RECIP 1.0: A Roadmap for Clinical Implementation

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Objective response evaluation in oncologic disease is a key endpoint of patient outcome. Response assessment has been performed using tumor measurements at the individual lesion level. For example, RECIST 1.1 defines progression on CT images on the basis of a change in lesion diameter or occurrence of new lesions (*1*), whereas PERCIST 1.0 adapts metabolic measurements to evaluate response using FDG PET imaging (*2*). In prostate cancer, the Prostate Cancer Working Group criteria define progression as occurrence of at least 2 new lesions for a bone scan and otherwise follow RECIST 1.1 definition for CT images (*3*). The bone scan index calculated on a bone scan was the first attempt to evolve response evaluation from traditional lesion-level measurements to whole-body tumor burden assessment; however, its standardization and clinical implementation have met with mixed success (*4*).

Prostate-specific membrane antigen (PSMA) PET/CT is a relatively new imaging modality for prostate cancer that has received regulatory approval within the past 4 y. Although its superior diagnostic accuracy compared with conventional imaging has been established, definitive evidence of its role for treatment monitoring of prostate cancer is still being generated. Response criteria for PSMA PET needed to be rationally designed, simple enough for routine use, yet accurate and validated by multicenter clinical evidence.

With this intent, RECIP 1.0 was proposed in 2022 as the first standardized framework to evaluate treatment response in prostate cancer using PSMA-targeted PET/CT imaging (*5*). RECIP 1.0 introduced the concept of using measurements of total tumor volume and lesions in PSMA PET imaging to monitor therapeutic efficacy in prostate cancer. In a direct comparison with other response frameworks applied to PSMA PET/CT, such as Prostate Cancer Working Group 3, PERCIST, and PSMA PET progression, RECIP achieved the highest interreader reliability and highest prognostic accuracy (*6*). The RECIP framework incorporates evaluation of 2 parameters: responses in PSMA-positive total tumor volume (PSMA-VOL) and status of the occurrence of new lesions (Table 1). PSMA-VOL was shown to be a relevant spatial biomarker with high prognostic value across the prostate cancer clinical states (*7*). qPSMA was the first software tool developed to enable whole-body tumor quantification specifically using PSMA PET/CT imaging (*8*), but several other tumor quantification software have been used to determine RECIP 1.0 (*9–13*). The original RECIP 1.0 incorporated quantitative changes in PSMA-VOL, and cutoff definition for changes in PSMA-VOL obtained using qPSMA was established (response, ≥30% decrease; progression, ≥20% increase). Among several cutoffs tested, the ones established achieved the highest prognostic value for overall survival in patients with biochemical recurrence of prostate cancer and late-stage metastatic castration-resistant prostate cancer (*5,9*). Importantly, these cutoff definitions are software agnostic and can be applied to any quantification tool in the future (*5*). More sophisticated approaches for tumor segmentation using artificial intelligence technologies were developed subsequently for commercial use, but they are not widely available (*14*). Head-to-head comparison among different quantification software and the impact of their output on calculating RECIP 1.0 is warranted.

To overcome the limited availability of tumor quantification tools, Gafita et al. (*15*) investigated whether responses in PSMA-VOL can be determined accurately with visual interpretation by nuclear medicine specialists. Responses in PSMA-VOL were evaluated qualitatively by means of side-by-side comparison of baseline and follow-up maximum-intensity projection (MIP) PET images. Additionally, review of axial images was performed to confirm MIP findings or for lesion-based analysis in borderline cases. The study found an excellent agreement (84%) among 5 readers and almost perfect agreement (94%) between visual assessment by physicians and quantitative assessment by segmentation software of responses in PSMA-VOL. These strikingly positive findings encouraged investigators to add a new component to the RECIP framework: visual evaluation of responses in PSMA-VOL using PSMA PET MIP images to determine RECIP 1.0. Validation of visual RECIP in early-stage prostate cancer in patients with low tumor burden is warranted before its clinical implementation in this setting.

Although standardizing the interpretation of PET MIP images for tumor response evaluation was conceptualized within the RECIP 1.0 framework, visual comparison of MIP PET images is commonly used in daily practice during interpretation of pairs of PET/CT scans in oncology. In fact, comparison of MIP PET images is typically the first assessment nuclear medicine specialists perform at the beginning of interpreting pairs of PET/CT scans. However, the purpose of comparing MIP PET images has been limited to providing an estimation of disease response.

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TABLE 1
RECIP 1.0 Definition

Criteria	Definition
New lesion	Any new focal uptake of PSMA ligand
	• Higher than surrounding background
	• With tumor SUV_{max} > blood-pool SUV_{max}
	• Not present on baseline scan (tumor SUV_{max} < blood-pool SUV_{max}), with tumor uptake not attributable to physiologic uptake or pitfalls
	Any new malignant lesion detected on follow-up CT images independent of PSMA ligand uptake
RECIP 1.0	
RECIP-CR	Absence of any PSMA uptake on follow-up PET scan
RECIP-PR	Significant reduction (quantitatively, ≥30%) in PSMA-VOL without appearance of new lesions
RECIP-PD	Significant increase (quantitatively, ≥20%) in PSMA-VOL with appearance of new lesions
RECIP-SD	None of the above

CR = complete response; PR = partial response; PD = progressive disease; SD = stable disease.

Formal response assessment and reporting are performed using traditional individual lesion-level measurements. The comparison of MIP PET images had not been included in formal tumor response assessment primarily because of a lack of standardization and a lack of trust in the method itself due to being traditionally perceived as oversimplified and imprecise. Nevertheless, an international survey found that visual RECIP 1.0 was implemented in PSMA PET/CT clinical reports during PSMA theranostics at 11% of participating institutions (*16*), highlighting that the nuclear medicine community is slowly adopting this methodology to determine objective response in prostate cancer. Of note, visual RECIP has been validated in advanced prostate cancer only. Evaluation of interreader agreement and prognostic accuracy of visual RECIP in early-stage prostate cancer is required before its clinical implementation in this setting.

However, 2 crucial aspects needed to be addressed to enable clinical implementation of PSMA PET MIP assessment in radiology reports: first to standardize image interpretation and second to provide educational tools to physicians to acquire experience in reading images. Data on visual RECIP 1.0 generated by Gafita et al. (*15*) were based on image interpretation performed by physicians with significant experience in PSMA PET/CT imaging. To support clinical translation of RECIP 1.0, an online platform for education was developed (http://recip-criteria.com), including comprehensive guidelines for interpreting response in PSMA PET/CT images by RECIP 1.0 (http://recip-criteria.com/guidelines).

The timing of follow-up imaging is also a crucial factor to consider. Although clinical trials typically follow a standardized schedule (every 8 or 12 wk (*3*)), in clinical practice, the timing of assessments can vary depending on the therapeutic agent and prostate cancer clinical state. In metastatic castration-resistant prostate cancer, interim PSMA PET/CT is typically performed after 2 or 3 cycles of PSMA-targeted therapeutic radiopharmaceuticals, androgen receptor–signaling inhibitors, or ^{223}Ra therapy. In contrast, during taxane-based chemotherapy, only an end-of-treatment scan is typically performed. In early-stage prostate cancer, there are no established imaging time points, and imaging is typically triggered by rising prostate-specific antigen values to confirm and localize disease progression.

Several unmet needs are to be addressed to ensure successful clinical implementation of RECIP 1.0. First, education of physicians on PSMA PET MIP methodology is a crucial step toward implementation of visual RECIP 1.0 in practice on a large scale. Second, RECIP has been validated for response evaluation during PSMA theranostics (*11,12,17*), hormonal therapy (androgen deprivation therapy or androgen receptor–signaling inhibitors) (*13,18,19*), and ^{223}Ra therapy (*10*). Validation of these findings in larger patient multicentric cohorts as well as evaluation of the RECIP role in monitoring the efficacy of taxane-based chemotherapy is warranted. Third, the role of cross-sectional imaging (contrast-enhanced CT or MRI) in conjunction with PSMA PET imaging has not been addressed. Of particular interest is the prognostic role of new PSMA-negative lesions (e.g., in the liver) or new organ involvement (*20*), which may carry a different prognostic significance. An international multicentric effort investigating this topic is ongoing. Nevertheless, the current RECIP 1.0 definition classifies new lesions on CT or MRI as a new lesion independent of PSMA expression status. Fourth, implementation of RECIP 1.0 in clinical trials in which serial PSMA PET/CT scans are being performed is imperative to determine its prognostic value as a time-to-event endpoint. When PSMA PET/CT is performed at multiple time points (e.g., every 8 or 12 wk), the most recent follow-up scan should be compared with the previous scan. No flare phenomenon has been reported with PSMA PET/CT; therefore, progression can be documented on the first follow-up scan. Lastly, given the considerable clinical value of PSMA-VOL, accurate software solutions for tumor quantification are urgently needed, and open-source software may be an option for rapid dissemination.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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