brain. Pleural and peritoneal carcinomatosis has newly been introduced as an "other" distant region.

2.1.2. Assessment of intraprostatic lesions

The PRIMARY score was integrated for the assessment of intraprostatic lesions. The 5-point PRIMARY score combines intraprostatic pattern and intensity on PSMA-PET (Table 2) [7]. Score results were associated with the presence of clinically significant cancer in biopsy-naïve men with suspected prostate cancer and have been established on the basis of ^{68}Ga-PSMA-11 uptake patterns. One PRIMARY score will be assigned on a patient basis for the most clinically significant intraprostatic pattern. PRIMARY scores 1–2 are negative and therefore reported as miT0 in PROMISE V2, whereas PRIMARY scores 3–5 will be assigned to the miT2, miT3, or miT4 category depending on the presumed disease extent. The PRIMARY score was developed in a post hoc analysis using data from the prospective PRIMARY trial in men with suspected prostate cancer prior to biopsy [7,8].

PRIMARY design is based on the following assumptions: (1) prostate cancer is more likely to arise in the peripheral zone and (2) some background uptake in PSMA-PET can be observed in the transition and especially central zones. Therefore, no minimum threshold is required for the peripheral zone, and focal activity at least twice the background activity is required for the transition and central zones to suspect prostate cancer. In the PRIMARY trial, significant prostate cancer was present in all patients with very high PSMA uptake (maximum standardized uptake value >12) [7,8]. The PRIMARY score assessment resulted in sensitivity of 88% for the detection of clinically significant prostate cancer in the post hoc analysis (specificity: 64%, positive predictive value: 76%, negative predictive value: 81%) [7].

2.1.3. PSMA-expression score

The PSMA-expression score 4-point scale was retained with a minor modification (Table 3 and Supplementary Fig. 3). We replaced "equal or higher than the reference organ" with "higher than the reference organ." The PSMA-expression score is applicable only to lesions with morphologic correlate >10 mm diameter to ensure suitable spatial resolution. A PSMA-expression score of $\geq$2 is regarded as suspicious for malignancy on a per-lesion base and generally required for the eligibility of PSMA radioligand therapy [18]. Especially in patients with advanced disease, it is encouraged to report the highest and lowest scores to illustrate the spectrum of disease positivity.

2.2. Standardized longitudinal assessments of PSMA-PET in clinical trials

Recent data indicate that PSMA-PET–derived measurements have high retest repeatability, facilitating its use for longitudinal disease monitoring [19,20]. Preliminary data propose the PSMA-derived tumor volume as an overall survival

Table 1 – Whole-body miTNM staging system for standardized PSMA-PET interpretation

Local tumor (T)			
miT0		No local tumor	
miT2		Organ-confined tumor	
	u	Unifocality	
	m	Multifocality	
miT3		Non–organ-confined tumor	
	a	Extracapsular extension	
	b	Tumor invades seminal vesicle(s)	
miT4		Tumor invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall	
miTr		Presence of local recurrence after radical prostatectomy	
Intrapelvic nodes (N)			
miN0		No positive pelvic lymph nodes	
miN1		Single lymph node region harbors lymph node metastases, report location by a standardized template	Lymph node regions: II internal iliac, laterality (L/R) EI external iliac, laterality (L/R) OB obturator, laterality (L/R) PS presacral OP other pelvic
miN2		Multiple ($\geq$2) lymph node regions harbor lymph node metastases, report location(s) by a standardized template	
Distant metastases (M)			
miM0		No distant metastasis	
miM1		Distant metastasis	
	a	Distant lymph node region(s)	miM1a regions: CI common iliac, laterality (L/R) RP retroperitoneal SD supradiaphragmatic OE inguinal and other extrapelvic
	b	Bone(s), additionally report pattern and involved bone(s) in case of unifocal or oligometastatic	Bone uptake patterns: uni unifocal oligo oligometastatic ($n \leq 3$) diss disseminated dmi diffuse marrow involvement
	c	Other site(s), additionally report involved organ (hep, pul, adrenal, brain, other). Other includes pleural or peritoneal invasion	

PSMA-PET = prostate-specific membrane antigen targeting positron emission tomography.

Table 2 – PRIMARY score, its relation with the PSMA-expression score and respective miT category

PRIMARY score	Pattern and intensity[a]	PSMA expression score	Local tumor (T) extent
1	No dominant intraprostatic pattern on PSMA. Low grade activity	0–1	miT0
2	Diffuse transition zone activity or symmetrical central zone activity that does not extend to the prostate margin on CT	1–2	miT0
3	Focal transition zone activity visually twice above background	2–3	miT2, miT3, or miT4
4	Focal peripheral zone activity (no minimum intensity).	1–3	miT2, miT3, or miT4
5	Intense uptake (visual very high intensity or SUV_{max} >12)	3	miT2, miT3, or miT4

CT = computed tomography; PSMA = prostate-specific membrane antigen; SUV_{max} = maximum standardized uptake value.
Modified with permission from Emmett et al. [7].
[a] Quantitative parameters for the PRIMARY score were established using ^{68}Ga-PSMA-11.

prognosticator, for example, in patients undergoing PSMA radioligand therapy [21,22]. A decrease of PSMA-derived tumor volume during treatment is associated with prolonged survival, if loss of PSMA expression is ruled out as a confounder [11,23,24]. We recommend the use of semiautomated approaches (such as aPROMISE, qPSMA, MICIIS/PARS, MIM, LIFEx etc.) for quantification as an exploratory endpoint (see the Supplementary material for methodological details) [22,25–27].

Here, we propose standardized parameters for longitudinal reporting of PSMA-PET for clinical trials enabling multiple time point assessment (Table 4 and Fig. 1B). Baseline and follow-up analyses of PSMA-PET in the context of clinical trials should include miTNM, lesion count (up to a defined maximum), occurrence of new lesions, and tumor volume. These parameters allow for response assessment in accordance with existing or new classification systems.

Two classification systems for response assessment have already been proposed, which include descriptive elements (eg, number of new lesions, diameter of hottest lesion), and volumetric assessment (Table 5): the PPP criteria are focusing on single lesions and are therefore more suitable for limited systemic disease as often seen in mHSPC. The RECIP framework has been developed and validated based on data from PSMA radioligand therapy and may be more amendable in the mCRPC setting [10,11]. RECIP or PPP yielded higher prognostic value and inter-reader reliability than adapted RECIST 1.1, adapted PCWG3, or adapted PERCIST criteria [28]. Reporting schemes for standardized longitudinal assessment of PSMA-PET are provided in the Supplementary material.

3. Evidence synthesis

Here, we present the updated PROMISE V2 framework including the modified miTNM system, PSMA-expression score for whole-body staging, and integration of the PRIMARY score for local disease assessment [7,29]. Examples for PROMISE in clinical routine are presented in Supplementary Fig. 4. For clinical trials, PROMISE V2 now reports a standardized template for collecting the various imaging parameters for miTNM, PPP, RECIP and tumor volume assessments.

The standardized reporting framework of PROMISE V2 has potential utility across a range of indications including staging of high-risk patients, biochemical recurrence, and evaluation of suitability for ^{177}Lu-PSMA radioligand therapy. These indications are now recommended in the guidelines on the criteria for appropriate use, based on high-level evidence [30]. Future research will also define utility of PSMA-PET for initial diagnosis of prostate cancer and evaluate the PRIMARY score integrated in PROMISE V2 [7].

So far, the miTNM classification was employed in prospective clinical trials, for example, by Fendler et al. [3] in patients with biochemical recurrence and Hope et al. [4] for pelvic lymph node staging in newly diagnosed intermediate- to high-risk prostate cancer. Both studies contributed to the regulatory approval of ^{68}Ga-PSMA-11 in December 2020 [31].

Several software tools have been designed to integrate miTNM staging. For example, aPROMISE (EXINI Diagnostics AB, Lund, Sweden) and PylarifyAI (Lantheus, North Billerica, MA, USA) were developed to facilitate the PSMA-PET analysis according to the miTNM criteria [26]. Mint Medical (Heidelberg, Germany) is integrating the miTNM classification in their reporting suite. Two open-source implementations of miTNM (ePROMISE and TNM stager) allowing standardized reporting are likewise available [32,33].

Current evidence for the prognostic value of PROMISE was extracted from Web of Science (Clarivate Analytics,

Table 3 – Updated PSMA expression score

Score	Reported PSMA expression	Uptake (PROMISE V1)	Uptake (PROMISE V2)	PSMA status for PSMA radioligand therapy[a] [18]
0	No	Below blood pool	Equal to or lower than blood pool	Negative
1	Low	Equal to or above blood pool and lower than liver[b]	Equal to or lower than liver[b] and higher than blood pool	Negative
2	Intermediate	Equal to or above liver[b] and lower than parotid gland	Equal to or lower than parotid gland and higher than liver[b]	Positive
3	High	Equal to or above parotid gland	Higher than parotid gland	Positive

PROMISE = prostate cancer molecular imaging standardized evaluation; PSMA = prostate-specific membrane antigen.
[a] For detailed criteria of selecting patients for PSMA radioligand therapy including lesion size and nature of lesions (lymph node, bone, and visceral), see the work of Kuo et al. [47].
[b] For PSMA ligands with liver dominant excretion (eg, [^{18}F]F-PSMA1007), the spleen is recommended as the reference organ instead of the liver.

Table 4 – Qualitative and quantitative imaging parameters for clinical trial PET interpretation

Category		PRIMARY (miT) or PSMA expression (all other) score	PSMA VOL of subregion (ml)	Diameters[a]	Total number of PET-positive lesions[b]	Any new lesion not previously detected on PSMA-PET
Local tumor (T)						
miT2–4		One hottest lesion[c]	Total	One hottest lesion (if feasible)[d]	*N*	No/yes (one)/yes (two or more)
miTr		One hottest lesion[c]	Total	One hottest lesion (if feasible)[d]	*N*	No/yes (one)/yes (two or more)
Intrapelvic nodes (N)						
miN1 or N2		One hottest lesion[c]	Total	One hottest lesion	*N*	No/yes (one)/yes (two or more)
Distant metastases (M)						
miM1						
	a	One hottest lesion[c]	Total	One hottest lesion	*N*	No/yes (one)/yes (two or more)
	b	One hottest lesion[c]	Total	One hottest lesion	Pattern (Table 1) and *N* lesions (only for oligo and diss)	No/yes (one)/yes (two or more)
	c	One hottest lesion[c]	Total	One hottest lesion	*N*	No/yes (one)/yes (two or more)
Total tumor volume (not only the sum of target lesions) is given in milliliters.						

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; VOL = volume.
[a] As per RECIST1.1 if measurable on CT or MRI, optional data for exploratory purpose or for follow-up lesion validation only.
[b] Report up to five or ">5" lesions for each category: T, N, M1a, M1b (oligo), M1b (diss), or M1c.
[c] The highest PRIMARY (miT) or PSMA expression (all other) score of the hottest lesion.
[d] Lesion diameter might be retrieved from additional MRI data.

Table 5 – Current frameworks for response assessment using PSMA-PET: PPP and RECIP [10,11]

Criteria	Definition
PPP	
PD	1. Volume increase of any metastasis ≥30% and consistent clinical/lab data Or 2. Two or more new PSMA-positive lesions Or 3. One new PSMA-positive lesion and consistent clinical/lab data
Non-PD	All other
RECIP	
PD	Total tumor volume increase ≥20% and new lesions
PR	Total tumor volume decrease ≥30% without new lesions
CR	Absence of any PSMA uptake on PET
SD	All other

CR = complete remission; CT = computed tomography; PD = progressive disease; PET = positron emission tomography; PPP = PSMA-PET progression; PR = partial remission; PSMA = prostate-specific membrane antigen; RECIP = Response Evaluation Criteria in PSMA-PET/CT; SD = stable disease.

Philadelphia, PA, USA) using these parameters: Original Research, abstract keywords (PSMA AND positron AND survival) OR (RECIP AND PSMA AND survival) OR (PPP AND PSMA AND survival). From 82 search results, 25 (30.5%) clinical studies that analyzed the association between PROMISE related parameters and oncologic outcome were selected (Supplementary Table 1). Two studies (8%) were prospective, and two studies (8%) included patients from mixed prospective and retrospective cohorts.

In total, 18 studies demonstrate that the location of prostate cancer metastases on PET is a prognosticator of outcome (Supplementary Table 1, miTNM) [34]. Emmett et al. [35] demonstrated a correlation between progression-free interval and tumor location prior to salvage radiotherapy. The rate of 3-yr freedom from progression dropped from local (miTr), nodal (miN1/2), and distant lymph nodes (miM1a) to bone and visceral (miM1b/c) disease [35]. Further studies demonstrated an association between miTNM disease location and survival or recurrence rate in the setting of initial surgery, radiotherapy of the prostate, salvage surgery, salvage radiotherapy, or metastases-directed therapy (Supplementary Table 1).

The miM1c lesions, especially liver metastases with potential dedifferentiation or neuroendocrine differentiation, are associated with short overall survival, as shown for ^{177}Lu-PSMA radioligand therapy [36–38]; miM1b and miM1c (liver) locations were independently associated with short overall survival in patients assessed for PSMA radioligand therapy eligibility [39].

Four studies report an association between visual PSMA-expression score in accordance with PROMISE and survival following ^{177}Lu-PSMA radioligand therapy (Supplementary Table 1, PSMA expression). Specifically, a low PSMA-expression score is a negative prognosticator of overall survival after ^{177}Lu-PSMA radioligand therapy [40–43]. The PSMA-expression score initially defined in 2018 is an easy and intuitive score, and its previous version has served as a template for assessing PSMA-PET screening examinations, for example, in the VISION or RESIST-PC prospective studies [18,44]. Notably, the PSMA-expression score has been modified slightly and aligned with the interpretation in the VISION study [18]. We propose standardized reporting of the lowest and highest PSMA-expression scores for any patient with N1/M1 disease. This provides a quick reference on target expression when PSMA radioligand therapy is considered.

We now provide a summary of imaging parameters to be recorded for response assessment including template documents in the Supplement. Imaging parameters recorded by

PROMISE V2 can be utilized to assess treatment response according to PPP or RECIP, but also future response criteria. We strongly believe that anatomical reporting of lesion distribution (locoregional vs distant and visceral) is important given the known association with survival. Lesion reporting should be supplemented by quantification of tumor volume changes for PPP or RECIP assessment. A recent study demonstrates an association between response according to PPP and overall survival [45]. RECIP was established in a retrospective multicenter study on overall survival following ^{177}Lu-PSMA radioligand therapy and was further validated in an independent mCRPC cohort [28,46].

4. Conclusions

Here, we report the updated PROMISE V2 framework for the standardized reporting of PSMA-PET for research and clinical routine. PROMISE V2 provides harmonized miTNM categories, improved assessment of local disease, and a slightly modified PSMA-expression score. Additionally, we propose a reporting template for response assessment in clinical trials by defining qualitative and quantitative imaging parameters to be recorded. These templates serve as a basis for current and future response assessment frameworks.

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Peer Review Summary

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