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Original Article

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Predicting early outcomes in patients with intermediate- and high-risk prostate cancer using prostate-specific membrane antigen positron emission tomography and magnetic resonance imaging

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Objectives

To identify predictors of early oncological outcomes in patients who opt for robot-assisted laparoscopic radical prostatectomy (RARP) for localized prostate cancer (PCa), including conventional prognostic variables as well as multiparametric magnetic resonance imaging (mpMRI) and prostate-specific membrane antigen (PSMA) positron emission tomography (PET).

Patients and Methods

This observational study included 493 patients who underwent RARP and extended pelvic lymph node dissection (ePLND) for unfavourable intermediate- or high-risk PCa. Outcome measurement was biochemical progression of disease, defined as any postoperative prostate-specific antigen (PSA) value ≥0.2 ng/mL, or the start of additional treatment. Cox regression analysis was performed to assess predictors for biochemical progression, including initial PSA value, biopsy Grade Group (GG), T-stage on mpMRI, and lymph node status on PSMA PET imaging (miN0 vs miN1).

Results

The median (interquartile range) total follow-up of all included patients without biochemical progression was 12.6 (7.5–22.7) months. When assessing biochemical progression after surgery, initial PSA value (per doubling; odds ratio [OR] 1.22, 95% confidence interval [CI] 1.07–1.40; $P = 0.004$), biopsy GG ≥4 vs GG 1–2 (OR 1.83, 95% CI 1.18–2.85; $P = 0.007$), T-stage on mpMRI (rT3a vs rT2: OR 2.13, 95% CI 1.39–3.27; $P = 0.001$; ≥rT3b vs rT2: OR 4.78, 95% CI 3.20–7.16; $P < 0.001$) and miN1 on PSMA PET imaging (OR 2.94, 95% CI 2.02–4.27; $P < 0.001$) were independent predictors of early biochemical progression of disease.

Conclusion

Initial PSA value, biopsy GG ≥4, ≥rT3 disease on mpMRI and miN1 disease on PSMA PET were predictors of early biochemical progression after RARP. Identifying these patients with an increased risk of early biochemical progression after surgery may have major implications for patient counselling in radical treatment decisions and on patient selection for modern (neo-)adjuvant and systematic treatments.

Keywords

prostate cancer, PSMA PET imaging, multiparametric MRI, oncological outcome, biochemical progression, #ProstateCancer, #PCSM

Introduction

Although the majority of patients with prostate cancer (PCa) will be free of disease after robot-assisted laparoscopic radical prostatectomy (RARP) [1], a substantial percentage of patients (20–40%) who undergo RARP will experience biochemical recurrence (BCR) of disease after first having an undetectable PSA level. Some patients even retain a persistently measurable PSA without first having an undetectable PSA level (i.e. biochemical persistence of disease) early after RARP, which has been associated with poor oncological outcome [2–5].

There are several established preoperative prognostic factors at diagnosis that can be used to predict the risk of recurrence after surgery, including clinical tumour stage, biopsy Grade Group (GG) according to International Society of Urological Pathology (ISUP), serum PSA levels, and findings on multiparametric MRI (mpMRI) [6–9]. Over the last few years, prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT has been increasingly used in the primary staging of patients with PCa, prior to RARP, in which the detection of metastases has improved substantially, compared to conventional imaging techniques [10], such as bone scintigraphy or CT. Hofman et al. [11] reported an overall sensitivity of PSMA PET/CT for the detection of metastatic disease of 85%, compared to 38% when using conventional imaging.

In patients with recurrent disease after RARP, restaging PSMA PET findings have proved to be predictive for the oncological outcome of salvage therapies [12]. However, only few studies reported on the additional value of staging PSMA PET/CT for predicting the risk of (biochemical) recurrence after RARP. These studies showed that patients with lymph node metastatic disease on PSMA PET/CT [13], or higher tumour intensity of the primary tumour on PSMA PET/CT [14], have an increased risk of developing BCR after RARP on univariate analyses. Whether PSMA PET/CT could be used along with well-recognized prognostic factors, as mentioned earlier, to predict the risk of biochemical progression after surgery in patients with localized PCa, remains largely unknown.

Previously, nomograms have been developed, such as the Briganti nomogram [6] or the Memorial Sloan Kettering Cancer Centre (MSKCC) nomogram, that are able to predict the final pathological tumour stage (pT) and the histological presence of lymph-node metastases (pN) after surgery [9]. Since pathological T-stage is a limited surrogate for the final oncological outcome, studies that use BCR as an endpoint are clinically more meaningful for patients and their physicians. Using common preoperative prognostic factors as well as the diagnostic data obtained from staging PSMA PET/CT, the present study was conducted to predict early biochemical progression of disease in patients after RARP and ePLND.

Patients and Methods

Study Design and Patient Inclusion and Exclusion Criteria

This study was conducted by the Prostate Cancer Network Netherlands, comprising the Amsterdam University Medical Centre (UMC), VU University Medical Centre and the Netherlands Cancer Institute (NCI), in the period between March 2017 and April 2020. Approval from the institutional review boards of both hospitals was obtained, with the need to receive informed consent waived (VUmc2019.586 and IRBd20-041).

This observational retrospective study included 493 patients with unfavourable intermediate- and high-risk PCa, based on the National Comprehensive Cancer Network (NCCN) classification [15], who underwent both PSMA PET imaging and mpMRI prior to RARP and ePLND for histologically proven PCa. From all included patients, preoperative data were collected including age at surgery, initial PSA measurements, clinical T-stage, biopsy GG, mpMRI findings and PSMA PET findings. A prerequisite for inclusion in the present study was at least one PSA measurement after RARP in order for biochemical progression of disease to be assessed as a primary outcome measure. Patients were excluded from the analyses if they underwent neoadjuvant testosterone-lowering treatment, if they did not have any (biochemical) follow-up after surgery, did not undergo ePLND or staging with PSMA PET imaging or if they had evidence of distant metastases on staging PSMA PET.

Multiparametric MRI Imaging

All patients were preoperatively staged with an mpMRI using the requirements specified by the Prostate Imaging-Reporting and Data System (PI-RADS) score v2.1 [16]) at the Amsterdam UMC, the NCI and all referring hospitals (23 in total). Sequences consisted of an axial unenhanced T1 sequence, three orthogonally oriented T2 sequences and axial diffusion-weighted and dynamic contrast-enhanced sequences. Radiological staging was based on the mpMRI findings, using the PI-RADS score v2.1 [16]. rT1c classification was defined as a PI-RADS score $\leq$2, rT2 as PI-RADS 3–5 lesion with no extracapsular extension, rT3a as evidence of extracapsular extension on mpMRI, and rT3b as evidence of seminal vesical invasion. All scans were reported by expert radiologists.

Prostate-Specific Membrane Antigen PET Imaging

All PSMA PET scans were performed in accordance with local protocol and interpreted in the clinical setting at the

Amsterdam UMC, the NCI and all referring hospitals. For the study, both available ^{18}F-fluorinated variants of PSMA (^{18}F-DCFPyL and ^{18}F-PSMA-1007) and gallium 68 (^{68}Ga)-PSMA-11 tracers were accepted. The ^{18}F-PSMA tracers were synthesized via direct radiofluoration at an on-site cyclotron facility, whereas ^{68}Ga-PSMA-11 was produced using on-site ^{68}Ga-generators compliant with the Good Manufacturing Practices guidelines [17,18]. PET images were performed from mid-thigh to skull base, with a median (interquartile range [IQR]) approximate tracer incubation time of 117 (60–120) min after a median (IQR) dose of 271 (203–310) MBq for ^{18}F-DCFPyL, 48 (44–60) min post-injection after a median (IQR) dose of 103 (95–145) MBq for ^{68}Ga-PSMA-11, and 90 min post-injection after a median (IQR) dose of 284 (253–305) MBq for ^{18}F-PSMA-1007.

Positron emission tomography images were combined with either a low-dose CT scan (120–140 kV, 40–80 mAs with dose modulation), a diagnostic CT scan (130kV, 110mAs) or MRI for anatomical correlation. All PET images were corrected for scatter, decay and random coincidences; attenuation correction was performed using CT or MRI.

Image Interpretation of PSMA PET Imaging

Scan interpretation was performed in participating centres by experienced nuclear medicine physicians. A scan was considered 'positive' if at least one lesion was suggestive of PCa (i.e. focal, higher tracer uptake compared to the surrounding tissues, incompatible with physiological uptake). In line with the PROMISE criteria [19], loco-regional lymph node metastases on PSMA PET were defined as lymph nodes in the true pelvis (miN1).

Extended Pelvic Lymph Node Dissection and Histopathological Evaluation

All ePLNDs were performed by experienced urological surgeons affiliated with one of the participating institutions. An ePLND was performed at least up to and including the bifurcation of the common iliac artery, along the external iliac (the distal limit being the deep circumflex vein and femoral canal), the internal iliac vessels and the obturator fossa. The lateral boarder was the genitofemoral nerve and the peri-vesical fat medially. Lymph node specimens were examined by dedicated uropathologists according to ISUP protocols [20]. A pathological lymph node (pN) assessment, either pN0 or pN1, was provided for each case.

Postoperative Follow-up and Outcome Measures

Patients were followed up postoperatively with PSA measurement every 3 months in the first year after RARP, twice in the second year after RARP, and yearly thereafter. Biochemical persistence was defined as any detectable first serum PSA value after RARP (≥0.1 ng/mL) at least 6 weeks after surgery, whereas biochemical progression was defined as any PSA value ≥0.2 ng/mL after RARP, or the start of additional treatment (e.g. salvage radiation therapy, hormonal therapy) [21]. Biochemical progression-free survival (bPFS) was defined as the time from surgery until biochemical progression, or from the time of surgery to the time of last follow-up in case no biochemical progression occurred.

Statistical Analyses

A multivariable logistic regression analysis was performed to assess potential predictors for biochemical persistence. Moreover, a multivariable Cox regression analysis assessing biochemical progression of disease was executed. The following preoperative variables were considered: initial PSA value (continuous; per doubling), biopsy GG (categorical), radiological T-stage on mpMRI (categorical) and lymph node status on PSMA PET (dichotomous). To further explore the effect of the number of pelvic lymph nodes on PSMA PET imaging on biochemical progression after surgery, univariable Cox regression analysis was performed. All statistical tests were two-sided, and differences were considered statistically significant at P values of <0.05. Statistical analysis was carried out with the Statistical Package for Social Sciences (SPSS, IBM; v26).

Results

Patient Characteristics

In total, 493 patients with unfavourable intermediate- and high-risk PCa who underwent mpMRI and a PSMA PET prior to RARP and ePLND, and who had at least one PSA measurement documented after surgery were included. Characteristics of patients included in the studied cohort are presented in Table 1. The median (IQR) age of all patients at surgery was 68 (64–72) years. The median (IQR) initial PSA value was 10.8 (7.2–20.0) ng/mL. Biopsy GG 1 was found in 15 patients (3%), GG 2 in 84 patients (17%), GG 3 in 126 patients (26%), GG 4 in 147 patients (30%) and GG 5 in 121 patients (24%). A clinical T-stage of cT1 was observed in 173 patients (35%), cT2 in 271 patients (55%) and ≥cT3 in 49 patients (10%). According to the NCCN risk classification [15], 156 patients (32%) were considered to have unfavourable intermediate-risk, 172 (35%) high-risk and 165 (33%) very-high-risk disease.

Imaging Prior to RARP

Assessing the radiological T-stage on mpMRI, 276 patients (56%) had <rT3 disease, 126 patients (26%) had rT3a and 91 patients (18%) had ≥rT3b disease (Table 1). Furthermore, 431 patients (87%) had a PSMA PET negative for (any) metastatic

Table 1 Preoperative characteristics of patients who underwent multiparametric MRI and prostate-specific membrane antigen positron emission tomography prior to robot-assisted laparoscopic radical prostatectomy and extended pelvic lymph node dissection.

	All included patients (*n* = 493)
Age at surgery, years	68 (64–72)
Initial PSA value, ng/mL	10.8 (7.2–20.0)
Time between MRI and surgery, days	93 (62–126)
Time between PSMA PET and surgery, days	59 (36–83)
Clinical T-stage; *n* (%)	
cT1	173 (35)
cT2	271 (55)
cT3-4	49 (10)
Biopsy Grade Group according to ISUP, *n* (%)	
1 (Gleason score 3 + 3 = 6)	15 (3)
2 (Gleason score 3 + 4 = 7)	84 (17)
3 (Gleason score 4 + 3 = 7)	126 (26)
4 (Gleason score = 8)	147 (30)
5 (Gleason score ≥ 9)	121 (24)
NCCN risk group, *n* (%)	
Unfavourable intermediate risk	156 (32)
High risk	172 (35)
Very high risk	165 (33)
PSMA PET findings, *n* (%)	
miN0	431 (87)
miN1	62 (13)
mpMRI findings, *n* (%)	
Radiological T-stage	
Negative (rT1c) / organ-confined disease (rT2)	276 (56)
Extracapsular extension (rT3a)	126 (26)
≥ Seminal vesicle invasion (≥ Rt3b)	91 (18)
PI-RADS score	
1–2	16 (3)
3–5	463 (94)
Missing	14 (3)

ISUP, International Society of Urological Pathology; NCCN, National Comprehensive Cancer Network; PET, positron emission tomography; PI-RADS, Prostate Imaging- Reporting and Data System; PSMA, prostate-specific membrane antigen. Data are median (interquartile range) unless otherwise specified.

Table 2 Final histopathological results of the radical prostatectomy specimen of all included patients.

	All included patients (*n* = 493)
Pathological T-stage, *n* (%)	
pT2	180 (36)
pT3a	186 (38)
pT3b	126 (26)
pT4	1 (<1)
Specimen Grade Group according to ISUP, *n* (%)	
1 (Gleason score 3 + 3 = 6)	4 (1)
2 (Gleason score 3 + 4 = 7)	148 (30)
3 (Gleason score 4 + 3 = 7)	184 (37)
4 (Gleason score = 8)	45 (9)
5 (Gleason score ≥9)	112 (23)
Surgical margin status, *n* (%)	
Negative	298 (60)
Positive	194 (40)
Missing	1 (<1)
Pathological lymph node status, *n* (%)	
pN0	367 (74)
pN1	126 (26)
Median (IQR) number of lymph nodes removed	18 (13–24)

IQR, interquartile range; ISUP, International Society of Urological Pathology.

disease, and 62 patients (13%) had PSMA-avid lesions suggestive of pelvic lymph node metastases (miN1). Of these 62 patients, 22 (35%) had suspicious lymph nodes on mpMRI as indicated by the radiologist.

Histopathological Examination

The histopathological data are shown in Table 2. The majority of patients had no evidence of lymph node metastatic disease (pN0; 367 patients, 74%), while 126 patients (26%) had pN1 disease at histopathological evaluation. In total, a median (IQR) of 18 (13–24) pelvic lymph nodes was removed per patient.

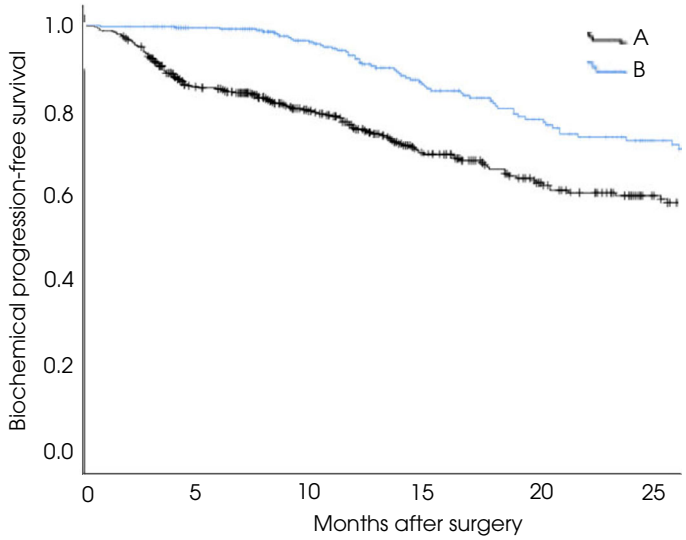
Follow-up After RARP

The median (IQR) total follow-up of all included patients without biochemical progression was 12.6 (7.5–22.7) months. Of the 493 included patients, 77 (16%) had biochemical persistence after RARP, with a median (IQR) first PSA value after RARP of 0.3 (0.2–0.8) ng/mL, after a median (IQR) of 100 (74–122) days post-surgery. One year after RARP and ePLND, 25% (76/299 patients) had biochemical progression of disease (i.e. bPFS rate of 75%), while the bPFS rate was 64% (87/136 patients) 2 years after RARP (Fig. 1a). When assessing BCR, by only including patients with undetectable PSA values after RARP, the 1-year bPFS was 94% (221/236 patients), while bPFS was 81% (87/107 patients) 2 years after RARP (Fig. 1b).

In total, 125/493 patients (25.4%) underwent a PSMA PET/CT after RARP, in case of biochemical progression of disease, at a median (IQR) PSA value of 0.3 (0.2–0.7) ng/mL. Of these 125 patients, 70 (14.2%) had biochemical persistence of disease, and 55 (11.2%) had BCR. The detection rate of PSMA PET in patients with biochemical persistence was found to be 59% (41/70) at a median PSA value of 0.5 ng/mL, vs a detection rate of 38% (21/55) at a median PSA value of 0.3 ng/mL in patients with BCR.

On restaging PSMA PET/CT, 35 patients (28%) had disease limited to the pelvic area (either local recurrent/residual disease [miTr], miN1, or both) and 27 patients (22%) had evidence of distant metastatic disease. Of all patients with miN1 disease solely on restaging PSMA PET/CT (28 patients), 10/28 (36%) had persistent lymph node metastatic disease on PSMA PET/CT, whereas 18/28 patients (64%) had recurrent pelvic lymph node metastatic disease. Of the 10 patients with persistent lymph nodes after ePLND, seven developed biochemical persistence of disease, and in three

Fig. 1 (A) Kaplan–Meier curve assessing biochemical progression-free survival of all included patients who underwent robot-assisted laparoscopic radical prostatectomy (RARP) and extended pelvic lymph node dissection (ePLND). (B) Kaplan–Meier curve assessing biochemical progression-free survival of all patients with an undetectable PSA value after RARP and ePLND.



patients the PSA value first became undetectable, before BCR developed.

Multivariable Logistic Regression Analysis

On multivariable logistic regression analysis, radiological rT3b disease on mpMRI (odds ratio [OR] 5.46 [95% CI 2.89–10.3]; $P < 0.001$) and pelvic lymph node metastatic disease (miN1) on PSMA PET imaging (OR 3.56 [95% CI 1.88–6.74]; $P < 0.001$) were significantly associated with biochemical persistence of disease after RARP, whereas the initial PSA value (per doubling; OR 1.25 [95% CI 0.99–1.59]; $P = 0.060$), biopsy GG (GG 3 vs GG 1–2: OR 0.69 [95% CI 0.28–1.72], $P = 0.43$; GG ≥4 vs GG 1–2: OR 1.73 [95% CI 0.85–3.55], $P = 0.13$) and radiological T-stage rT3a (OR 1.85 [95% CI 0.95–3.60]; $P = 0.071$) were not (Table 3).

Cox Regression Analysis

When assessing biochemical progression in a Cox regression analysis, higher initial PSA values (per doubling; OR 1.23 [95% CI 1.07–1.41]; $P = 0.004$), biopsy GG ≥4 vs 1–2 (OR 1.84 [95% CI 1.18–2.85]; $P = 0.007$), T-stage on mpMRI (rT3a vs rT2: OR 2.13 [95% CI 1.39–3.26], $P = 0.001$; ≥rT3b vs rT2: OR 4.79 [95% CI 3.20–7.17], $P < 0.001$) and miN1 on PSMA PET imaging (OR 2.94 [95% CI 2.03–4.27]; $P < 0.001$) were independent predictors of early biochemical progression of disease, whereas biopsy GG 3 vs 1–2 (OR 0.95 [95% CI 0.53–1.71]; $P = 0.87$) was not (Table 3).

Number of Lymph Nodes on PSMA PET Imaging

In the present study, only 35% of patients (8/23) with two or more suspicious lymph node metastases on PSMA PET were biochemical progression-free 1 year after surgery. On univariable Cox regression analysis, the number of pelvic lymph node metastases on PSMA PET was significantly associated with biochemical progression: one pelvic lymph node metastasis vs no metastatic disease resulted in an OR of 3.06 (95% CI 1.91–4.91; $P < 0.001$); two or more pelvic lymph node metastases on PSMA PET vs no metastatic disease resulted in an OR of 5.70 [95% CI 3.61–9.00;

Table 3 Multivariable logistic regression and Cox regression analysis assessing the impact of several preoperative prognostic factors on biochemical persistence and biochemical progression of disease

	Multivariable logistic regression on BCP		Cox regression on biochemical progression of disease at last follow-up	
	OR (95% CI)	*P*	OR (95% CI)	*P*
log2 (initial PSA value)	1.25 (0.99–1.59)	0.060	1.23 (1.07–1.41)	**0.004**
Biopsy Grade Group				
1–2 (Gleason score 3 + 3 = 6 and 3 + 4 = 7)	Reference		Reference	
3 (Gleason score 4 + 3 = 7)	0.69 (0.28–1.72)	0.43	0.95 (0.53–1.71)	0.87
≥4 (Gleason score ≥ 8)	1.73 (0.85–3.55)	0.13	1.84 (1.18–2.85)	**0.007**
Radiological T stage; n (%)				
< rT3	Reference		Reference	
rT3a	1.85 (0.95–3.60)	0.071	2.13 (1.39–3.26)	**0.001**
≥ rT3b	5.46 (2.89–10.3)	<**0.001**	4.79 (3.20–7.17)	<**0.001**
PSMA PET findings				
miN0	Reference		Reference	
miN1	3.56 (1.88–6.74)	<**0.001**	2.94 (2.03–4.27)	<**0.001**

BCP, biochemical persistence; OR, odds ratio; PET, positron emission tomography; PSMA, prostate-specific membrane antigen. Significant values are visualized in bold.

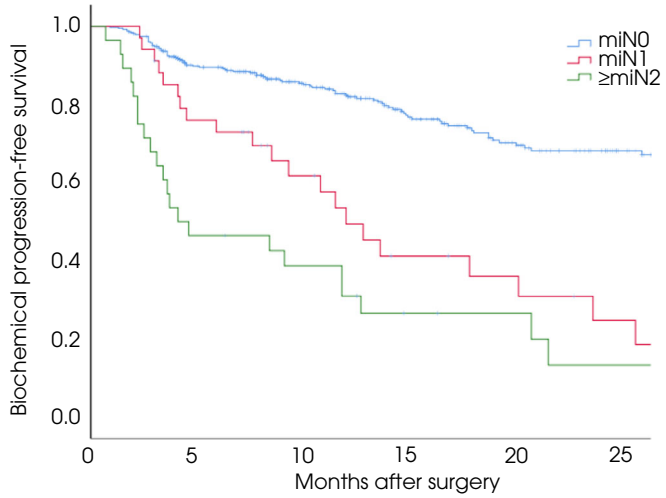
$P < 0.001$; Fig. 2]. When excluding patients with miN0 on PSMA PET, patients with two or more pelvic lymph node metastases on PSMA PET had a shorter median time to biochemical progression of disease, compared to patients with one regional lymph node metastasis on PSMA PET (4.1 vs 12.0 months; log-rank test, $P = 0.05$).

Discussion

Before offering curative treatment in men with localized PCa, clinicians need to accurately evaluate patients' wishes and available prognostic factors to objectively counsel them on treatment decisions that will result in the best possible oncological outcome. Previously, this prediction of oncological outcome was based on the clinical stage of the tumour (cT), on the initial PSA value, on biopsy GG and sometimes on mpMRI findings [6,7]. We assessed whether early biochemical progression of disease after RARP and ePLND could be predicted in patients who were preoperatively staged with conventional prognostic factors combined with both mpMRI and modern PSMA PET imaging.

In the present study, 16% of all included patients had biochemical persistence after RARP with an additional 9% of patients developing BCR (i.e. a detectable PSA level after initially being unmeasurable) in the first year after surgery. We found that in addition to the previously known clinical variables of initial PSA level, biopsy GG and ≥rT3 on mpMRI, miN1 disease on PSMA PET was an independent predictor of early biochemical progression after RARP and ePLND. As only the minority of patients had PI-RADS scores 1–2 (3%), we were not able to include this variable in our analyses.

Fig. 2 Kaplan–Meier curve assessing biochemical progression-free survival of all included patients who underwent robot-assisted laparoscopic radical prostatectomy and extended pelvic lymph node dissection, stratified by preoperative findings on prostate-specific membrane antigen positron emission tomography.



Number at risk

miN0	431	325	233	151	106	71
miN1	34	25	16	9	7	4
≥miN2	28	13	10	5	4	2

Conventional imaging techniques for the staging of localized PCa using CT and bone scintigraphy have limited sensitivity for the detection of both lymph node and distant metastatic disease [11]. PSMA PET as a new staging tool may improve the selection of patients suitable for curative treatment because of its enhanced sensitivity and specificity compared to conventional imaging [10,11]. Consequently, a substantial percentage of patients with undetected metastatic disease on conventional imaging will currently refrain from curative treatment, as distant metastatic disease is present on PSMA PET imaging. Therefore, currently available predicting models for biochemically recurrent disease after surgery such as those developed for the MSKCC and the Briganti nomograms may at present not be applicable in patients staged with modern imaging techniques.

Moreover, local staging with mpMRI has been increasingly used over the last few years and is recommended in the current European Association of Urology (EAU) guidelines [21]. Rayn et al. [22] showed that the addition of the mpMRI findings to standard clinical nomograms significantly improved the predictive ability for organ-confined disease ($P < 0.001$), extracapsular extension ($P = 0.003$) and seminal vesicle invasion ($P = 0.011$) after RARP. Similar findings were reported by Feng et al. [23]. By contrast, Weaver et al. [24] and Jansen et al. [25] showed that mpMRI did not provide additional risk discrimination over the MSKCC nomogram-based model alone.

In a systematic review evaluating the discriminative capabilities of the Briganti [6], Partin [8] and MSKCC nomograms [9], it was shown that neither of the nomograms was superior to another in predicting the presence of lymph node involvement [26]. The pooled areas under the curve (AUCs) for the Briganti, Partin and MSKCC nomograms were 0.793, 0.778 and 0.780, respectively. The Mantel–Haenszel-derived comparison of AUC values revealed no statistical differences of predictive capabilities for Briganti vs Partin ($P = 0.23$), Briganti vs MSKCC ($P = 0.83$) and Partin vs MSKCC ($P = 0.26$). Based on these results, the authors commented that patients and clinicians may use any of these nomograms without significant advantages. As the Briganti, Partin and MSKCC nomograms were developed before mpMRI and PSMA PET/CT were implemented into clinical practice, it remains to be established whether the predictive

capabilities of these nomograms are sustained in the presence of these modern imaging tools. Indeed, in a multicentre study including 497 patients undergoing RARP and ePLND, Gandaglia et al. [7] adopted mpMRI and MRI-targeted biopsies into a predictive model for lymph node invasion and were able to identify candidates for ePLND. They found the AUC of the model to be 0.86, substantially higher compared to other predicting models without using mpMRI as one of the included variables (AUC 0.81–0.82). Based on these findings, mpMRI may have an important role in identifying patients for ePLND.

From the literature, it is known that biochemical persistence of disease or early biochemical relapse after surgery is associated with early radiological progression of disease and with overall survival [2–5,21]. Studies on the prediction of oncological relapse after surgery based on preoperative variables, including modern imaging techniques, are limited. In 2018, Kjölhede et al. [27] showed that metastatic disease on pre-treatment choline PET/CT was an independent predictor for developing BCR and skeletal metastases after local treatment. In addition, in a recent study by van Leeuwen et al. [13] assessing PSMA PET/CT, miN1 on PSMA PET/CT was found to be highly predictive for biochemical persistence on univariate logistic regression analysis, while several other preoperative and histopathological variables (initial PSA value, clinical T-stage, surgical margin status) were not. Moreover, Roberts et al. [14] found that a higher intensity of the primary tumour on PSMA PET/CT was correlated with BCR after RARP. In the present study, the predictive role of PSMA PET for the development of biochemical progression is confirmed.

It remains questionable whether patients with one or multiple risk factors for biochemical progression of disease at diagnosis are suitable candidates for RARP and ePLND only. It might well be that these patients are better candidates for a multimodality approach such as by combined treatment with external beam radiation therapy (EBRT) and/or androgen deprivation therapy (ADT). Indeed, according to the EAU guidelines, patients with clinical T3b disease, clinical T4 disease or clinical N+ disease should only undergo RARP as part of multi-modal therapy [21]. The optimal treatment regimen in this specific patient group remains to be defined and is a topic of ongoing research and clinical trials. However, all currently available studies assessing this were performed before the introduction of more sensitive imaging methods, such as mpMRI and PSMA PET/CT. Due to their enhanced sensitivity, the number of patients diagnosed with at least T3b disease, or N+ disease preoperatively, has probably increased substantially. Nevertheless, in the present study, rT3b disease on mpMRI and miN1 disease on PSMA PET/CT were the strongest predictors of biochemical progression after RARP. This might suggest as yet undetected distant (oligo-)metastatic disease at primary staging. In these patients, (neo-)adjuvant treatment may be worthwhile investigating. In addition, in patients with oligometastatic disease, local treatment by means of EBRT, combined with lifelong ADT has been suggested to improve overall survival compared to ADT alone [28,29]. Multiple studies showed that radical prostatectomy is a useful alternative for EBRT in case of newly diagnosed metastatic disease [30,31]. With PSMA PET as a new imaging method, enhanced visualization is achieved, therefore treatment of oligometastatic disease to postpone ADT is aided. The present study confirms that RARP and ePLND is an appealing option for local treatment, even in patients with preoperative risk factors for biochemical progression of disease.

The present study has the limitations inherent to its retrospective nature. Firstly, mpMRI and PSMA PET scans were interpreted in a clinical setting, therefore, no dual-reading was performed. Moreover, different radiotracers, PET scanners and scan protocols were combined in this study. However, the differences in diagnostic accuracy of PSMA PET across different radiotracers and among different observers seems to be limited. Secondly, it is possible that some of our cohort had early biochemical progression of disease, due to an incomplete ePLND, resulting in persistent pelvic lymph node metastases. Thirdly, as the aim of the present study was to identify preoperative predictors of early oncological outcomes after RARP and ePLND, strong independent variables, such as surgical margin status, could not be included in the analyses. Lastly, because of the relatively short follow-up time, we were limited to the use of early biochemical progression after surgery as one of our primary outcome variables, instead of more solid oncological outcomes, such as time to radiological progression of disease, time to development of castration-resistant PCa, or, ultimately, overall survival. Nevertheless, biochemical progression of disease is a surrogate of overall survival [21]. Therefore, we believe our results may aid the decision whether to apply (neo-)adjuvant treatment in patients planned to undergo RARP and ePLND.

In conclusion, in the present study, a higher initial PSA value, a biopsy GG ≥4, ≥rT3 disease on mpMRI and miN1 disease on PSMA PET were predictors for early biochemical progression of disease after RARP, whereas biopsy GG3 was not. Identifying patients with an increased risk of biochemical progression of disease after surgery may have implications for patient counselling in radical treatment decisions, on the predicted outcome of therapy and on patient selection for modern (neo-)adjuvant and systematic treatments.

Disclosure of Interest

None declared.

References

1 **Hull GW**, **Rabbani F**, **Abbas F**, **Wheeler TM**, **Kattan MW**, **Scardino PT**. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. *J Urol* 2002; 167(Pt 1): 528–34

2 **Ploussard G**, **Staerman F**, **Pierrevelcin J et al**. Predictive factors of oncologic outcomes in patients who do not achieve undetectable prostate specific antigen after radical prostatectomy. *J Urol* 2013; 190: 1750–6

3 **Wiegel T**, **Bartkowiak D**, **Bottke D et al**. Prostate-specific antigen persistence after radical prostatectomy as a predictive factor of clinical relapse-free survival and overall survival: 10-year data of the ARO 96–02 trial. *Int J Radiat Oncol Biol Phys* 2015; 91: 288–94

4 **Preisser F**, **Chun FKH**, **Pompe RS et al**. Persistent prostate-specific antigen after radical prostatectomy and its impact on oncologic outcomes. *Eur Urol* 2019; 76: 106–14

5 **Meijer D**, **Donswijk ML**, **Bodar YJL et al**. Biochemical persistence of prostate-specific antigen after robot-assisted laparoscopic radical prostatectomy: tumor localizations using PSMA PET/CT imaging. *J Nucl Med* 2020. https://doi.org/10.2967/jnumed.120.252528

6 **Briganti A**, **Larcher A**, **Abdollah F et al**. Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. *Eur Urol* 2012; 61: 480–7

7 **Gandaglia G**, **Ploussard G**, **Valerio M et al**. A novel nomogram to identify candidates for extended pelvic lymph node dissection among patients with clinically localized prostate cancer diagnosed with magnetic resonance imaging-targeted and systematic biopsies. *Eur Urol* 2019; 75: 506–14

8 **Huang Y**, **Isharwal S**, **Haese A et al**. Prediction of patient-specific risk and percentile cohort risk of pathological stage outcome using continuous prostate-specific antigen measurement, clinical stage and biopsy Gleason score. *BJU Int* 2011; 107: 1562–9

9 **Memorial Sloan Kettering Cancer Centre**. Prostate cancer nomograms: pre-radical prostatectomy. 2020. Available at: https://www.mskcc.org/nomograms/prostate/pre_op. Accessed January 4 2021

10 **Perera M**, **Papa N**, **Roberts M et al**. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur Urol* 2020; 77: 403–17

11 **Hofman MS**, **Lawrentschuk N**, **Francis RJ et al**. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet* 2020; 395: 1208–16

12 **Emmett L**, **Tang R**, **Nandurkar R et al**. 3-Year freedom from progression after (68)Ga-PSMA PET/CT-triaged management in men with biochemical recurrence after radical prostatectomy: results of a prospective multicenter trial. *J Nucl Med* 2020; 61: 866–72

13 **van Leeuwen PJ**, **Donswijk M**, **Nandurkar R et al**. Gallium-68-prostate-specific membrane antigen ((68) Ga-PSMA) positron emission tomography (PET)/computed tomography (CT) predicts complete biochemical response from radical prostatectomy and lymph node dissection in intermediate- and high-risk prostate cancer. *BJU Int* 2019; 124: 62–8

14 **Roberts MJ**, **Morton A**, **Donato P et al**. (68)Ga-PSMA PET/CT tumour intensity pre-operatively predicts adverse pathological outcomes and progression-free survival in localised prostate cancer. *Eur J Nucl Med Mol Imaging* 202148: 477–82. https://doi.org/10.1007/s00259-020-04944-2

15 **Mohler JL**, **Antonarakis ES**, **Armstrong AJ et al**. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2019; 17: 479–505

16 **Padhani AR**, **Weinreb J**, **Rosenkrantz AB**, **Villeirs G**, **Turkbey B**, **Barentsz J**. Prostate imaging-reporting and data system steering committee: PI-RADS v2 status update and future directions. *Eur Urol* 2019; 75: 385–96

17 **Bouvet V**, **Wuest M**, **Jans HS et al**. Automated synthesis of [(18)F] DCFPyL via direct radiofluorination and validation in preclinical prostate cancer models. *EJNMMI Res* 2016; 6: 40

18 **Ravert HT**, **Holt DP**, **Chen Y et al**. An improved synthesis of the radiolabeled prostate-specific membrane antigen inhibitor, [(18) F] DCFPyL. *J Labelled Comp Radiopharm* 2016; 59: 439–50

19 **Eiber M**, **Herrmann K**, **Calais J et al**. Prostate cancer molecular imaging standardized evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. *J Nucl Med* 2018; 59: 469–78

20 **Egevad L**, **Delahunt B**, **Evans AJ et al**. International society of urological pathology (ISUP) grading of prostate cancer. *Am J Surg Pathol* 2016; 40: 858–61

21 **Mottet NBJ**, **Briers E**, **Bolla M et al**. *EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer*, Arnhem, The Netherlands: EAU Guidelines Office., 2020

22 **Rayn KN**, **Bloom JB**, **Gold SA et al**. Added value of multiparametric magnetic resonance imaging to clinical nomograms for predicting adverse pathology in prostate cancer. *J Urol* 2018; 200: 1041–7

23 **Feng TS**, **Sharif-Afshar AR**, **Wu J et al**. Multiparametric MRI improves accuracy of clinical nomograms for predicting extracapsular extension of prostate cancer. *Urology* 2015; 86: 332–7

24 **Weaver JK**, **Kim EH**, **Vetter JM et al**. Prostate magnetic resonance imaging provides limited incremental value over the memorial sloan kettering cancer center preradical prostatectomy nomogram. *Urology* 2018; 113: 119–28

25 **Jansen BHE**, **Nieuwenhuijzen JA**, **Oprea-Lager DE et al**. Adding multiparametric MRI to the MSKCC and Partin nomograms for primary prostate cancer: Improving local tumor staging? *Urol Oncol* 2019; 37: 181.e1–181.e6

26 **Cimino S**, **Reale G**, **Castelli T et al**. Comparison between Briganti, Partin and MSKCC tools in predicting positive lymph nodes in prostate cancer: a systematic review and meta-analysis. *Scand J Urol* 2017; 51: 345–50

27 **Kjolhede H**, **Almquist H**, **Lyttkens K**, **Bratt O**. Pre-treatment (18)F-choline PET/CT is prognostic for biochemical recurrence, development of bone metastasis, and cancer specific mortality following radical local therapy of high-risk prostate cancer. *Eur J Hybrid Imaging* 2018; 2: 16

28 **Boeve LMS**, **Hulshof M**, **Vis AN et al**. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical Trial: Data from the HORRAD Trial. *Eur Urol* 2019; 75: 410–8

29 **Parker CC**, **James ND**, **Brawley CD et al**. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018; 392: 2353–66

30 **Culp SH**, **Schellhammer PF**, **Williams MB**. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. *Eur Urol* 2014; 65: 1058–66

31 **Knipper S**, **Beyer B**, **Mandel P et al**. Outcome of patients with newly diagnosed prostate cancer with low metastatic burden treated with radical prostatectomy: a comparison to STAMPEDE arm H. *World J Urol* 2020; 38: 1459–64

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Abbreviations: ADT, androgen deprivation therapy; AUC, area under the curve; BCR, biochemical recurrence; bPFS, biochemical progression-free survival; EBRT, external beam radiation therapy; ePLND, extended pelvic lymph node

dissection; EAU, European Association of Urology; 68Ga, gallium 68; GG, Grade Group; IQR, interquartile range; ISUP, International Society of Urological Pathology; mpMRI, multiparametric MRI; NCCN, National Comprehensive Cancer Network; NCI, Netherlands Cancer Institute; PCa, prostate cancer; MSKCC, Memorial Sloan Kettering Cancer Centre; OR, odds ratio; PET, positron emission tomography; PI-RADS, Prostate Imaging- Reporting and Data System; PSMA, prostate-specific membrane antigen; RARP, robot-assisted laparoscopic radical prostatectomy; UMC, University Medical Centre.