

## Original Article

# External validation of the Memorial Sloan Kettering Cancer Centre and Briganti nomograms for the prediction of lymph node involvement of prostate cancer using clinical stage assessed by magnetic resonance imaging

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## Objectives

To evaluate the impact of using clinical stage assessed by multiparametric magnetic resonance imaging (mpMRI) on the performance of two established nomograms for the prediction of pelvic lymph node involvement (LNI) in patients with prostate cancer.

## Patients and Methods

Patients undergoing robot-assisted extended pelvic lymph node dissection (ePLND) from 2015 to 2019 at three teaching hospitals were retrospectively evaluated. Risk of LNI was calculated four times for each patient, using clinical tumour stage (T-stage) assessed by digital rectal examination (DRE) and by mpMRI, in the Memorial Sloan Kettering Cancer Centre (MSKCC; 2018) and Briganti (2012) nomograms. Discrimination (area under the curve [AUC]), calibration, and the net benefit of these four strategies were assessed and compared.

## Results

A total of 1062 patients were included, of whom 301 (28%) had histologically proven LNI. Using DRE T-stage resulted in AUCs of 0.71 (95% confidence interval [CI] 0.70–0.72) for the MSKCC and 0.73 (95% CI 0.72–0.74) for the Briganti nomogram. Using mpMRI T-stage, the AUCs were 0.72 (95% CI 0.71–0.73) for the MSKCC and 0.75 (95% CI 0.74–0.76) for the Briganti nomogram. mpMRI T-stage resulted in equivalent calibration compared with DRE T-stage. Combined use of mpMRI T-stage and the Briganti 2012 nomogram was shown to be superior in terms of AUC, calibration, and net benefit. Use of mpMRI T-stage led to increased sensitivity for the detection of LNI for all risk thresholds in both models, countered by a decreased specificity, compared with DRE T-stage.

## Conclusion

T-stage as assessed by mpMRI is an appropriate alternative for T-stage assessed by DRE to determine nomogram-based risk of LNI in patients with prostate cancer, and was associated with improved model performance of both the MSKCC 2018 and Briganti 2012 nomograms.

## Keywords

prostate cancer, nomogram, lymph node involvement, extended pelvic lymph node dissection, external validation, staging, #PCSM, #ProstateCancer, #uroonc

## Introduction

Assessment of pelvic lymph node involvement (LNI) by extended pelvic lymph node dissection (ePLND) is an essential component of the general staging evaluation in patients with newly diagnosed prostate cancer selected for radical prostatectomy, and is indicated in patients with a risk of LNI above 5% [1]. Even minimal tumour involvement of the lymphatic system is thought to have a pivotal impact on disease prognosis and should be established to identify patients with an increased risk of disease recurrence [2].

Currently, advances within the field of clinical imaging, particularly prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)-CT, are rapidly evolving. However, since the sensitivity of PSMA PET-CT for the detection of LNI in primary prostate cancer is only moderate, it cannot yet replace ePLND to exclude LNI [3,4]. Thus, ePLND remains the preferred option for nodal staging in primary prostate cancer [1].

Performing ePLND in patients undergoing radical prostatectomy is associated with unfavourable intra- and peri-operative outcomes, including symptomatic lymphocele development (in up to 18%), bleeding (2.7%), infections (3.6%), and ureteric damage (0.8%), whereas there is no high-level evidence for a direct therapeutic effect [5,6]. ePLND should therefore be reserved for carefully selected patients.

Both the European Association of Urology (EAU) and the National Comprehensive Cancer Network guidelines recommend the use of nomograms to guide patient selection for ePLND [1,7]. Several of these prediction tools have been developed over the years [8]. The Memorial Sloan Kettering Cancer Centre (MSKCC) pre-radical prostatectomy (update 2018) and Briganti 2012 nomograms are the two most established models [9,10]. In a recent validation study using a contemporary cohort of patients with prostate cancer, the 2012 Briganti and 2018 MSKCC nomograms were identified as the most accurate prediction tools available, with reported areas under the curve (AUC) of 0.76 and 0.75, respectively [8].

Both the MSKCC 2018 and Briganti 2012 nomograms include clinical tumour stage (T-stage) assessed by digital rectal examination (DRE) as one of the input variables [9,10]. However, recent guideline updates include the recommendation for performing multiparametric MRI (mpMRI) prior to prostate biopsy [1,11]. As a result, MRI staging information will become increasingly available in newly diagnosed patients. In addition, mpMRI potentially enables a more accurate estimation of local tumour extent compared with DRE [12]. However, it is not clear if the use of T-stage assessed by mpMRI (mpMRI T-stage) results in more accurate nomogram-based LNI risk prediction.

In the present study, therefore, we evaluate whether replacing DRE T-stage by mpMRI T-stage results in a more accurate LNI risk prediction by the MSKCC 2018 and Briganti 2012 nomograms.

## Patients and Methods

### Study Population

After receiving institutional review board approval, patients diagnosed with prostate cancer undergoing ePLND between January 2015 and September 2019 at three Dutch teaching hospitals (St Antonius Hospital Nieuwegein/Utrecht, Hospital Group Twente Almelo/Hengelo, and Canisius Wilhelmina Hospital Nijmegen) were included.

Patients underwent ePLND either combined with radical prostatectomy or prior to radiation therapy. In general, patients with a risk of LNI >5% (based on DRE T-stage), calculated using the MSKCC web calculator [9] were considered as candidates for ePLND. However, deviations were allowed at the discretion of the treating urologist.

Digital rectal examination T-stage, mpMRI T-stage, preoperative prostate-specific antigen (PSA), highest International Society of Urological Pathology (ISUP) grade observed on most recent preoperative biopsy, total number of biopsy cores taken on systematic biopsy and relative number of cores containing prostate cancer on systematic biopsy were collected. Patients were included if they underwent systematic biopsies with or without MRI-guided target biopsy and mpMRI for local staging prior to ePLND. Patients undergoing salvage ePLND or those who received androgen deprivation therapy prior to ePLND were excluded.

### Covariates and Endpoints

Prostate-specific antigen, DRE T-stage, mpMRI T-stage, total number and relative number of positive biopsy cores as well as pathological lymph node status were collected during standard clinical practice. Biopsy grading was performed according to the new Gleason Grade group classification [13].

Digital rectal examination was performed during the primary diagnostic evaluation by urologists with >5 years of experience in diagnosing and staging prostate cancer. DRE consisted of systematic palpation of all prostate regions including both lateral sides, the posterior region and the sulcus. DRE was performed in either the dorsal lithotomy or lateral position. Findings were reported according to the clinical classification of the American Joint Committee on Cancer [14].

During the study period, 3-Tesla MRI scanners were used at the three institutions. Radiological reporting was performed by dedicated uro-radiologists. Reporting was done according

to the Prostate Imaging – Reporting and Data System (PI-RADS) version 2 guidelines [15]. mpMRI T-stages were defined as T2a (unilateral suspicious lesion, involving <50% of the prostatic lobe), T2b (unilateral suspicious lesion, involving >50% of the prostatic lobe), T2c (bilateral suspicious lesion), T3a (definite or high degree of suspicion for extraprostatic extension), T3b (definite or high degree of suspicion of seminal vesicle invasion) and T4 (invasion of adjacent structures). The MRI protocols used at the three institutions are presented in the Supporting Information (Table S1).

The ePLND template included removal of nodes overlying the external iliac vessels, internal iliac artery, and the nodes located within the obturator fossa [16].

All resected nodal tissue was submitted for pathological evaluation, which was performed by experienced uro-pathologists. The total number of lymph nodes found in the tissue and the number of nodes containing prostate cancer metastasis were assessed. Histopathological evaluation was performed in accordance with the ISUP consensus statement on handling and staging of radical prostatectomy specimens [17].

### Statistical Analysis

The risk of LNI was estimated a total of four times per patient: using both the MSKCC and Briganti 2012 nomograms, with both DRE and mpMRI T-stage. Other covariates used for LNI risk calculation included most recent preoperative serum PSA level, highest ISUP grade found on either systematic or target biopsy, as well as the number of positive cores and the total number of cores taken on systematic biopsy. Model discrimination was quantified using the AUC, and refers to the probability of a random patient with histologically proven LNI (pN1) having a higher predicted risk than a random patient without histologically proven LNI (pN0) [18]. Classification plots showing the true- and false-positive rates per risk threshold were used to visualize discriminatory ability [19]. Model calibration, which refers to the agreement between observed and predicted LNI, was assessed by plotting calibration curves [18]. Calibration-in-the-large indicates whether predicted probabilities are systematically too low or too high. Perfect calibration is characterized by a calibration-in-the-large of 0, and a calibration slope of 1 [18]. The scaled Brier score, which is the average squared difference between the actual outcomes (i.e. LNI) and predicted probabilities, was also determined. A scaled Brier score close to 1 shows overall poor predictive ability, whereas a scaled Brier score of 0 corresponds to perfect risk prediction of the model [18]. Decision-curve analysis was performed to determine the net benefit of the models over multiple clinically relevant thresholds. The calculated net benefit of the models was compared to the

scenarios of treating either all or no patients [20]. A systematic analysis was performed to determine the number of patients (with or without LNI) in whom ePLND would be advised, for LNI risk thresholds between 1% and 15%. Missing data were handled by using multiple imputations by chained equations [21]. A total of 10 imputed datasets were created. Model performance measures were estimated by bootstrapping each imputed dataset 500 times. To select the best-performing approach, the different approaches were compared head-to-head by estimating in how many bootstrap samples a specific approach resulted in the highest pooled AUC measure. Statistical analysis was performed using R v3.6.3. (R Project for Statistical Computing, www.r-project.org).

## Results

### Study Population

A total of 1062 patients fulfilled the inclusion criteria. Overall, 301 patients (28%) had histologically confirmed LNI. The median number of lymph nodes removed was 20 (interquartile range 13–25). A total of 21 patients (2%) had one or more covariates missing, including DRE T-stage ( $N = 11$ ), mpMRI T-stage ( $N = 2$ ), and biopsy data ( $N = 8$ ). Baseline characteristics of the study cohort are presented in Table 1.

### Model Performance Using DRE or mpMRI T-stage

Initial validation included use of DRE T-stage. Discrimination in terms of AUC was 0.71 (95% CI 0.70–0.72) for the MSKCC and 0.73 (95% CI 0.72–0.74) for the Briganti nomogram. Mean predicted probability for LNI was 24% for the MSKCC and 21% for the Briganti nomogram, where the observed LNI rate was 28% (Table S2). On visual exploration of calibration plots, we also observed systematic underestimation of the predicted risk of both nomograms, particularly for risk thresholds between 0% and 30% (Fig. 1A and B).

When using mpMRI T-stage, discrimination in terms of AUC increased to 0.72 (95% CI 0.71–0.73) for the MSKCC and 0.75 (95% CI 0.74–0.76) for the Briganti model (Table S2). The mean predicted probability for LNI changed to 30% for the MSKCC and 27% for the Briganti nomogram (Table S2). As shown in the calibration plots, the agreement between predicted and observed probabilities was comparable (both moderate calibration) for both DRE T-stage and mpMRI T-stage. Calibration intercepts were closer to 0 when using mpMRI instead of DRE for both the MSKCC (0.04 [95% CI 0–0.08] vs 0.08 [95% CI 0.04–0.12]) and the Briganti nomogram (0.05 [95% CI 0–0.08] vs 0.10 [95% CI 0.06–0.13]; Table S2). In a head-to-head comparison, calculating the LNI

**Table 1** Baseline characteristics of the validation cohort.

	Overall	pN0	pN1
Patients, <i>N</i> (%)	1062 (100)	761 (72)	301 (28)
Hospital, <i>N</i> (%)			
SAH	258 (24)	186 (24)	72 (24)
HGT	246 (23)	159 (21)	87 (29)
CWH	558 (53)	416 (55)	142 (47)
Median (IQR) age, years	67 (63–71)	68 (63–71)	67 (63–71)
Median (IQR) PSA, ng/mL	10 (6.6–18)	9.3 (6.2–16)	13 (7.8–22)
Median (IQR) total cores	10 (10–12)	10 (9–12)	10 (10–12)
Data on total cores missing <i>N</i> (%)	5 (0)	4 (1)	1 (0)
Median (IQR) total positive cores	5 (3–8)	5 (3–7)	7.1 (3.3)
Data on positive cores missing <i>N</i> (%)	6 (1)	5 (1)	1 (0)
Median (IQR) percentage of positive cores	0.50 (0.33–0.75)	0.50 (0.25–0.67)	0.75 (50–100)
Data on percentage of positive cores missing <i>N</i> (%)	7 (1)	6 (1)	1 (0)
Biopsy ISUP grade, <i>N</i> (%)			
1	78 (7)	65 (9)	13 (4)
2	245 (23)	191 (25)	54 (18)
3	280 (26)	202 (27)	78 (26)
4	253 (24)	189 (25)	64 (21)
5	201 (19)	110 (14)	91 (30)
Missing	5 (0)	4 (0)	1 (0)
DRE T-stage, <i>N</i> (%)			
T1c	384 (36)	301 (40)	83 (28)
T2a	328 (31)	248 (33)	80 (27)
T2b	84 (8)	57 (7)	27 (9)
T2c	77 (7)	52 (7)	35 (12)
T3a	169 (16)	103 (14)	66 (22)
T3b	7 (1)	3 (0)	4 (1)
T4	3 (0)	1 (0)	2 (0)
Missing	10 (1)	6 (1)	4 (1)
mpMRI T-stage, <i>N</i> (%)			
T1c	40 (4)	36 (5)	4 (1)
T2a	301 (28)	250 (33)	51 (17)
T2b	41 (4)	29 (4)	12 (4)
T2c	120 (11)	103 (14)	17 (6)
T3a	376 (35)	261 (34)	115 (38)
T3b	160 (15)	69 (9)	91 (30)
T4	22 (2)	12 (2)	10 (3)
Missing	2 (0)	1 (0)	1 (0)
Biopsy type, <i>N</i> (%)			
TRUS-guided SB	694 (65)	479 (63)	215 (71)
TRUS-SB + MRI-TB	368 (35)	282 (37)	86 (29)
Median (IQR) total nodes resected	20 (13–25)	17 (12–24)	20 (14–28)

CWH, Canisius Wilhelmina Hospital; HGT, Hospital Group Twente; IQR, interquartile range; MRI-TB, magnetic resonance image-guided target biopsy; SAH, St Antonius Hospital; SB, systematic biopsy. Percentages may not total 100 due to rounding.

risk using mpMRI T-stage with the Briganti nomogram led to higher AUCs in all bootstrap samples, compared with Briganti DRE T-stage as well as both DRE T-stage and mpMRI T-stage with the MSKCC nomogram.

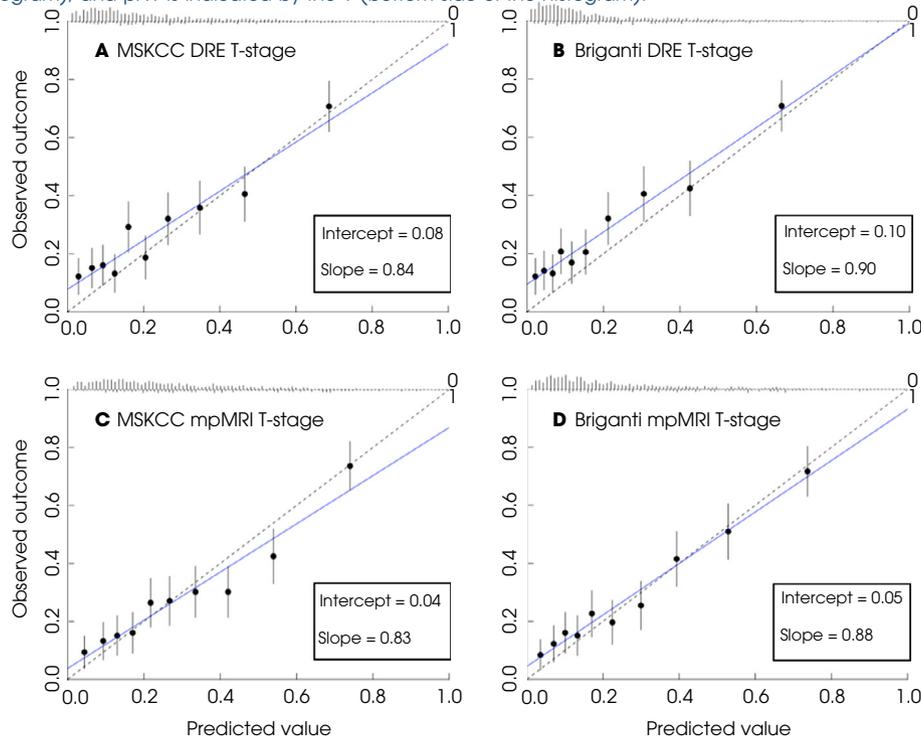
### Clinical Usefulness

Using mpMRI T-stage resulted in a higher true-positive rate and a higher false-positive rate for the detection of positive lymph nodes for all risk thresholds, compared to using DRE T-stage (Fig. 2). Use of mpMRI T-stage led to increased sensitivity for the detection of LNI for all risk thresholds in both models, countered by a lower specificity, compared with DRE T-stage. In Tables S3 and S4, total numbers of missed

LNI cases per risk threshold are presented, combined with rates of performed ePLND and number of positive LNI cases. For all thresholds, the number of missed LNI cases was lower when mpMRI T-stage was used, countered by higher rates of unnecessary ePLND (pN0).

Decision-curve analysis revealed that use of mpMRI T-stage in both nomograms resulted in higher net benefits, compared with DRE T-stage, for the risk thresholds between 5% and 20%. Net benefits for both the MSKCC and Briganti nomograms, using mpMRI T-stage, were comparable for this range of risk thresholds. For risk thresholds ranging from 20% to 30%, the combined use of mpMRI T-stage with the Briganti nomogram would lead to the highest net benefit (Fig. 3).

**Fig. 1** Calibration plots of both nomograms based on DRE T-stage (**A** and **B**) and mpMRI T-stage (**C** and **D**). MSKCC, Memorial Sloan Kettering Cancer Centre. A histogram displayed at the top of each calibration plot shows the distribution of predicted risks for pN0 and pN1 cases. pN0 is indicated by the 0 (top side of the histogram), and pN1 is indicated by the 1 (bottom side of the histogram).



## Discussion

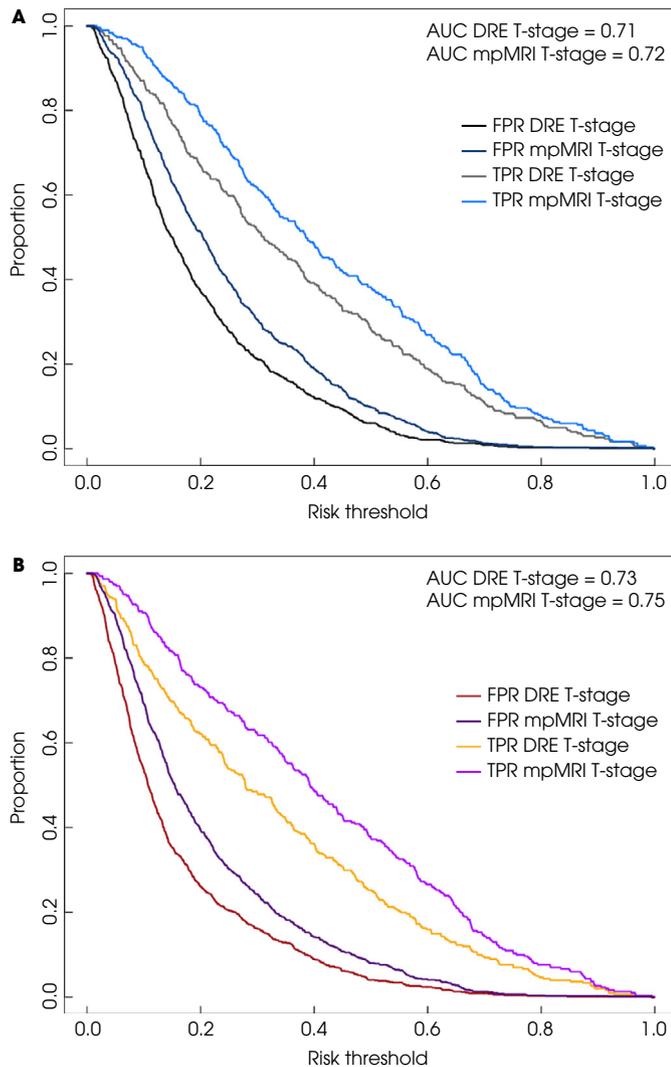
Use of mpMRI T-stage for nomogram-based LNI risk assessment resulted in higher AUC, comparable agreement between predicted and observed probabilities, and higher net benefit compared with DRE T-stage, in both the MSKCC 2018 and Briganti 2012 nomograms. In our study population, use of DRE T-stage would lead to overall LNI risk underestimation in the clinically relevant range of risk thresholds (0–30%). In the head-to-head comparison, combined use of the mpMRI T-stage with the Briganti 2012 nomogram resulted in the most accurate LNI risk prediction.

Our study acknowledges the robustness of both the MSKCC 2018 and Briganti 2012 nomograms, since model performance was still fair to good, even when the model was applied in a patient population with substantially higher prevalence of the predicted outcome compared with the development populations. In our cohort, LNI prevalence (28%) was substantially higher compared to both the MSKCC (7% [internal communication MSKCC research team]) and Briganti (8%) populations [10]. Therefore, our results show both models are applicable in a contemporary patient cohort. In addition, our analysis confirmed that mpMRI T-stage can be safely used as an impute parameter for these nomograms, even leading to improved accuracy of the predicted LNI risk compared with DRE T-stage.

The present study's main findings add to the available body of literature supporting the additional value of mpMRI information for predicting presence of LNI in prostate cancer. For example, Porphiglia et al. [22] showed that MRI has an important role in LNI risk prediction in patients with a nomogram-predicted risk <5%. Huang et al. [23] demonstrated that addition of PI-RADS score improved model discrimination in terms of AUC for both nomograms, increasing from 75% to 86% for Briganti and from 79% to 88% for MSKCC, respectively.

Recently, two new nomograms have been introduced, including mpMRI and target biopsy features such as maximum diameter of the index lesion and maximum percentage of tumour involvement in one core [24,25]. Of these, the 2019 Briganti nomogram was recently externally validated, showing excellent characteristics, including an AUC of 79% and high agreement between predicted and observed probabilities for risk thresholds below 35% [26]. In their head-to-head comparison, the 2019 Briganti nomogram outperformed the Briganti 2017 and MSKCC 2018 nomograms in terms of discrimination, calibration and net benefit. Although these new nomograms potentially enable improved LNI risk prediction due to the addition of mpMRI-guided target biopsy, they both include complex features which may not always be available in clinical practice, such as maximum diameter of the index lesion on mpMRI and

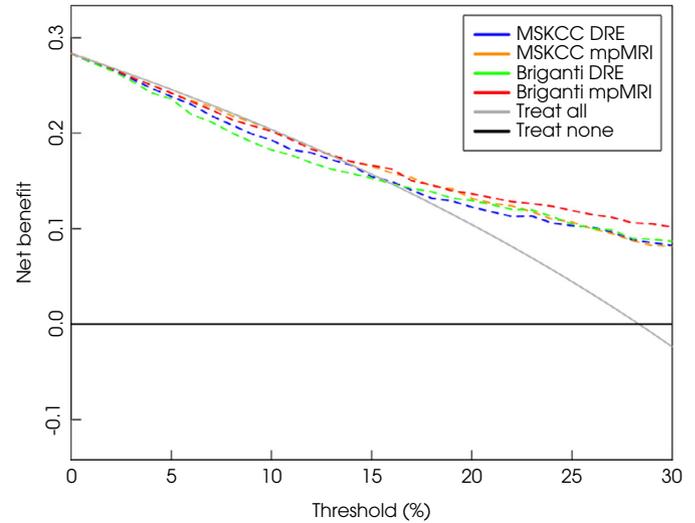
**Fig. 2** Classification plots of both nomograms displaying false positive rate (FPR) and true positive rate (TPR) established using both DRE T-stage and multiparametric MRI (mpMRI) T-stage with (A) the Memorial Sloan Kettering Cancer Centre 2018 and (B) the Briganti 2012 nomogram. AUC, area under the curve.



highest tumour length in millimetres of all biopsy cores taken [24,25]. In addition, more external validation studies are warranted to confirm the accuracy of these new nomograms in external patient populations as model transportability needs to be adequate to prevent systematic wrong decision-making.

Our results do not support the statements in a recent position paper on prostate cancer staging by Paner *et al.* [27], who suggested that DRE should not be replaced by mpMRI for establishing clinical T-stage. In the present study, mpMRI outperformed DRE in terms of AUC for nomogram-based LNI risk prediction, as the use of mpMRI T-stage resulted in higher AUCs for all bootstrap samples. This is most likely the

**Fig. 3** Decision curves for the four performed validation scenarios compared to the default strategies. MSKCC, Memorial Sloan Kettering Cancer Centre.



consequence of the main advantage that mpMRI has over DRE for determining local tumour extent, which is the visualization of the prostate gland as a whole and improved detection of non-organ-confined disease. Our study group has confirmed this in a recent study, as the reported sensitivity for the detection of non-organ-confined disease was significantly lower for DRE compared with mpMRI (51% vs 12%;  $P < 0.001$ ) [28].

Although our main study results favour the use of mpMRI T-stage for nomogram-based LNI risk prediction, there are arguments against replacing DRE with mpMRI T-stage that should be mentioned. First, disadvantages of MRI include reader interobserver variability and quality differences regarding mpMRI reading [27]. However, a previous study by Angulo *et al.* [29] showed interobserver inconsistency also to be an issue for DRE, resulting in a low ability to reproduce clinical staging on DRE among multiple examiners.

Second, use of mpMRI compared with DRE would lead to upstaging of clinical T-stage in one-third of patients [28]. Although mpMRI can provide valuable prognostic information for specific patients, including those with non-organ-confined disease which was not detected during DRE, the high upstaging rates bear the risk of overstaging and hence overtreatment in patients with favourable-risk disease [28].

To select patients for ePLND, it remains important to take into account patient's preferences, age and prognostic tumour parameters other than those included in the nomograms to distinguish the patients who would benefit from additional ePLND from those in whom this intervention would potentially do more harm than good.

In addition, the trade-off between subjecting node-negative patients to the concomitant risks of ePLND vs the potential advantages of ePLND in the specific node-positive subgroup, remains to be explored. Future studies should focus on finding the optimum risk threshold at which the benefits of ePLND, at best, outweigh the harms.

Although the present study has several strengths, such as the inclusion of a multicentre cohort representing a real-world prostate cancer population and a large study sample with a sufficient number of events for adequate external validation, it also has some limitations. Firstly, the data used in the study were derived from routine clinical practice, and no central review of DRE, mpMRI and histopathological evaluation was performed. Secondly, the majority of the data were collected retrospectively, which could have led to measurement bias. Lastly, the indication to perform an ePLND in this patient cohort was derived from nomogram-based LNI risk estimation (risk of LNI >5%). Even though this is in accordance with current EAU guideline recommendations, and reflects contemporary clinical practice, it could have introduced bias due to the selection of patients for ePLND with higher risk of LNI (reflected by the relatively high LNI prevalence). For instance, selecting patients with higher risk of LNI (and prevalence) could explain the counterintuitive finding on decision-curve analysis, showing that a 'treat-all' approach would lead to higher net benefit compared with nomogram-based selection for risk thresholds between 0% and 15%.

In conclusion, the MSKCC and Briganti 2012 nomograms were found to be adequate models for the prediction of LNI in patients with prostate cancer when using either mpMRI T-stage or DRE T-stage. The use of mpMRI T-stage led to improved model discrimination, equal calibration, and lower rates of missed LNI cases. Using the mpMRI T-stage with the Briganti 2012 nomogram was shown to be the most accurate strategy for LNI risk prediction.

## Disclosure of Interest

None declared.

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Abbreviations: AUC, area under the curve; EAU, European Association of Urology; ePLND, extended pelvic lymph node dissection; ISUP, International Society of Urological Pathology; LNI, lymph node involvement; mpMRI, multiparametric MRI; MSKCC, Memorial Sloan Kettering Cancer Centre; PET, positron-emission tomography; PI-RADS, Prostate Imaging – Reporting and Data System; PSMA, prostate-specific membrane antigen; T-stage, clinical tumour stage.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** MRI protocols used at each hospital.

**Table S2.** Model performance parameters after pooling for DRE T-stage and mpMRI T-stage.

**Table S3.** Systematic analysis of the MSKCC 2018 nomogram-derived cut-offs to discriminate patients with from patients without LNI when using DRE T- or mpMRI T-stage.

**Table S4.** Systematic analysis of the Briganti 2012 nomogram-derived cut-offs to discriminate patients with from patients without LNI when using DRE T or mpMRI T-stage.