INTRODUCTION

The utilization and importance of multiparametric magnetic resonance imaging (mpMRI) for the diagnosis and treatment of prostate cancer (PCa) is continuously increasing worldwide [1]. The current role of mpMRI in the clinical field of PCa is diverse, including cancer screening, biopsy guidance, staging, and recurrence evaluation [2]. In addition,
mpMRI facilitates the enhanced assessment of the tumor stage, including extraprostatic extension (EPE), seminal vesicle invasion, nodal status, and adjacent anatomical structures [3].

Over the last 10–20 years, the use of radical prostatectomy (RP) for primary management has practically increased in patients with localized high-risk PCa [4]. RP performed as initial monotherapy may be considered to have the potential benefits of confirming final pathological cancer staging, chance of cure without additional therapy, reduced rates of symptomatic local recurrence, and avoidance of possible complications due to medical castration therapy or radiotherapy. For the main goals of RP, including oncological safety and optimization of functional outcomes, accurate prediction of pathological EPE is crucial for surgical planning decisions [5, 6].

Although almost urologists today utilize mpMRI to determine the presence of any degree of EPE [7], the accuracy of EPE on mpMRI of PCa remains controversial [8]. A recent meta-analysis study reported that MRI has high specificity of 91% but poor and heterogeneous sensitivity of 55% for localized PCa staging [9]. To increase the accuracy of EPE prediction of mpMRI, several studies have used novel risk models that combine mpMRI with other clinical parameters [10-14]. In current guidelines, mpMRI-related parameters are not currently included in risk group stratification and were limited to its role in selecting active surveillance targets [15, 16]. Therefore, evaluating the relationship between risk group stratification on the pivotal guideline and suspicious EPE on mpMRI is essential to accurately predict pathological EPE.

In this study, we aimed to determine the effect of mpMRI on EPE prediction in the final pathology after RP according to the National Comprehensive Cancer Network (NCCN) risk stratification in patients with clinically localized PCas.

**MATERIALS AND METHODS**

1. **Patient Cohort**

This retrospective study of patients in a single tertiary medical center was approved by the Ethics Committee of the Kyungpook National University Chilgok Hospital (IRB No. KNUCH 2023-02-012). This study enrolled consecutive 444 patients diagnosed with PCas after transrectal ultrasound (TRUS)-guided prostate needle biopsy who underwent RP with a staging mpMRI between March 2020 and December 2021. After the exclusion of 41 patients who underwent biopsy using MRI-TRUS fusion prostate biopsy technique and 63 patients who received neoadjuvant therapy, a total of 340 patients were analyzed.

2. **Patient Evaluation**

1) **mpMRI**

In our center’s RP protocol, every patient scheduled for surgery underwent staging 3-Tesla mpMRI (Discovery MR750, GE Healthcare, Chicago, IL, USA) unless MRI was contraindicated. mpMRI was performed without an endorectal coil. Most of the patients underwent mpMRI at our center, and images were read by an experienced radiologist according to Prostate Imaging Reporting and Data System (PIRADS) v2.1 recommendations. The definition of suspicious EPE on mpMRI was defined as with or without EPE, regardless of the degree of EPE. Regarding the evaluation of EPE probability, “capsular contact,” “abutment,” or “bulge without gross EPE” were considered negative for suspicious EPE and “loss of prostate capsule,” “bulging with irregular or spiculate margin,” “asymmetry or invasion of the neurovascular bundles,” “gross obliteration of the rectoprostatic angle,” and “gross EPE” were considered positive for suspicious EPE on mpMRI.

2) **Histopathological analysis**

The Gleason grade groups (GGGs) of the prostate needle biopsy tissue and RP specimens were evaluated by an experienced pathologist according to the International Society of Urological Pathology (ISUP) grading [17]. All RP specimens were reviewed by 2 experienced pathologists according to ISUP. Pathological T stages after RP were assessed according to the American Joint Committee on Cancer guidelines, and the pathological EPE was defined as the case any malignant glands were found outside the prostatic capsule [18]. The seminal vesicle invasion on its own was not classified as EPE.
3. Study Design and Outcome Measurements

To assess EPE in the final pathology, patients were stratified to low (LR), favorable intermediate (FIR), unfavorable intermediate (UIR), and high risk (HR) groups according to the NCCN risk stratification: LR, clinical stage T1, T1c, T2a, GGG 1, and prostate-specific antigen (PSA) <10 ng/mL; FIR, clinical stage T2b or PSA levels between 10 and 20 ng/mL or GGG 2 plus <50% positive biopsy cores; UIR, ≥50% positive biopsy cores and/or GGG 3 and/or clinical stage T2b-c and/or PSA 10–20 ng/mL; HR, clinical stage ≥T3a or PSA levels >20 ng/mL or GGG ≥4 [16]. We assessed the performance evaluation of mpMRI for the prediction of EPE in the final pathology according to the NCCN risk stratification. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of suspicious EPE on mpMRI for pathological EPE were assessed in each group. Variables that can be potentially associated with pathological EPE included age at diagnosis, index PSA, prostate volume, PSA density, maximum percentage of the tumor length in a positive core, total positive core rate, GGG on the prostate needle biopsy, preoperative clinical stage, NCCN risk stratification, and suspicious EPE on mpMRI. Univariate and multivariate analyses were used to evaluate the predictors of EPE in the final pathology after RP.

4. Statistical Analysis

Categorical variables were reported as rates and were tested by Fisher exact test or the χ² test, as appropriate. Univariate analysis was performed using the χ² test. Multivariate analysis was performed using logistic regression analysis. All statistical analyses were performed in IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the clinical, radiological, and pathological characteristics of 340 patients. The mean age at diagnosis was 66.4±6.2 years, the mean index PSA was 8.7±6.3 ng/mL, and the mean prostate volume was 33.6±12.0 mL. ISPU GGG on prostate needle biopsy was 36.8% in GG1, 21.5% in GG2, 19.1% in GG3, 20.9% in GG4, and 1.8% in GG5. Based on the NCCN risk stratification, 113 patients (33.2%) were in the LR group, 50 (14.7%) in the FIR group, 94 (27.6%) in the UIR group, and 83 (24.4%) in the HR group.

Regarding the final pathology after RP, 203 patients (59.7%) had organ-confined disease, whereas 137 patients (40.3%) had EPE. Suspicious EPE on mpMRI was observed in 65 of 137 patients (47.4%) with EPE in the final pathology after RP, whereas it was observed in only 10.8% (22 of 203) of patients with organ-confined disease (p<0.001). Moreover, the index PSA, mean prostate volume, PSA density, maximum percentage of the tumor length in a positive core, total positive core rate, GGG on the prostate needle biopsy, clinical stage, PIRADS score and NCCN risk stratification showed a significant difference between patients with EPE and without EPE. In the final pathology report after RP, the positive surgical margin (PSM) rate and ISUP GGG were significantly higher in the EPE group.

Table 2 shows the results of the univariate analysis of the correlation between suspicious EPE on mpMRI and EPE in the final pathology according to the NCCN risk stratification. Suspicious EPE on mpMRI was observed in 10 patients (8.8%) in the LR group, 9 (18.0%) in the FIR group, 31 (33.0%) in the UIR group, and 37 (44.6%) in the HR group. In the final pathology report, EPE was observed 21 patients (18.6%) in the LR group, 15 (30.0%) in the FIR group, 53 (56.4%) in the UIR group, and 48 (57.8%) in the HR group. Suspicious EPE on mpMRI and EPE in the final pathology showed a significant correlation in the FIR, UIR, and HR groups (p=0.015, p=0.004, and p<0.001, respectively), but not in the LR group (p=1.000). Multivariate analysis was performed with variables that can be potentially associated with pathological EPE. The multivariate analysis also showed similar results to the univariable analysis. Suspicious EPE on mpMRI was a significant predictive factor for EPE in the final pathology in the FIR, UIR, and HR groups (p=0.004, p=0.011, and p<0.001, respectively). In other variables except suspicious EPE on mpMRI, age at diagnosis showed a statistically significant difference in EPE at final pathology prediction (p=0.004) in the FIR group (Supplementary Table 1). The maximum percentage of the tumor length in a positive core and the total positive core rate on biopsy were found to be statistically significant predictors for pathological...
EPE in the UIR group (p=0.012 and p=0.030, respectively) (Supplementary Table 2). In the HR group, suspicious EPE on mpMRI was the only predictor for pathological EPE (Supplementary Table 3). However, no variable showed statistical significance in the LR group (Supplementary Table 4).

Overall, sensitivity, specificity, PPV, and NPV of prediction for pathological EPE on staging mpMRI were 47.5%, 89.2%, 74.7%, and 71.5%, respectively. Table 3 reveals the sensitivity, specificity, PPV, and NPV of suspicious EPE on mpMRI predicting EPE in the final pathology according to the NCCN risk stratification. The sensitivity of suspicious EPE on mpMRI for pathological EPE was 9.5% in the LR, 40.0% in FIR, 45.3% in UIR, and 68.8% in HR groups. In addition,
the PPV was 2.0% in the LR, 66.7% in FIR, 77.4% in UIR, and 89.2% in HR groups. Specificity and NPV ranged from 82.9% to 91.4% and from 54.0% to 81.6% in each group, respectively.

**DISCUSSION**

In the current era when the role of mpMRI has been increasing in the diagnosis and treatment of PCa, improving the accuracy of EPE prediction using mpMRI in patients with clinically localized PCa undergoing RP is essential. In this study, we investigated the fractionized value of mpMRI for EPE prediction in the final pathology after RP according to the NCCN risk stratification of clinically localized PCa. This study revealed that mpMRI showed distinct values for the prediction of EPE in the final pathology according to the NCCN risk stratification. A strong correlation was observed between suspicious EPE on mpMRI and EPE in the final pathology in the FIR, UIR, and HR groups, except in the LR group. The LR group also showed relatively low sensitivity and PPV compared with other groups. This emphasized that the accurate assessment of the tumor status including mpMRI-related parameters and risk stratification is crucial when planning for correct surgical techniques. Therefore, these decisions may promote the optimization of postoperative functional outcomes without compromising oncological outcomes.

Despite unavoidable adverse effects, including postoperative erectile dysfunction and postprostatectomy incontinence, RP has demonstrated a significant survival benefit compared with expectative management in clinically detected localized PCa [19]. Preoperative risk stratification of patients with clinically localized PCa is relevant for patient-tailored treatment planning. Specifically, accurate EPE prediction is critical for the primary goal of RP to achieve oncological safety and maximize functional outcomes by minimizing PSM while maximizing safe nerve-sparing surgery. Moreover, EPE is associated with a higher risk of PSM, biochemical recurrence, metastatic disease, and cancer-specific mortality [15, 20]. Although several nomograms such as CAPRA [21], Kattan nomograms [22], Epstein criteria [23], and Partin tables [24] have investigated the prediction of adverse pathologies including EPE and oncological outcomes, a recent study revealed that even the most widely used versions of Partin tables showed poor discriminative performance in predicting EPE [25]. Several nomograms have not yet included imaging modalities such as MRI in EPE prediction; thus, a specific approach including parameters observed in prostate-specific imaging is necessary.

The introduction of mpMRI for the diagnosis and treatment of PCa has brought progress through several advantages over the conventional methods that depended on PSA, DRE, and TRUS-guided biopsy [26]. In particular,
mpMRI helps in the selection of active surveillance or radical local therapy by clarifying clinical insignificance through visualization of the area and enhancing the detection and characterization of high-risk diseases [27]. In addition, mpMRI facilitates the enhanced assessment of the tumor stage, including EPE, seminal vesicle invasion, nodal status, and adjacent anatomical structures, which are crucial for surgical planning such as for nerve-sparing surgery, bladder neck-sparing surgery, and extent of apical dissection, and pelvic lymph node dissection [7, 27-29]. Among them, the prediction of pathological EPE may pivotally affect surgical planning decision through the implementation status and degree of NS [30-32]. Nowadays, most urologists utilize MRI to determine the presence of any degree of EPE [32].

Currently, the accurate prediction of EPE is increasingly challenging through imaging studies in the preoperative radiological evaluation of clinically localized PCa. In recent decades, many studies have tried to predict EPE through widespread dissemination and significant improvements of MRI in the diagnostic field of PCa [9, 32, 33]. In a diagnostic meta-analysis, de Rooij et al. [9] reported the diagnostic accuracy of MRI for local PCA staging. The study reported that MRI has a high specificity of 91% but poor and heterogeneous sensitivity of 55% for local PCA staging. They concluded that MRI is not sensitive enough to detect the tumor growth outside the prostate. Otherwise, Schiavina et al. [32] reported the effect of mpMRI to guide the NS surgical plan in patients with PCa who underwent robot-assisted RP. They showed that preoperative mpMRI changed the surgical plan in nearly half and significantly lowered overall PSMs compared with the control group without mpMRI (12.4% vs. 24.1%). The discrepancy regarding the accuracy of MRI for EPE prediction may be explained by broad differences in study design, measurement metrics, EPE definitions, and clinical practices (different prevalence of EPE, different scan quality, pre- or postbiopsy performance, different experience of radiologists, etc.) [34, 35].

Although the role of mpMRI in predicting adverse pathology has gradually been increased, PCa risk categories including the NCCN risk stratification do not yet include mpMRI-derived parameters. Because MRI information alone is relatively unreliable in predicting EPE [9], the additional use of clinical and biopsy parameters can increase the predictive accuracy. At MRI initiation in PCa, Wang et al. [30] evaluated MRI findings and clinical data for EPE prediction. They revealed that MRI findings add incremental value to EPE prediction compared with a model containing only clinical variables. Recently, Mehralivand et al. [31] demonstrated that an MRI-based EPE grading system showed higher accuracy for the prediction of pathologic EPE, and clinical features plus MRI grading had the highest diagnostic performance for EPE prediction. In addition, Falagario et al. [6] demonstrated a different area under the curve for EPE prediction using mpMRI in patients with HR PCa compared with LR disease. Contrastingly, Dinneen et al. [34] reported that the improvement in scan quality could increase the prediction accuracy of mpMRI. They showed that their data on EPE prediction using a Likert scale demonstrate the excellent ability of mpMRI, better than previous studies (sensitivity of 90.4% and NPV of 96%). The authors agreed that, like other studies, predicting EPE with MRI alone has limitations. Therefore, we evaluated EPE prediction on mpMRI based on NCCN risk stratification, which is the most commonly used simple risk stratification in patients with clinically localized PCa who underwent RP. This study found a strong correlation between suspicious EPE on mpMRI and final pathology for the intermediate and HR groups, except for the LR group. Recently, several studies have tried to develop nomograms including MRI-related parameters, ISUP grade group, and PSA density for predicting pathological EPE [11-14]. Heetman et al. [13] showed that a EPE-predicting nomogram could reduce PSM rates in patients planned for RP. Other nomograms presented by Soeterik et al. [14] and Nyarangi-Dix et al. [12] demonstrated an excellent AUC range of 0.82 and 0.86, respectively. The MR radiomic analysis, a more futuristic model, combined with radiology interpretation aid the MSKCC nomogram in predicting EPE in high- and nonfavorable intermediate-risk patients, showing the highest AUC [36].

This study has several limitations to consider. First, this retrospective study included a relatively small number of patients. Second, this study was conducted by relying on the interpretation of a single radiologist with high levels of mpMRI expertise. Therefore, a multicenter study that can consider and analyze interreader variability and mpMRI
acquisition protocol is necessary. In addition, the clinical, radiologic, and pathological findings, which may affect the interpretation, were not concealed to each radiologist and pathologist. These limitations warrant future larger, multi-institution, prospective studies.

CONCLUSIONS

In this study, suspicious EPE on mpMRI showed different values for the prediction of EPE in the final pathology according to the NCCN risk stratification. A strong correlation was observed between suspicious EPE on mpMRI and EPE in the final pathology in the FIR, UIR, and HR groups but not in the LR group. By using this in surgical planning, such as in nerve-sparing surgery, the oncologic safety and functional outcome of RP can be increased, and the accuracy can be increased by adding variables for each risk group.

NOTES

- Supplementary Materials: Supplementary Tables 1-4 can be found via https://doi.org/10.22465/juo.234600160008.
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