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Stage Migration on Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography in Comparison to Conventional Imaging in Patients with High-risk Prostate Cancer Referred for Radiation Therapy: Results from the Phase 2/3 THUNDER Trial

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Abstract

Background and objective: In high-risk prostate cancer, the proPSMA trial showed upstaging with prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) in 14% of patients. We hypothesised that the probability of stage migration in a patient population referred for curative-intent radiotherapy would be higher. Here we report stage migration results according to PSMA PET/CT in the first year of inclusion in the phase 2/3 THUNDER trial (NCT06282588).

Methods: Patients with high-risk prostate cancer screened between December 2023 and December 2024 in the THUNDER trial with both conventional imaging (CT, bone scintigraphy) and PSMA PET/CT within 16 weeks before screening were included (n = 142). Stage migration according to the TNM classification versus the molecular imaging (miTNM) classification (PROMISE v2 criteria) was assessed using descriptive statistics.

Key findings and limitations: PSMA PET/CT led to stage migration in 43 patients, of whom 42 (30%) were upstaged and one (1%) was downstaged. Upstaging to miN1–2 disease occurred in 32 patients (23%), and to miM1a–c disease in 19 patients (13%). The probability of upstaging increased with the number of high-risk features. In the

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subgroup meeting the STAMPEDE M0 high-risk criteria (n = 73), PSMA PET/CT upstaged 27 patients (37%), including upstaging to miM1a–c disease in 14 (19%). Limitations include the absence of central review of the imaging procedures.

Conclusions and clinical implications: One-third of patients with high-risk prostate cancer referred for curative-intent radiotherapy were upstaged on PSMA PET/CT. This finding supports the use of PSMA PET/CT for staging, especially in patients with multiple high-risk features, and suggests a need for treatment adaptations accordingly, which will be further investigated in the THUNDER trial.

ADVANCING PRACTICE

What does this study add?

This study demonstrated that in comparison to conventional imaging, prostate-specific membrane antigen positron (PSMA) positron emission tomography/computed tomography (PET/CT) led to upstaging in 30% of patients with high-risk prostate cancer referred for radiotherapy. The probability of upstaging increased with the number of high-risk features. These findings emphasise the importance of PSMA PET/CT for accurate staging and suggest a need for treatment adaptation accordingly. The phase 2/3 THUNDER trial will investigate these treatment adaptations and their impact on metastasis-free survival.

Clinical Relevance

In the prospective THUNDER trial, PSMA PET/CT led to upstaging in 30% of patients with high-risk prostate cancer referred for radiotherapy, escpecially in patients with multiple high-risk features. These findings support the clinical utility of PSMA PET/CT over conventional imaging to guide treatment decisions in this setting, which will be further investigated in the THUNDER trial.

Patient Summary

In patients with high-risk prostate cancer being considered for radiation therapy, a type of scan called PSMA PET/CT (prostate-specific membrane antigen positron emission tomography/computed tomography) detected metastatic spread more frequently than CT and bone scans, and led to identification of a higher disease stage in 30% of patients. This was mainly seen in patients with multiple high-risk features. These findings highlight the importance of using PSMA PET/CT for disease staging to plan treatment accordingly, which is currently being investigated in the THUNDER trial.

1. Introduction

Patients with prostate cancer presenting with one or more high-risk features at diagnosis have a higher likelihood of harbouring metastatic disease, so accurate imaging is essential for disease staging and selecting the optimal treatment strategy. Conventional imaging modalities such as computed tomography (CT) and bone scintigraphy have traditionally been used for staging; however, their sensitivity and specificity are limited [1,2]. Prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT has emerged as a more accurate imaging modality for prostate cancer staging [3,4]. PSMA PET/CT uses radiolabelled PSMA ligands that selectively bind to the extracellular domain of PSMA, a transmembrane protein overexpressed in prostate cancer cells, which allows visualisation of metastatic lesions as small as 3–5 mm [5,6]. The multicentre randomised phase 3 proPSMA trial demonstrated that PSMA PET/CT had 27% greater accuracy in comparison to conventional imaging in detecting nodal and distant metastases in high-risk prostate cancer. This led to nodal or distant metastasis upstaging in 14% of patients, which can have a significant impact on treatment strategies [3]. The proPSMA trial included patients who underwent either curative-intent surgery or radiotherapy. However, patients referred for radiotherapy typically present with a greater number of high-risk features than patients for whom surgery is recommended [7]. Thus, we hypothesised that the rate of upstaging with PSMA PET/CT is higher in the former group, which has not previously been tested.

The aim of this preplanned substudy of the THUNDER trial (ClinicalTrials.gov NCT06282588) was to investigate stage migration in patients with high-risk prostate cancer referred for curative-intent radiotherapy using data from the first year of trial inclusion.

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2. Patients and methods

2.1. Study design and participants

Patients who provided written informed consent to participate in the two-part phase 2/3 THUNDER trial between December 13, 2023 and December 12, 2024 were included in this study. In the THUNDER trial, patients with histopathologically proven high-risk local or locally advanced prostate cancer (defined as any of the following: prostate-specific antigen (PSA) >20 ng/ml, stage T3–4, International Society of Urological Pathology (ISUP) grade group ≥4, or cN1 disease) were screened for study inclusion. Both conventional imaging and PSMA PET/CT had to be performed within 16 weeks before the screening visit. A complete list of the inclusion and exclusion criteria is provided in the Supplementary material. Patients with metastatic lesions on conventional imaging (cM1) at screening were excluded from further participation in the interventional part of THUNDER, but were included in this study on the screening phase of the trial. To reduce the patient burden, from March 2024 it was decided to no longer require additional bone scintigraphy in cases in which PSMA PET/CT showed no bone lesions, as the proPSMA trial showed that the probability of a true-positive bone scintigraphy result in cases with negative PSMA PET/CT findings is <2% [3]. This amendment was discussed with the steering committee and the independent data monitoring committee, and was approved by the ethics committee and governing bodies.

Patients included in the trial enter either a phase 2 treatment de-intensification or a phase 3 treatment intensification trial. At inclusion, patients undergo conventional imaging, PSMA PET/CT imaging and a genomic classifier (GC) test (Decipher Biosciences, San Diego, CA, USA). Patients without PSMA-positive lesions outside the prostate [8] and a GC score <0.60 enter the de-intensification phase 2 trial, receiving radiotherapy to the prostate and/or pelvic lymph nodes (PLNs) with 24 months of darolutamide, for which quality of life is the primary endpoint. All other patients enter the randomised phase 3 trial comparing radiotherapy to the prostate and/or PLNs plus 24 months of androgen deprivation therapy (ADT) with darolutamide or placebo, for which metastasis-free survival is the primary endpoint.

2.2. Imaging procedures

Contrast-enhanced CT, bone scintigraphy, and PSMA PET/CT scans were performed according to local procedures at each site and were assessed locally. All PSMA PET tracers were allowed. Results from the CT scan for the combined PSMA PET/CT imaging at screening could be used for conventional imaging. The TNM classification was used for reporting of positive lesions on CT and bone scintigraphy. Assessment of N stage was based on findings from CT or magnetic resonance imaging. The PROMISE v2 framework was used for reporting of PSMA-positive lesions on PSMA PET/CT [8]. Equivocal lesions on both conventional and PSMA PET/CT imaging were not counted.

2.3. Study outcomes

The primary aim of this THUNDER substudy was to report any migration in N and/or M stage on PSMA PET/CT in comparison to conventional imaging. Secondary objectives were to evaluate N stage and M stage migration separately, and to assess the effect of the number of high-risk features on the likelihood of stage migration. An additional subgroup analysis was conducted for patients who met the high-risk M0 criteria from the STAMPEDE trial [9].

2.4. Statistical analysis

Descriptive statistics were used to assess rates of stage migration. Continuous variables were reported as the median and interquartile range (IQR). Results for categorical variables were reported as the number and proportion of patients. Logistic regression analysis was conducted to identify significant predictors of upstaging to miM1 disease.

3. Results

3.1. Patient characteristics

Between December 13, 2023 and December 12, 2024, 153 patients were screened for inclusion in the THUNDER trial, of whom 11 were excluded (Fig. 1). The baseline characteristics of the study cohort of 142 patients are shown in Table 1. Some 59% of these men had at least two high-risk features (PSA >20 ng/ml, stage T3–4, ISUP grade group ≥4, or cN1 disease). Conventional imaging showed regional metastases (cN1) in 27 men (19.0%), of whom five (3.5%) also had distant metastases (cM1). The PSMA radiotracers used for PSMA PET/CT imaging are listed in Supplementary Table 1.

3.2. Stage migration

PSMA PET/CT detected positive PLNs in 40.8% of patients (vs 19.0% on CT), positive abdominal distant lymph nodes in 12.0% (vs 0.7% on CT), visceral lesions in 1.4% (vs 0.7% on CT), and bone lesions in 7.7% (vs 1.4% on CT and 2.7% on bone scintigraphy; Table 2). No positive lymph nodes above the diaphragm were observed in the study cohort.

Figure 2 shows the differences in staging between PSMA PET/CT and conventional imaging. Stage migration was

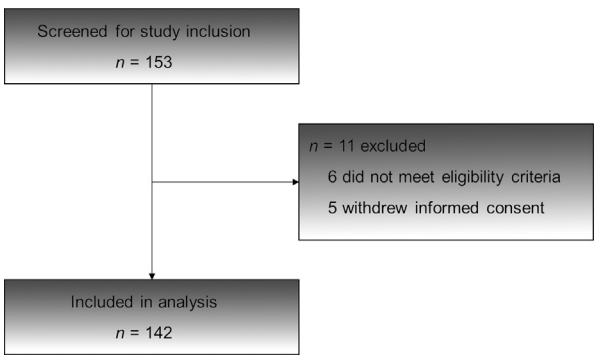

Fig. 1 – Flow diagram for the study.

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Table 1 – Baseline characteristics for the cohort of 142 patients

Parameter	Result
Median age, yr (IQR)	75 (69–78)
Median PSA, ng/ml (IQR)	14.3 (8.0–32.7)
PSA >20 ng/ml, *n* (%)	54 (38)
Stage ≥T3, *n* (%)	87 (61)
ISUP grade group, *n* (%)	
1	4 (3)
2	11 (8)
3	23 (16)
4	35 (25)
5	69 (49)
ISUP grade group ≥4, *n* (%)	104 (73)
Stage cN1, *n* (%)	27 (19)
Stage cM1, *n* (%)	5 (4)
Number of high-risk features, *n* (%) [a]	
1	58 (41)
2	48 (34)
3	26 (18)
4	10 (7)
Imaging performed, *n* (%)	
CT scan	142 (100)
Bone scintigraphy [b]	113 (80)
PSMA PET/CT	142 (100)

BS = bone scintigraphy; CT = computed tomography; IQR = interquartile range; ISUP = International Society of Urological Pathology; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.
[a] High-risk features: PSA >20 ng/ml, stage T3–4, ISUP grade group ≥4, or cN1 disease.
[b] In 29 patients with no bone lesions on PSMA PET/CT, bone scintigraphy was not performed because of the low probability of true positive findings [3], with the aim of reducing the patient burden.

Table 2 – Findings on conventional imaging and PSMA PET/CT

Location	Positivity rate (%)		
	CT (*n* = 142)	BS (*n* = 113)	PSMA PET/CT (*n* = 142)
Positive pelvic LNs (N1–2)	19.0	–	40.8
Positive extrapelvic LNs (M1a) [a]	0.7	–	12.0
Positive bone lesions (M1b)	1.4	2.7	7.7
Positive visceral lesions (M1c)	0.7	–	1.4

BS = bone scintigraphy; CT = computed tomography; LNs = lymph nodes; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
[a] All M1a lesions detected were below the diaphragm.

observed in 43 patients, of whom 42 (30%) were upstaged and one (1%) was downstaged. Specifically, 23 patients with cN0M0 had miN1–2M0 disease, 13 with cN0M0 had miM1 disease, and six with cN1M0 had miM1 disease. The patient with downstaging had cN1M0 and miN0M0 disease.

Regarding N stage, PSMA PET/CT detected positive PLNs that were not detected on conventional imaging in 32 patients (23%). Among these patients, PSMA PET/CT revealed one positive PLN in 14 patients, and multiple positive PLNs in 18 patients. In terms of M stage, PSMA PET/CT revealed distant metastases that were not detected on conventional imaging in 19 patients (13%). Of these, ten had miM1a disease (nine with one to three extrapelvic lymph nodes, one with more than five extrapelvic lymph nodes), eight had miM1b disease (seven with one to three bone lesions and one with five bone lesions), and one had miM1c disease (penile metastasis). In the five patients with cM1 disease on conventional imaging, PSMA PET/CT confirmed this finding. In one of these patients, PSMA PET/CT identified three additional bone lesions (conventional imaging identified one bone lesion). PSMA PET/CT did not reveal any additional lesions in the remaining four patients; one had M1a disease (more than five extrapelvic lymph nodes), two had M1b disease (both had one to three bone lesions), and one had M1c disease (two liver lesions).

Furthermore, the PSMA PET/CT upstaging rate was higher for patients with a greater number of high-risk features (Fig. 3). For example, among the patients with four high-risk features, 30% were upstaged to miM1 disease, whereas the upstaging rate to miM1 was 7% in the group with one high-risk feature. Univariate logistic regression analysis revealed that the number of high-risk features was significantly associated with upstaging to miM1 disease (odds ratio per additional high-risk feature: 1.86, 95% confidence interval 1.13–3.07; $p = 0.014$). The individual high-risk features (PSA >20 ng/ml, stage ≥T3, ISUP grade group ≥4, or cN1 disease) taken separately had no predictive value.

3.3. *Subgroup analysis for patients meeting the STAMPEDE M0 high-risk criteria*

The STAMPEDE M0 high-risk criteria (either cN1M0 disease or two of the following: stage ≥T3, PSA >40 ng/ml, ISUP grade group ≥ 4) [9] were met by 73 of the 142 men in the study cohort (51%). Upstaging was observed in 27 patients (37%), with distant metastases in 14 patients (19%). Some 21 patients with localised disease on conventional imaging were upstaged to either pelvic nodal disease (*n* = 13), miM1a disease (*n* = 5), miM1b disease (*n* = 2), or miM1c disease (*n* = 1), while six patients with pelvic nodal disease on conventional imaging were upstaged to either miM1a (*n* = 3) or miM1b disease (*n* = 3; Supplementary Fig. 1).

4. Discussion

Our prospective study showed that PSMA PET/CT led to upstaging in 30% of patients with high-risk prostate cancer referred for curative-intent radiotherapy, including upstaging to miN1–2 disease in 23% and to miM1 disease in 13% of all patients. In addition, the risk of upstaging to miM1 disease increased from 7% for patients with one high-risk feature to 30% for patients with four high-risk features. These findings support the use of PSMA PET/CT for staging, and provide a rationale for prioritising the use of PSMA PET/CT in patients presenting with multiple high-risk features.

The proPSMA trial [3] reported nodal or distant metastatic upstaging in 14% of high-risk prostate cancer patients intended for surgery or radiotherapy, which is half the rate observed in our study. This can likely be attributed to the fact that our patient cohort included only high-risk prostate cancer patients referred for radiotherapy with more high-risk features. In comparison to the proPSMA trial, our cohort had higher proportions of patients with PSA >20 ng/ml (38%

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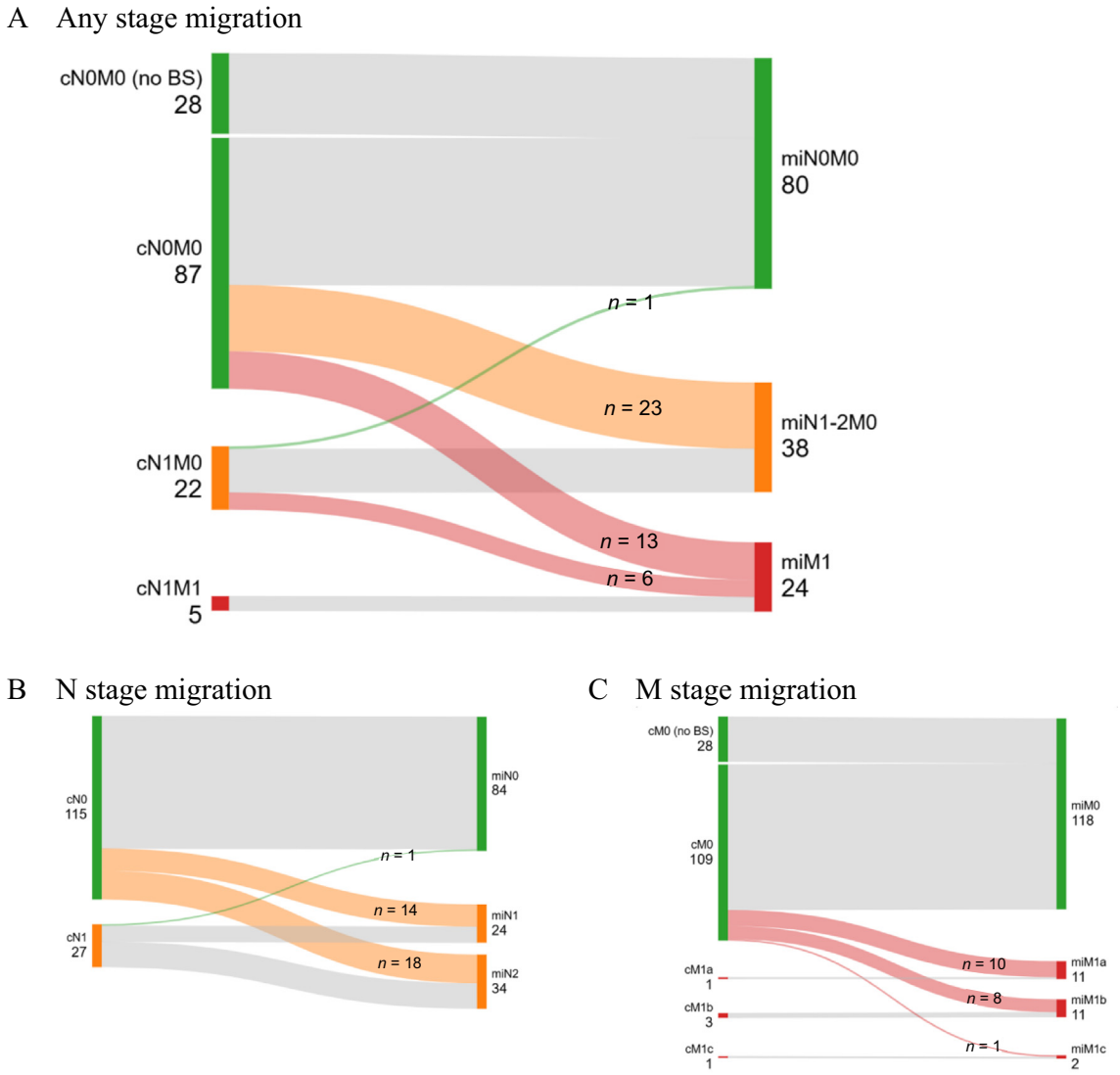

Fig. 2 – Prostate-specific membrane antigen positron emission tomography/computed tomography findings in comparison to conventional imaging. (A) Any stage migration. (B) N stage migration. (C) M stage migration. BS = bone scintigraphy.

vs 22%), stage ≥T3 (61% vs 27%), ISUP grade group ≥4 (73% vs 64%), and cN1 disease (19% vs 9%). A similar trend was observed when comparing our findings to those reported by Hruby et al [10], whose analysis for a cohort with intermediate- or high-risk prostate cancer before definitive radiotherapy revealed upstaging in 21% and miM1 upstaging in 6% of patients. Interestingly, Ravi et al [11] found that patients with multiple risk factors or cN1 disease had worse survival than patients with one risk factor. Together, these results suggest that patients with multiple high-risk features have more aggressive disease with a higher risk of upstaging on PSMA PET/CT and worse survival outcomes. A recent multi-institutional study involving more than 6000 patients staged with PSMA PET/CT revealed that the PET/CT result is at least prognostic [12]. The authors conclude that despite the prognostic value of PSMA PET/CT, they would only recommend this imaging modality as standard practice if a benefit or at least lack of harm is proven when treatment is adapted to the PET/CT result. Although our report focuses on the upstaging potential of PSMA PET/CT in a high-risk population, the primary goal of the trial is to address this fundamental question of whether treatment tailored according to PSMA PET/CT findings improves clinical outcomes.

In the THUNDER trial, patients with extraprostatic disease on PSMA PET/CT or a high Decipher GC score will be randomised to standard-of-care radiotherapy and 2 years of ADT plus either 2 years of placebo or 2 years of darolutamide. In the STAMPEDE M0 trial, addition of abiraterone to radiotherapy and ADT significantly improved metastasis-free survival and overall survival for men with high-risk cM0 prostate cancer [9]. In our study, 37% of patients meeting the STAMPEDE M0 criteria were upstaged, and 19% had distant metastatic disease on PSMA PET/CT at prostate cancer diagnosis. In the STAMPEDE trial, the 6-year metastasis-free survival was 82% in the combination therapy group and 69% in the control group. The fact that almost one in five of these patients could have had distant metas-

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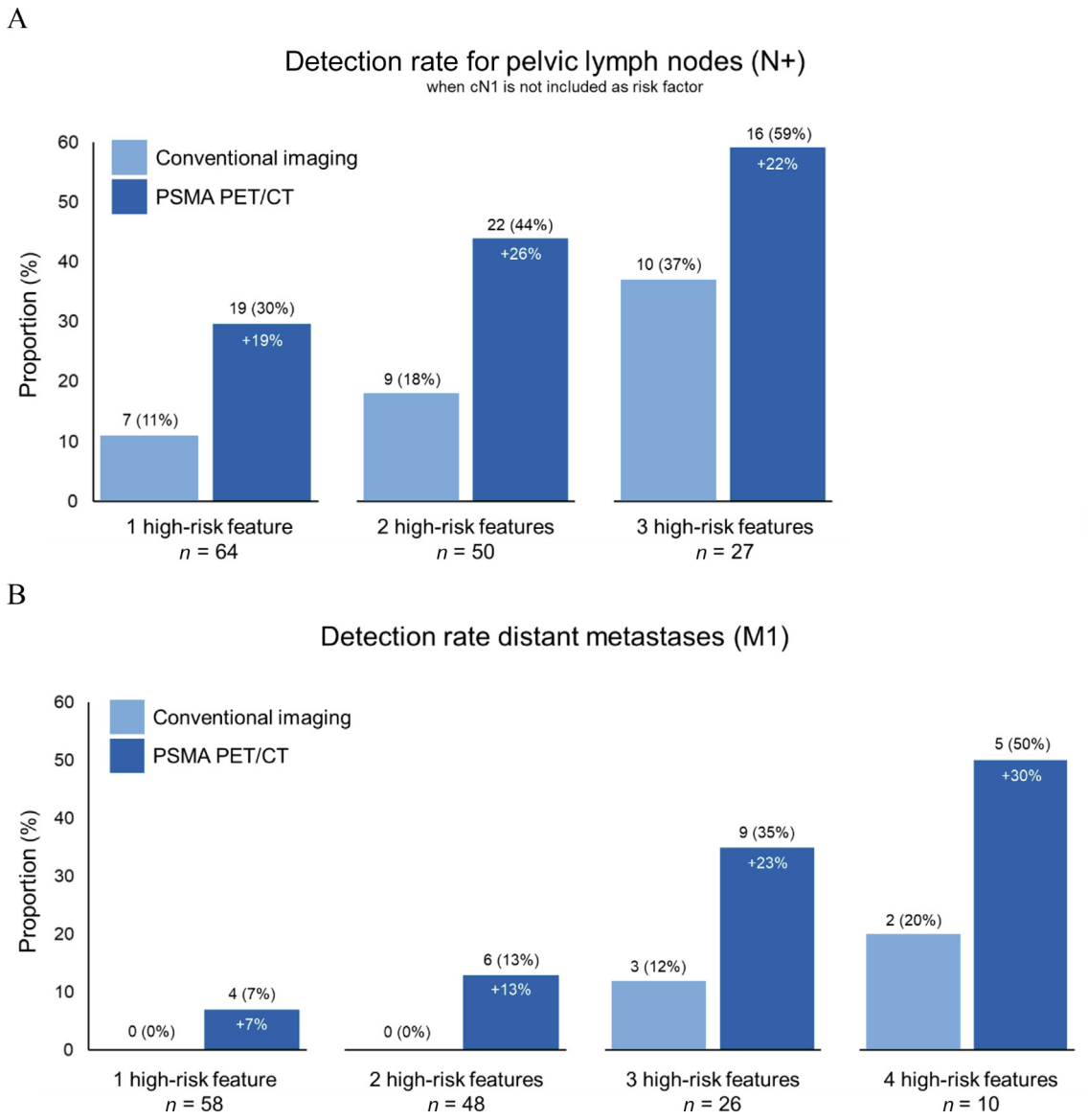

Fig. 3 – Detection rate on PSMA PET/CT according to the number of high-risk features for (A) pelvic lymph nodes (high-risk features: PSA > 20 ng/ml, T stage ≥3, ISUP grade group ≥4) and (B) distant metastases (high-risk features: PSA >20 ng/ml, T stage ≥3, ISUP grade group ≥4, cN1 disease). CT = computed tomography; ISUP = International Society of Urological Pathology; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

tases on PSMA PET/CT raises the question of whether the benefit of abiraterone observed was not mainly driven by this subgroup of patients.

Strengths of our study include the prospective design, large patient cohort, and standardised reporting of PSMA PET/CT scans. Limitations include the fact that patients with multiple unequivocal metastases on conventional imaging were not screened for inclusion in the THUNDER trial and therefore were potentially missed. Some patients with localised disease on PSMA PET/CT did not undergo bone scintigraphy to minimise the patient burden, which may have resulted in underestimation of downstaging. In addition, PSMA PET/CT may yield false-positive findings for regional lymph node metastases, although this risk is relatively low, with specificity of ~94% reported [13]. Furthermore, scans were interpreted by a single reader, without blinding to prior imaging, and different PSMA tracers were used. However, interobserver agreement for PSMA PET/CT is substantial to excellent. Agreement is highest for regional lymph node and bone metastases, and somewhat lower for soft-tissue metastases and local tumour assessment [14,15]. A structured approach based on the PROMISE criteria was used to minimise interobserver variability in the study, as it has been demonstrated that this yields excellent compartment-based scores indicating excellent agreement, even among readers with varying experience [13].

5. Conclusions

In patients with high-risk prostate cancer referred for radiotherapy, who present with more high-risk features than the overall high-risk prostate cancer population, PSMA PET/CT

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led to upstaging in 30% of cases, and upstaging to miM1 disease in 13%. The risk of upstaging increased with the number of high-risk features. The THUNDER trial will investigate if adapting treatment strategies accordingly can improve metastasis-free survival.

Author contributions: Fleur Kleiburg 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.

Study concept and design: Ost, Kleiburg.
Acquisition of data: Ost, Dirix, Fonteyne, Bral, De Troyer, Sautois, Lamande, Liefhooghe, Grisay, Meersschout, Vandermeulen, Jullian, Staelens, Poelaert, Strijbos, Verschueren, Goffin, Withofs.
Analysis and interpretation of data: Kleiburg, Ost.
Drafting of the manuscript: Kleiburg, Ost.
Critical revision of the manuscript for important intellectual content: Ost, Dirix, Fonteyne, Bral, De Troyer, Sautois, Lamande, Liefhooghe, Grisay, Meersschout, Vandermeulen, Jullian, Staelens, Poelaert, Strijbos, Verschueren, Goffin, Withofs.
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Appendix A. Supplementary data

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