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Brief Report

Association Between the PRIMARY Score at Staging Prostate-specific Membrane Antigen Positron Emission Tomography and Overall Survival Among Patients with Newly Diagnosed Prostate Cancer: Findings from the International, Multicenter PROMISE Registry

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Abstract

The PRIMARY score was implemented in Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) version 2 to improve accuracy for the diagnosis of clinically significant prostate cancer using prostate-specific membrane antigen (PSMA) positron emission tomography (PET). We reviewed overall survival (OS) for patients who underwent PSMA PET for initial staging to evaluate the prognostic value of PRIMARY in a large, international, multicenter cohort. The cohort comprised 1889

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patients who underwent PSMA PET for initial staging of prostate cancer at investigator sites across Europe and Australia between 2012 and 2021. Hazard ratios (HRs) with 95% confidence interval (CI) were calculated for PRIMARY scores to identify predictors of OS. Complete-case head-to-head comparisons were conducted for Prostate Imaging-Reporting and Data System (PI-RADS) versus PRIMARY scores, and cT stage versus PRIMARY scores. We present preliminary findings up to January 31, 2025, when 231 deaths had occurred. PRIMARY score 5 (HR 1.5, 95% CI 1.0–2.3; $p = 0.045$) was associated with shorter OS. Improvements in C index values confirmed the added prognostic value of the PRIMARY score when combined with PI-RADS or cT stage. PRIMARY score 5 on initial PSMA PET is prognostic for shorter OS. There is ongoing long-term follow-up in the PROMISE registry (NCT06320223, promise-pet.org).

ADVANCING PRACTICE

What does this study add?
For the first time we confirm the prognostic value of PROMISE and PRIMARY using a large international multicenter cohort of patients who underwent prostate-specific membrane antigen (PSMA) positron emission tomography (PET) at initial staging.

Clinical Relevance
This large international registry analysis provides the first evidence that a PRIMARY score of 5 on initial staging PSMA PET is independently associated with shorter overall survival in patients with prostate cancer, offering additive prognostic value when combined with PI-RADS or clinical T stage. However, the results should be interpreted with caution given the retrospective design, heterogeneous imaging protocols, and relatively short follow-up, which may limit generalizability. Nevertheless, these findings support the potential role of standardized PSMA-PET metrics in refining risk stratification and informing treatment strategies in patients with prostate cancer at the time of first diagnosis. Associate Editor: Gianluca Giannarini, MD.

Patient Summary
We looked at the value of tools called the PROMISE criteria and the PRIMARY score in predicting the prognosis for patients with prostate cancer who undergo a newer type of scan called PSMA PET (prostate-specific membrane antigen positron emission tomography).

The standard for diagnosis of prostate cancer (PC) in men is multiparametric magnetic resonance imaging (mpMRI) in accordance with the Prostate Imaging-Reporting and Data System (PI-RADS), and subsequent biopsy [1]. The additive diagnostic accuracy of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) to mpMRI has been evaluated [2,3]. On the basis of its practical value, the 5-point PRIMARY score, developed to describe local PSMA PET findings and optimize cancer diagnosis [4], was implemented in Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) v2 [5]. The PRIMARY score combines the intraprostatic pattern and site and PSMA activity. Score 1 (no intraprostatic pattern) and score 2 (diffuse transition-zone or symmetric central-zone activity without focal uptake) are deemed "benign" patterns, while score 3 (focal transition-zone activity two times higher than the background), score 4 (focal peripheral-zone activity), and score 5 (maximum standardized uptake value [SUV_{max}] $\geq$12) are deemed "malignant" patterns [4]. When combined with mpMRI, PSMA PET significantly improves the sensitivity and negative predictive value for detection of clinically significant PC (csPC) over mpMRI alone [6]. However, to the best of our knowledge, the PRIMARY score has not yet been associated with survival in a large, international, multicenter cohort. Here we report on the prognostic value of the PRIMARY score for overall survival (OS) in a primary staging subgroup from the PROMISE registry study (ClinicalTrials.gov NCT06320223).

We present preliminary findings for a subgroup of patients at initial staging ($n = 1889$). Inclusion criteria and central data collection for the PROMISE registry have previously been described [7] and are presented in more detail in the Supplementary material.

Patient data, including laboratory parameters, histopathology, clinical data, and conventional imaging reports according to local site practice, were screened to

classify patients in an initial staging subgroup. The patients included had not received definitive primary therapy before PSMA PET imaging.

All patients underwent ^{68}Ga-based or ^{18}F-based PSMA PET-computed tomography (CT) or whole-body PET-MRI between December 6, 2012 and October 15, 2021 for initial staging of PC.

In alignment with the PROMISE v2 criteria [5], PRIMARY scores were retrospectively assigned on the basis of PSMA PET images and clinical PET reports. Data for clinical parameters (Gleason grade group, cT stage, and prostate-specific antigen [PSA] at the time of PSMA PET) were collected when available. PI-RADS scores for MRI results were collected when available.

The primary endpoint of OS was defined as time from PSMA PET to death from any cause. Follow-up was calculated as the time from PSMA PET to the last day the patient was known to be alive. Vital status for patients was requested from ongoing therapy schedules, electronic medical records, or cancer registry data sets according to local site practice.

Cox proportional-hazard ratios (HRs) with 95% confidence interval (CI) were calculated for the PRIMARY score. Multivariable Cox regression was performed for patients with complete data sets for Gleason grade group, PSA level at PET, and cT stage at diagnosis (complete-case analysis).

Head-to-head subgroup analyses were performed for patients with complete data for PI-RADS and PRIMARY scores (n = 366), and for patients with cT stage and PRIMARY scores (n = 960). cT stage was defined on the basis of clinical results without PET. Separate Cox proportional-hazard models were built for the PRIMARY score, PI-RADS score, and cT stage. The additive value of the PRIMARY score when combined with either the PI-RADS score or cT stage was measured in terms of the C index for combined Cox proportional-hazard models. Internal bootstrap validation was conducted by running 1000 bootstrap replicates for the combined models. We used R v4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses, with statistical significance set at $p < 0.05$.

Baseline characteristics of the initial staging subgroup are presented in Supplementary Table 1. In total, 231 patients had died by January 31, 2025. The majority of patients had PRIMARY score 4 (n = 642, 34%) or score 5 (n = 810, 43%); 437 patients (23%) had PRIMARY score 1–3.

Univariable regression analysis revealed that PRIMARY score 5, miT3b/T4 stage, and all PROMISE categories of locoregional or distant disease were predictors for shorter OS (Fig. 1).

Multivariable regression results (n = 925) are presented in Supplementary Fig. 1. PRIMARY score 3 and stages cT2 and cT4 were predictors for worse OS, while Gleason grade group and PSA were risk factors, but did not reach statistical significance.

We tested the additive value of the PRIMARY score when combined with the PI-RADS score or with cT stage (Table 1). The C index values were 0.68 (95% CI 0.58–0.77) for PI-RADS + PRIMARY, and 0.65 (95% CI 0.59–0.71) for cT stage + PRI-

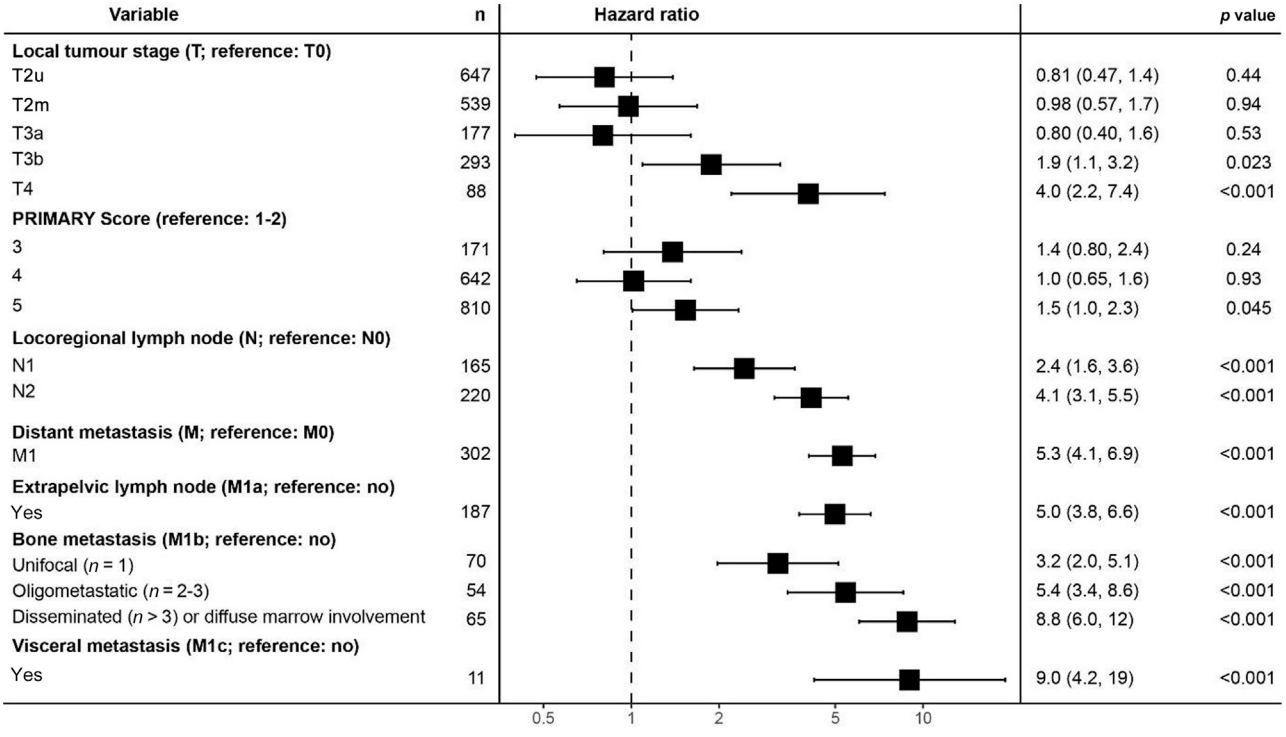

Fig. 1 – Univariable regression results for PROMISE and PSMA PET metrics in the initial staging subgroup (n = 1889) for identification of potential predictors of overall survival. Estimates are the hazard ratio with 95% confidence interval. T, N, and M stages refer to the molecular imaging TNM classification (miTNM). PROMISE = Prostate Cancer Molecular Imaging Standardized Evaluation; PSMA = prostate-specific membrane antigen; PET = positron emission tomography.

Table 1 – Additive predictive value of the PRIMARY score in separate combined models with PI-RADS or cT stage (complete-case analysis)

Cox regression model	C index (95% CI)
PI-RADS model (*n* = 366)	
PRIMARY score	0.61 (0.49–0.72)
PI-RADS score	0.63 (0.54–0.72)
PI-RADS score + PRIMARY score	0.68 (0.58–0.77)
cT stage model (*n* = 960)	
PRIMARY score	0.58 (0.52–0.63)
cT stage	0.63 (0.57–0.68)
cT stage + PRIMARY score	0.65 (0.59–0.71)

CI = confidence interval; PI-RADS = Prostate Imaging-Reporting and Data System.

MARY. Optimism-corrected C index values were 0.60 for PI-RADS + PRIMARY, and 0.64 for cT stage + PRIMARY.

It has been shown that the PRIMARY score improves cancer diagnosis, and the score was incorporated into the PROMISE v2 framework for reporting PSMA PET to better characterize prostate findings with this imaging modality [5]. The PRIMARY score is a 5-point system comprising a combination of the intraprostate pattern (diffuse or focal), site (transition or peripheral zone), and intensity ($SUV_{max} \geq 12$) to overcome the limitations of benign PSMA activity, which is common within the prostate and reduces specificity. While PRIMARY scores of 1–4 focus on the pattern and site independent of intensity, PRIMARY score 5 is based on the PSMA intensity of the index lesion. It is known that greater PSMA intensity in the primary prostate tumor predicts both higher grade group and poorer outcomes following definitive primary therapy. PRIMARY score 5 thus provides information on tumor biology and aggressiveness on the basis of PSMA expression independent of other features such as prostatic pattern and site.

The OS prediction probability for csPC detected using the PRIMARY score alone was comparable to that using PI-RADS scores or clinical results without PET (cT stage). However, our results confirm the additive OS predictive value of the PRIMARY score when combined with either PI-RADS scores or cT stage.

Our study demonstrates for the first time the prognostic value of the PRIMARY score at initial staging of biopsy-confirmed PC. A PROMISE score of 5 was associated with shorter OS. We will continue to collect PRIMARY score data in our PROMISE registry (NCT06320223, promise-pet.org) for further analysis over longer OS follow-up.

Author contributions: Madeleine J. Karpinski had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data sharing statement: Access to the summary of participant data can be approved on an individual basis by an independent review committee on reasonable request after publication. Requests should be directed to the corresponding author.

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Supplementary material

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