The effect of 5-alpha reductase inhibitors on the detection of prostate cancer with multiparametric magnetic resonance imaging and prostate biopsy

Mefail Aksu[1], Ural Oğuz[1], Serdar Aslan[2], Erhan Demirelli[1], Özay Demiray[3], Birgül Tok[4], Doğan Sabri Tok[1], Ercan Öğreden[1]

[1]Department of Urology, Giresun University School of Medicine, Giresun, Turkey

[2]Department of Radiology, Giresun University School of Medicine, Giresun, Turkey

[3]Department of Urology, Ministry of Health, Giresun Training and Research Hospital, Giresun, Turkey

[4]Department of Pathology, Giresun University School of Medicine, Giresun, Turkey

Aim To evaluate the effect of 5 alpha-reductase inhibitor (5-ARI) treatment on prostate cancer detection by multi-parametric magnetic resonance imaging (mpMRI).

Methods We retrospectively collected data on 429 patients who underwent mpMRI before prostate biopsy in the Urology Department of Giresun University Training and Research Hospital between March 2018 and December 2021. The patients were categorized as those who had never been treated with 5-ARI (n = 359) and those who were treated with 5-ARI for more than six months (n = 70). The two groups were compared in terms of age, mpMRI findings, and pathology results.

Results The number of patients with Prostate Imaging-Reporting and Data System (PIRADS) 3 score was significantly higher in the 5-ARI group (37.1% vs 20.6%; $P = 0.009$). The groups did not differ in terms of malignant pathological findings (48.5% in the non-5-ARI vs 47.1% in the 5-ARI group; $P = 0.505$). The detection rates of malignant pathological findings in PIRADS 3 and PIRADS 5 patients were similar between the 5-ARI and non-5-ARI group. However, malignancy detection rate in PIRADS 4 patients was significantly higher in the non-5-ARI group ($P = 0.031$). In the non-5-ARI group, the sensitivity was 56.4% and the specificity was 79.7%. In the 5-ARI group, the sensitivity was 84.9% and the specificity was 56.8%.

Conclusion In patients with suspected prostate cancer, 5-ARI intake may alter lesion mpMRI characteristics and PIRADS distribution on mpMRI. 5-ARI intake should be reported to the radiologist.

Prostate cancer is the most common type of cancer in male patients, ranking second (behind lung cancer) in terms of cancer-related mortality. The lifetime risk of prostate cancer is one in nine (1). Due to the high incidence of prostate cancer, appropriate diagnostics, treatment, and follow-up are important. Prostate cancer is suspected based on the results of prostate-specific antigen (PSA) test and digital rectal examination, and the definitive diagnosis is made by prostate biopsy (2). In addition, magnetic resonance imaging (MRI) has been used since the 1980s as a non-invasive imaging method in the diagnosis and staging of the disease, monitoring its local spread, and the detection of lymph node metastases (3,4). Multiparametric magnetic resonance imaging (mpMRI) encompasses several different MRI techniques, such as T2 weighted (T2W) imaging for anatomical evaluation, diffusion-weighted imaging (DWI) for functional evaluation, dynamic contrast imaging (DCI), and MR proton spectroscopy (3).

5-alpha reductase inhibitors (5-ARI) are a first-line treatment widely used for benign prostatic hyperplasia (BPH) (5-7). More than half of men affected by BPH develop symptomatic disease between the ages of 50 and 70 (8), which is the recommended age for early detection of pros-

tate cancer (9). 5-ARI treatment after three to six months reduces the need for surgery by approximately 50% and prostate volume by 25% (10,11). It also reduces serum PSA levels by 50% after six months (12).

Some studies have shown that 5-ARI reduces the detection of prostate cancer and alters PIRADS scores of lesions visible on mpMRI (13-15). However, other studies investigating the effects of 5-ARI on MRI detection of prostate cancer have yielded conflicting results. In light of these findings, we aimed to evaluate how prostate cancer is affected radiologically and pathologically by the use of 5-ARI.

PATIENTS AND METHODS

In this retrospective study, we reviewed the medical records of 756 patients who underwent transrectal ultrasound cognitive prostate biopsy in the Urology Department of Giresun University Training and Research Hospital between March 2018 and December 2021. The study enrolled patients who had undergone mpMR imaging, including DWI, T2W, and DCI sequences, before biopsy. Patients taking 5-ARI for less than 6 months or irregularly were excluded. The final sample involving 429 patients
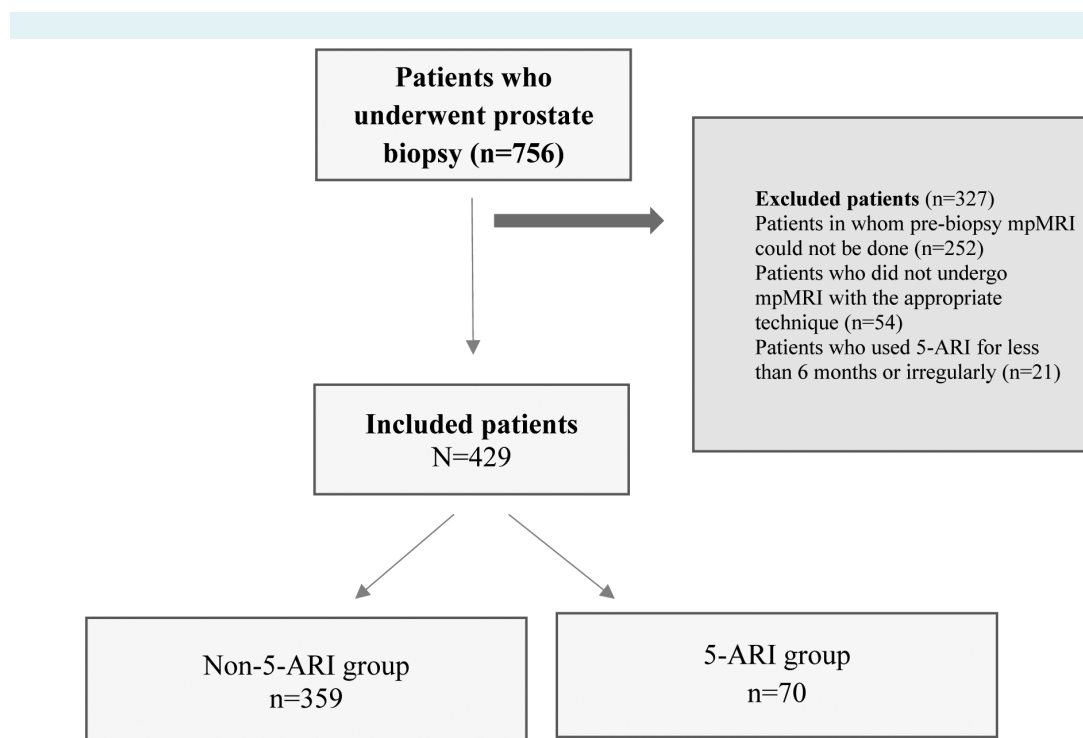

FIGURE 1. Study flowchart. 5-ARI – 5 alpha-reductase inhibitors; mpMRI –multiparametric magnetic resonance imaging.

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(Table 1) was categorized into those who had never taken 5-ARI (n = 359) and those who were taking 5-ARI for more than 6 months (n = 70) (Figure 1). We gathered data on age, PSA, PSA density (PSAD), prostate volume, mpMRI findings, and pathology results. The study was approved by the Clinical Research Ethics Committee of the Ministry of Health Kanuni Training and Research Hospital.

Total serum PSA levels were determined with an electrochemiluminescence immunoassay using the cobas® 8000 modular analyzer, series e-602 module (Roche Diagnostics, Indianapolis, IN, USA). We gathered data on measured PSA rather than on corrected PSA because of different periods of 5-ARI usage. PSAD was calculated by dividing PSA by prostate volume, obtained from MR images.

mpMR images (DWI, T2W, DCI) were evaluated by a radiologist with 10 years of uroradiology experience. mpMRI findings were graded according to the Prostate Imaging-Reporting and Data System (PIRADS), v. 2 (3), evaluation categories. Laboratory findings and pathology reports were evaluated according to the ISUP grading system (16).

Statistical analysis

The normality of distribution of continuous variables was tested with a Kolmogorov-Smirnov test. Variables are presented as means and standard deviations, or medians and interquartile ranges (IQR). Categorical variables were compared with a χ^2 test, and continuous variables with a Mann-Whitney U test. We used receiver-operating characteristic (ROC) curves to assess the diagnostic performance of mpMRI in detecting prostate cancer. Sensitivity and specificity were calculated. P values below 0.05 were considered significant. Statistical analysis was carried out with SPSS, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The mean age did not significantly differ between the groups (66.57 in the non-ARI group vs 68.66 in the ARI group; $P = 0.055$). The median PSA and median PSAD were significantly higher in the non-ARI group (7.12 ng/mL vs 5.37 ng/mL, $P = 0.001$; 0.14 vs 0.10; $P = 0.006$, respectively). There was no difference in prostate volume (non-ARI group: 60.2 cm³ vs 59.9 cm³ in the ARI group; $P = 0.835$)

In the non-5-ARI group, the sensitivity was 56.4%, and the specificity was 79.7%. In the 5-ARI group, the sensitivity was 84.9%, and the specificity was 56.8%. Areas under the curve (AUC) in the non-5-ARI group and ARI group were 0.673 (95% CI 0.621-0.721) and 0.754 (95% CI 0.636-0.849), respectively (Figure 2).

When MRI results were compared, in the non-5-ARI group, PIRADS 3 was found in 74 patients (20.6%), PIRADS 4 in 150 patients (41.8%), and PIRADS 5 in 135 patients (37.6%). In the 5-ARI group, PIRADS 3 was found in 26 patients (37.1%), PIRADS 4 in 26 patients (37.1%), and PIRADS 5 in 18 patients (25.7%). The number of patients with PIRADS 3 was significantly higher in the 5-ARI group than in the non-5-ARI group (37.1% vs 20.6%; $P = 0.009$) (Table 1).

The malignancy detection rate in patients with PIRADS 3 score was 36.5% in the 5-ARI group and 19.3% in the non-5-ARI group ($P = 0.105$). The malignancy detection rates in patients with PIRADS 4 (32% vs 53.9%) and PIRADS 5 (71.9% vs 77.8%) were higher in the 5-ARI group, but the difference was significant only for the PIRADS 4 group ($P = 0.031$ and $P = 0.597$, respectively) (Figure 3). There was no significant difference in total malignant pathological findings between the groups (48.5% in the non-ARI group, 47.1% in the ARI group; $P = 0.505$) (Table 1).

TABLE 1. Prostate Imaging-Reporting and Data System (PIRADS) distributions and pathological results in the group not using 5 alpha-reductase inhibitors (5-ARI) and the group using 5-ARI

| | | Group | | | | | | χ^2 test | |
| | | non-5-ARI | | 5-ARI | | total | | | |
		n	%	n	%	n	%	χ^2	p
PIRADS	3	74	20.6	26	37.1	100	23.3	9.496	0.009
	4	150	41.8	26	37.1	176	41.0		
	5	135	37.6	18	25.7	153	35.7		
	total	359	100.0	70	100.0	429	100.0		
Pathology	benign	185	51.5	37	52.9	222	51.7	1.365	0.505
	malign	174	48.5	33	47.1	207	48.3		
	total	359	100.0	70	100.0	429	100.0		

DISCUSSION

This study showed that in patients with suspected prostate cancer, 5-ARI intake may alter lesion MRI characteristics and PIRADS distribution on mpMRI. The number of patients with PIRADS 3 lesions was higher in the 5-ARI group. In both groups, the cancer detection rate in patients with PIRADS 3 lesions was lower than in patients with PIRADS 4 and PIRADS 5 lesions.

In some studies, the use of 5-ARI affected the detection of prostate cancer and the interpretation of mpMRI (13-15). For example, Andriole et al reported that, compared with placebo, 5-ARI reduced the risk of prostate cancer by low-
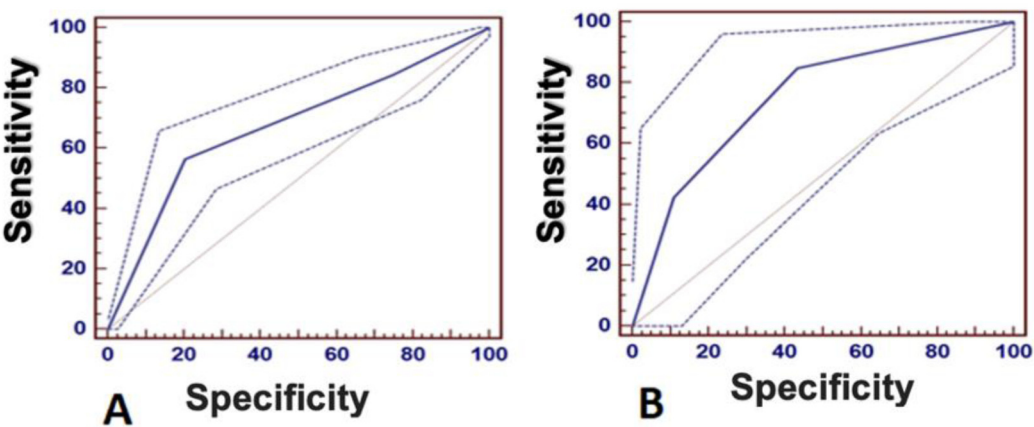

FIGURE 2. Receiver operating characteristic curve of multiparametric magnetic resonance imaging in (**A**) the group not using 5 alpha-reductase inhibitors (area under the curve: 0.673; 5% confidence interval 0.621-0.721); (**B**) the group using 5 alpha-reductase inhibitors (area under the curve: 0.754; 95% confidence interval 0.636-0.849).

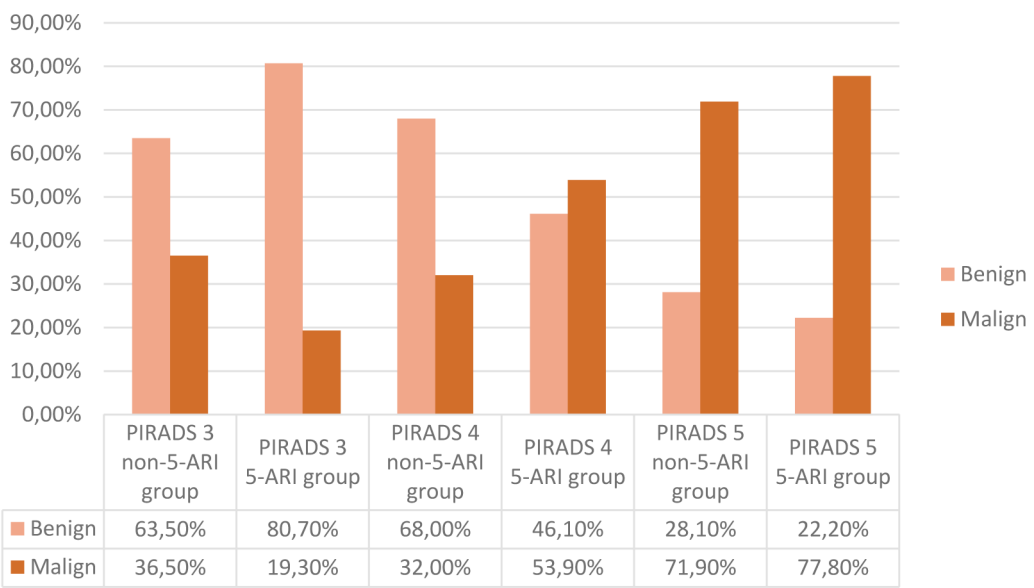|	PIRADS 3 non-5-ARI group	PIRADS 3 5-ARI group	PIRADS 4 non-5-ARI group	PIRADS 4 5-ARI group	PIRADS 5 non-5-ARI group	PIRADS 5 5-ARI group
Benign	63,50%	80,70%	68,00%	46,10%	28,10%	22,20%
Malign	36,50%	19,30%	32,00%	53,90%	71,90%	77,80%

FIGURE 3. Prostate Imaging-Reporting and Data System (PIRADS) subgroup malignancy rates in the group not using 5 alpha-reductase inhibitors (5-ARI) and the group using 5-ARI.

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ering the level of dihydrotestosterone, but the detected malignancies were of higher grade (13). Iczkowski et al reported that 5-ARI affected cellular involution and epithelial shrinkage of the prostate tissue, and increased the stromal/epithelial ratio in prostate cancer (17). 5-ARI can induce significant phenotypic changes in both benign and cancerous prostate tissue. In the MAPPED study (14), patients treated with 5-ARI experienced a reduction in prostate cancer volume on T2WI compared with placebo-treated patients ($P < 0.0001$). In this context, the intake of 5-ARI is expected to affect the interpretation of mpMRI (18,19).

However, other studies investigating the effects of 5-ARI on the quantitative parameters of cancerous and benign prostate lesions have yielded conflicting results. Giganti et al found that 0.5 mg 5-ARI, administered daily for six months, did not significantly affect T_2 contrast or T_2 relaxation values in men under active surveillance for prostate cancer (18). In a retrospective study involving 20 patients, Starobinets et al found a lower discrimination ability of T2WI between prostate cancer and benign tissue in the 5-ARI group than in controls, but for functional MR measurements, the discrimination was higher in the 5-ARI group (19).

In the study by Bekci et al, the sensitivity of mpMRI for detecting prostate cancer was 96%, and the specificity was 43% (20). At the same time, Loggitsi et al reported the sensitivity and specificity of mpMRI for prostate cancer to be 53% and 90.3%, respectively (21). In a meta-analysis of 3857 patients, the sensitivity of PIRADS v. 2-guided mpMRI to detect prostate cancer was 89% and the specificity was 73% (22). In our study, the sensitivity in the non-5-ARI group was 56.4%, and the specificity was 79.7%. In the 5-ARI group, the sensitivity was 84.9%, and the specificity was 56.8%. The sensitivity and specificity values in the non-5-ARI group were similar to those reported in previous studies. However, the sensitivity in the 5-ARI group was higher.

In our study, AUC analysis showed that the predictive ability of mpMRI to detect prostate cancer in the 5-ARI group was higher than in the non-5-ARI group. 5-ARI may cause more pronounced radiological changes in non-malignant prostate tissues; accordingly, mpMRI may have greater sensitivity in the detection of the cancerous area.

Giganti et al (15) showed that 5-ARI treatment increased tumor apparent diffusion coefficient and reduced conspicuity on DWI. The authors concluded that the prostate biopsy threshold in mpMRI should be lower in patients who used

5-ARI than in the general population (15). In our study, the number of patients with PIRADS 3 lesions was significantly higher in the group using 5-ARI. In addition, although the result was not significant, PIRADS≥4 lesions were less frequently observed in the 5-ARI group. This suggests that the use of 5-ARI may decrease the contrast enhancement of the lesions and DWI sequence visibility.

Other studies found similar PIRADS score distributions as in our study (23,24). In a study designed similarly to ours, Kim et al found a significant difference in the prostate cancer detection rate between the 5-ARI and non-5-ARI groups only in the PIRADS category ≥4 (75.0% vs 53.7%, $P = 0.031$) (25). Wang et al (26) observed a comparable distribution of PIRADS categories between the 5-ARI and non-5-ARI group. However, the overall prostate cancer detection was significantly reduced in the 5-ARI group (68.0% vs 46.3%) (26). The recently reported Prostate MRI Outcomes Database study concluded that 5-ARI exposure did not affect the PIRADS distribution (27). In this study, a higher rate of high-grade prostate cancer (ISUP>3) was observed in 5-ARI users with PIRADS 5 compared with 5-ARI non-users.

The total malignancy rates of both groups were similar. Although patients with PIRADS 3 and 5 scores from both groups had similar malignancy rates, 5-ARI patients with PIRADS 4 had a significantly higher malignancy rate. This finding should be taken into consideration in clinical practice.

Our study has some limitations. Although there is no prospective study about this topic in the literature, the retrospective nature of the study can be considered a limitation. Second, we did not evaluate the effect of 5-ARI on the clinically significant cancer because of the low number of patients in the subgroups.

In conclusion, our findings suggest that taking 5-ARI increases the sensitivity of mpMRI in detecting cancer but decreases its specificity. In addition, the malignancy rate in PIRADS 4 was higher in patients using 5-ARI. In light of the present findings, urologists and radiologists should be more cautious when interpreting the MRI findings in patients using 5-ARI.

to be submitted; all authors agree to be accountable for all aspects of the work.

Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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